Profiling and Identification of Post-Transcriptional Regulatory Molecules for Human Cancer Cachexia

by

Ashok Narasimhan

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Medical Sciences - Laboratory Medicine and Pathology
University of Alberta

Abstract

Cancer cachexia (CC) is a multifactorial syndrome characterized by severe depletion of skeletal muscle, with or without fat loss. A majority of cancer patients with incurable cancer are affected with cachexia and it remains an unmet medical need. Gene expression changes at the transcriptional level have been studied for CC in both humans and rodents. However, post-transcriptional regulatory mechanisms likely play a role in CC and are not addressed in the literature on human subjects, and are the focus of this thesis. It is well known that the sex-specific expression of genes contributes to traits and phenotypes. The role of autosomal expression of genes and their regulation at a post-transcriptional level in skeletal muscle from cancer cachexia patients has not been explored to account for the sex-specific differences in cachexia prevalence or severity. I hypothesize that CC, a manifestation of the net effect of complex host-tumor interactions and underlying molecular mechanisms, involves dysregulation of miRNAs and splice variants in skeletal muscle contributing to the pathophysiology of CC in a sex-specific manner.

The objectives of the thesis are (i) to profile miRNAs expressed in skeletal muscle biopsies and to identify Differentially Expressed (DE) miRNAs associated with human CC using Next Generation Sequencing (NGS), (ii) to profile Alternatively Spliced Genes (ASGs) from human skeletal muscle biopsies and to identify differentially expressed alternatively spliced genes (DASGs) associated with human CC using Human Transcriptome Array 2.0 (HTA 2.0) and (iii) to profile and identify sex-specific miRNAs and Differentially Expressed Isoform specific gene expression (DEI) for human CC.

Study subjects were classified based on the international consensus definition and diagnostic criteria for CC. Forty-two cancer patients were classified into 22 cachectic cases and 20 non-cachectic cancer controls who had no weight loss over a period of six months compared to their pre-illness weight. For identifying sex-specific expression differences, 22 cases and 20 controls were further stratified by sex. Body composition analysis was carried out using computed tomography (CT) taken prior to surgery. Total RNA was isolated from *rectus abdominis* muscle and used for NGS and HTA 2.0 arrays. Representative signatures were validated using qRT-PCR for cross platform concordance. Partek Genomics Suite v6.6 and SPSS v16 were used for bioinformatics and statistical analyses, respectively. Ingenuity pathway analysis (IPA) was used to identify canonical pathways and network analysis for biological interpretation.

777 miRNAs were profiled and 82 miRNAs with read counts of ≥ 5 in 80% of samples were retained for analysis. Eight miRNAs were DE (up-regulated, fold change of ≥ 1.4 at $p < 0.05$). IPA identified pathways related to myogenesis and inflammation. qRT-PCR analysis of representative miRs showed a similar direction of effect ($p < 0.05$), as observed in NGS. 8960 ASGs were identified, of which 922 DASGs (772 up-regulated, 150 down-regulated) were observed with ≥ 1.4 fold change and $p < 0.05$. Representative DASGs validated by semi-quantitative RT-PCR confirmed the primary findings from the HTA 2.0. Identified DASGs were associated with myogenesis, adipogenesis, protein ubiquitination and inflammation. Up to 10% of the DASGs exhibited cassette exon (exon included or skipped) as a predominant form of AS event. Other forms of AS events such as intron retention and alternative promoters were also observed. Sex-specific expression was observed both at the miRNA and at the DEI

levels. 10 upregulated miRNAs in males and 3 upregulated miRNAs in females were identified with ≥ 1.4 FC and $p < 0.05$. 1324 and 372 DEIs were identified in males and females, respectively. Pathways associated with skeletal muscle atrophy were predominant in males, whereas adipogenesis pathways were more common in females. Although the same upstream regulators were identified, their downstream targets were different between sexes. In all, my study has shown for the first time that post-transcriptional regulatory molecules are indeed associated with the pathophysiology of CC and are expressed in a sex-specific manner. This may potentially spur interests to address finer molecular mechanisms as an approach to personalized therapeutics development based on sex. Independent replications of the study findings are warranted. Functional characterization of the identified molecules may offer insights into their biological significance in cancer cachexia.

Preface

This thesis is an original study conducted by Ashok Narasimhan. Human skeletal muscle biopsies were collected after obtaining written informed consent from patients and this was approved by the Conjoint Health Research Ethics Board at the University of Calgary (Ethics ID E-17213). Further, post-biopsy molecular profiling of samples and collection of patient information was conducted under ethics protocol ETH-21709, which was approved by Health Research Ethics Board of Alberta (HREBA) – Cancer Committee.

Work from chapter 2 has been published in a peer-reviewed journal. The contributions from all the authors are listed below.

Chapter 2 - Small RNAome profiling from human skeletal muscle: Novel miRNAs and their targets associated with cancer cachexia

A version of this chapter has been published in J Cachexia Sarcopenia Muscle. 2017 Jan 6. doi: 10.1002/jcsm.12168. [Epub ahead of print].

Author list – Ashok Narasimhan, Sunita Ghosh, Cynthia Stretch, Russell Greiner, Oliver F Bathe, Vickie Baracos, Sambasivarao Damaraju

Contributions – Ashok Narasimhan performed data analysis for NGS and array datasets, conducted qRT-PCR experiments, analyzed and interpreted the data. Ashok Narasimhan and Sunita Ghosh performed statistical analysis. Cynthia Stretch provided clinical annotation for the study subjects. Muscle biopsies were provided by Oliver Bathe. Vickie Baracos provided CT analysis data and interpretations. Sambasivarao Damaraju is the principal investigator of the project who conceived the study and designed the experiments with Ashok Narasimhan. Manuscript preparation was by Ashok Narasimhan and Sambasivarao Damaraju. All contributing authors reviewed the manuscript and provided edits and suggestions

Dedicated to

To my ever-supportive parents and dear wife

Acknowledgements

I would like to thank my supervisor Dr. Sambasivarao Damaraju for offering his expertise on various facets of Omics platform, providing exceptional support and guidance during the tenure. I have learnt much about scientific writing and how to handle science with utmost integrity. He has been very instrumental in helping me finish my thesis and its related manuscripts within this time frame. As a part of the learning process, he has also played an important role in developing my interpersonal skills. He taught me science as a philosophy and to apply to day-to-day life. His door was always open for discussions all through the day. His 'anytime for students' approach is something that I would like to imbibe throughout my scientific career.

I would like to thank my co-supervisor Dr. Vickie Baracos. Her energy and wealth of information never ceases to amaze me and often overwhelms me. Every time I walk in to her office, I always come back with contentment knowing that I have learnt something new. If not cachexia, there is always arts, history and museums to discuss. Her philosophy about life and how to take it easy has impacted me positively. I am extremely fortunate to have worked and interacted with such a lovely person.

I would like to thank Dr. Russell Greiner for serving as a part of my committee. Some of his intriguing questions during our interaction have made me travel beyond boundaries in search of answers. I would also like to thank him for all his valuable inputs for my manuscripts.

I would like to thank Dr. Oliver Bathe for his expertise in surgical oncology and insights into cachexia from the clinician perspective. Without his help in providing the access to the clinical specimens, my research into cachexia would not have been complete. His constructive feedback on my manuscripts was very helpful and improved on the overall content of the manuscript. I would also like to thank Dr. Sunita Ghosh for teaching me the statistical rigor needed to do science and also for offering her statistical expertise during my studies. During our interactions, her words of wisdom on science and life have always enlightened me. It was a wonderful experience to work with her.

I would like to thank Dr. Teresa Zimmers and Dr. Toshifumi Yokota for being part of my examining committee. I am thankful to Dr. Monika Keelan for being an examiner for my candidacy exam and for also chairing my examinations. She has played an important role in motivating me during different stages of the graduate program with positive words and has been a pillar of support.

I would like to profoundly thank Ms. Cheryl Titus for helping me with various administrative work and for always welcoming us with a smile even during her busy schedule. I would like to thank Mr. Ronald Marinas and Ms. Femka Williams for their administrative support. I would like to thank Ms. Jennifer Dufour, Ms. Lillian Cook and Mr. Mesfin Fanta for their technical assistance and also for being great colleagues.

I would like to thank my colleague, friend Ms. Mahalakshmi Kumaran for her excellent support. On several occasions, she has helped me to understand some of the toughest concepts with utmost ease. It has been a memorable experience working with her. My special thanks to Dr. Seyyed Mohammad Kazemi Bajestani and Ms. Lisa Martin for readily sharing their knowledge on cachexia and for all the wonderful discussions that I have had with them.

I would like to thank Alberta Cancer Research Biobank/Canadian Breast Cancer Foundation for housing the precious muscle biopsies, without which this study could not have been possible. I would like to immensely thank all the study participants. I would also like to acknowledge Canadian Institutes of Health Research for providing the operating funds to Dr. Damaraju and Dr. Baracos.

I am indebted to my family for all their support. My parents, sister and in-laws have always showered me with love which has helped me brave through all situations with consummate ease. I am eternally thankful to my childhood friends Mr. Siddharth Rukmangathan and Dr. Kaushik Prakash for being part of the extended family and for supporting me all my life. Finally, I would like to thank my wife, my best half and my lab colleague – Preethi Krishnan, for her unconditional love and support. Her presence and calmness have indeed made this journey more meaningful and I will cherish this all my life.

Table of contents

List of Tables

List of Figures

Abbreviations

AS	Alternative Splicing
ASG	Alternatively Spliced Genes
ASV	Alternative Splice Variants
BMI	Body Mass Index
CC	Cancer Cachexia
CNS	Central Nervous System
CRP	C Reactive Protein
CNV	Copy Number Variants
DASG	Differentially Expressed Alternatively Spliced Genes
DE	Differentially Expressed
FABP4	Fatty Acid Binding Protein 4
FAR1	Fatty Acyl-CoA Reductase 1
FOXO	Forkhead box O
FTO	Fat Mass and Obesity Associated
GWAS	Genome Wide Association Studies
HIV1	Human Immunodeficiency Virus
HTA 2.0	Human Transcriptome Array
IGF1	Insulin Growth Factor 1
IL1	Interleukin-1
IL1β	Interleukin-1β
MAC	Murine Adenocarcinoma 16
MAFBX	Muscle Atrophy F-Box Protein
miRNAs	microRNAs
MRI	Magnetic Resonance Imaging
MURF1	Muscle RING Finger containing protein 1
NFKB	Nuclear Factor Kappa B Subunit 1
NGS	Next generation sequencing
PAX7	Paired Box 7
piRNAs	PIWI-Interacting RNAs

SMAD2	SMAD Family Member 2
snoRNAs	Small Nucleolar RNAs
TNFα	Tumor Necrosis Factor-α
UPP	Ubiquitin Proteasome system
WL	Weight Loss

1 Introduction and Review of Literature

1.1 Cancer Cachexia

Cancer Cachexia (CC) is a paraneoplastic syndrome characterized by severe depletion of skeletal muscle with or without fat loss. The condition cannot be reversed by conventional nutritional support (1, 2). CC is distinct from malnutrition, starvation and age-related muscle loss. It is estimated that one in four Canadians will die of cancer and cachexia may account for 30% of cancer-related deaths (3-5). Patients with CC have poor response to treatment, decreased performance status and decreased quality of life that ultimately impacts on their survival (6). The incidence of cachexia varies according to the cancer type. The highest incidence of cachexia is observed in patients with pancreatic cancer, gastric cancer, esophageal cancer and lung cancer (7-9). The cardinal diagnostic criterion of cachexia is the presence of involuntary weight loss, and in many studies in the past percent weight loss served as the sole diagnostic criterion. More recently attention has been paid to defining CC in a clinical setting more rigorously including additional key dimensions (10-12).

One of the challenges in CC research was to develop a consensus definition and diagnostic criteria to classify patients in a clinical setting. This was first addressed in 2008 where a generic definition of cachexia was proposed (1). In 2011, an international consensus definition and provisional diagnostic criteria for CC emerged. The definition was: “CC is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Cachexia pathophysiology is characterized by “a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism” (2). Several published studies in the recent years have increasingly adopted these definitions and provisional diagnostic criteria, attesting to the acceptance amongst the cachexia research community (13).

1.2 Molecular mechanisms underlying CC pathophysiology

1.2.1 Host-tumor interactions

Several mechanisms exist to explain the complexity involved in CC pathophysiology. One of the driving forces of CC pathophysiology is the involvement of complex host-tumor interactions; our understanding is still evolving (14-17). The presence of tumor eventually leads to aberrant host responses. The presence of a tumor affects the homeostasis of the human system, thereby leading to metabolic alterations in carbohydrate, protein and lipid metabolism (3). Systemic inflammation is also considered as one of the classic features of CC (17, 18). Systemic inflammation induced by tumor lead to aberrant host response, such as increased acute phase response (18). It has been reported that elevated levels of C-reactive protein (CRP) are associated with weight loss in CC (19, 20). Apart from these mechanisms, other factors such as appetite regulation (21, 22), neuro-endocrine alterations (23, 24), tumor-derived factors (25-27) and tumor microenvironment (28) have also been shown as potential contributors to CC pathophysiology. The above-mentioned mechanisms have profound implications in skeletal muscle (29-31) and adipose tissue (25, 32-34), eventually leading to cachexia. As mentioned before, the effects of host-tumor interactions in CC remains to be fully understood. The effect of CC on skeletal muscle will be discussed below which also forms the basis of my thesis.

1.3 Effect of CC on skeletal muscle from experimental models

1.3.1 Mechanisms associated with protein turnover

Skeletal muscle atrophy is one of the hallmarks of CC. Our understanding of various mechanisms associated with skeletal muscle atrophy commences from animal models. In a healthy state, there is always maintenance of steady protein turnover. In cachexia, there is an increased protein degradation and reduced protein synthesis accompanied with loss of myofibrillar proteins (3). One of the well-studied pathways contributing to muscle protein degradation is the ubiquitin proteasome pathway (UPP) (35). Khal et al. reported that activation of ubiquitin proteasome system leads to tremendous muscle loss and more than 10% weight loss in rodents (36). There are other

mechanisms, such as calpain-dependent mechanisms, that are activated upstream of UPP and which release the myofilaments that are subsequently ubiquitinated (37, 38). Another mechanism that has been an area of intense research is the role of autophagy in cancer biology (39) and in particular skeletal muscle and CC (40, 41). Autophagy has a central role in muscle homeostasis and evidence suggests that dysregulation of autophagy-related genes leads to muscle atrophy. A recent study also demonstrated that overexpression of autophagy-related genes is indeed observed in skeletal muscle of cachectic patients, eventually leading to skeletal muscle atrophy (42).

1.3.2 Signaling pathways associated with protein turnover and skeletal muscle wasting

Many inter- and intra-cellular signaling pathways are associated with protein turnover and in turn with muscle wasting. Inflammatory and tumor-derived mediators trigger a cascade of events leading to muscle wasting. Myostatin, a member of the transforming growth factor (TGF-β) family and a negative regulator of muscle mass, is overexpressed in cachexia and decreases protein synthesis through SMAD2 signaling (43). Myostatin through SMAD signaling can lead to FOXO activation, leading to an increased expression of ubiquitin ligases such as muscle atrophy F-box protein (MAFBX) and muscle RING finger-containing protein 1 (MURF1), which causes proteolysis of myofibrillar protein (3, 44, 45). Pro-inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α) and Interleukin-1 (IL-1) act through the NF-KB pathway and MAP kinase (MAPK) pathways to bring about muscle protein degradation (46). Glucocorticoids also act via FOXO, leading to up-regulation of the UPP, causing muscle atrophy (47). Insulin-like growth factor 1 (IGF-1), known for promoting protein synthesis via PI3K-AKT-mTOR pathways, is also suppressed in cachexia, leading to decreased protein synthesis (3). Angiotensin, a molecule in the renin-angiotensin system plays an important role in increasing protein degradation and decreasing protein synthesis by generating free radicals and inhibiting the IGF-1 signaling pathway (48).

1.3.3 Other contributory mechanisms to skeletal muscle atrophy

There are many other mechanisms that have been shown to contribute to muscle atrophy. One of the well-studied mechanisms in recent decade is the role of the central nervous system (CNS) in skeletal muscle atrophy. The hypothalamus is considered a master regulator of energy homeostasis. Inflammation induced in the CNS by Interleukin-1β (IL-1β) alone was shown to activate a catabolic program in muscle (3, 49, 50). The imbalance between orexigenic and anorexigenic signals affects appetite regulation. Molecules such as IL-1β, TNF-α play an important role in appetite regulation which eventually leads to muscle atrophy (51). Some of the recent advances made in the field of CC include the role of the muscle and tumor microenvironment in bringing about muscle atrophy. In cachexia, deregulation of Pax7 (transcription factor) under the influence of NFKB, impairs myogenic cell differentiation and prevents recovery of damaged muscle fibers. Overexpression of Pax7 leads to an increase in muscle wasting (52). It has been demonstrated that differences in the tumor microenvironment may have an impact on the progression of CC, mediated through the circulating tumor factors (53). Lastly, tumor-derived microvesicles have been shown to induce apoptosis of skeletal muscle (54). Many of these identified molecules and mechanisms await validation in human studies.

1.4 Perspective of CC from human studies

1.4.1 Clinical perspective and definition of CC

An overall definition for cachexia was proposed in 2006 by Evans et al. (1). As cachexia is observed in chronic heart failure, chronic kidney disease and cancer, the initial definition was generalized for all of the above-mentioned chronic conditions. From that point in time, significant progress has been made in understanding the clinical aspects of cachexia. Utilization of imaging techniques such as computed tomography (CT) has aided in the distinction between muscle and adipose tissues of patients in disease conditions (discussed subsequently). In cancer research, CT has been used effectively in assessing the presence of sarcopenia (severe depletion of muscle) along with fatty muscle detected as increased intermuscular adipose tissue and lowered values of muscle radiodensity (55-58). Although severe depletion of muscle (leading to net weight loss) is also seen in other chronic diseases, the mechanisms through which it can

occur in cancer may be different. Based on international collaborations and improved understanding of CC pathophysiology in the recent years, international consensus diagnostic criteria for CC was proposed in 2011. The proposed diagnostic criteria for CC were: (i) > 5% pre-illness weight loss (WL) over a period of six months; or (ii) > 2% WL with Body Mass Index (BMI) <20; or (iii) sarcopenia (defined by skeletal muscle index cut-points using CT) and >2%WL.

Reduced muscle mass has been suggested to be responsible for the morbidity and mortality associated with cancer cachexia (59). Diagnostic imaging has added to the diagnostic criteria, because for many patients the presence of muscle loss is obscured by their large overall weight and fat mass. Cachexia can be present in patients who do not appear thin or emaciated. It has been shown that patients with obesity along with sarcopenia have as poor a prognosis as those who appear underweight (60). Studies have shown that severe skeletal muscle depletion was an independent prognostic factor of survival (59). Recently, a grading system was proposed based on BMI and weight loss that showed that both initial BMI and weight loss are independently predictive of survival and that increasing weight loss is predictive of mortality across the entire range of BMI (61). These studies are significant as it continuously helps in improving our understanding of CC from the clinical standpoint.

1.4.1.1 Role of CT in assessing body composition

Measurement of body composition was not commonly- done in cancer patients until imaging techniques advanced and began to be used to guide the clinical decisions. The 3rd lumbar vertebra is used as a standard landmark for analyzing the total muscle and fat cross-sectional areas as these showed strong correlation to the whole body muscle and adipose tissue (59, 60, 62). Cross-sectional muscle area is normalized to patient stature (m^2) to calculate the skeletal muscle index (SMI) (cm^2/m^2). Muscle radiation attenuation (MA) (measured in Hounsfield Units, HU) is also captured for these patients. Radiation attenuation is a physical property of elements standardized to a scale that is anchored at -1000 HU (air) and 0 HU (water). Human tissue radiation attenuation values vary between approximately -200 HU for adipose tissue, 30-60 HU for muscle and organs and +400 HU for bone. Sarcopenia status is assigned based on age and sex-adjusted SMI values as

described earlier (60, 62). Use of CT has its own advantages. For example, as described above, a majority of cancer patients have a BMI of more than 25 kg/m^2 with few presenting with BMI of < 20 kg/m^2 due to the presence of obesity. However, there are conditions wherein a cancer patient may have BMI equated to overweight or obese but may be undergoing profound loss of skeletal muscle. In the absence of a CT, it would be difficult to assess the skeletal muscle depletion that could be hidden owing to their body weight. Many conditions such as sarcopenia, sarcopenic obesity (increased fat mass and reduced muscle mass), myosteatosis (deposition of fat in muscle) could be ascertained using CT imaging that is gaining increasing prominence as clinically important resources to ascertain the body composition and associated prognosticators or phenotypes. Sarcopenic obesity and myosteatosis were shown to be associated with poor survival in cancer patients (59, 63). Population-based cut-points have been estimated for sarcopenia, and these are being continuously improvised. Recent efforts have led to the development of age-adjusted, sex-specific cut-offs for defining the sarcopenic status of cancer patients (64). In all, combining the body composition measurements with traditional weight loss in classifying cancer patients for cachexia status could lead to a more robust classification of patients. Based on this premise, I have also classified the study subjects by combining weight loss information with body composition measurements. While muscle loss with age is a slow but gradual process, CC associated muscle loss is very rapid (rate of loss is an order of magnitude higher). In recognition of these differences, age-adjusted, sex-specific cut-offs from a large cohort of cancer patients are adopted as described earlier for the CC associated muscle depletion.

1.4.2 Summary of molecular perspectives in human CC

More than 40% of body weight is comprised of skeletal muscle and that muscle is used for performing various functions. Tissue-specific gene expression in muscle is important to carry out normal physiological functions. In cachexia, many of these genes may be dysregulated, which may contribute to muscle wasting. Current mechanistic understanding of gene expression and its regulation in CC has come from animal models. However, many of the molecules from animal models remain to be validated in human CC. Conflicting reports emerged when studies were compared between model systems

and humans (11). This could be due to the heterogeneity of CC as a condition that exists in human when compared to rodent models. For example, the genes involved in UPP components were invariably shown to be upregulated in preclinical models but conflicting reports have emerged when investigated in human skeletal muscle (65). To address these existing discrepancies, more studies need to be conducted using human samples. However, acquiring human samples for CC is very challenging and can be considered a rarity. Apart from the known mechanisms, many recently identified mechanisms at the cellular level had never been studied for CC in humans. Few of these challenges mentioned already highlights the immense amount of work that needs to be done in the field of CC to bridge the existing gap between animal and human studies. To uncover newer mechanisms or test the prevailing hypotheses in CC pathophysiology to a human setting requires clinically well-annotated muscle biopsy specimens from cancer patients, combined with advancements in technology.

1.4.2.1 Gene expression studies using microarray

The majority of the molecular understanding has come from the top-down approach, wherein a candidate molecule (for instance gene/mRNA) is investigated in greater depth to understand its role in a disease condition. Since CC is a multifactorial syndrome, there is a need to identify multiple genes for a phenotype. This was not possible earlier due lack of technological advancements. The advent of human genome project has played an important role in revolutionizing molecular biology. The introduction of high-throughput array based technologies such as microarray, aids in identifying expression levels of thousands of genes simultaneously at a genome-wide level. Identifying many genes at a snapshot can do two things: it can help confirm the previous gene findings associated with a phenotype and may also identify newer molecules associated (not previously associated) with a phenotype, which may give more insights about a phenotype under study.

1.4.2.1.1 Gene expression studies for human CC using microarray

So far, limited numbers of microarray-based gene expression studies have been addressed using human muscle biopsy specimens for CC and these experiments tried to capture the changes at the transcriptional level. For instance, Stephens et al.

identified 83 genes to be associated with CC using *rectus abdominis* muscle (11). When the 83 gene signatures were correlated with weight loss, CAMK2B was positively correlated to weight loss. Unfortunately, these authors did not have any muscle loss data. The study also highlighted that genes such as E3 ligases did not have similar direction of expression as observed in animal models. In the gene expression study carried out by Gallagher et al., paired muscle biopsies were obtained before and after removal of tumor. They showed that genes associated with protein turnover and metabolic alterations were restored to normal after tumor removal (10). Overall, these studies emphasized that there is a relative alteration in expression of genes observed in patients with CC when compared against a control group. This study used n = 21 microarray samples (18 cases and 3 controls). Although these are significant contributions, it also highlights the paucity of human muscle biopsy availabile for carrying out such studies. It is also interesting to note that other than the above-mentioned studies, to the best of my knowledge, gene expression studies conducted using microarray for human CC are uncommon. Microarray studies compare gene expression in cases vs. controls. These studies yield differential expression of genes, viz., mRNA profiles of hundreds or even thousands of genes. Hereafter I use the term "association study" to describe studies on DE of genes (and isoforms or transcripts) wherein the two phenotypes considered are labelled as a case and a control.

1.4.2.1.2 Case-control study design

The case-control study design has been used to identify many disease-related genes in hundreds of phenotypes ranging from diabetes (66), atherosclerosis (67) to CC (11). Normally, the study involves the use of apparently healthy controls against the affected cases associated with the phenotype under study, to identify the relative gene expression differences between the groups. While this is the norm, the same design may be adopted for several other scenarios where a case or a control status is defined and also the research question being addressed. For example, some of the gene expression microarray studies have used human skeletal muscle biopsies obtained from cancer patients for both cases and controls. Cancer patients with cachexia were classified as cases, whereas cancer patients with no cachexia were classified as controls. While it is possible to obtain muscle biopsies from cancer patients who are undergoing surgery, the

same may not be possible for healthy individuals for whom the biopsy is an unnecessarily invasive procedure. In rare instances, muscle biopsies may be obtained from individuals who are undergoing abdominal surgery for non-tumor-related conditions. These can be considered as apparently healthy controls and has been used in very few studies (11, 68). Muscle biopsies obtained from cancer patients can be classified into cachectic cases and non-cachectic controls. The advantage of using this binary is that the effect of cancer-related cachexia may be captured. Healthy controls are used to detect the effect of cancer and not the effect of cachexia vs. non-cachectic individuals. Therefore, to study the effect of variations among the cancer patients (cachectic vs. non-cachectic), here I have used muscle biopsies from cancer patients for both cases and controls.

1.5 Advancements in high-throughput technologies

1.5.1 Evolution of microarrays

Rapid technological advancements made in the post-genomic era has given us platforms with a better resolution corresponding to improved accuracy in the results (69). The array technology used in the above mentioned CC studies were the traditional microarray or earlier versions of the array. These arrays are 3' biased; i.e., oligo-dT primers anneal to the poly-A tail of the transcript and the reverse transcriptase often does not transcribe the entire length of the longer mRNAs, resulting in the capture of exonic regions from the 3' end and 5' exons are missed or under-represented. These microarrays also have less genome coverage. For example, if a gene has 10 exons, the probes for 3' arrays are designed only to a couple of exons from the 3' end of the array. The limitation of 3' arrays led to the development of an exon array with the probes distributed throughout the entire gene. In the 3' arrays, the primers attach to the poly-A-tail of mRNAs whereas the exon arrays utilize random primers, effectively eliminating 3' bias. Improved understanding of various complex molecular mechanisms was paralleled with advancements in the existing technology. In the post-genomic era, it was increasingly recognized that measuring gene expression was a reflection of an overall picture. During mRNA processing, there are many intermediary mechanisms that occur within a gene before it gets translated into protein. It is recognized that more than 90 % of human genes are alternatively spliced (see detailed explanations in Chapter 3), which therefore led to

the development of human transcriptome array 2.0 (HTA 2.0). This array contains both the coding and the non-coding portions of the genome covering every gene with 10 probes per exon. HTA 2.0 is the most comprehensive array that has been developed to date. Use of exon arrays and HTA 2.0 has led to more accurate results when compared with the traditional 3' arrays (70). The fact that HTA 2.0 also covers the non-coding portion of the genome, offers an opportunity to identify novel molecules associated with the disease and also underlying mechanisms that may have been missed in earlier technology. Many of the gene expression studies for various diseases had been carried out using microarrays (71). They are relatively cost-effective and the data generation process is also fairly quick. However, array technologies are also affected by certain inherent issues such as limited dynamic range of detection (four orders of magnitude). Further, the array platforms do not offer insights into non-annotated regions of the genome, mutations, and fusion transcripts. One should, therefore, consider Next Generation Sequencing (NGS) to overcome these limitations and sequence the genome in an unbiased manner (all transcripts are sequenced regardless of annotation and the data can be re-visited as the genome is continuously being annotated as discussed in the next section).

1.5.2 Next generation sequencing platform

Next Generation Sequencing (NGS) allows sequencing of millions of reads in parallel, thereby offering more coverage than any other existing array-based platforms. Studies on transcriptome profiling, both at transcriptional (mRNA level) and at post-transcriptional level (isoforms) (72), non-coding RNA profiling (73), and mutational detection can all be performed using NGS. NGS can also be used to identify rarer transcripts, allele-specific gene expression, and gene-fusion. There are many advantages using NGS: (i) specificity and sensitivity of NGS is higher where it can capture molecules present in low abundance (10 orders of magnitude) compared to array-based technology (74), (ii) NGS captures absolute read counts and is capable of capturing reads with even a single nucleotide difference, (iii) Sequence information can be used to study different RNA populations. For example, in case of small non-coding RNAs, if alignment files were generated to study the role of microRNAs (miRNAs), the same file can also be

re-aligned to other small non-coding RNAs such as piRNAs, snoRNAs and tRNAs to any genome build of interest. This is not possible when an array-based technology is used for studying only one class of molecules at a time. Conversely, NGS has its own technical and experimental biases such as batch effects and biases in sample preparation (75). Moreover, large volumes of data are generated, the analysis and interpretation of data are quite complex. Another important issue to consider is the cost involved in performing NGS experiments. For every class of molecules to be studied, the protocols involved are complex and are equally expensive.

In summary, every technology has its own advantages and limitations. The use of any platform purely depends on the kind of research question under study. Therefore decision making should be based on the combination of valid research questions aided by the use of proper technological platform. For example, if the aim of a project is to identify isoform specific gene expression and not any rarer isoforms or gene fusions, it would be sufficient to use HTA 2.0 arrays. There is also evidence to suggest that exon measurements are more sensitive in HTA 2.0 when compared to RNA sequencing (76). These strategies need to be considered until such time the sequencing technologies can be made available at affordable cost.

1.6 Existing gaps in CC literature

From the literature review, it is evident that: (i) most literature on CC is from animal models, (ii) few studies have been carried out using human muscle biopsy samples (owing to the difficulty in obtaining samples), (iii) conflicting results were obtained when findings from animal models were extrapolated to human studies and (iv) there have only been a few human transcriptome studies to understand the pathophysiology of CC using microarrays.

(a) The role of post-transcriptional gene regulatory mechanisms for CC has not been addressed in humans and very few studies have been carried out to date in model systems. The central dogma of molecular biology, proposed in 1958, stated that DNA is transcribed to RNA, which eventually translates to proteins. Between 1970 and 1980, there were additional layers of information that were added to the existing central dogma, a reflection of our ever-improving

understanding of molecular biology. These additional layers are the intermediary mechanisms between transcription and translation. It was once thought that when a DNA is transcribed into mRNA, it will invariably be translated into proteins to carry out their functions. However, with our latest understanding, we realize that the transcribed mRNA may have other outcomes. These mRNAs or genes may be either silenced by molecules present higher in the hierarchy leading to gene regulation, which in turn affects protein synthesis. The molecules that bring about gene silencing are a class of small non-coding RNAs and the most studied subclass is the microRNA or miRNAs, also called miRs (77). It is also recognized that a single mRNA can give rise to different isoforms, giving rise to different proteins that may perform different functions. This mechanism is known as Alternative Splicing (78-80). These two different mechanisms that regulate gene expression and generate different isoforms are types of post-transcriptional gene regulatory mechanisms.

(b) CC is found to be more prevalent in men, compared to women. It has been reported that weight loss and skeletal muscle loss are greater in male cancer patients, compared to female cancer patients (55). In addition, clinical studies in CC have shown a dimorphic pattern in lower limb muscle mass and its functions. It has been reported that the mechanical quality of the muscle progressively declines in females, relative to males. Physical function and quality of life scores were reduced in male cachectic patients but not in females (81). Clearly, a sexually dimorphic pattern exists in the prevalence and severity of CC. However, the molecular mechanisms that contribute to these differences have not been studied to date for human CC. Here, I have focused on the post-transcriptional regulatory molecules to comprehend the overall and sex-specific differences at the molecular level.

Addressing these gaps may help us identify new molecules associated with CC, understand their biological relevance, and gain insights into pathophysiology. A brief summary of these regulatory mechanisms and their role in sexual dimorphism is explained in subsequent sections.

1.7 microRNAs and Cancer Cachexia

The non-coding part of the genome previously dubbed as “genomic junk” is increasingly being recognized as playing varied regulatory roles in normal physiological processes. One such class of small non-coding RNAs is the microRNAs (miRNAs), which are 18-25 nucleotides in length and are considered global regulators of gene expression. They were discovered in 1993 in *C. elegans* (82). miRNAs are highly conserved across species (83). They bring about translational repression or mRNA degradation by primarily binding to 3’ untranslated region (3’UTR) of mRNA. miRNAs are both pleiotropic and redundant in nature, i.e., a single miRNA can target hundreds of target genes and multiple individual miRNAs may act upon the same gene, respectively (84). They play a role in normal physiological processes such as cell differentiation and apoptosis in skeletal muscle (85). A suite of miRNAs called as myomiRs were shown to be involved in myogenesis (86). Dysregulation of miRNAs is associated with various disease states. For example, deregulation of miRNAs were shown to be associated with myotonic dystrophy and Duchenne Muscular Dystrophy (DMD) (87). In rodent models, it was shown that overexpression of miRNAs lead to apoptosis of skeletal muscle thereby contributing to muscle atrophy (54). However, the role of miRNAs in human skeletal muscle has never been studied for CC. Studying this aspect may help us identify the different miRNAs that are associated with CC. As miRNAs act a step higher in the hierarchy by regulating gene expression (mRNAs), identification of mRNA targets may help us in understanding different pathways that may be involved in CC pathophysiology, a novel aspect of my study. This may eventually help us targeting those pathways that may reduce the activity of muscle atrophy thereby improve the quality of life in patients suffering from CC.

1.8 Alternative splicing and Cancer Cachexia

Alternative splicing (AS) is another post-transcriptional regulatory mechanism where multiple isoforms are generated from a single pre-mRNA. This is a crucial intermediate step between transcription and translation, which leads to an increase in proteome diversity (79, 80). Mechanism of AS is complex and precise, leading to flawless splicing of introns and joining of exons (88). To precisely accomplish the

splicing process there are regulatory proteins, namely splicing enhancers and silencers, that help in activating and suppressing splice site recognition, respectively (89). Recent studies have shown that more than 90% of genes in humans are alternatively spliced (90) and that aberrant splicing contributes to the pathogenesis of diseases such as cancer and skeletal muscle-related diseases, including muscular dystrophy (88) and myotonic dystrophy (91) . Interestingly, among several other tissues, muscle was one of the first in which AS was observed, in contractile protein genes (92). Alternative Splice Variants (ASVs) have been reported as biomarkers for pancreatic cancer (71), colorectal cancer, and skeletal muscle-related diseases (88, 93). ASVs identified from DMD are now targeted for therapy through clinical trials, emphasizing the importance of ASVs in disease pathology (94). However, the role of AS in CC has never been studied. Studying AS may help us understand isoform-specific expression and also helps us identify the affected exon in the expressed isoform. This has been made possible only by major technological advancements where every exon (even putative exons based on *in silico* predictions) of every isoform has been captured to give a finer resolution capture of the expression.

It is now demonstrated that exon arrays accurately capture the individual exons in a gene compared to a 3' biased arrays. In the 3' biased arrays, the expression of probe intensities on a microarray may in some genes, encompass isoforms and yet, these isoforms are not individually distinguished (69). As with 3' biased conventional arrays, the exon arrays offer the flexibility to also interrogate the data for the whole gene level expression but the signals are estimated as average signal intensity from all probes spanning all isoforms. Traditional microarrays with 3' bias, do not offer insights into the exon from which a probe is arrayed and upon hybridization, the probe intensities are not traceable to specific isoforms. However, it is increasingly recognized that it is the isoform (called "transcripts" for the remainder of my thesis) of a gene that is expressed in a tissue-specific manner but not the gene *per se* (95, 96). Quite often, in the literature, the gene often represents mRNA, but the specific isoform is not obvious and it is difficult to make finer interpretations, as isoforms are tissue-specific and each tissue may express different isoforms. The relative abundance of each isoform is, therefore, important to confer the phenotype and these subtle distinctions were not captured in previous profiling

studies. Therefore, studying AS may help us identify the specific isoforms and exons affected for CC leading to a finer understanding of the underlying mechanisms, constituting a novel aspect of my study.

1.9 Sexual dimorphism and Cancer Cachexia

Sexual Dimorphism is observed at every level, ranging from tissue, chromosomes and even at the cellular level (97, 98). Sex-specific differences have been observed in physiological and pathological states such as diabetes, obesity and cancer (99-101). There is evidence to suggest that sexual dimorphism has an enormous impact in terms of adverse drug reactions and can have severe implications (102, 103). However, few studies to date addressed the role of sexual dimorphism in CC. As explained in section 1.6, men and women show differences in the prevalence and severity of CC. It is recognized that men are more muscular and women have more fat (104). Baracos et al. have reported that men lose more muscle and weight than women and are more prone to CC (55). This already depicts that there are some dimorphic patterns exhibited between sexes in CC. This would also mean that to attain these changes in disease states, there might be changes at the molecular level as well. Therefore, clinical observations at the body composition levels need to be taken forward to understand if these changes are indeed reflected at the molecular levels in CC to understand if sex-specific expression patterns really exist. Although sex-specific adverse drug reaction has not been observed in CC to date, this scenario is still possible . If there are indeed going to be differences observed at the molecular level between sexes, this may have an impact in the way the future studies are designed for clinical trials.. Interestingly, molecular changes at the post-transcriptional level for Sexual Dimorphism in human CC have never been studied.

The novelty of my thesis not only lies in the hitherto unexplored post-transcriptional regulation in skeletal muscle in patients with cancer cachexia, but also in the utilization of the same biopsy material to profile both miRNAs and splice variants to identify sex-specific signatures. This has enabled me to interrogate the targets for miRNAs to specific isoforms of mRNAs as an approach to functionally validate the targets.

1.10 Hypothesis

Dysregulation of miRNAs and mRNA splice variants in skeletal muscle affect pathways contributing to the pathophysiology of CC in a sex-specific manner.

1.11 Specific objectives of thesis

Specific objectives of my thesis were:

(i) To profile miRNAs expressed in skeletal muscle biopsies and to identify Differentially Expressed (DE) miRNAs associated with human CC using Next Generation Sequencing (Addressed in Chapter 2).

(ii) To profile alternatively spliced genes (ASGs) from human skeletal muscle biopsies and to identify differentially expressed alternatively spliced genes (DASGs) associated with human CC on a genome-wide scale using Human Transcriptome array 2.0 (Addressed in Chapter 3)

(iii) To profile and identify sex-specific miRNAs and isoform-specific gene expression for human CC

The three specific objectives have been organized into distinct chapters. Objective 1 is described in chapter 2 of this thesis. Objectives 2 and 3 form chapters 3 and 4 of this thesis, respectively. Overall discussion, conclusions and future directions are explained in chapters 5 and 6, respectively.

1.12 References

1. Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clinical nutrition. 2008;27(6):793-9.

2. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology. 2011;12(5):489-95.

3. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nature reviews Cancer. 2014;14(11):754-62.

4. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. American Journal of Medicine. 1980;69(4):491-7.

5. Farkas J, von Haehling S, Kalantar-Zadeh K, Morley JE, Anker SD, Lainscak M. Cachexia as a major public health problem: frequent, costly, and deadly. Journal of cachexia, sarcopenia and muscle. 2013;4(3):173-8.

6. Muscaritoli M, Bossola M, Aversa Z, Bellantone R, Rossi Fanelli F. Prevention and treatment of cancer cachexia: new insights into an old problem. European journal of cancer. 2006;42(1):31-41.

7. Tan BH, Fladvad T, Braun TP, Vigano A, Strasser F, Deans DA, et al. P-selectin genotype is associated with the development of cancer cachexia. EMBO molecular medicine. 2012;4(6):462-71.

8. Tisdale MJ. Mechanisms of cancer cachexia. Physiological reviews. 2009;89(2):381-410.

9. Fearon KC, Baracos VE. Cachexia in pancreatic cancer: new treatment options and measures of success. HPB : the official journal of the International Hepato Pancreato Biliary Association. 2010;12(5):323-4.

10. Gallagher IJ, Stephens NA, MacDonald AJ, Skipworth RJ, Husi H, Greig CA, et al. Suppression of skeletal muscle turnover in cancer cachexia: evidence from the

transcriptome in sequential human muscle biopsies. Clinical cancer research : an official journal of the American Association for Cancer Research. 2012;18(10):2817-27.

11. Stephens NA, Gallagher IJ, Rooyackers O, Skipworth RJ, Tan BH, Marstrand T, et al. Using transcriptomics to identify and validate novel biomarkers of human skeletal muscle cancer cachexia. Genome Med. 2010;2(1):1.

12. Kulyte A, Lorente-Cebrian S, Gao H, Mejhert N, Agustsson T, Arner P, et al. MicroRNA profiling links miR-378 to enhanced adipocyte lipolysis in human cancer cachexia. American journal of physiology Endocrinology and metabolism. 2014;306(3):E267-74.

13. Op dK, Langen RC, Minnaard R, Kelders MC, Snepvangers FJ, Hesselink MK, et al. Pre-cachexia in patients with stages I–III non-small cell lung cancer: Systemic inflammation and functional impairment without activation of skeletal muscle ubiquitin proteasome system. Lung cancer. 2012;76:112-7.

14. MacDonald N, Easson AM, Mazurak VC, Dunn GP, Baracos VE. Understanding and managing cancer cachexia. Journal of the American College of Surgeons. 2003;197(1):143-61.

15. Kern KA, Norton JA. Cancer cachexia. Journal of Parenteral and Enteral Nutrition. 1988;12(3):286-98.

16. Skipworth RJ, Stewart GD, Dejong CH, Preston T, Fearon KC. Pathophysiology of cancer cachexia: much more than host-tumour interaction? Clinical nutrition. 2007;26(6):667-76.

17. Argiles JM, Busquets S, Toledo M, Lopez-Soriano FJ. The role of cytokines in cancer cachexia. Current Opinion in Supportive & Palliative Care. 2009;3(4):263-8.

18. Onesti JK, Guttridge DC. Inflammation based regulation of cancer cachexia. Biomed Res Int. 2014;2014:168407.

19. Fearon KC, Voss AC, Hustead DS, Cancer Cachexia Study G. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. The American journal of clinical nutrition. 2006;83(6):1345-50.

20. Mahmoud FA, Rivera NI. The role of C-reactive protein as a prognostic indicator in advanced cancer. Curr Oncol Rep. 2002;4(3):250-5.

21. Guillory B, Splenser A, Garcia J. The role of ghrelin in anorexia-cachexia syndromes. Vitamins & Hormones. 2013;92:61-106.

22. Steinman J, DeBoer MD. Treatment of cachexia: melanocortin and ghrelin interventions. Vitamins & Hormones. 2013;92:197-242.

23. Inui A. Neuropeptide Y: a key molecule in anorexia and cachexia in wasting disorders? Molecular medicine today. 1999;5(2):79-85.

24. Inui A, Meguid MM. Cachexia and obesity: two sides of one coin? Current Opinion in Clinical Nutrition & Metabolic Care. 2003;6(4):395-9.

25. Bing C, Bao Y, Jenkins J, Sanders P, Manieri M, Cinti S, et al. Zinc-alpha2-glycoprotein, a lipid mobilizing factor, is expressed in adipocytes and is up-regulated in mice with cancer cachexia. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(8):2500-5.

26. Cahlin C, Korner A, Axelsson H, Wang W, Lundholm K, Svanberg E. Experimental cancer cachexia: the role of host-derived cytokines interleukin (IL)-6, IL-12, interferon-gamma, and tumor necrosis factor alpha evaluated in gene knockout, tumor-bearing mice on C57 Bl background and eicosanoid-dependent cachexia. Cancer research. 2000;60(19):5488-93.

27. Kir S, White JP, Kleiner S, Kazak L, Cohen P, Baracos VE, et al. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. Nature. 2014;513(7516):100-4.

28. He WA, Berardi E, Cardillo VM, Acharyya S, Aulino P, Thomas-Ahner J, et al. NF-kappaB-mediated Pax7 dysregulation in the muscle microenvironment promotes cancer cachexia. Journal of Clinical Investigation. 2013;123(11):4821-35.

29. Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L, Clarke BA, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. Science. 2001;294(5547):1704-8.

30. Gomes MD, Lecker SH, Jagoe RT, Navon A, Goldberg AL. Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(25):14440-5.

31. Suzuki ASAIJ. The temporal specific role of WNT/β-catenin signaling during myogenesis. Journal of Nature and Science. 2015;1(8).

32. Tisdale MJ. Catabolic mediators of cancer cachexia. Current Opinion in Supportive & Palliative Care. 2008;2(4):256-61.

33. Das SK, Hoefler G. The role of triglyceride lipases in cancer associated cachexia. Trends in molecular medicine. 2013;19(5):292-301.

34. Thompson MP, Cooper ST, Parry BR, Tuckey JA. Increased expression of the mRNA for hormone-sensitive lipase in adipose tissue of cancer patients. Biochimica et biophysica acta. 1993;1180(3):236-42.

35. Argiles JM, Lopez-Soriano FJ. The ubiquitin-dependent proteolytic pathway in skeletal muscle: its role in pathological states. Trends in pharmacological sciences. 1996;17(6):223-6.

36. Khal J, Wyke SM, Russell ST, Hine AV, Tisdale MJ. Expression of the ubiquitin-proteasome pathway and muscle loss in experimental cancer cachexia. British journal of cancer. 2005;93(7):774-80.

37. Hasselgren PO, Wray C, Mammen J. Molecular regulation of muscle cachexia: it may be more than the proteasome. Biochemical and biophysical research communications. 2002;290(1):1-10.

38. Smith IJ, Aversa Z, Hasselgren PO, Pacelli F, Rosa F, Doglietto GB, et al. Calpain activity is increased in skeletal muscle from gastric cancer patients with no or minimal weight loss. Muscle Nerve. 2011;43(3):410-4.

39. Mathew R, Karantza-Wadsworth V, White E. Role of autophagy in cancer. Nature reviews Cancer. 2007;7(12):961-7.

40. Penna F, Costamagna D, Pin F, Camperi A, Fanzani A, Chiarpotto EM, et al. Autophagic degradation contributes to muscle wasting in cancer cachexia. The American journal of pathology. 2013;182(4):1367-78.

41. Penna F, Baccino FM, Costelli P. Coming back: autophagy in cachexia. Current opinion in clinical nutrition and metabolic care. 2014;17(3):241-6.

42. Aversa Z, Pin F, Lucia S, Penna F, Verzaro R, Fazi M, et al. Autophagy is induced in the skeletal muscle of cachectic cancer patients. Sci Rep. 2016;6:30340.

43. Bonnieu A, Carnac G, Vernus B. Myostatin in the Pathophysiology of Skeletal Muscle. Current Genomics. 2007;8(7):415.

44. Tisdale MJ. Mechanisms of cancer cachexia. Physiol Rev. 2009;89(2):381-410.

45. Elkina Y, von Haehling S, Anker SD, Springer J. The role of myostatin in muscle wasting: an overview. Journal of cachexia, sarcopenia and muscle. 2011;2(3):143-51.

46. Inacio Pinto N, Carnier J, Oyama LM, Otoch JP, Alcantara PS, Tokeshi F, et al. Cancer as a Proinflammatory Environment: Metastasis and Cachexia. Mediators Inflamm. 2015;2015:791060.

47. Schakman O, Kalista S, Barbe C, Loumaye A, Thissen JP. Glucocorticoid-induced skeletal muscle atrophy. The international journal of biochemistry & cell biology. 2013;45(10):2163-72.

48. Yoshida T, Tabony AM, Galvez S, Mitch WE, Higashi Y, Sukhanov S, et al. Molecular mechanisms and signaling pathways of angiotensin II-induced muscle wasting: potential therapeutic targets for cardiac cachexia. The international journal of biochemistry & cell biology. 2013;45(10):2322-32.

49. Braun TP, Zhu X, Szumowski M, Scott GD, Grossberg AJ, Levasseur PR, et al. Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic-pituitary-adrenal axis. The Journal of experimental medicine. 2011;208(12):2449-63.

50. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nature reviews Clinical oncology. 2013;10(2):90-9.

51. Inui A, Meguid MM. Cachexia and obesity: two sides of one coin? Current opinion in clinical nutrition and metabolic care. 2003;6(4):395-9.

52. He WA, Berardi E, Cardillo VM, Acharyya S, Aulino P, Thomas-Ahner J, et al. NF-kappaB-mediated Pax7 dysregulation in the muscle microenvironment promotes cancer cachexia. The Journal of clinical investigation. 2013;123(11):4821-35.

53. Matsuyama T, Ishikawa T, Okayama T, Oka K, Adachi S, Mizushima K, et al. Tumor inoculation site affects the development of cancer cachexia and muscle wasting. Int J Cancer. 2015;137(11):2558-65.

54. He WA, Calore F, Londhe P, Canella A, Guttridge DC, Croce CM. Microvesicles containing miRNAs promote muscle cell death in cancer cachexia via TLR7. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(12):4525-9.

55. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. The American journal of clinical nutrition. 2010;91(4):1133S-7S.

56. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2008;33(5):997-1006.

57. Du Y, Karvellas CJ, Baracos V, Williams DC, Khadaroo RG, Acute C, et al. Sarcopenia is a predictor of outcomes in very elderly patients undergoing emergency surgery. Surgery. 2014;156(3):521-7.

58. Antoun S, Baracos VE, Birdsell L, Escudier B, Sawyer MB. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2010;21(8):1594-8.

59. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47.

60. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncology. 2008;9(7):629-35 7p.

61. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(1):90-9.

62. Esfandiari N, Ghosh S, Prado CM, Martin L, Mazurak V, Baracos VE. Age, Obesity, Sarcopenia, and Proximity to Death Explain Reduced Mean Muscle Attenuation in Patients with Advanced Cancer. The Journal of frailty & aging. 2014;3(1):3-8.

63. Esfandiari N, Ghosh S, Prado CMM, Martin L, Mazurak V, Baracos VE. Age, Obesity, Sarcopenia, and Proximity to Death Explain Reduced Mean Muscle Attenuation in Patients with Advanced Cancer. The Journal of frailty & aging. 2014;3(1):3-8.

64. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Seminars in cell & developmental biology. 2016;54:2-10.

65. D'Orlando C, Marzetti E, Francois S, Lorenzi M, Conti V, di Stasio E, et al. Gastric cancer does not affect the expression of atrophy-related genes in human skeletal muscle. Muscle Nerve. 2014;49(4):528-33.

66. Reece EA, Ji I, Wu YK, Zhao Z. Characterization of differential gene expression profiles in diabetic embryopathy using DNA microarray analysis. Am J Obstet Gynecol. 2006;195(4):1075-80.

67. Laguna JC, Alegret M. Regulation of gene expression in atherosclerosis: insights from microarray studies in monocytes/macrophages. Pharmacogenomics. 2012;13(4):477-95.

68. Op den Kamp CM, Gosker HR, Lagarde S, Tan DY, Snepvangers FJ, Dingemans AM, et al. Preserved muscle oxidative metabolic phenotype in newly diagnosed non-small cell lung cancer cachexia. Journal of cachexia, sarcopenia and muscle. 2015;6(2):164-73.

69. Lee C, Roy M. Analysis of alternative splicing with microarrays: successes and challenges. Genome Biol. 2004;5(7):231.

70. Kapur K, Xing Y, Ouyang Z, Wong WH. Exon arrays provide accurate assessments of gene expression. Genome biology. 2007;8(5):R82.

71. Arafat H, Lazar M, Salem K, Chipitsyna G, Gong Q, Pan TC, et al. Tumor-specific expression and alternative splicing of the COL6A3 gene in pancreatic cancer. Surgery. 2011;150(2):306-15.

72. Mutz KO, Heilkenbrinker A, Lonne M, Walter JG, Stahl F. Transcriptome analysis using next-generation sequencing. Curr Opin Biotechnol. 2013;24(1):22-30.

73. Krishnan P, Ghosh S, Wang B, Li D, Narasimhan A, Berendt R, et al. Next generation sequencing profiling identifies miR-574-3p and miR-660-5p as potential novel prognostic markers for breast cancer. BMC genomics. 2015;16:735.

74. Tam S, de Borja R, Tsao MS, McPherson JD. Robust global microRNA expression profiling using next-generation sequencing technologies. Laboratory Investigation. 2014;94(3):350-8.

75. Taub MA, Corrada Bravo H, Irizarry RA. Overcoming bias and systematic errors in next generation sequencing data. Genome Med. 2010;2(12):87.

76. Xu W, Seok J, Mindrinos MN, Schweitzer AC, Jiang H, Wilhelmy J, et al. Human transcriptome array for high-throughput clinical studies. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(9):3707-12.

77. Bartel DP. MicroRNAs. Cell.116(2):281-97.

78. Black DL. Mechanisms of alternative pre-messenger RNA splicing. Annual review of biochemistry. 2003;72:291-336.

79. Boue S, Letunic I, Bork P. Alternative splicing and evolution. Bioessays. 2003;25(11):1031-4.

80. Faustino NA, Cooper TA. Pre-mRNA splicing and human disease. Genes & development. 2003(4):419.

81. Stephens NA, Gray C, MacDonald AJ, Tan BH, Gallagher IJ, Skipworth RJ, et al. Sexual dimorphism modulates the impact of cancer cachexia on lower limb muscle mass and function. Clinical nutrition. 2012;31(4):499-505.

82. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75(5):843-54.

83. Lall S, Grun D, Krek A, Chen K, Wang YL, Dewey CN, et al. A genome-wide map of conserved microRNA targets in C. elegans. Current biology : CB. 2006;16(5):460-71.

84. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281-97.

85. Liang Y, Ridzon D, Wong L, Chen C. Characterization of microRNA expression profiles in normal human tissues. BMC genomics. 2007;8:166.

86. Guller I, Russell AP. MicroRNAs in skeletal muscle: their role and regulation in development, disease and function. Journal of Physiology. 2010;588(Pt 21):4075-87.

87. Li X, Li Y, Zhao L, Zhang D, Yao X, Zhang H, et al. Circulating Muscle-specific miRNAs in Duchenne Muscular Dystrophy Patients. Molecular TherapyNucleic Acids. 2014;3:e177.

88. Pistoni M, Ghigna C, Gabellini D. Alternative splicing and muscular dystrophy. RNA biology. 2010;7(4):441-52.

89. Gamazon ER, Stranger BE. Genomics of alternative splicing: evolution, development and pathophysiology. Human genetics. 2014;133(6):679-87.

90. Lu ZX, Jiang P, Xing Y. Genetic variation of pre-mRNA alternative splicing in human populations. Wiley Interdisciplinary Reviews. 2012;3(4):581-92.

91. Perfetti A, Greco S, Fasanaro P, Bugiardini E, Cardani R, Garcia-Manteiga JM, et al. Genome wide identification of aberrant alternative splicing events in myotonic dystrophy type 2. PloS one. 2014;9(4):e93983.

92. Llorian M, Smith CW. Decoding muscle alternative splicing. Current opinion in genetics & development. 2011;21(4):380-7.

93. Fan X, Tang L. Aberrant and alternative splicing in skeletal system disease. Gene. 2013;528(1):21-6.

94. Kole R, Leppert BJ. Targeting mRNA splicing as a potential treatment for Duchenne muscular dystrophy. Discovery Medicine. 2012;14(74):59-69.

95. Sekiyama Y, Suzuki H, Tsukahara T. Functional gene expression analysis of tissue-specific isoforms of Mef2c. Cellular and molecular neurobiology. 2012;32(1):129-39.

96. Mosthaf L, Grako K, Dull TJ, Coussens L, Ullrich A, McClain DA. Functionally distinct insulin receptors generated by tissue-specific alternative splicing. The EMBO journal. 1990;9(8):2409-13.

97. Penaloza C, Estevez B, Orlanski S, Sikorska M, Walker R, Smith C, et al. Sex of the cell dictates its response: differential gene expression and sensitivity to cell death inducing stress in male and female cells. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2009;23(6):1869-79.

98. Yang X, Schadt EE, Wang S, Wang H, Arnold AP, Ingram-Drake L, et al. Tissue-specific expression and regulation of sexually dimorphic genes in mice. Genome research. 2006;16(8):995-1004.

99. Choi M, Choi JW, Chaudhari HN, Aseer KR, Mukherjee R, Yun JW. Gender-dimorphic regulation of skeletal muscle proteins in streptozotocin-induced diabetic rats. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2013;31(2-3):408-20.

100. Grove KL, Fried SK, Greenberg AS, Xiao XQ, Clegg DJ. A microarray analysis of sexual dimorphism of adipose tissues in high-fat-diet-induced obese mice. International journal of obesity. 2010;34(6):989-1000.

101. Clocchiatti A, Cora E, Zhang Y, Dotto GP. Sexual dimorphism in cancer. Nature reviews Cancer. 2016;16(5):330-9.

102. Martin L. Diagnostic criteria for cancer cachexia: data versus dogma. Current opinion in clinical nutrition and metabolic care. 2016;19(3):188-98.

103. Roeland EJ, Ma JD, Nelson SH, Seibert T, Heavey S, Revta C, et al. Weight loss versus muscle loss: re-evaluating inclusion criteria for future cancer cachexia interventional trials. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2016.

104. Wells JC. Sexual dimorphism of body composition. Best practice & research Clinical endocrinology & metabolism. 2007;21(3):415-30.

2 Small RNAome profiling from human skeletal muscle: Novel miRNAs and their targets associated with cancer cachexia[1]

2.1 Introduction

Cancer Cachexia (CC) is a multifactorial syndrome characterized by severe depletion of skeletal muscle with or without fat loss. The pathophysiology includes systemic inflammation, reduced food intake and negative energy and protein balance (1). Patients with CC have poor treatment response, reduced survival and a severe compromise in their quality of life (2). CC is characterized by complex host-tumor interactions that remain to be fully elucidated. Tumor-derived mediators lead to aberrant host tissue responses. Several proinflammatory and procachectic cytokines released from tumor cells contribute to systemic inflammation in the host, and lead to metabolic alterations (3). Genes (mRNA) involved in the pathophysiology of CC have been fairly well studied (4, 5). However, the role of finer post-transcriptional gene regulatory mechanisms and its implications on CC at the whole genome level has not been comprehensively explored.

MicroRNAs (miRs, 18-25 nt) are a class of small non-coding RNAs (ncRNAs) that are considered as global regulators of gene expression. They primarily bind to 3' untranslated region (3'UTR) of mRNA and cause either translational repression or mRNA degradation, depending on the degree of complementarity shared between the two molecules (6). Myo-miRs, a suite of miRs highly enriched in skeletal muscle, are known to play a role in myogenesis (7). For example, miR-1 and miR-133 regulate skeletal muscle proliferation and differentiation (8). Similarly, diverse roles of miRs have been reported in the physiological process such as adipogenesis, exercise and in general, health and disease states (9-11) and have also been identified as promising biomarkers for many diseases (12, 13). Recent evidence has suggested that miR-21 and miR-378 promote muscle cell apoptosis and lipolysis, respectively in CC (14, 15). While these studies have focused on animal models and human adipose tissues, it remains to be explored if miRs

[1]A version of this chapter has been published. Narasimhan et al., 2017. J Cachexia Sarcopenia Muscle.
 I would like to thank Jennifer Dufour and Lillian Cook for providing technical assistance.

identified from human muscle associate with CC pathophysiology and can also act as potential biomarkers. Biomarkers for CC have previously been identified from preclinical models (16, 17). Nonetheless, many of these molecules are far from being universally accepted as these are yet to be validated in human subjects.

Whole genome miR profiling using Next Generation Sequencing (NGS) are increasingly being utilized, as NGS offers better sensitivity and specificity compared to hybridization techniques (18). However, comprehensive profiling of miRs for CC using NGS platform has not yet been attempted. I hypothesized that deregulation of miRs contributes to the etiology of CC. The study objectives were (i) to profile human skeletal muscle expressed miRs, (ii) to identify differentially expressed (DE) miRs between cachectic and non-cachectic cancer patients, (iii) to identify mRNA targets for the DE miRs to gain mechanistic insights and (iv) to explore the prognostic and predictive potential of miRs. I report eight novel miRs associated with CC pathophysiology. I have also identified gene targets (mRNA) for the miRs and potential regulation of canonical pathways by these miR-mRNA pairs.

2.2 Methods

I performed all the experiments and analysis, unless otherwise indicated in the text.

2.2.1 Recruitment of study subjects and acquisition of muscle samples

Skeletal muscle biopsies from patients who underwent laparotomy at the Foothills Medical Centre between 2006 and 2013 were obtained from the University of Calgary Hepatopancreaticobiliary/Gastrointestinal Tumor Bank. Patients were approached for consents in pre-admission clinics (outpatient) prior to surgery. All patients provided written informed consent for study participation and the study was approved by the Conjoint Health Research Ethics Board at the University of Calgary (Ethics ID E-17213). Biopsies of *rectus abdominus* were taken at the start of the surgery using sharp dissection, immediately frozen in liquid nitrogen to minimize ischemic shock post devitalization, and stored at -80ºC until further use. Post biopsy molecular profiling of samples for NGS and collection of patient information was conducted under ethics

protocol ETH-21709, which was approved by Health Research Ethics Board of Alberta (HREBA) - Cancer Committee.

2.2.2 Study design and clinical annotation of cases[2]

Weight loss (WL) information of patients (n = 42) was retrieved from medical charts. Computed Tomography (CT) scans were available for the majority of the samples (n = 35) and these were accessed for quantification of skeletal muscle and fat components. Patients were classified as Cachectic based on the international consensus framework for CC; patients belonging to any one of the three diagnostic criteria were considered cachectic (more than 5% pre-illness weight loss (WL) for a period of six months, BMI <20 with any degree of weight loss >2% and lumbar skeletal sarcopenia, as defined by muscle index cut points using computed tomography) (1). Non-Cachectic cancer patients - had no WL over a period of six months compared to their pre-illness weight. The exclusion criteria include: (i) patients with no clinical chart or recorded WL information, (ii) below 18 years and (iii) inability to give written informed consent. A subset of age-matched patients in the bank meeting the above inclusion criteria and with available biopsies and WL histories were accessed; of these 22 were cachectic cases (with mean weight loss of 11.8 ± 6.6%; hereafter referred to as cases) and 20 were non-cachectic controls (hereafter referred to as controls). One of these patients had completed a course of chemotherapy (neoadjuvant) before surgery but had not received any chemotherapy four weeks prior to surgery. The remaining patients did not receive any chemotherapy before surgery.

Pancreatic and colorectal cancer (with liver metastasis) patients were considered for the present study from the collection of biopsies from the Hepatopancreaticobiliary/Gastrointestinal Tumor Bank to minimize the number of tumor types. Tumor stage is reported according to American Joint Committee on Cancer v7.

CT Image quantification: 20 cases and 15 controls had a single CT prior to surgery (70.75 ± 45.24 in days). The quantification protocol has been explained elsewhere in detail (19, 20). Briefly, the third lumbar vertebrae were used as a standard landmark to measure the cross sectional muscle area (cm^2) and normalized to their stature (m^2) to calculate the skeletal muscle index (SMI) (cm^2/m^2). Muscle attenuation (MA)

[2]Sambasivarao Damaraju conceived the study and designed the experiments with Ashok Narasimhan.

(Hounsfield Units) was also captured for these patients. Sarcopenia status was assigned based on age and sex adjusted SMI values, as described earlier (21).

2.2.3 RNA extraction and Next Generation Sequencing (NGS) profiling

Total RNA from muscle biopsies were isolated using Trizol (Sigma-Aldrich, Oakville, ON, Canada) and purified using Qiagen's RNeasy Maxi kit (Mississauga, ON, Canada). Quantification of RNA was done using Nanodrop 1000 Spectrophotometer. All of the above-mentioned protocols were carried out according to the manufacturer's instructions.

Services from PlantBiosis Ltd (Lethbridge, Alberta, Canada; http://www.plantbiosis.com/) were used from small RNA library preparation up to the generation of alignment files (.bam files), as described earlier (22). All the samples were sequenced in a single batch in a single lane to avoid batch effects. Sequencing of small RNA was done using Truseq Small RNA sequencing kit (Illumina), TruSeq SR Cluster Kit v5-CS-GA (Illumina) and TruSeq SBS Kit v5-GA (Illumina), according to manufacturer's instructions. The samples were sequenced using MiSeq platform with 36 bases single-end protocol. Base calling and demultiplexing was performed using MiSeq Reporter FastQ workflow. Cutadapt 1.4.1 (https://pypi.python.org/pypi/cutadapt/1.4.1) was used to trim the adapters. Only reads with a quality score of more than 30 on the Sanger scale were considered. Quality control for sequenced reads before and after adapter trimming was performed using FastQC v0.11.3 software. BWA aligner version 0.6.1 was used to align trimmed reads to the reference genome (23) (human genome 19 build), downloaded from Illumina iGenome website. Samtools version 0.1.18 was used to convert sequence aligned data file (.sam files) to its binary format (.bam format) which was used for downstream analyses. The raw files and normalized counts of the NGS data have been submitted to Gene Expression Omnibus (GEO accession ID GSE75473).

2.2.4 Identification of differentially expressed miRs

Partek Genomics Suite 6.6 (PGS 6.6) was used to analyze the .bam files generated from NGS experiment. Raw data was filtered to include miRs with more than or equal to 5 read counts in at least 80% of the samples and was normalized using Reads per

Kilobase per Million (RPKM) method (24). Differentially Expressed (DE) miRs were identified with a Fold Change (FC) of $\geq$ 1.4 and $p < 0.05$ using one-way ANOVA. The DE miRs were also subjected to permutation test (n = 10,000) and miRs with permuted p-values < 0.05 were considered for subsequent analysis.

2.2.5 qRT-PCR validation of the identified miRs

From the eight DE miRs identified from NGS, representative miRs: hsa-miR-3184-3p, hsa-let-7d-3p and hsa-miR-1296-5p were selected and validated using qRT-PCR. Total RNA was reverse transcribed using TaqMan MicroRNA Reverse transcription kit. RNU6B was used as the internal control. qPCR was performed using 7900HT Fast Real-Time PCR System (Applied Biosystems). The 20µL reactions for each sample were run in triplicates according to manufacturer's protocol. The following thermal cycler conditions were used for reverse transcription: 30 min. at 16ºC, 30 min. at 42ºC and 5 min. at 95ºC and the following conditions were used for qPCR: 50ºC for 2 mins, 95º C for 20 sec. and 40 cycles of 95ºC and 60ºC for 1 sec and 20 sec, respectively. Data analysis was carried out using $2^{-\Delta\Delta Ct}$ method (25).

2.2.6 Target predictions and putative functional annotation for mRNA targets of DE miRs

Detailed description of the in-house muscle transcriptome gene (mRNA) expression data generated using Agilent platform are elaborated elsewhere (26) and has been deposited in Gene Expression Omnibus repository (GSE41726). Initially, independent muscle biopsies (non-matched data sets) were used for miR profiling (this study, n=42) and mRNA profiling (n=90, a previous study GSE41726 from the same lab). Briefly, using the same definitions as in the miR study, 29 cachectic cases (WL $\geq$ 5%) and 61 weight stable controls (WS) were used to identify DE mRNAs. PGS 6.6 was used for differential expression analysis. Raw intensity files were quantile normalized, log 2 transformed and DE mRNAs were identified at $\geq$ 1.4 FC and $p < 0.05$ using one-way ANOVA. The direct binding of miR to 3'UTR of the mRNA is one of the most commonly recognized mechanisms in post-transcriptional silencing of genes (27, 28). However, miRs may exert influence on target mRNAs in an indirect manner (29) and

hence I considered all miR-mRNA correlations. I interrogated the mRNA data showing inverse and similar directional effect of expression between miR and mRNA (i.e. miR up-regulated and its corresponding mRNA down-regulated and both miR and mRNA being up-regulated/down-regulated) to understand the biological role of identified miRs in CC (22). Putative gene targets for DE miRs were predicted *in silico* using TargetScan 7.0 (30), based on the complementary binding of the seed region of miRs with 3'UTR of mRNAs. These predicted targets were then overlapped with the DE genes identified from in-house muscle transcriptome dataset. Ingenuity pathway analysis (IPA) was used to identify pathways for the overlapped gene targets of eight DE miRs. I have further interrogated the mRNA targets (GSE85017) for the miRs in matched data sets, albeit of lower sample size (n=42), compared to the unmatched mRNA data set (n=90, GSE41726). Independent confirmation of findings from two sources, matched and unmatched data sets, as an approach for functional validation of targets in a tissue-specific context would strengthen the study findings.

2.2.7 Statistical analysis

Data are presented as mean ± standard deviation. Independent t-test and chi-square test were used for continuous and categorical variables, as appropriate. Sample size estimation was done using the following parameters: $\alpha = 0.05$, $\beta = 80\%$ and a fold difference of 1.4 or more in miR expression. 19 samples per group were required to conduct the study (http://bioinformatics.mdanderson.org/MicroarraySampleSize/) to meet the statistical power and identify differentially expressed miRs with confidence.

2.2.8 Identification of miRs as prognostic and predictive factors

One of the objectives of this study was to identify miRs associated with Overall Survival (OS). OS was defined as the time period between the date of surgery and the date of death. The median follow-up period was 1060 days (Range: 6 to 2041 days), from the date of muscle biopsy accrual until the last follow-up date (March 2014). Of the 42 patients, 19 died and 23 were alive at the time of completion of this study.

(i) Prognostic value: I considered DE miRs as continuous variables and subjected the miRs to univariate Cox proportional hazards regression model. For OS, a composite risk

score was constructed for each sample using the parameter estimates (co-efficient) and the normalized counts obtained for the eight DE miRs. Receiver operating characteristics (ROC) curve was used to determine the optimal cut-point for the composite risk score. This was done to dichotomize the 42 samples into high risk and low risk groups. Hazard ratios (HR) along with 95% confidence intervals were reported for univariate and multivariate analyses. For multivariate analysis, the risk score was adjusted for age, BMI and tumor type, where appropriate. Log-rank test was carried out to identify if any significant difference existed between the survival curves of two risk groups.

(ii) Predictive value: The association between the weight change (loss vs. stable) group and the miRNA score (composite risk score) was tested using binary logistic regression. Univariate and multivariate logistic regression models are reported. For the multivariate model, I adjusted for age and BMI as continuous variables and tumor type (colorectal vs. pancreas) as a dichotomous variable. Odds ratio (OR) and the corresponding 95% confidence interval are reported. P-value <0.05 was used to define statistical significance. Two-sided tests were used for the comparisons. All statistical analyses were conducted using SPSS v16.0 and SAS (SAS Institute Inc., Cary, NC) v 9.3.

2.3 Results

2.3.1 Patient Demographics and body composition analysis

I selected the 42 patients who met the study criteria with information on age, gender, BMI, tumor type and physician-documented WL information. There was no significant difference between cases and controls in age, gender and tumor type. BMI was found to be significant between the groups ($p = 0.01$) (Table 2.1). I investigated if the CT derived body composition measurements also are in concordance with the phenotypes of cachexia in the study cohort (Table 2.2). I observed expected trends in SMI values between cases and controls, ($p = 0.07$ for SMI). MA was found to be reduced in cases compared to controls and was significant at $p = 0.04$.

Table 2.1 Patient Demographics

Characteristics	Cachectic cases (n=22)	Non-cachectic controls (n=20)	P-values
Weight loss, % mean	11.8 ± 6.6	-	
Age (mean, in years) [Range]	64.9 ± 10.1 [40-83]	63.6 ± 7.9 [45-76]	0.6 [a]
Tumor type (n) Pancreatic Colorectal	 12 10	 7 13	0.2 [b]
Tumor Stage (n) I II III IV	 2 3 2 15	 1 3 0 16	0.6 [c]
Gender (n) Male Female	 9 13	 9 11	0.7 [b]
Body Mass Index (mean, in kg/m2) [Range]	24.35 ± 2.5 [19-29]	27.02 ± 3.7 [20-40]	0.01 [a]

a= unpaired t-test, b= chi-square test, c= Fisher's exact test

***Table 2.1*:** Data represented as mean ± standard deviation. Statistical analyses were carried out using SPSS v16. Independent t-test was conducted for age and Body Mass Index. Chi-square test was carried out for tumor type and gender. $p<0.05$ was considered statistically significant.

Table 2.2 Body composition analysis for the study subjects

Characteristics	Cachectic cases (n = 20)	Non-cachectic controls (n = 15)	P- values
Cross sectional skeletal muscle area (cm^2)[a] *Male* *Female*	 139.5 ± 15.4 96.2 ± 14.6	 158 ± 12.9 103.5 ± 14.1	0.2
Skeletal muscle index (cm^2/m^2)[a] *Male* *Female*	 45.3 ± 5.9 36.3 ± 5.6	 49.1± 3.1 41.52± 7.43[a]	0.07
Z-Score	-0.7 ± 0.7	-0.08 ± 0.86	0.03
Total adipose tissue[a] *Male* *Female*	 226.8 ± 84.5 328.8 ± 126.4	 266.29 ± 77.2 302.2 ± 122.7	0.9
Muscle attenuation (HU)[a] *Male* *Female*	 34.14 ± 8.7 29.46 ± 7.3	 39.8 ± 6.9 36.42 ± 8.4	0.04

a = unpaired t-test

Table 2.2: Body composition was calculated for the subset of patients (n=35) who had CT prior to surgery. Statistical analysis was conducted between cases and controls. Muscle attenuation values were significant in the overall comparison between cachectic cases and non-cachectic controls. Z- score is the difference expressed in standard deviation of patients' values from age and gender specific mean values (21).

2.3.2 Technical variation, data processing and identification of DE miRs using NGS

Earlier reports suggested that the technical variance arising from the NGS platform is minimal (31). This has been validated in the current investigation as well. Technical replicates of 4 samples (2 cases and 2 controls) were sequenced. Excellent concordance was observed ($r > 0.99$) between the replicates, suggesting that technical variance in the data is absent or minimal due to experimental procedures adopted (Table 2.3).

Table 2.3 Technical replicates

Samples	Pearson correlation (r)
Case 1 vs Case 1 replicate	0.9998*
Case 2 vs Case 2 replicate	0.9997*
Control 1 vs Control 1 replicate	0.9999*
Control 2 vs Control 2 replicate	0.9999*

***Table 2.3*:** Pearson correlation test was carried out for the four technical replicates. The r- value for all the replicates were above 0.99. * indicates the obtained values have a statistical significance of $p<0.05$. Cases indicate cachectic cases and control indicate non-cachectic controls.

7,926,299 and 9,155,808 reads were obtained from cases and controls (n = 42), respectively. 97.12 % (7,698,807) and 97.35% (8,913,914) of reads were retained after adapter trimming in cases and controls, respectively. 87.78% (6,758,570) of reads in cases and 87.64% (7,812,866) of reads in controls were aligned to the reference genome, of which 9.55% (646,069) of reads in cases and 8.14% (636,748) of reads in controls mapped to miRs (Table 2.4) and had read length distribution from 18-25 nucleotides (Figure 2.1).

Table 2.4 Descriptive statistics for the data obtained from NGS

Samples	Total reads	Reads retained after adapter trimming	Aligned reads	Reads mapped to miRNAs
Cachectic Cases (n = 22)	7,926,299	7,698,807 (97.12%)	6,758,570 (87.78%)	646,069 (9.55%)
Non-cachectic Controls (n =2 0)	9,155,808	8,913,914 (97.32%)	7,812,866 (87.64%)	636,748 (8.14%)

Table 2.4: Step-wise filtering of NGS data is shown starting from total reads obtained from NGS for both cases and controls to reads mapped to miRNA. Furthermore, the reads mapped to miRNA were subjected to differential expression analysis.

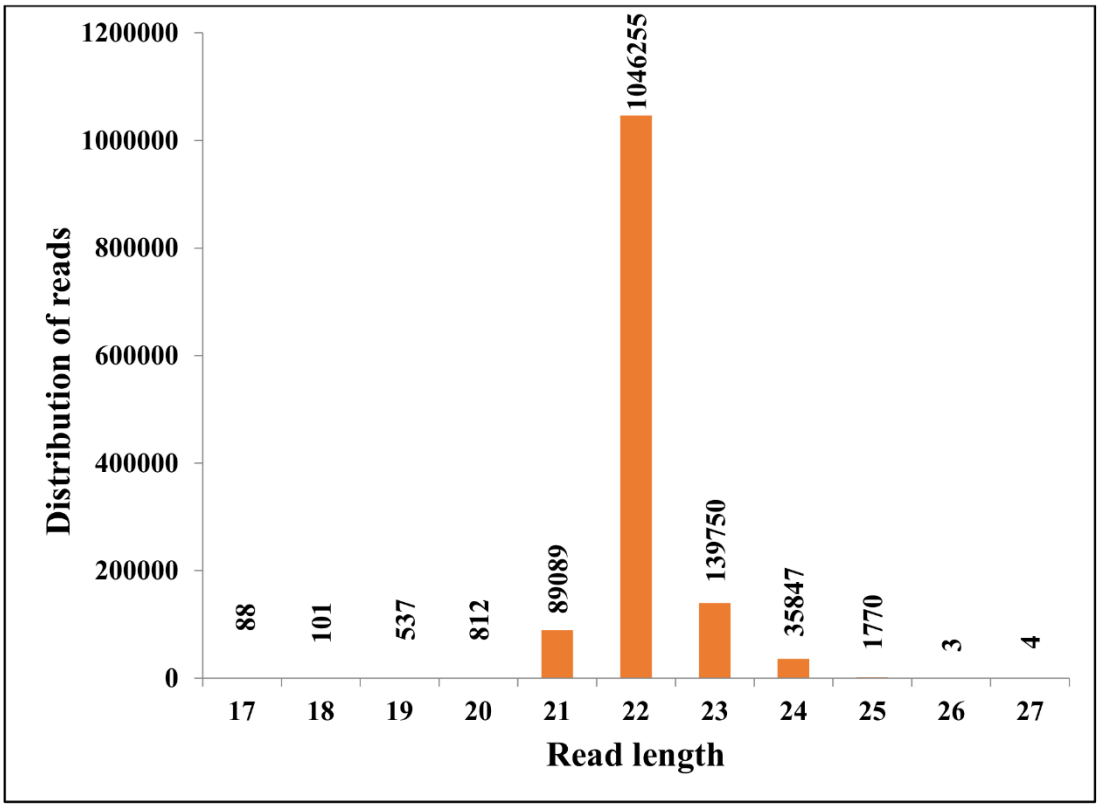


Figure 2.1 Length distribution of reads aligned to miRs

Figure 2.1: The aligned read length ranges from 17 to 27 nucleotides with the maximum distribution of reads captured between 18-25 nucleotides (reflecting miRNA read length).

777 miRs were profiled from the skeletal muscle tissues (out of a total of 2,588 miRs annotated in miRbase v20, of which only a subset can be tissue specific). 82 miRs were retained after filtering (> 5 read counts in 80% of samples) and were subjected to DE analysis. A total of eight miRs were found to be up-regulated with a FC of $\geq$ 1.4, $p < 0.05$ and with false discovery rate (FDR) ranging from 0.21 - 0.22. Permutation tests (n = 10,000) for the eight DE miRs were carried out and were also found to be significant with permuted $p<0.05$. The eight up-regulated DE miRs were hsa-miR-3184-3p, hsa-miR-423-5p, hsa-let-7d-3p, hsa-miR-1296-5p, hsa-miR-345-5p and hsa-miR-532-5p, hsa-miR-423-3p, hsa-miR-199a-3p (Table 2.5). No down-regulated miRs were identified in the current study under the stringent data filters applied and with the current sample size.

Table 2.5 Differentially expressed (DE) miRNAs

miRNA	p-value	FDR[a]	Permutation p-value	Fold Change (Cachectic cases vs. Non-cachectic controls)	Direction of fold change
hsa-let-7d-3p	0.01	0.21	0.01	1.48	Up
hsa-miR-345-5p	0.02	0.21	0.02	1.47	Up
hsa-miR-423-5p	0.009	0.21	0.009	1.42	Up
hsa-miR-532-5p	0.02	0.21	0.02	1.48	Up
hsa-miR-1296-5p	0.03	0.22	0.03	1.44	Up
hsa-miR-3184-3p	0.009	0.21	0.008	1.42	Up
hsa-miR-423-3p	0.01	0.21	0.01	1.43	Up
hsa-miR-199a-3p	0.03	0.22	0.01	2.01	Up

a- FDR- False Discovery rate

Table 2.5: All eight differentially expressed miRNAs were up-regulated in cachectic cases with a fold change of ≥ 1.4 at $p<0.05$. Permutation test was carried out (n=10,000) for these eight miRNAs to rule out observation by chance. The permuted p-value was significant for all the eight differentially expressed miRNAs. FDR for all eight DE miRNAs were also represented.

2.3.3 Validation of select miRs using qRT-PCR

Representative miRs hsa-miR-3184-3p, hsa-let-7d-3p and hsa-miR-1296-5p were validated in an independent platform - qRT-PCR. All three miRs showed similar direction of expression as observed in NGS with significant p-values ($p < 0.05$) (Figure 2.2).

Figure 2.2 qRT-PCR validation of miRs

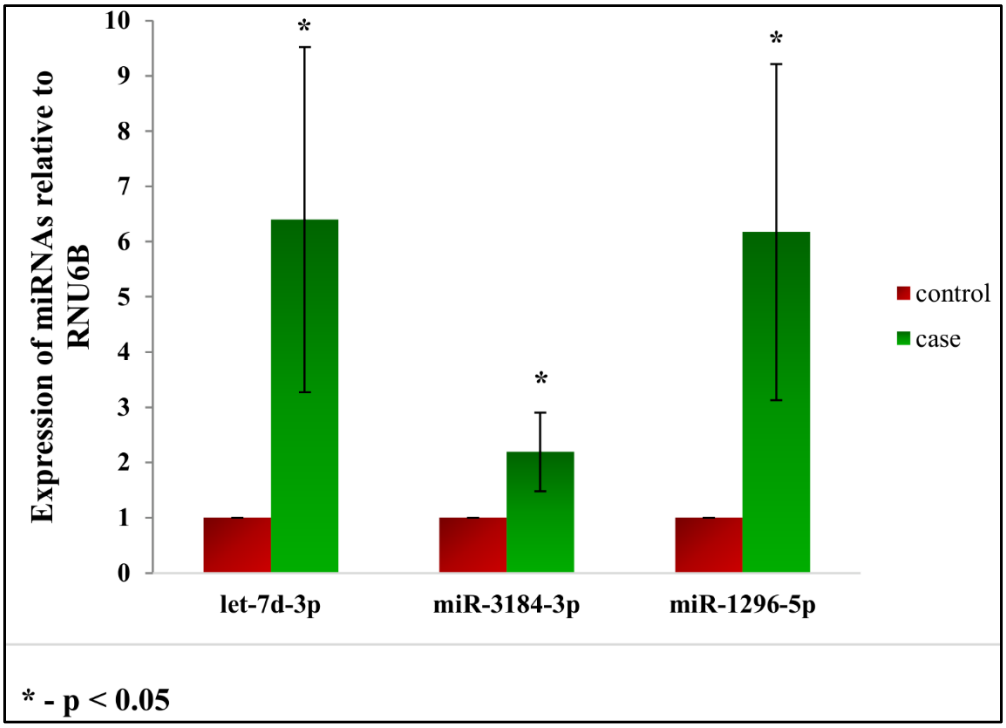


Figure 2.2: Representative miRNAs were validated using qRT-PCR. Similar direction of effect was observed as seen in next generation sequencing with a statistical significance of $p<0.05$.

2.3.4 Gene expression (GE) studies for identification of putative targets for DE miRs

TargetScan identified 20,988 mRNAs as potential targets for eight DE miRs. TargetScan *in-silico* predicted targets included mRNAs from muscle and non-muscle cell and tissue types. Therefore, to identify tissue-specific gene (mRNA) targets for the DE miRs, an in-house muscle transcriptome dataset was used (26). 353 mRNAs with a FC of > 1.4 and $p < 0.05$ were identified between cachectic cases (> 5% WL) and non-cachectic controls (WS), of which 127 were up-regulated and 226 were down-regulated (data not shown). Since I do not know a priori which among the 353 mRNAs serve as potential targets for the DE miRs in our study, I mapped the 353 mRNAs to the 25,348 mRNA targets predicted by TargetScan. In this analysis, I identified 191 mRNA targets as potentially regulated by the eight DE miRs (Table 3b). Up to 70% of the targets identified

were down-regulated, which is expected as a consequence of the binding of miRs to 3'UTRs of mRNAs leading to post-transcriptional gene silencing. To further confirm the direction of expression of these targets, an independent gene expression study for matched samples was conducted using Affymetrix Human Transcriptome Array 2.0 (GSE85017). I compared the direction of expression of the identified 233 mRNA targets in this independent dataset. I found 77% (147/191) of the mRNA targets expressed in the same direction, in these comparisons regardless of the p-value and fold change (data not shown). Further, the direction of expression of 10 representative mRNA targets chosen for discussion (see below) is indicated in Table 2.7. Although the p-value and fold change of these 10 mRNA targets were small in the independent dataset, perhaps due to the small sample size, I have confirmed the direction of expression in matching samples.

Table 2.6 Summary of Target Identification

miRNA	# Targets identified by target scan	# DE gene targets identified by in-house datasets
hsa-let-7d-3p	479	4
hsa-miR-345-5p	3515	34
hsa-miR-423-5p	4437	41
hsa-miR-532-5p	3227	32
hsa-miR-1296-5p	2007	13
hsa-miR-3184-3p	3531	28
hsa-miR-423-3p	779	14
hsa-miR-199a-3p	3013	25

Table 2.6: DE miRs were mapped to TargetScan 7.0. The identified gene targets from TargetScan 7.0 were overlapped to in-house muscle transcriptome dataset to identify tissue-specific gene targets for DE miRNA. The identified targets were interrogated for pathway analysis using IPA to understand the potential biological roles of the miRNAs in CC.

Table 2.7 Comparison of mRNA targets regulated by the differentially expressed miRs from two independent transcriptome datasets

Gene	GSE41726 Fold change (p-value) (unmatched dataset)	GSE85017 Fold change (p-value) (matched dataset)
NOV	-1.61 (0.02)	-1.1 (0.4)
COL1A1	-1.98 (0.04)	-1.1 (0.5)
CYR61	1.55 (0.01)	1.45 (0.01)
SQLE	-1.49 (0.03)	-1.05 (0.4)
FADS2	-1.47 (0.0003)	-1.1 (0.02)
DLK1	-1.6 (0.0007)	-1.2 (0.005)
CAMK2A	-1.47 (0.008)	-1.06 (0.06)
BMPR1B	1.43 (0.01)	1.05 (0.002)
HTR2A	-1.55 (0.007)	-1.05 (0.2)
GREM1	-1.94 (0.003)	-1.04 (0.4)

Table 2.7: Representative mRNA target expressions were compared from two independent human skeletal muscle transcriptome studies. Direction of expression is similar in both the datasets, when the stringency between data sets for absolute p-value and fold change are relaxed due to the small sample size.

2.3.5 Pathway analysis using IPA

The 191 mRNA targets identified for eight DE miRs were subjected to IPA to identify the corresponding pathways and understand their biological relevance (Table 2.8). The identified targets are known to play a role in adipogenesis, myogenesis (SULF1, BMPR1B, DLK1), inflammation and innate immune response (RPS6KA6) and also in signal transduction pathways (SFRP4, DKK2) that may directly or indirectly contribute to the phenotype of CC (see discussion for details).

Table 2.8 List of significant pathways identified from IPA

Ingenuity Canonical Pathways	Molecules	miRNA-ID
Actin Cytoskeleton Signaling	FN1	hsa-miR-199a-3p
Adipogenesis pathway	DLK1	hsa-miR-345-5p, hsa-miR-423-5p, hsa-miR-3184-3p
BMP signaling pathway	GREM1 BMPR1B SULF 1	hsa-miR-345-5p, hsa-miR-3184-3p, hsa-miR-199a-3p hsa-miR-3184-3p hsa-miR- 532-5p
Calcium signaling	CAMK2A	hsa-hsa-miR-423-3p
Cholesterol Biosynthesis I	SQLE	hsa-miR-3184-3p
CNTF Signaling	RPS6KA6	let-7d-3p, hsa-miR-1296-5p, hsa-miR-199a-3p, hsa-miR-532-5p
Energy metabolism	NYP1R	hsa-miR-532-5p
GDNF Family Ligand-Receptor Interactions	RET	hsa-miR-423-5p, hsa-miR-3184-3p
Glucocorticoid Receptor Signaling	PGR	let-7d-3p, hsa-miR-1296-5p, hsa-miR-423-5p
Glutamate Receptor Signaling	SLC1A7	hsa-miR-345-5p
IGF-1 Signaling	CYR61, NOV	hsa-miR-345-5p
IL-6 Signaling	COL1A1	hsa-miR-345-5p, hsa-miR-423-5p
IL-8 Signaling	EIF4EBP1	hsa-miR-423-5p, hsa-miR-199a-3p
Insulin Receptor Signaling	EIF4EBP1	hsa-miR-423-5p
Integrin Signaling	CAPN6	let-7d-3p, hsa-miR-1296-5p, hsa-miR-345-5p, hsa-miR-423-5p, hsa-miR-3184-3p
Mitochondrial Dysfunction	SOD2	hsa-miR-345-5p, hsa-miR-423-5p, hsa-miR-3184-3p, hsa-miR-199a-3p
mTOR Signaling	RPS6KA6 EIF4EBP1	let-7d-3p, hsa-miR-1296-5p, hsa-miR-199a-3p hsa-miR-423-5p, hsa-miR-199a-3p
NF-κB Signaling	BMPR1B	hsa-miR-3184-3p
Oleate Biosynthesis II	FADS2	hsa-miR-423-5p
Phospholipase C Signaling	BLNK	hsa-miR-345-5p
Regulation of Cellular Mechanics by Calpain Protease	CAPN6	let-7d-3p, hsa-miR-1296-5p, hsa-miR-345-5p, hsa-miR-423-5p, hsa-miR-3184-3p
Serotonin Receptor Signaling	HTR2A	let-7d-3p, hsa-miR-1296-5p, hsa-miR-3184-3p, hsa-miR-199a-3p
TGF-β Signaling	BMPR1B	hsa-hsa-miR-3184-3p
Wnt/β-catenin Signaling	SFRP4	let-7d-3p, hsa-miR-1296-5p, hsa-miR-3184-3p

Table 2.8: All miRs selected for this analysis showed up-regulation. Majority of the genes indicated in the table showed down-regulation. Note that common molecules between pathways reflect in the redundancy of the genes due to multiple miRs regulating the same pathway.

2.3.6 miRs as potential independent prognostic factors

The eight DE miRs were considered as continuous variables and were subjected to a univariate cox proportional hazards regression model. The parameter estimates thus obtained were used for constructing a risk score. A risk score cut-point was estimated to dichotomize the patients into high risk and low risk groups. Samples above the cut-point of 7.6 was considered high risk and less than or equal to 7.6 as low risk, following which the risk score was treated as a categorical variable for univariate cox model. The risk score showed a trend towards significance after adjusting for potential confounding factors (age, BMI and tumor type) in the multivariate analysis. The high risk group had a shorter OS when compared to the low risk group [Hazard ratio: 2.32 (0.88 - 6.06), p = 0.08, Table 2.9]. The log-rank p-value was significant in survival analysis between two risk groups (p = 0.001, Fig 2.3).

Table 2.9 Univariate and multivariate results for overall survival

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Risk Score	3.49 (1.51-8.04)	0.003	2.32 (0.88-6.06)	0.08
Age	0.99 (0.94-1.04)	0.81	0.95 (0.89-1.00)	0.07
BMI	0.97 (0.86-1.10)	0.67		
Tumor Type	0.21 (0.09-0.50)	0.0005	0.22 (0.07-0.63)	0.005

HR = Hazards ratio, CI = Confidence Interval

Table 2.9: Risk score and other clinical parameters were subjected to univariate cox proportional hazards model. In the multivariate analysis, risk score was marginally significant after adjusting for all potential confounders (age, BMI and tumor type).

Figure 2.3 Kaplan–Meier plot for risk score

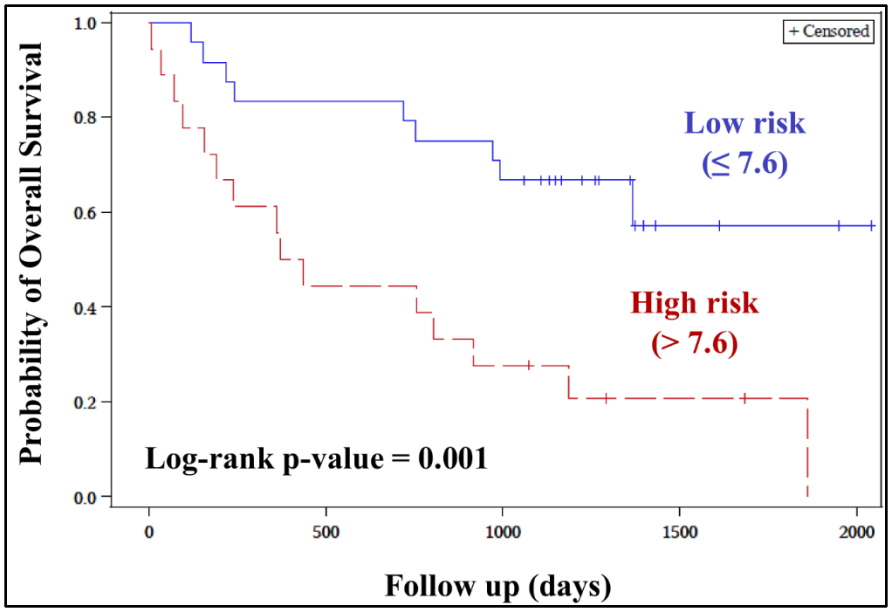


Figure 2.3: Kaplan–Meier plot was constructed to assess the survival function of high-risk group vs. the low-risk group, based on the risk score. The high risk group had a shorter OS when compared to the low risk group. The log rank p-value was significant in survival analysis between the two risk groups.

2.3.7 miRs as potential independent predictive factors

The association between the dichotomous risk score obtained from OS analysis for eight miR signature and weight change (cases vs controls) was analyzed using binary logistic regression. Results from this analysis indicated that the dichotomous risk score is an independent predictor of weight change. The odds of weight loss were 7 times higher in patients with a high risk score compared to the low risk score patients. When adjusted for age, BMI and tumor type, the odds were still higher, about 7.95 times higher (1.44 - 43.97 at 95% confidence interval, Table 2.10). Area under the curve (AUC) was found to be 0.84 after adjusting for potential confounding factors (age, BMI and tumor type). The wider confidence interval observed may be attributed to a relatively small sample size used in the study.

Table 2.10 Univariate and multivariate analysis for logistic regression

Parameter	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Risk Score (High Score vs. Low Score)	7.00 (1.73- 28.3)	0.006	7.95 (1.44 – 44.0)	0.01
Age	0.99 (0.92-1.06)	0.8		
BMI	0.72 (0.53-0.96)	0.03	0.66 (0.45-0.96)	0.03
Tumor Type (Colorectal vs. Pancreas)	0.45 (0.13-1.56)	0.21		

OR= Odds ratio, CI= Confidence Interval

Table 2.10: The odds of weight loss was 7.95 times higher in patients with high risk score compared to low risk score after adjusting for potential confounders.

2.4 Discussion

I identified eight novel DE miRs from human skeletal muscle and also identified the potential contributions of miR-mRNA correlations to the pathophysiology of CC. All eight DE miRs were up-regulated, and none of the miRs reported here have been directly studied in the context of CC. This is the first study where NGS technology was used to comprehensively profile miRs on a genome-wide scale for CC.

42 cancer patients were chosen and stratified as cases and controls for the study. BMI was less in cachectic cases when compared to controls ($p = 0.01$, Table 2.1). In the current study, although cachectic cases have BMI in the overweight range, they have lost more than 10% of their weight in previous six months. In this population (Canada) considered for the study, weight loss regardless of BMI (32), as well as the combination of sarcopenia and weight loss, was shown to be associated with poor prognosis. Body composition analysis indicated that MA was reduced in cases compared to controls ($p = 0.04$). Previous studies suggest that cancer patients with reduced attenuation exhibit reduced survival. In terms of attenuation values, I have observed a similar trend as

reported in literature with large sample sizes (33). The reduced attenuation values in cases indicate that these muscles could have been infiltrated by fat.

Using an independent in-house muscle transcriptome dataset, I interrogated tissue (muscle) specific mRNA signatures to identify potential miRNA targets. The transcriptome dataset serves as a proxy for functional validation of eight DE miRs to gain mechanistic insights. A list of mRNA targets and inferred pathways for DE miRs is given in Table 2.8. However, further cell-based assays would help confirm the specific targets and their regulation by their corresponding miRs. A brief discussion on eight DE miRs, their interacting partners (mRNAs) and their biological relevance to CC is described below. There is a paucity of literature for the identified miRs associated with human CC and hence these comparisons are of high relevance.

(i) Transferrin receptor (TFRC) was identified as a putative target for *let-7d-3p,* in addition to three other targets. While let-7d-3p was up-regulated in CC, its corresponding target, TFRC was observed to be relatively down-regulated in weight losing patients. Let-7 members play a role in aging; higher levels of let-7 were observed in elderly subjects. They affect muscle cell proliferation by downregulating the target genes, eventually leading to reduced regenerative capacity of muscle (34). Transferrin, the ligand for TFRC, has been associated with myogenic differentiation, and downregulation of TFRC may impair myogenic differentiation. Furthermore, the expression of TFRC was observed to be down-regulated in skeletal muscle and heart muscle in hereditary hemochromatosis and during muscle atrophy in conditions such as diabetes and uremia (35, 36). However the role of TFRC in the context of CC remains to be elucidated.

(ii) Gene targets identified for *miR-345-5p* include NOV, COL1A1 and CYR61. While miR-345-5p was up-regulated in CC, its targets NOV and COL1A1 were down-regulated in the muscle transcriptome dataset, whereas CYR61 was found to be up-regulated. NOV and CYR61 are known to be involved in IGF-1 signaling via the AKT and mTOR pathway (37), impairment of which is related to suppression of protein synthesis leading to muscle atrophy. COL1A1 is an extracellular matrix protein and its downregulation in animal models is reported to be associated with skeletal muscle atrophy. let-7d-3p and miR-345-5p regulate genes such as TFRC and COL1A1 (also

known as atrogin signatures) that are known to be involved in skeletal muscle atrophy in diverse disease states including CC (36).

(iii) SQLE and FADS2 were the down-regulated gene targets in muscle transcriptome dataset for *miR-423-5p and miR-3184-3p*; these miRs were up-regulated, and occur as clusters that are located within 10 kb distance (38). As they arise from the same clusters, their p-value, fold changes and direction of expression in the current study were found to be similar. Both these genes were found to be associated with lipid biosynthesis (Table 2.8) which is severely compromised in cachectic states. These genes contribute to sterol biosynthesis and fatty acid dehydrogenation. Additionally, miR-423-5p also regulates genes associated with energy homeostasis such as leptin. Perturbed levels of leptin in orexigenic and anorexigenic signals circuit and its impact on body weight regulation are fairly well understood. While increased leptin levels are observed in obesity, the opposite effect is seen in CC (39). Leptin expression is low (but not lost) in mature skeletal muscle but its expression is high in myocytes (40). Indeed, a similar trend was observed in our muscle transcriptome dataset, wherein leptin was down-regulated in cases, relative to controls (data not shown). A similar argument may also be extended to miR-423-5p, which is up-regulated in CC (found in this study) and down-regulated in morbid obese patients (41). miR-423-5p regulates DLK1 (down-regulated in our study), which is known to be involved in skeletal muscle hypertrophy (42). However, the effect of this downregulation in CC needs to be further elucidated in the future using model systems. miR-423-3p, which is derived from the same precursor miR as that of miR-423-5p, regulates CAMK2A (down-regulated in this study), which is involved in calcium signaling. While CAMK2B is associated with inducing weight loss in CC (4), the role of CAMK2A remains to be elucidated.

miR-3184-3p, up-regulated in the current study, is involved in Wnt/β-catenin signaling, which plays a role in myogenic differentiation (43) and a defective signaling has been found to have an impact in muscle developmental defects (44). The targets of miR-3184-3p include BMPR1B and GREM1 which are up and down-regulated, respectively in the muscle transcriptome dataset. They are involved in BMP signaling and Transforming Growth Factor beta (TGF-β) signaling, deregulation of which may contribute to CC (45).

(iv) Targets identified for *miR-532-5p* (up-regulated) in this study include SULF1, RPS6KA6 and NPY1R. While SULF1 plays a role in regulating BMP signaling and is also required for somite development (46), NPY1R is involved in appetite regulation. The action of NeuropeptideY (NPY) in energy metabolism is carried out through NPY1R and other NPY receptors (47) and their roles have been widely implicated in the pathogenesis of cachexia (48). RPSKA6 is involved in CNTF signaling (see below).

(v) The targets identified for *miR-1296-5p* are HTR2A and RPS6KA6; both these genes were down-regulated in muscle transcriptome dataset. HTR2A plays a role in serotonin signaling. Altered serotonin signaling has been demonstrated to have an impact on food intake in cachectic mouse models (49). Serotonin was also shown to be involved in myogenesis by promoting longitudinal growth of muscle fibres (50). RPS6KA6 (also regulated by miR-532-5p) is involved in CNTF signaling. CNTF is expressed in both central and peripheral nervous systems and has been shown to induce cachexia in model systems, when injected systemically (51).

(vi) EIF4EBP1 (up-regulated) was one of the targets identified for *miR-199a-3p.* EIF4EBP1 has been demonstrated to be involved in mTOR signaling, which regulates muscle protein synthesis. This signaling pathway is shown to be impaired in cachectic states by the action of IL-6 (52). The other targets of miR-199a-3p are HTR2A and RPS6KA6.

Overall, based on these insights and inferences, the pleiotropic and redundant roles of miRs are observed against their binding partners regulating different pathways.

Biomarkers identified to-date in CC, though promising, are not ready for translation to clinic. One of the foremost concerns is the availability of well annotated specimens for the discovery stages of the studies in sufficient numbers. Sample sizes used for gene expression studies are critical for confidence in the study findings. While it is important to have large number of samples, it is equally imperative to recognize the difficulties in obtaining biopsy material with detailed clinical annotations for CC phenotype. Despite these challenges, the current study had sample size of 42 for miR profiling and a sample size of 90 for mRNA profiling, well above the sample sizes used in earlier gene expression profiling experiments (4). Nevertheless, validating the identified biomarkers

in independent datasets with larger sample size is warranted to confirm the study findings. Although the study has identified several targets and pathways that have potential implications in CC, as judged from the miR-mRNA correlations, further characterization of the identified targets using model systems is needed to validate the overall biological relevance of the pathways. This would enable us to delineate the role of these identified miRs in CC and also gain functional insights.

Recent studies have highlighted the role of miRs as biomarkers from serum in myotonic dystrophy (53); it remains to be seen if this could be extended to CC in future. In this proof of principle study, I have demonstrated potential utility of miRs as prognostic and predictive factors from muscle biopsies. However, muscle biopsy is invasive for routine analysis. Therefore, clinical application of the current findings awaits development of alternative methodologies and study designs to make it feasible in clinical setting. To understand the disease trajectory of CC, longitudinal studies can be conducted in plasma and serum as the same may not be possible with muscle biopsies. However, until such time the challenges and logistics involved to carry out such investigations are addressed, muscle biopsy remains the best option for CC biomarker and discovery studies. Identification and characterization of miRs that drive CC followed by functional testing in preclinical models may eventually lead to clinical trials to determine the efficacy of certain miRs for CC treatment.

2.5 Conclusions

I identified eight novel miRs that could potentially contribute to the etiology of CC and as promising biomarkers. Continuing efforts in validating the miR signatures in independent cohorts and characterization of the identified miRs to understand its biological relevance to CC may eventually lead to the use of miRs as diagnostics or therapeutics.

2.6 References

1. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology. 2011;12(5):489-95.

2. Tan BH, Fearon KC. Cachexia: prevalence and impact in medicine. Current Opinion in Clinical Nutrition & Metabolic Care. 2008;11(4):400-7.

3. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nature reviews Cancer. 2014;14(11):754-62.

4. Stephens NA, Gallagher IJ, Rooyackers O, Skipworth RJ, Tan BH, Marstrand T, et al. Using transcriptomics to identify and validate novel biomarkers of human skeletal muscle cancer cachexia. Genome Medicine. 2010;2(1):1.

5. Gallagher IJ, Stephens NA, MacDonald AJ, Skipworth RJ, Husi H, Greig CA, et al. Suppression of skeletal muscle turnover in cancer cachexia: evidence from the transcriptome in sequential human muscle biopsies. Clinical Cancer Research. 2012;18(10):2817-27.

6. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281-97.

7. Guller I, Russell AP. MicroRNAs in skeletal muscle: their role and regulation in development, disease and function. Journal of Physiology. 2010;588(Pt 21):4075-87.

8. Chen JF, Mandel EM, Thomson JM, Wu Q, Callis TE, Hammond SM, et al. The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation. Nature genetics. 2006;38(2):228-33.

9. Sharma M, Juvvuna PK, Kukreti H, McFarlane C. Mega roles of microRNAs in regulation of skeletal muscle health and disease. Frontiers in Physiology. 2014;5:239.

10. Chen L, Hou J, Ye L, Chen Y, Cui J, Tian W, et al. MicroRNA-143 regulates adipogenesis by modulating the MAP2K5-ERK5 signaling. Sci Rep. 2014;4:3819.

11. Ahn J, Lee H, Jung CH, Jeon TI, Ha TY. MicroRNA-146b promotes adipogenesis by suppressing the SIRT1-FOXO1 cascade. EMBO molecular medicine. 2013;5(10):1602-12.

12. Romaine SP, Tomaszewski M, Condorelli G, Samani NJ. MicroRNAs in cardiovascular disease: an introduction for clinicians. Heart. 2015;101(12):921-8.

13. Li X, Li Y, Zhao L, Zhang D, Yao X, Zhang H, et al. Circulating Muscle-specific miRNAs in Duchenne Muscular Dystrophy Patients. Molecular TherapyNucleic Acids. 2014;3:e177.

14. Kulyte A, Lorente-Cebrian S, Gao H, Mejhert N, Agustsson T, Arner P, et al. MicroRNA profiling links miR-378 to enhanced adipocyte lipolysis in human cancer cachexia. American Journal of Physiology - Endocrinology & Metabolism. 2014;306(3):E267-74.

15. He WA, Calore F, Londhe P, Canella A, Guttridge DC, Croce CM. Microvesicles containing miRNAs promote muscle cell death in cancer cachexia via TLR7. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(12):4525-9.

16. Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L, Clarke BA, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. Science. 2001;294(5547):1704-8.

17. Gomes MD, Lecker SH, Jagoe RT, Navon A, Goldberg AL. Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(25):14440-5.

18. Tam S, de Borja R, Tsao MS, McPherson JD. Robust global microRNA expression profiling using next-generation sequencing technologies. Laboratory Investigation. 2014;94(3):350-8.

19. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncology. 2008;9(7):629-35.

20. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47.

21. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Seminars in cell & developmental biology. 2016;54:2-10.

22. Krishnan P, Ghosh S, Wang B, Li D, Narasimhan A, Berendt R, et al. Next generation sequencing profiling identifies miR-574-3p and miR-660-5p as potential novel prognostic markers for breast cancer. BMC genomics. 2015;16(1):735.

23. Li H, Durbin R. Fast and accurate short read alignment with Burrows–Wheeler transform. Bioinformatics. 2009;25(14):1754-60.

24. Mortazavi A, Williams BA, McCue K, Schaeffer L, Wold B. Mapping and quantifying mammalian transcriptomes by RNA-Seq. Nat Meth. 2008;5(7):621-8.

25. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods. 2001;25(4):402-8.

26. Stretch C, Khan S, Asgarian N, Eisner R, Vaisipour S, Damaraju S, et al. Effects of sample size on differential gene expression, rank order and prediction accuracy of a gene signature. PLoS ONE [Electronic Resource]. 2013;8(6):e65380.

27. Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell.75(5):855-62.

28. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell.75(5):843-54.

29. Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can up-regulate translation. Science. 2007;318(5858):1931-4.

30. Agarwal V, Bell GW, Nam J-W, Bartel DP. Predicting effective microRNA target sites in mammalian mRNAs. Elife. 2015;4.

31. Marioni JC, Mason CE, Mane SM, Stephens M, Gilad Y. RNA-seq: an assessment of technical reproducibility and comparison with gene expression arrays. Genome research. 2008;18(9):1509-17.

32. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(1):90-9.

33. Esfandiari N, Ghosh S, Prado CM, Martin L, Mazurak V, Baracos VE. Age, Obesity, Sarcopenia, and Proximity to Death Explain Reduced Mean Muscle Attenuation in Patients with Advanced Cancer. The Journal of frailty & aging. 2014;3(1):3-8.

34. Drummond MJ, McCarthy JJ, Sinha M, Spratt HM, Volpi E, Esser KA, et al. Aging and microRNA expression in human skeletal muscle: a microarray and bioinformatics analysis. Physiological Genomics. 2011;43(10):595-603.

35. Rodriguez A, Hilvo M, Kytomaki L, Fleming R, Britton R, Bacon B, et al. Effects of iron loading on muscle: genome-wide mRNA expression profiling in the mouse. BMC genomics. 2007;8(1):379.

36. Lecker SH, Jagoe RT, Gilbert A, Gomes M, Baracos V, Bailey J, et al. Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. The FASEB Journal. 2004;18(1):39-51.

37. Rommel C, Bodine SC, Clarke BA, Rossman R, Nunez L, Stitt TN, et al. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. Nature cell biology. 2001;3(11):1009-13.

38. Zhang X, Azhar G, Wei JY. The expression of microRNA and microRNA clusters in the aging heart. PLoS ONE [Electronic Resource]. 2012;7(4):e34688.

39. Inui A, Meguid MM. Cachexia and obesity: two sides of one coin? Current Opinion in Clinical Nutrition & Metabolic Care. 2003;6(4):395-9.

40. Rigmor S, Vigdis A, Hege Thoresen G, Eili Tranheim K, Christian AD, Arild CR, et al. Leptin expression in human primary skeletal muscle cells is reduced during differentiation. Journal of cellular biochemistry. 2005;96(1):89.

41. Ortega FJ, Mercader JM, Catalan V, Moreno-Navarrete JM, Pueyo N, Sabater M, et al. Targeting the circulating microRNA signature of obesity. Clinical chemistry. 2013;59(5):781-92.

42. Waddell JN, Zhang P, Wen Y, Gupta SK, Yevtodiyenko A, Schmidt JV, et al. Dlk1 is necessary for proper skeletal muscle development and regeneration. PLoS ONE [Electronic Resource]. 2010;5(11):e15055.

43. Jones AE, Price FD, Le Grand F, Soleimani VD, Dick SA, Megeney LA, et al. Wnt/beta-catenin controls follistatin signalling to regulate satellite cell myogenic potential. Skeletal Muscle. 2015;5:14.

44. Suzuki ASAIJ. The temporal specific role of WNT/β-catenin signaling during myogenesis. Journal of Nature and Science. 2015;1(8).

45. Zimmers TA, Davies MV, Koniaris LG, Haynes P, Esquela AF, Tomkinson KN, et al. Induction of cachexia in mice by systemically administered myostatin. Science. 2002;296(5572):1486-8.

46. Meyers JR, Planamento J, Ebrom P, Krulewitz N, Wade E, Pownall ME. Sulf1 modulates BMP signaling and is required for somite morphogenesis and development of the horizontal myoseptum. Developmental biology. 2013;378(2):107-21.

47. Sohn J-W, Elmquist JK, Williams KW. Neuronal circuits that regulate feeding behavior and metabolism. Trends in neurosciences. 2013;36(9):504-12.

48. Inui A. Neuropeptide Y: a key molecule in anorexia and cachexia in wasting disorders? Molecular medicine today. 1999;5(2):79-85.

49. Dwarkasing JT, Boekschoten MV, Argilès JM, van Dijk M, Busquets S, Penna F, et al. Differences in food intake of tumour-bearing cachectic mice are associated with hypothalamic serotonin signalling. Journal of cachexia, sarcopenia and muscle. 2015;6(1):84-94.

50. Suchismita C, Tingqing G, Teresa T, Weiping C, Murphy Dennis L, McPherron Alexandra C. Effects of serotonin on skeletal muscle growth. BMC Proceedings. 2012:O3.

51. Henderson JT, Seniuk NA, Richardson PM, Gauldie J, Roder JC. Systemic administration of ciliary neurotrophic factor induces cachexia in rodents. Journal of Clinical Investigation. 1994;93(6):2632-8.

52. Durham WJ, Dillon EL, Sheffield-Moore M. Inflammatory burden and amino acid metabolism in cancer cachexia. Current Opinion in Clinical Nutrition & Metabolic Care. 2009;12(1):72-7 6p.

53. Koutsoulidou A, Kyriakides TC, Papadimas GK, Christou Y, Kararizou E, Papanicolaou EZ, et al. Elevated Muscle-Specific miRNAs in Serum of Myotonic Dystrophy Patients Relate to Muscle Disease Progress. PLoS ONE [Electronic Resource]. 2015;10(4):e0125341.

3 Differentially expressed alternatively spliced genes in skeletal muscle from cancer patients with cachexia[1]

3.1 Introduction

Alternative splicing (AS, also used synonymously with the term 'alternatively spliced') is a crucial post-transcriptional gene regulatory mechanism that is involved in generating gene isoforms (used synonymously with the term "transcripts") from a single precursor mRNA, thereby increasing proteome diversity (1, 2). More than 90% of the human genes are alternatively spliced but such complexity is not observed in lower organisms (3). AS is regulated in a tissue-specific manner, with skeletal muscle exhibiting the highest number of alternatively expressed exons (4, 5), and is recognized to contribute to a wide range of physiological and cellular processes (6, 7). Aberrant splicing mechanisms due to splice site mutations also contribute to tumorigenesis (8, 9). Aberrant splicing mechanisms are known to be associated with various muscle-related pathologies such as Duchenne muscular dystrophy (DMD) (10). However, the contribution of AS dysregulation in human cancer cachexia is unknown.

Cancer cachexia (CC), a debilitating condition seen in advanced cancer patients is associated with involuntary weight loss and loss of lean body mass with or without loss of fat mass (11). CC can be seen as a consequence of complex host-tumor interactions eventually leading to a state of energy imbalance (12, 13). Degeneration of skeletal muscle and impaired myogenesis are prominent features in CC (14, 15). In vitro models suggested that AS plays a major role in myogenic differentiation in a spatiotemporal manner (16). Dysregulation of splicing mechanisms is observed in polygenic muscular diseases such as sporadic inclusion body myositis (17). It is therefore very likely that AS dysregulation contributes to CC pathophysiology.

Traditional gene expression arrays (at transcriptional level) have enabled researchers to identify many differentially expressed genes to understand the underlying biology in a disease specific context, especially in many cancer types (18). However, it is now possible to address gene regulatory mechanisms (post-transcriptional) at a finer level

[1]A version of this chapter has been resubmitted to Journal of Cachexia, Sarcopenia and Muscle after revisions.

with the availability of global microarrays and massive parallel sequencing technologies (19). In-vitro experiments have shown that isoform specific expressions delineate tumor associated signatures from non-tumor signatures more accurately (20). Given its importance in a disease context, it is imperative to understand the effect of AS in CC; here I chose to profile muscle tissue as skeletal muscle atrophy is a characteristic feature of CC. Recognizing the plasticity exhibited by the muscle tissue and AS being a dynamic mechanism, identifying tissue-specific isoforms may shed more light on CC pathophysiology, which remains a gap in the literature. The aims of the current study are (i) to profile alternatively spliced genes (ASGs) in CC on a genome-wide scale from human skeletal muscle biopsies and (ii) to identify differentially expressed alternatively spliced genes (DASGs) associated with the phenotype of CC. I report identification of several DASGs showing association to CC pathophysiology. Based on Gene Set Enrichment Analysis (GSEA) and Ingenuity Pathway Analysis (IPA), the identified genes appear to play a role in myogenesis, inflammation and ubiquitination.

3.2 Materials and Methods

I performed all the experiments and analysis, unless otherwise indicated in the text.

3.2.1 Procurement of muscle biopsies

Rectus abdominis muscle biopsies were obtained from University of Calgary Hepatopancreaticobiliary/Gastrointestinal Tumor Bank from pancreatic cancer and colorectal cancer patients with liver metastasis who underwent laparotomy at the Foothills hospital from 2006 to 2013. Tumor stage is reported according to American Joint Committee on Cancer v7. Standard procedures were followed for tissue procurement and storage. Specifically, biopsies of rectus abdominis muscle were taken by the operating surgeon within 30 minutes of the start of the surgery using sharp dissection, immediately flash frozen in liquid nitrogen to minimize ischemic shock post devitalization, and stored at -80ºC until further use. Written informed consent was obtained from all study participants which was approved by Conjoint Health Research Ethics Board at the University of Calgary (Ethics ID E-17213). Health Research Ethics Board of Alberta (HREBA) - Cancer Committee approved the current study protocol, i.e.,

transcriptome profiling and access to the patient's clinical information (protocol number ETH-21709).

The stratification of patients for the proposed association study was based on the International consensus diagnostic framework for CC (11). Patients were classified into: Cachectic cases, defined as those with either (i) > 5% pre-illness weight loss (WL) over a period of six months, (ii) > 2% WL with either Body Mass Index (BMI) <20, (iii) or sarcopenia (defined by skeletal muscle index cut-points using computed tomography, CT) with >2% WL. Non-Cachectic controls are defined as those who were weight stable (WS) cancer patients over a period of six months, compared to their pre-illness weight. Physician documented weight loss at first presentation of the patient in the clinic was used for the study. I excluded patients with no clinical chart, or no recorded WL information, who were below 18 years of age, or were unable to provide written consent. In all, 42 age-matched patients with pancreatic cancer and colorectal cancer with liver metastasis were selected for the study. Of these 42 patients, 22 were cachectic cases (hereafter referred to as cases) and 20 were non-cachectic controls (hereafter referred to as WS cancer patients). Eight patients (4 cachectic cases and 4 WS cancer patients) had completed a course of neoadjuvant chemotherapy but had not received any chemotherapy four weeks prior to surgery. The remaining study participants did not receive any chemotherapy before surgery.

3.2.2 Body composition analysis using CT

34 of the 42 patients in the study had a CT prior to surgery (71.51 ± 45.9 days). CT based body composition analysis was carried out using lumbar vertebrae (L3) as a standard landmark, as described elsewhere (21). Cross sectional muscle area (cm2), Skeletal muscle index (SMI) - cross sectional muscle area normalized to their stature (cm2/m2), total adipose tissue, and muscle radiation attenuation were measured. Muscle radiation attenuation was measured in Hounsfield Units (HU) and the ranges for these measurements are described elsewhere (21). Patients were classified sarcopenic based on the previously described SMI values (21, 22).

3.2.3 RNA Isolation and Integrity of RNA

Total RNA was isolated using TRIzol method and QIAGEN RNAeasy maxi kit (Mississauga, ON). Optical density (OD) 260/280 ratio was measured using Nanodrop and RNA integrity number (RIN) was assessed using Agilent Bio-analyzer 2100 for all the samples.

3.2.4 Human Transcriptome array 2.0 (HTA 2.0), Hybridization methods and data analysis

The HTA array 2.0 has been designed to capture all known and putative coding exons and coding gene exon-intron boundaries in the human genome. Ten probes span each exon and four probes span each exon-intron boundary (splice junctions). The array also contained non-protein coding transcripts, but these were not mined in the current study. Instead, I focused primarily on the protein coding gene transcripts (isoforms and exon level). The entire protocol was carried out as per the manufacturer's instructions (http://www.affymetrix.com). Briefly, 100 ng of total RNA was used as a starting material for labeling and hybridization. Hybridization was performed for 16 hours in Genechip hybridization oven 645 using the standard procedures (http://www.affymetrix.com). The washing and staining protocol was carried out using GeneChip fluidics station 450 according to manufacturer's protocol. The HTA 2.0 arrays were scanned using Affymetrix GCS 3000 7G scanner to generate the raw intensity CEL files for downstream analyses. Identification of Alternatively spliced genes and GSEA were carried out using Partek Genomics Suite 6.6 (PGS 6.6).

3.2.5 Analysis for Alternatively spliced genes (ASGs)

Exon level intensity estimates were generated using RMA method which includes background correction, quantile normalization and log 2 transformation. Exons that were not expressed in all of the samples were excluded from further analysis. In the AS analysis, PGS generates two results – at the transcript (isoform) level and at the exon level. Initially, at a transcript level, differentially expressed (DE) ASGs were identified between cases and WS cancer patients at a p-value of < 0.05 (Partek defined this as "alt-splice p-value"). At the exon level, the expression between cases and WS cancer patients

with $p < 0.05$ and FC $\geq$ 1.4 were identified using one-way ANOVA and these exons were mapped to their corresponding transcripts (isoforms). Final representation of data would, therefore, reflect a composite signature of the alternatively spliced gene transcripts overlapped with exon level results ($p < 0.05$, FC $\geq$ 1.4). These overlapped transcripts were called differentially expressed alternatively spliced genes (DASGs). The identified DASGs were used for subsequent GSEA and for IPA. Select DASGs were validated using semi-quantitative RT-PCR. The raw files and normalized counts have been submitted to Gene Expression Omnibus database (GEO accession ID-GSE85017).

3.2.6 Validation of representative DASGs using Semi-quantitative RT-PCR

1µg of total RNA was converted in to cDNA using High Capacity cDNA Reverse Transcription kit (Applied Biosystems) using the manufacturer's protocol. Reverse transcription was performed using the following thermal cycler conditions: 37ºC for 60 minutes and 95ºC for 5 minutes.

100 ng of cDNA was used for semi quantitative RT-PCR. Go Taq G2 Hotstart green Mastermix (Promega, Madison, Wisconsin, USA) was used. Primers were designed using primer 3 software (V 0.4.0) (http://bioinfo.ut.ee/primer3-0.4.0/) and Oligocalc (http://biotools.nubic.northwestern.edu/OligoCalc.html). Six DASGs (IFRD1, KCNQ5, DEPDC1, UBA3, FNDC1 and CNNM3) were validated in representative cases and WS cancer patients. The amplified products were separated using 2.5-3% agarose gel and stained using RedSafe stain solution (Intron Biotechnology) for visualization. Densitometric scans were used to quantify gel bands using Image J software and to calculate the ratios between the splice variants (23).

3.2.7 Functional annotation of the identified DASGs and identification of canonical pathways

GSEA was carried out using PGS 6.6 to understand the potential functions of the identified DASGs in CC pathophysiology. IPA was used for identifying the canonical pathways and upstream regulators for the DASGs.

3.2.8 Statistical Analyses

Patient demographics data were represented as mean ± standard deviation. Independent t-test and chi-square test were used for continuous and categorical variables, as appropriate. For the AS analysis, one-way ANOVA test was used to identify DASGs. $P < 0.05$ was considered as statistically significant for all analyses. To understand the association between DASGs and clinical factors, Pearson correlation test was carried out. For all the analyses, $p < 0.05$ was considered to be statistically significant.

3.3 Results

3.3.1 Patient demographics

No significant difference was observed in age, gender and tumor type, while BMI was significantly different between cases and WS cancer patients (Table 3.1). The results from the body composition analysis are represented in Table 3.2. SMI, z-score and MA was found to be significant between cases and WS cancer patients. Abnormally low MA has been observed in pathological conditions such as cancer, where there is an excess infiltration of fat in muscle against the normally observed levels (24).

3.3.2 RNA integrity

The 260/280 ratio for all the samples ranged from 1.6 - 1.8. The RIN (RNA Integrity Number) values for samples were between 5.9 and 8.9. Two samples had poor single cRNA yield (one of the intermediate steps leading to hybridization) and were not processed further in the study, leaving 40 samples for further analysis; 21 patients belonged to cases and 19 patients belonged to WS cancer patients.

Table 3.1 Patient Demographics

Characteristics	Cachectic cases (n=21)	Non-cachectic controls (n=19)	p-value
Weight loss (% mean)	11.4 ± 6.5	-	-
Age (mean, in years) [a] [Range]	65.7 ±10.5 [39-84]	64.2 ± 8.1 [46-77]	0.67
Tumor type [b] Pancreatic Colorectal	12 9	12 7	0.69
Gender [b] Male Female	8 13	9 10	0.55
Body Mass Index [a] (mean, in kg/m^2) [Range]	24.2 ± 3.6 [19-29]	26.9 ± 3.9 [21-40]	0.02
Tumor Stage [c] I II III IV	2 3 2 14	1 3 0 15	0.64

a= unpaired t-test, b= chi-square test, c= Fisher exact test

***Table 3.1*:** Statistical analyses were carried out using SPSS v16 and the data was represented as mean ± standard deviation. $p<0.05$ was considered statistically significant.

Table 3.2 CT derived Body composition analysis

Characteristics	Cachectic cases (n = 19)	Non-cachectic controls (n = 15)	p-value
Cross sectional skeletal muscle area (cm^2) [a]			
Male	137.8 ± 15.7	158 ± 12.9	0.17
Female	96.2 ± 14.6	103.5 ± 14.1	
Skeletal muscle index (cm^2/m^2)* [a]			
Male	44.6 ± 5.9	49.1± 3.1	0.05
Female	36.3 ± 5.6	41.52± 7.43	
Sarcopenia [b]			
Yes	16	8	0.06
No	3	7	
Z-Score[#]	-0.75 ± 0.7	-0.09 ± 0.9	0.04
Total adipose tissue [a]			
Male	215.6 ± 84.5	266.29 ± 77.2	0.9
Female	328.8 ± 126.4	302.2 ± 122.7	
Muscle attenuation (HU)[a]			
Male	32.9 ± 8.6*	39.8 ± 6.9	0.02
Female	29.5 ± 7.3*	36.4 ± 8.6	

a= unpaired t-test, b= Fisher's exact test, *- $p<0.05$

***Table 3.2*:** CT quantification was carried out for patients who had CT prior to surgery. Overall Muscle attenuation, Skeletal muscle index and Z-score was found to be significant between cases and controls. Sarcopenia status based on Martin et al classification was trending towards significance (p=0.06) (21).

[#] Z-score indicates how many standard deviations an element is from the mean value for cancer patients of the same age and sex.

3.3.3 Identification of DASGs associated with CC

HTA array data identified a total of 8,960 ASGs. At ≥ 1.4 fold change and $p < 0.05$, 922 DASGs were identified, of which 722 DASGs were up-regulated (Appendix Table 7.1) and 150 were down-regulated (Appendix Table 7.2).

3.3.4 Validation of representative DASGs using Semi-quantitative RT-PCR

Representative DASGs from HTA array were selected (Table 3.3) for semi-quantitative RT-PCR. The thermal cycle profiles and the primers sequences used are given in Table 3.4. The primer sequence for β- Actin (used as an internal control) was available in literature (25). Exons of 4 up-regulated DASGs (IFRD1, KCNQ5, DEPDC1, UBA3) and 2 down-regulated DASGs (FNDC1 and CNNM3) were validated (Figure 3.1 and Table 3.3, Table 3.5). IFRD1 and KCNQ5 were found to be associated with skeletal muscle differentiation (see GSEA results below). However, the roles of DEPDC1 and FNDC1 in skeletal muscle or CC are unknown. CNNM3 is vital for magnesium transport and magnesium is known to regulate muscle contraction (26). From the HTA 2.0 results, exon 3 of UBA3 (ENST00000415609) was found to be up-regulated in cases. However, designing the primer for this exon (transcript ID ENST00000415609) was not feasible because of the presence of an upstream cassette exon event in another UBA3 transcript (ENST00000361055). Since both these transcripts were identified in muscle tissues, I chose to validate a cassette exon event (reported in UCSC genome browser), present in exon 4 (transcript ID ENST00000361055).

If an exon of a particular DASG is up-regulated in cases, it means increased inclusion of an exon is observed in cases, relative to WS cancer patients. For example, exon 5 of IFRD1 was found to be up-regulated in cases and was identified as a cassette exon (exon included or skipped). Based on semi-quantitative RT-PCR, an increased inclusion of exon 5 was observed in cases relative to WS cancer patients. Similarly, if an exon was down-regulated in CC cases, an increased inclusion of an exon was observed in WS cancer patients relative to CC cases. Exon inclusion rate was calculated based on the ratio of long isoform / short isoform (27, 28). Exon inclusion rate (densitometric analysis of RT-PCR amplicons) was computed from the semi-quantitative RT-PCR data and these independent results were consistent with the findings from transcriptome array (Table 3.5). All five validated DASGs exhibited cassette exon property, one of the most common AS events.

Table 3.3 DASGs validated using semi-quantitative PCR and detected from HTA 2.0 arrays microarray

Gene	Gene ID	Probe set ID	AS event	Fold change	p-value
IFRD1	NM_001197079	PSR07011131	Exon 5 is a CE (up)	1.76	0.007
KCNQ5	NM_001160132	PSR06008716	Exon 9 is a CE (up)	1.51	0.005
DEPDC1	NM_001114120	PSR01043217	Exon 8 is a CE (up)	1.55	0.0002
FNDC1	ENST00000297267	PSR06013583	Exon 10 is a CE (down)	-1.32	0.0008
CNNM3	ENST00000305510	PSR02009044	Exon 2 is a CE (down)	-1.58	0.01

Table 3.3: AS events for all the validated DASGs were identified using UCSC genome browser (hg19). The direction of effect of the identified exons for DASGs are represented, with respect to the cachectic cases relative to controls, as indicated by: (up), up-regulated and (down), down-regulated.

Table 3.4 Primer sequence for the validated DASGs with their corresponding thermal profiles

Gene	Primer Sequence (5'→ 3')	Thermal cycle profiles	Expected Isoform (bp)
IFRD1	F: ACTGATAGCATTGAACGCTG CCTGA R: GGAGTGCTGCAAATAACAGTAGTGTC	36 cycles at 95ºC for 30 sec, 59ºC for 30 sec and 72ºC for 30 sec	Long form (329) Spliced form (171)
KCNQ5	F:ATTGCAACCTGGAAGCCACACTTGAAG R: GTTGAAGCTCCAGCTCTTCTGCACTT	34 cycles at 95ºC for 30 sec, 59ºC for 30 sec and 72ºC for 30 sec	Long form (267) Spliced form (210)
DEPDC1	F: TGACCTCCCTCACTGGGTATTATCTG R: GACCTCGTACCCATTGCATCATGAAG	36 cycles at 95ºC for 30 sec, 57ºC for 30 sec and 72ºC for 1 min	Long form (1209) Spliced form (357)
CNNM3	F: ACCATCACTCGTTTCTACAACCATCCG R: GAGCAGCTGAGGCGAGATTGTTACTT	34 cycles at 95ºC for 30 sec, 61ºC for 30 sec and 72ºC for 1 min	Long form (351) Spliced form (207)
FNDC1	F: TACAGTTGTCGCTGCATCTTGGGATG R: TTTCTGTCGACTGAAGATCCAGCTCC	36 cycles at 95ºC for 30 sec, 59ºC for 30 sec and 72ºC for 30 sec	Long form (494) Spliced form (305)
UBA3	F: TGGGAAGGTCGCTGGAACCATGTAAA R: GCGATGATAGAGTCCAGTCCACATAC	34 cycles at 95ºC for 30 sec, 59ºC for 30 sec and 72ºC for 35 sec	Long form (412) Spliced form (331)
β- Actin	F: CGGGAAATCGTGCGTGAC R: TGGAAGGTGGACAGCGAGG	32 cycles at 95ºC for 30 sec, 59ºC for 30 sec and 72ºC for 30 sec	443 bp *

*- The primer sequence of loading control was used from literature reported studies and optimized for the present study.

Table 3.5 Densitometry analysis for DASGs

Gene	Isoform Inclusion ratio	Cachectic cases (mean)	Non-cachectic controls (mean)	Fold change (Densitometric analysis)
IFRD1	Incl Ex 5/ Skip Ex 5	6.41	5.5	1.16
KCNQ5	Incl ex 9/ Skip Ex 9	1.66	1.39	1.2
DEPDC1	Incl ex 8/ Skip Ex 8	3.82	2.44	1.57
FNDC1	Incl Ex 10/Excl Ex 10	0.53	0.59	0.89
CNNM3	Incl Ex 2/Skip Ex 2	4.34	5.40	0.8
UBA3	Incl Ex 4/ Skip Ex 4	3.74	3.03	1.23

Table 3.5: Representative DASGs with cassette exon event were validated using semi-quantitative RT-PCR. Similar direction of effect was observed in both microarray and PCR experiments.

Figure 3.1 Semi-quantitative RT-PCR validation of AS event

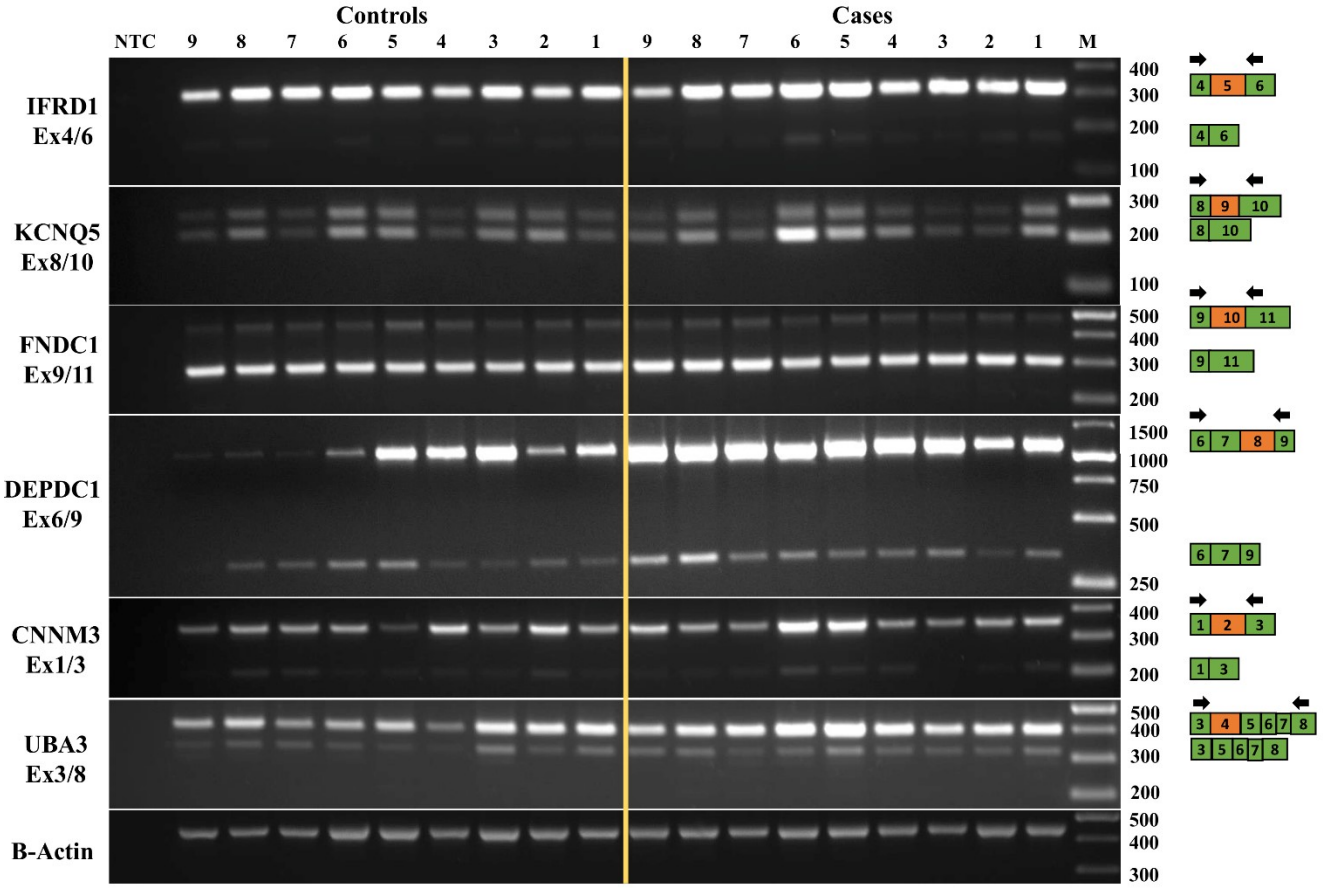


***Figure 3.1*:** The forward and reverse primers are represented by arrows that are designed from flanking constitutive exons. The exons identified in Human Transcriptome array (indicated in orange) exhibited similar direction of effect when validated in representative cases and WS cancer patients. All five validated DASGs exhibited cassette exon property. NTC is a non-template control and "M" is a DNA ladder marker. β- actin is used as an internal control.

Up to 10 % of the DASGs in the current study were identified to have cassette exons (exon present in some transcripts and absent in other isoforms). The next common splicing event observed in our study was alternate promoter usage (4.5% of identified DASGs had alternative transcription initiation sites, leading to isoform diversity). Other events identified were (i) variations in the sequence at the 3' and 5' positions in the splice donor-acceptor sites termed alternate 3' and 5' transcripts, (ii) alternate finish

(transcription ending at multiple sites and hence multiple isoforms), and (iii) intron retention. The definitions for each of the above AS events are adopted from the UCSC genome browser (https://genome.ucsc.edu/). The validation of AS events other than cassette exons are quite challenging and robust methods to validate diverse AS events are still in development.

3.3.5 DASGs and its biological relevance to CC using gene set enrichment analysis

The identified DASGs were associated with muscle structure and function (ENAH, ANKRD1), skeletal muscle differentiation (MEF2C, IFRD1 and KCNQ5), circadian rhythm (MKL1, QKI, ARNTL), inflammation (ADIPOR1, IL18), magnesium transport (CNNM3), protein ubiquitination (ANAPC1, UBB, UBC) and signaling pathways (DEPDC1, MAP2K5). A list of the DASGs with their respective functions is summarized in Table 3.6.

Table 3.6 Functional annotation of DASGs

Functions	Associated genes
Muscle	
Muscle structure and function	**DAAM1**, **PFN2**, **TRPM7**, **TPM3**, MYL6B, **ACTN2**, **PDE4D**, **RYR3**, **SLMAP**, **ANKRD1, ENAH, MYL5**
Skeletal muscle cell differentiation	**IGF1**, **LEMD3**, **MEF2C, PAXBP1**,**CYR61 , IFRD1, FLRT3, KCNQ5**
Extracellular matrix protein	**ADAM10**, *ADAM32*, *COL18A1, COL20A1,* **COL19A1**
Lipid Biosynthesis	*INPP4B***, PIGX, PLA2G2A,** *PLA2G15,* **SYNJ1, FABP4, FAR1, GK**
Inflammation	
Cytokine signaling and B cell activation	**ADIPOR**1, **PTPN2**, **IL18**, *CLCF1*, **PPM1B, BCL6**, **PTPRC, TGFBR2**
Protein ubiquitination and proteolysis	**UBE4B, UBE2B, USP45, PSMA5, HERC4, HUWE1, UBR5, UBA3, UBE2G2, FBXO11, USPL1, UBA6**
Signaling pathways	**DNM1L**, **MAP2K5**, **MKL1**, **NCF2**, **TNFRSF9, DEPDC1, ENAH**, **FYB**, **PIK3R1, JAK2, KIDINS220**, **NEDD9, CYR61**
Transcription factors	**INPP5F**, **CDCA7**
Circadian rhythm	**MKL1**, **QKI**, **SIK1, NCOR1**
mRNA-splicing	**CSTF3, SRSF10, SRSF3, SRSF4, SRSF5, SRSF6, TRA2A,** *CSTF1*

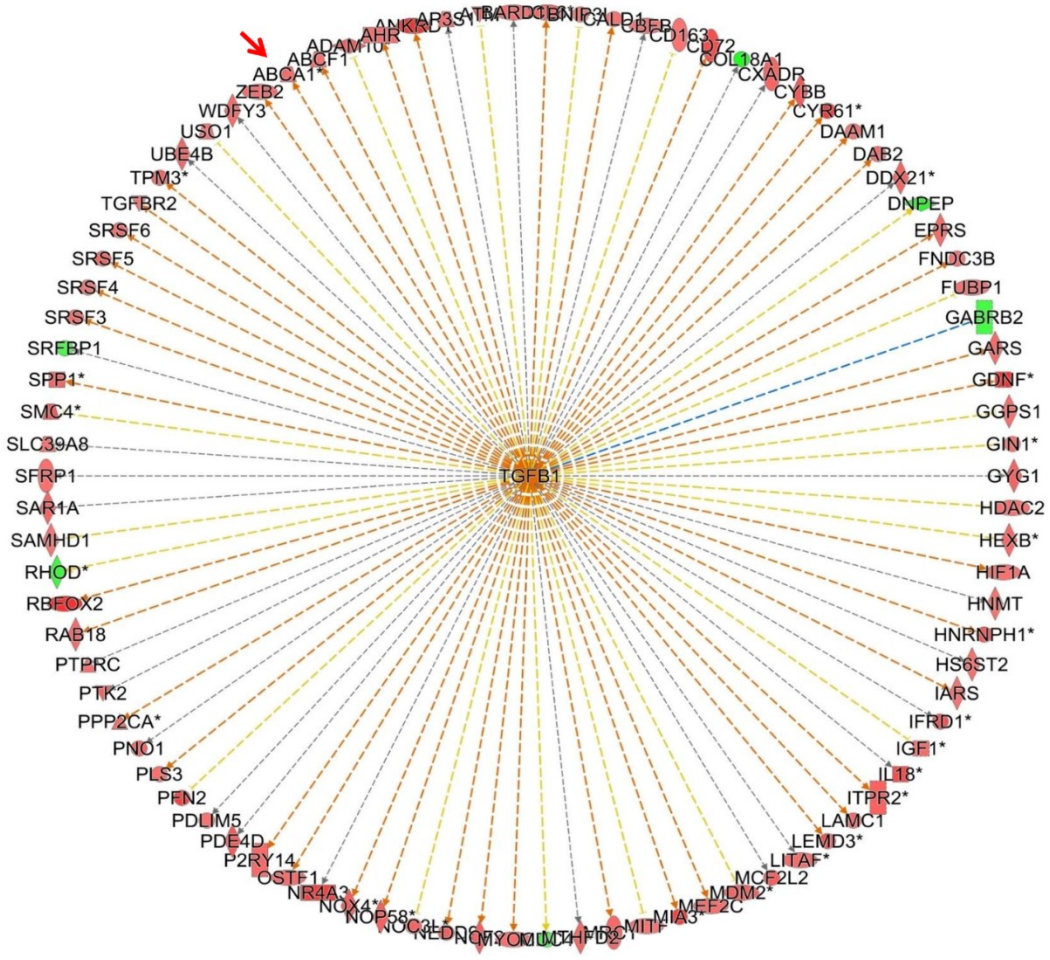
***Table 3.6*:** Gene set enrichment analysis was carried out using PGS 6.6. Clusters with $p < 0.05$ and enrichment score of more than 1.2 were considered significant in this study. Majority of the DASGs were associated with muscle structure and function that might be directly associated with skeletal muscle dysregulation. Other functions include inflammation, energy homeostasis, protein ubiquitination- dysregulation of all of these processes are well known to be associated with CC pathophysiology. The DASGs in bold are upregulated and the italicized genes are down-regulated in the study.

3.3.6 Canonical pathways Identified from IPA

83 canonical pathways were identified at $p<0.05$ (Appendix Table 7.3). Increased and decreased activity of a particular pathway is inferred based on the z-score. If the z-score is positive, then a pathway has an increased activity and negative for the decreased activity. The highly activated pathways include FLT3 signaling, IGF-1 signaling, IL-8 signaling, CNTF signaling and CXCR4 signaling (z-score range: 1.7-3.5). PTEN signaling was found to be decreased (z-score -1.732). While IGF-1 and IL-8 have been studied in the context of CC, FLT3 signaling is an emerging new pathway with a role in myogenic differentiation (28). Other significant pathways ($p < 0.05$) identified were protein ubiquitination pathway, glucocorticoid signaling and IL-4 signaling.

Many of the identified DASGs have not previously been associated with CC (29, 30). However, the pathways containing the DASGs were known to be associated with CC. The complete lists of canonical pathways are given in Appendix Table 7.3. While canonical pathways are informative, my interest was also to search for upstream modulators that affect several of the identified downstream effectors. In this search, I identified TFGB1 as one of the upstream regulators with activation z-scores of 3.1 with overlap p-value of 0.004 (Figure 3.2). The overlap p-value is an estimate of overlap between the DASGs identified in this study and the upstream regulator. Many of the upregulated DASGs were predicted to be activated rather than inhibited. A recent study had shown the effect of muscle dysfunction in CC through TGFB1 signaling. Activation of TGFB1 signaling in model systems led to an up-regulation of NOX-4 among other molecules which eventually leads to defective muscle contraction (31, 32). I also observed NOX-4 to be upregulated in the human skeletal muscle tissues, in support of previous observations.

Figure 3.2 TGFB1 as an upstream regulator identified by IPA along with its downstream targets.



List of downstream targets for TGFB1

ABCA1,ABCF1,ADAM10,AHR,ANKRD1,AP3S1,ATM,BARD1,BCL6,BNIP3L,CALD1,CBFB,CD163,CD72,COL18A1,CXADR,CYBB,CYR61,DAAM1,DAB2,DDX21,DNPEP,EPRS,FNDC3B,FUBP1,GABRB2,GARS,GDNF,GGPS1,GIN1,GYG1,HDAC2,HEXB,HIF1A,HNMT,HNRNPH1,HS6ST2,IARS,IFRD1,IGF1,IL18,ITPR2,LAMC1,LEMD3,LITAF,MCF2L2,MDM2,MEF2C,MIA3,MITF,MRC1,MTHFD2,MUC4,MYOCD,NCF2,NEDD9,NOC3L,NOP58,NOX4,NR4A3,OSTF1,P2RY14,PDE4D,PDLIM5,PFN2,PLS3,PNO1,PPP2CA,PTK2,PTPRC,RAB18,RBFOX2,RHOD,SAMHD1,SAR1A,SFRP1,SLC39A8,SMC4,SPP1,SRFBP1,SRSF3,SRSF4,SRSF5,SRSF6,TGFBR2,TPM3,UBE4B,USO1,WDFY3,ZEB2

Figure 3.2: Many of the upregulated DASGs were predicted to be (i) activated by TGFB1 (orange lines); (ii) inhibited by TGFB1 (blue lines); IPA identified molecules with no set predictions (gray lines) or those which could not be fit to a pattern of downstream molecules (yellow lines) are also illustrated. The DASGs highlighted in green are the down-regulated and the remaining DASGs are up-regulated. To facilitate readability of genes in the figure, I have listed the genes at the bottom of the figure and these have to be read in the clock-wise direction starting with the indicated red arrow.

3.3.7 Pearson correlation analysis for DASGs with body composition measurements

DASGs identified in gene set enrichment analysis (Table 3.6) were subjected to Pearson correlation test. DASGs identified with muscle structure and function, ubiquitination and inflammation were correlated to SMI; DASGs associated with lipid biosynthesis were correlated to Muscle radiation Attenuation. As CT was available for 34 patients, expression values from those samples were considered for these correlations with body composition measurements. ENAH (r= -0.38, p= 0.03), KCNQ5 (r= -0.36, p= 0.04), ROCK2 (r= -0.46, p=.006) were negatively correlated with SMI and MYL6B (r= 0.44, p= .009) was positively correlated to SMI. DASGs associated with inflammation such as BCL6 (r= -0.47, p= .004), TGFBR2 (r= -0.35, p= 0.04) were negatively correlated to SMI and ADIPOR1 (r= 0.34, p= 0.05) was positively correlated to SMI. INPP4B (r= 0.37, p= 0.04) was positively correlated with muscle radiation attenuation and PLA2G2A (r= -0.47, p= .005) and B4GALT4 (r= -0.37, p= 0.03) were negatively correlated to muscle radiation attenuation.

3.4 Discussion

This is the first study to identify DASGs associated with CC. It is recognized that different isoforms generated from the same pre-mRNA are expressed in a tissue specific manner (33) and these isoforms are known to perform diverse functions (34). Therefore, an understanding of the isoform specific expression in muscle tissue may explain the hidden complexity hitherto not revealed at the conventional gene level studies. Several DASGs that are involved in protein ubiquitination, skeletal muscle differentiation and inflammation were identified. These aforementioned mechanisms have been well-documented for their role in CC pathophysiology. Another mechanism which is slowly gaining prominence in CC pathophysiology is circadian rhythm (35). Many of the DASGs identified in this study have either not been previously reported in CC literature or were shown to be associated with other tissue types. For example, FNDC1 is associated with apoptosis of cardiomyocytes under hypoxic conditions (36). DEPDC1, a gene with a described role in bladder cancer (37) has not been reported to be associated with skeletal muscle functions. Independent confirmation of the described DASGs by

semi-quantitative RT-PCR gives us the confidence in the study findings that these are indeed expressed in skeletal muscle and may have a role in CC. It is currently known that >90% of all genes express multiple isoforms. With muscle having the highest number of alternatively expressed exons and skeletal muscle atrophy being a hall mark of CC, this study addresses a critical gap in literature by identifying the DASGs in CC pathophysiology using rectus abdominis muscle.

Many of the identified DASGs were associated with muscle structure and development, lipid biosynthesis, extracellular matrix, inflammation and protein ubiquitination (Table 3). Some of the identified DASGs have been reported to be associated with CC pathophysiology at the whole gene expression levels (38) but have not been explored at isoform levels. The ensuing discussion explains the potential role of representative DASGs identified from correlation analysis as well as from other DASGs identified in the study.

3.4.1 Extracellular matrix protein (ECM)

Collagen and its family members are one of the most abundant ECM proteins and we are now realizing that they are associated with a range of muscle diseases (39, 40). Collagen gene expression levels have been shown to be down-regulated in muscle tissue in various catabolic states, including CC (38). DASGs of collagen such as COL18A1 and COL20A1 were down-regulated in our current study, while COL19A1 was up-regulated. Matrix metalloproteinases (MMPs), an ECM remodeling enzymes, plays an important role in the breakdown of ECM components in normal physiological process and also in tissue turnover (41). ADAM 10, a cell surface protein identified in this study as associated with CC, has been shown to be a critical player in the maintenance of satellite cells (42). Up-regulation of this isoform in CC context needs to be elucidated in future experiments using model systems

3.4.2 Inflammation

Systemic inflammation is a hallmark of CC in which there is an imbalance between the levels of pro-inflammatory and anti-inflammatory cytokines (43). While Interleukin-1 (IL-1) and IL-6 have been implicated in the pathogenesis of CC (44, 45),

enhanced IL-18 levels have been associated with fat loss and cachexia (46) . Evidence suggests that mRNA levels of IL-18 are increased in the skeletal muscle of COPD patients when compared to controls and may potentially play a role in muscle wasting (47). Based on this premise, it could be conjectured that IL-18 isoforms may also play a role in cancer induced muscle wasting but this needs to be validated in future studies. ADIPOR1 is an adipokine molecule that is abundantly expressed in skeletal muscle. Its spliced isoforms have been shown to play a role during myogenesis and also in insulin sensitivity (48). Up-regulation of ADIPOR1 in the skeletal muscle of CC may potentially lead to impaired myogenesis. Both ADIPOR1 and IL-18 are involved in cytokine signaling, deregulation of which may contribute to CC pathophysiology. Other DASGs that are associated with cytokine signaling, B cell activation are listed in Table 3.

3.4.3 Lipid Biosynthesis and fatty infiltration in skeletal muscle

Abnormal deposition of fat in organs such as liver, muscle and bone are being recognized as pathogenic. While abnormal accumulation of fat in the liver (hepatosteatosis) is well documented (49), molecular mechanisms involved in fatty infiltration of skeletal muscle (myosteatosis) have not been addressed. Myosteatosis has been found to be associated with insulin resistance and is also known to reduce the survival period in cancer patients (24). In the present study, cachectic cases have lower muscle attenuation relative to WS cancer patients, which likely indicates the presence of fat accumulation in muscle. FABP4 has been reported to be expressed in skeletal muscle and play a role in fatty acid transport (50). FAR1, is studied for its role in β oxidation of fatty acids and acetyl-CoA translocation (51). Up-regulation of both these DASGs may potentially lead to accumulation of fat in skeletal muscle. Evidence also suggests that sphingolipid accumulation contributes to increased fat accumulation in skeletal muscle (52). The current study has identified DASGs such as B4GALT4 and ST8SIA5, which are associated with sphingolipid biosynthesis. With the potential role of the abovementioned DASGs leading towards lipogenesis and adipogenesis, it may be inferred that they may play a role in conferring the fatty muscle characteristics.

3.4.4 Protein Ubiquitination

Skeletal muscle depletion is characteristic of CC that could be attributed to an imbalance between protein synthesis and breakdown. In CC, we observe increased protein degradation or decreased protein synthesis or sometimes, both. One of the well-studied pathways for muscle atrophy is the Ubiquitin Proteasome Pathway (UPP) (13). Some of the identified DASGs such as UBA3, UBE2B, UBE2G2, PSMA5 and UBR5 have been implicated to play a role in protein ubiquitination. PSMA5 was shown to be upregulated in various catabolic states in animal models [38] and our study also found its isoform to be up-regulated. UBE2B was also shown to be up-regulated in-vitro leading to myofibrillar protein loss (53). The current study has also identified UBE2B to be up-regulated. Results from in vivo and in vitro models suggest that UBR5 acts as an activator of smooth muscle differentiation by stabilizing myocardin protein (54). While not much has been reported on spliced isoforms of UBR5, sequencing studies in mantle cell lymphoma (MCL) have identified a high number of lethal mutations in MCL patients which includes splice site mutations (55). However, defective splicing of UBR5 on muscle and muscle related conditions has not been investigated yet. Other upregulated DASGs associated with ubiquitination may also play a role in protein degradation pathways but have not been reported in the CC literature.

3.4.5 Skeletal muscle function and differentiation

Approximately 5% of the DASGs identified were associated with skeletal muscle function in some capacity, ranging from muscle structure to extracellular matrix protein (Table 3.6). ROCK2, identified in this study, plays a role in myoblast fusion during myogenesis by interacting with an RNA binding protein (56) ACVR2A, up-regulated in the current study, belongs to the member of TGF-β family. ACVR2A is involved in BMP signaling and plays a role in maintaining muscle mass. Their functional role in CC pathophysiology needs to be elucidated in future studies (57) FLRT3 is a cell surface protein that is expressed during the somite development, and plays a role in cell adhesion and in FGF signaling (58). However, their role in adult skeletal muscle and in disease states remains to be established.

AS and the isoforms produced may have varied (and in some instances, opposing) roles in the cellular context. One of the best studied examples is the BCL2 gene, whose long form is anti-apoptotic and whose short form is pro-apoptotic (59). While high levels of long forms of BCL2 helps cancer cells to evade apoptosis, the opposite effect occurs when cell exhibits high levels of short forms of BCL2. Possibly several of the identified ASGs identified in our study may have such functions; this needs to be experimentally validated in future studies. Also, upstream molecular events leading to alternative splicing need to be explored independently.

Genome-wide profiling of ASGs has helped unravel a large number AS events. It has helped in making rapid strides towards understanding and identifying the many ASGs that are dysregulated in a disease context. As with any genome-wide profiling studies, there are potential limitations, and these need to be addressed in future studies. Firstly, replication of findings using independent samples is required; and secondly, the identified signatures need to be interrogated for their putative biological roles in the context of CC. Overall, this study has comprehensively catalogued various molecules that could be affected in CC due to aberrant splicing mechanisms.

To put the current study into perspective: this is one of the largest sample sizes used to-date for profiling AS in human skeletal muscle and CC literature. I recognize that independent validation of findings is needed and international collaborations are sought to gain access to the rare and precious source of skeletal muscle biopsies from cancer affected patients. Being the first study in CC and AS, I chose to profile as many samples as possible and not split the samples into discovery and validation stages to preserve statistical power. If muscle biopsies from patients affected by different tumor types are accrued, this can also help us identify tumor-specific cachexia signatures, which may aid in therapeutic interventions in future, to support the premise of personalized medicine.

3.5 References

1. Kornblihtt AR, Schor IE, Allo M, Dujardin G, Petrillo E, Munoz MJ. Alternative splicing: a pivotal step between eukaryotic transcription and translation. Nature reviews Molecular cell biology. 2013;14(3):153-65.

2. Mironov AA, Fickett JW, Gelfand MS. Frequent alternative splicing of human genes. Genome research. 1999;9(12):1288-93.

3. Keren H, Lev-Maor G, Ast G. Alternative splicing and evolution: diversification, exon definition and function. Nature Reviews Genetics. 2010;11(5):345-55.

4. Castle JC, Zhang C, Shah JK, Kulkarni AV, Kalsotra A, Cooper TA, et al. Expression of 24,426 human alternative splicing events and predicted cis regulation in 48 tissues and cell lines. Nature genetics. 2008;40(12):1416-25.

5. Llorian M, Smith CW. Decoding muscle alternative splicing. Current opinion in genetics & development. 2011;21(4):380-7.

6. Futatsugi A, Kuwajima G, Mikoshiba K. Tissue-specific and developmentally regulated alternative splicing in mouse skeletal muscle ryanodine receptor mRNA. Biochemical Journal. 1995;305(Pt 2):373-8.

7. Arafat H, Lazar M, Salem K, Chipitsyna G, Gong Q, Pan TC, et al. Tumor-specific expression and alternative splicing of the COL6A3 gene in pancreatic cancer. Surgery. 2011;150(2):306-15.

8. Faustino NA, Cooper TA. Pre-mRNA splicing and human disease. Genes & development. 2003(4):419.

9. Ward AJ, Cooper TA. The pathobiology of splicing. Journal of Pathology. 2010;220(2):152-63.

10. Pistoni M, Ghigna C, Gabellini D. Alternative splicing and muscular dystrophy. RNA biology. 2010;7(4):441-52.

11. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology. 2011;12(5):489-95.

12. Kern KA, Norton JA. Cancer cachexia. JPEN Journal of parenteral and enteral nutrition. 1988;12(3):286-98.

13. Skipworth RJ, Stewart GD, Dejong CH, Preston T, Fearon KC. Pathophysiology of cancer cachexia: much more than host-tumour interaction? Clinical nutrition. 2007;26(6):667-76.

14. Dodson S, Baracos VE, Jatoi A, Evans WJ, Cella D, Dalton JT, et al. Muscle wasting in cancer cachexia: clinical implications, diagnosis, and emerging treatment strategies. Annual review of medicine. 2011;62:265-79.

15. Penna F, Costamagna D, Fanzani A, Bonelli G, Baccino FM, Costelli P. Muscle Wasting and Impaired Myogenesis in Tumor Bearing Mice Are Prevented by ERK Inhibition. PloS one. 2010;5(10):1-11.

16. Bland CS, Wang ET, Vu A, David MP, Castle JC, Johnson JM, et al. Global regulation of alternative splicing during myogenic differentiation. Nucleic acids research. 2010;38(21):7651-64.

17. Cortese A, Plagnol V, Brady S, Simone R, Lashley T, Acevedo-Arozena A, et al. Widespread RNA metabolism impairment in sporadic inclusion body myositis TDP43-proteinopathy. Neurobiol Aging. 2014;35(6):1491-8.

18. Clarke PA, te Poele R, Wooster R, Workman P. Gene expression microarray analysis in cancer biology, pharmacology, and drug development: progress and potential. Biochemical pharmacology. 2001;62(10):1311-36.

19. Eswaran J, Horvath A, Godbole S, Reddy SD, Mudvari P, Ohshiro K, et al. RNA sequencing of cancer reveals novel splicing alterations. Nature Publishing Group; 2013.

20. Zhang Z, Pal S, Bi Y, Tchou J, Davuluri RV. Isoform level expression profiles provide better cancer signatures than gene level expression profiles. Genome Medicine. 2013;5(4):1-13.

21. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47.

22. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Seminars in cell & developmental biology. 2016;54:2-10.

23. Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. Nat Meth. 2012;9(7):671-5.

24. Esfandiari N, Ghosh S, Prado CM, Martin L, Mazurak V, Baracos VE. Age, Obesity, Sarcopenia, and Proximity to Death Explain Reduced Mean Muscle Attenuation in Patients with Advanced Cancer. The Journal of frailty & aging. 2014;3(1):3-8.

25. Liu J, Xiao Y, Xiong HM, Li J, Huang B, Zhang HB, et al. Alternative splicing of apoptosis-related genes in imatinib-treated K562 cells identified by exon array analysis. Int J Mol Med. 2012;29(4):690-8.

26. Potter JD, Robertson SP, Johnson JD. Magnesium and the regulation of muscle contraction. Federation proceedings. 1981;40(12):2653-6.

27. Gardina PJ, Clark TA, Shimada B, Staples MK, Yang Q, Veitch J, et al. Alternative splicing and differential gene expression in colon cancer detected by a whole genome exon array. BMC genomics. 2006;7:325.

28. Ge Y, Waldemer RJ, Nalluri R, Nuzzi PD, Chen J. Flt3L is a novel regulator of skeletal myogenesis. Journal of cell science. 2013;126:3370-9.

29. Tisdale MJ. Mechanisms of cancer cachexia. Physiol Rev. 2009;89(2):381-410.

30. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nature reviews Cancer. 2014;14(11):754-62.

31. Waning DL, Mohammad KS, Reiken S, Xie W, Andersson DC, John S, et al. Excess TGF-ß mediates muscle weakness associated with bone metastases in mice. Nature medicine. 2015;21(11):1262-71.

32. Guttridge DC. A TGF-ß pathway associated with cancer cachexia. Nature medicine. 2015;21(11):1248-9.

33. Sekiyama Y, Suzuki H, Tsukahara T. Functional gene expression analysis of tissue-specific isoforms of Mef2c. Cellular and molecular neurobiology. 2012;32(1):129-39.

34. Mosthaf L, Grako K, Dull TJ, Coussens L, Ullrich A, McClain DA. Functionally distinct insulin receptors generated by tissue-specific alternative splicing. The EMBO journal. 1990;9(8):2409-13.

35. Tsoli M, Schweiger M, Vanniasinghe AS, Painter A, Zechner R, Clarke S, et al. Depletion of White Adipose Tissue in Cancer Cachexia Syndrome Is Associated with Inflammatory Signaling and Disrupted Circadian Regulation. PloS one. 2014;9(3):1-12.

36. Sato M, Hiraoka M, Suzuki H, Sakima M, Mamun AA, Yamane Y, et al. Protection of Cardiomyocytes from the Hypoxia-Mediated Injury by a Peptide Targeting the Activator of G-Protein Signaling 8. PloS one. 2014;9(3):1-9.

37. Kanehira M, Harada Y, Takata R, Shuin T, Miki T, Fujioka T, et al. Involvement of upregulation of DEPDC1 (DEP domain containing 1) in bladder carcinogenesis. Oncogene. 2007;26(44):6448-55.

38. Lecker SH, Jagoe RT, Gilbert A, Gomes M, Baracos V, Bailey J, et al. Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. The FASEB Journal. 2004;18(1):39-51.

39. Gelse K, Pöschl E, Aigner T. Collagens—structure, function, and biosynthesis. Advanced Drug Delivery Reviews. 2003;55(12):1531.

40. Bönnemann CG. The collagen VI-related myopathies: muscle meets its matrix. Nature ReviewsNeurology. 2011;7(7):379-90.

41. Sorsa T, Tjäderhane L, Salo T. Matrix metalloproteinases (MMPs) in oral diseases. Oral diseases. 2004;10(6):311-8.

42. Mizuno S, Yoda M, Shimoda M, Tohmonda T, Okada Y, Toyama Y, et al. A Disintegrin and Metalloprotease 10 (ADAM10) Is Indispensable for Maintenance of the Muscle Satellite Cell Pool. The Journal of biological chemistry. 2015;290(47):28456-64.

43. Argiles JM, Busquets S, Toledo M, Lopez-Soriano FJ. The role of cytokines in cancer cachexia. Current opinion in supportive and palliative care. 2009;3(4):263-8.

44. Moldawer LL, Georgieff M, Lundholm K. Interleukin 1, tumour necrosis factor-alpha (cachectin) and the pathogenesis of cancer cachexia. Clinical Physiology. 1987;7(4):263-74.

45. Cahlin C, Korner A, Axelsson H, Wang W, Lundholm K, Svanberg E. Experimental cancer cachexia: the role of host-derived cytokines interleukin (IL)-6, IL-12, interferon-gamma, and tumor necrosis factor alpha evaluated in gene knockout, tumor-bearing mice on C57 Bl background and eicosanoid-dependent cachexia. Cancer research. 2000;60(19):5488-93.

46. Murphy AJ, Kraakman MJ, Kammoun HL, Dragoljevic D, Lee MKS, Lawlor KE, et al. IL-18 Production from the NLRP1 Inflammasome Prevents Obesity and Metabolic Syndrome. Cell Metabolism. 2016;23(1):155-64.

47. Petersen AMW, Penkowa M, Iversen M, Frydelund-Larsen L, Andersen JL, Mortensen J, et al. Elevated levels of IL-18 in plasma and skeletal muscle in chronic obstructive pulmonary disease. Lung. 2007;185(3):161-71.

48. Ashwal R, Hemi R, Tirosh A, Gordin R, Yissachar E, Cohen-Dayag A, et al. Differential expression of novel adiponectin receptor-1 transcripts in skeletal muscle of subjects with normal glucose tolerance and type 2 diabetes. Diabetes. 2011;60(3):936-46.

49. Younossi ZM, Afendy A, Stepanova M, Hossain N, Younossi I, Ankrah K, et al. Gene expression profile associated with superimposed non-alcoholic fatty liver disease and hepatic fibrosis in patients with chronic hepatitis C. Liver Int. 2009;29(9):1403-12.

50. Furuhashi M, Saitoh S, Shimamoto K, Miura T. Fatty Acid-Binding Protein 4 (FABP4): Pathophysiological Insights and Potent Clinical Biomarker of Metabolic and Cardiovascular Diseases. Clinical Medicine InsightsCardiology. 2015;8:23-33.

51. bin Yusof MT, Kershaw MJ, Soanes DM, Talbot NJ. FAR1 and FAR2 regulate the expression of genes associated with lipid metabolism in the rice blast fungus Magnaporthe oryzae. PloS one. 2014;9(6):e99760-e.

52. Momin AA, Park H, Portz BJ, Haynes CA, Shaner RL, Kelly SL, et al. A method for visualization of "omic" datasets for sphingolipid metabolism to predict potentially interesting differences. Journal of lipid research. 2011;52(6):1073-83.

53. Polge C, Leulmi R, Jarzaguet M, Claustre A, Combaret L, Béchet D, et al. UBE2B is implicated in myofibrillar protein loss in catabolic C2C12 myotubes. Journal of cachexia, sarcopenia and muscle. 2016;7(3):377-87.

54. Hu G, Wang X, Saunders DN, Henderson M, Russell AJ, Herring BP, et al. Modulation of Myocardin Function by the Ubiquitin E3 Ligase UBR5. Journal of Biological Chemistry. 2010(16).

55. Meissner B, Kridel R, Lim RS, Rogic S, Tse K, Scott DW, et al. The E3 ubiquitin ligase UBR5 is recurrently mutated in mantle cell lymphoma. Blood. 2013;121(16):3161-4.

56. Singh RK, Xia Z, Bland CS, Kalsotra A, Scavuzzo MA, Curk T, et al. Rbfox2-coordinated alternative splicing of Mef2d and Rock2 controls myoblast fusion during myogenesis. Molecular cell. 2014;55(4):592-603.

57. Lee SJ, Reed LA, Davies MV, Girgenrath S, Goad ME, Tomkinson KN, et al. Regulation of muscle growth by multiple ligands signaling through activin type II receptors. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(50):18117-22.

58. Haines BP, Wheldon LM, Summerbell D, Heath JK, Rigby PWJ. Regulated expression of FLRT genes implies a functional role in the regulation of FGF signalling during mouse development. Developmental biology. 2006;297:14-25.

59. Schwerk C, Schulze-Osthoff K. Regulation of apoptosis by alternative pre-mRNA splicing. Molecular cell. 2005;19(1):1-13.

4 Sexual dimorphism in human cancer cachexia – a preliminary study into miRNA/mRNA expression and their regulatory mechanisms in human skeletal muscle

4.1 Introduction

Sex-specific gene expression differences are observed at tissue, chromosome and cellular levels, and as such, sexual dimorphism in humans is relatively well recognized with profound consequences at physiological and molecular levels in conferring phenotypes and traits (1, 2). Studies using various model systems have helped understand that different physiological processes are guided by a set of genes in a sex-specific manner. These dimorphic patterns have also been observed in disease specific context, especially in conditions such as obesity, diabetes, cancer and adverse drug reactions (3-6). These observations indicate that both sexes may have evolved different mechanisms in conferring a disease or responses to changing environmental stimuli. Mouse models have also been found to exhibit sexual dimorphism patterns of gene expression in cardiac atrophy condition (7). However, the impact of sexual dimorphism on human Cancer Cachexia (CC) remains unexplored at the molecular level.

CC is a multifactorial syndrome characterized by severe depletion of skeletal muscle, with or without fat loss (8). Effect of sexual dimorphism has been observed in lower limb muscle function in CC (9). Body composition analysis has revealed that males have more lean body mass while females have more fat mass (10). Recent evidence also suggests that overall weight loss and skeletal muscle loss is more prevalent in male cancer patients, when compared to female cancer patients (11). Although the sexual dimorphism patterns have been captured at the imaging and anthropometric levels, it has never been linked to molecular level changes in human CC. Comprehending these molecular changes may help us identify sex-specific mechanisms contributing to a disease phenotype, which might add a newer dimension to our understanding of CC.

The aim of this preliminary study was to investigate if there are sex-specific molecular differences for CC. I addressed this question by studying regulatory mechanisms at the post-transcriptional level, i.e., microRNAs (miRNAs) and gene expression at the isoform level from human skeletal muscle biopsies. miRNAs are small non-coding RNAs ranging from 18-25 nucleotides in length. They are considered as post-transcriptional regulators of gene expression by binding predominantly to 3' untranslated region of mRNAs, leading either to mRNA degradation or translational repression, based on the degree of complementarity shared between the two molecules (12). I have earlier shown that miRNAs may be potentially associated with the pathophysiology of CC using human skeletal muscle biopsies. In the present study, I extend these observations (utilizing the same sample sets, GEO accession ID - GSE75473) to interrogate for sex-specific differences that exist at miRNA expression (13).

It is widely recognized that human genes are capable of producing multiple isoforms (also known as transcripts) from a single mRNA by the process of alternative splicing mechanisms thereby increasing proteome diversity (14, 15). There are also evidence to suggest that both miRNA and gene expression at the isoform level exhibit sexual dimorphism patterns (16, 17), but the same has not been studied for CC yet, in human skeletal muscle. Further, regulation of isoform specific gene expression by miRNAs has also not been studied. Traditional gene expression studies using microarrays (3' biased and not exon level resolution) provide gene level changes that are derived from the signal averaged expressions from potential multiple isoforms and as such, do not offer the finer level of resolution at the isoform level. I hypothesized that post-transcriptional regulatory mechanisms may contribute to CC pathophysiology in a sex-specific manner. The objectives of our preliminary study were: (i) to identify differentially expressed (DE) miRNAs associated with CC independently for sexes, (ii) to identify differentially expressed genes at the isoform level (hereafter referred to as DEI) for sexes, (iii) to identify canonical pathways for the DEI and its relevance to CC, (iv) to identify DEI as targets for DE miRNAs and identify canonical pathways to understand the biological relevance using matched samples, and (v) to validate representative miRNAs and DEI using qRT-PCR. Several differences were identified between genders at miRNA, DEI

expression, pathway and at the network levels, indicating that sexual dimorphism may play an important role at the molecular level in CC pathophysiology.

4.2 Methods

I performed all the experiments and analysis, unless otherwise indicated in the text.

4.2.1 Sample selection and muscle biopsies procurement for the study

Complete details of sample selection and procurement of muscle biopsies have been explained elsewhere (13). Written informed consent was obtained from all the patients who participated in the study. The study was approved by Conjoint Health Research Ethics Board at the University of Calgary (Ethics ID E-17213). Molecular profiling of the study samples was carried out under the ethics protocol ETH-21709, approved by Health Research Ethics Board of Alberta (HREBA) - Cancer Committee.

Samples were stratified into cachectic cases and non-cachectic controls based on the international consensus definition for cancer cachexia as described (8, 13). 42 patients, belonging to pancreatic cancer and colorectal cancer with liver metastasis, were selected for the study, of which 9 males and 13 females were cachectic cases (hereafter referred to as cases), while 9 males and 11 females were non-cachectic controls (hereafter referred to as controls).

4.2.2 Body composition analysis

CT images were available for 35 patients prior to surgery (70.75 ± 45.24 in days). The 3rd lumbar vertebra is used as a standard landmark in quantifying the muscle and fat cross sectional area, as described (18). Cross-sectional area (cm^2) and radio density of rectus abdominis muscle (Hounsfield units), and adipose tissue were measured. Cross-sectional muscle area was normalized to individual's stature to obtain the skeletal muscle index (SMI, cm^2/m^2). Sarcopenia status was assigned to patients based on the previously described age and sex adjusted SMI values (18, 19).

4.2.3 Total RNA extraction

Total RNA was isolated using Trizol (Sigma-Aldrich, Oakville, ON, Canada) and QIAGEN maxi kit (Mississauga, ON). An aliquot of the isolated RNA was used for both

miRNA and DEI profiling. 260/280 ratio and RNA integrity number (RIN) were assessed using Nanodrop and Agilent Bio-analyzer 2100, respectively.

4.2.4 miRNA profiling using Next Generation Sequencing (NGS)

Details of the various processing steps involved in processing NGS data to generate the binary alignment files (.bam files) for downstream analysis are explained elsewhere (13). Briefly, after importing the .bam files to Partek genomics suite 6.6 (PGS 6.6), the data was normalized using RPKM method normalization. For both male and female groups, only miRNAs with ≥ 5 read counts in at least 75% of the samples (cases and controls inclusive) were used for differential expression. DE miRNAs were identified at ≥ 1.4 Fold Change (FC) and with $p < 0.05$. The raw data and .bam files were submitted to Gene expression Omnibus database (GEO accession ID - GSE75473).

4.2.5 Profiling of genes at the isoform level using Human Transcriptome Array 2.0

Samples used for miRNA profiling were also used for generating gene expression data at the isoform level using Human Transcriptome Array 2.0 (HTA 2.0). This array contains both protein coding and non-protein coding transcripts. For the current study, only the protein coding genes were considered for analysis. Total RNA was used for labeling and hybridization, according to manufacturers' protocol (http://www.affymetrix.com). After hybridization, washing and staining protocol was carried out and the array chips were scanned using Affymetrix GCS 3000 7G scanner. The .CEL files thus generated were used for downstream analysis using PGS 6.6. The intensity data was background corrected, log 2 transformed and quantile normalized. PGS identifies variations at the transcript and at the exon levels. All the analyses were conducted separately for males and females. Genes that exhibited ≥ 1.4 FC and $p < 0.05$ at the exon level, along with statistical significance ($p < 0.05$) at the transcript level were identified as DEI. The raw data and intensity files have been submitted to gene expression omnibus database (GEO accession ID - GSE85017).

4.2.6 Identifying canonical pathways and upstream regulators using Ingenuity Pathway Analysis (IPA)

The identified DEI were subjected to IPA to identify the canonical pathways. The aim was to identify overlapping and diverging pathways between sexes to understand the pathophysiology of CC. Upstream regulatory molecules and network analysis were also carried out using IPA.

4.2.7 Validation of representative signatures using qRT-PCR

Representative DE miRNAs and DEI identified from males and females were validated for cross-platform concordance using qRT-PCR. hsa-miR-3184-3p for females and hsa-let-7d-5p, hsa-miR-320a and hsa-miR-744-5p for males were validated. RNU-6B was used as an internal control. At the DEI level, NFKB1 (NM_003998), NMNAT1 (NM_022787) for males and MYL3 (NM_000258) for females were validated using TaqMan probes. GAPDH was used as an internal control. All the experiments were carried out in triplicates and for all the samples used in the study. For DEI, total RNA was converted to cDNA using high capacity cDNA reverse transcription kit (Life technologies). For miRNA, TaqMan stem-loop primers, which are known for their better specificity and sensitivity, were used for reverse transcription. 10 ng and 50 ng of RNA was used as starting material for miRNA and DEI, respectively. $2^{-\Delta\Delta Ct}$ method was used for fold expression calculation (20).

4.2.8 Statistical analysis

The data were represented as mean ± standard deviation. The difference between means was estimated using independent t-test for continuous variables. Fisher's exact test was used for categorical variables. $p < 0.05$ was considered statistically significant for all the tests.

4.3 Results

4.3.1 Patient Demographics and CT imaging results

The mean age, BMI and body composition measurements for males and females are represented in Table 4.1. In both the sexes, BMI was found to be lower in cases than

in controls. Also, cross sectional muscle area, SMI and MA were lower in cases compared to controls. However, MA was considerably less in females compared to males. Reduced muscle attenuation has been associated with poor survival in diseases such as cancer (21). It may also be an indication of pathological infiltration of fat into the muscle, which may impact muscle function and quality of life. Overall, in males, the skeletal muscle mass is higher, while the fat mass was present in higher proportions in females (Table 4.1). Statistical significance could not be reached for these comparisons for body measurements owing to the small sample size and stratification into males and females in independent association studies. However, I have earlier shown that the statistical analyses carried out between cases (n=22) and controls (n=22) for BMI and other body composition, parameters such as z-score (indicates how many standard deviations an element is from the mean value for cancer patients of the same age and sex), muscle attenuation were significant at $p < 0.05$, while SMI was trending towards significance (22).

Table 4.1 Demographics and body composition analysis for study subjects

Characteristics	Male		Female	
	Cachectic cases (n=9)	**Non-cachectic controls (n=9)**	**Cachectic cases (n=13)**	**Non-cachectic controls (n=11)**
Age (mean, in years)[a] [Range]	67.34 ± 5.53	62.78 ± 5.94	65.08 ± 10.32	64.27 ± 9.23
Tumor type (n) [b] Pancreatic Colorectal	 4 5	 3 6	 8 5	 4 7
Body Mass Index [a] (mean, in kg/m^2) [Range]	24.6 ± 1.04	26.36 ±2.64	24.2 ±3.1	27.56 ± 4.3
Tumor Stage [c] *I* *II* *III* *IV*	 1 2 0 6	 1 0 0 9	 1 1 2 9	 0 3 0 8
Cross sectional skeletal muscle area (cm^2) [a]	139.5 ± 15.4	158 ± 13	96.2 ± 14.6	103.5 ± 14.1
Skeletal muscle index (cm^2/m^2) [a]	45.3 ± 6.0	49.2 ± 3.1	36.3 ± 5.6	41.6 ± 7.4
Z-Score [a]	-0.6 ± 0.7	-0.33 ± 0.37	-0.7 ± 0.8	0.03 ± 1.1
Total adipose tissue [a]	226.9 ± 84.5	157.5 ± 46.5	328.8 ± 126.4	302.2 ± 122.8
Muscle attenuation [a] (HU)	34.1 ± 8.7	39.8 ± 6.9	27.6 ± 5.2	37.4 ± 8.7

a - Independent t-test; b - Chi-square test

***Table 4.1*:** In males, cross sectional muscle area, skeletal muscle index, and muscle attenuation were less in cases compared to controls. Mean between the groups was not statistically significant owing to small sample size. Nevertheless, there was an expected trend observed between cases and controls. As observed in males, similar trends were seen in females when cases and controls were compared but were not statistically significant. Overall muscle radiation attenuation was reduced in females compared to males.

4.3.2 Profiling and identification of DE miRNAs

In males, a total of 612 miRNAs were profiled. 103 miRNAs were retained after data filtering (> 5 RC in 75% of samples) and were considered for DE analysis. 10 miRNAs (hsa-miR-320a, hsa-let-7b-5p, hsa-miR-193b-5p, hsa-miR-744-5p, hsa-miR-92a-3p, hsa-let-7b-3p, hsa-let-7d-3p, hsa-miR-423-3p, hsa-miR-532-5p and hsa-miR-199a-3p) were identified as DE with ≥ 1.4 FC and $p < 0.05$. All the ten miRNAs were up-regulated in cases when compared with controls. Except miR-532-5p (present in X-chromosome), all the identified miRNAs were present in autosomes. Six of the ten DE miRNAs are novel and are specific for males, while the remaining four DE miRNAs are associated with CC as described in our earlier study (13).

In females, a total of 674 miRNAs were profiled. 106 miRNAs were retained after filtering and were used for identifying DE miRNAs. 3 miRNAs (hsa-miR-3184-3p, hsa-miR-423-5p and hsa-miR-1296-5p) were identified as DE with ≥ 1.4 FC and $p < 0.05$. Here again, all the miRNAs were up-regulated in cases when compared to controls and were present in autosomes. None of the DE miRNAs in females showed overlap with DE miRNAs from males. These findings should be interpreted with caution due to the small sample size used in this preliminary study. The current study has not identified any down-regulated miRNAs at the specified cut-off in both sexes but the use of larger sample size may help identify DE down-regulated miRNAs. The list of DE miRNAs for males and females are presented in Table 4.2. All of the previously reported miRNAs associated with CC have retained statistical significance even in this stratified analysis. However, when the DE miRNAs identified from male and female groups were compared, no miRNA was found in common between the two sexes, indicating a possible sexual dimorphic expression pattern.

Table 4.2 List of DE miRNAs

miRNA	p-value	Fold change	Direction of fold change
DE miRNAs in males			
hsa-miR-320a	0.01	1.75	Up
hsa-let-7b-5p	0.01	1.55	Up
hsa-miR-193b-5p	0.02	1.74	Up
hsa-miR-744-5p	0.02	1.78	Up
hsa-miR-92a-3p	0.03	1.51	Up
hsa-let-7b-3p	0.04	1.57	Up
hsa-let-7d-3p	0.04	1.60	Up
hsa-miR-423-3p	0.04	1.53	Up
hsa-miR-532-5p	0.04	1.76	Up
hsa-miR-199a-3p	0.05	2.88	Up
DE miRNAs in females			
hsa-miR-3184-3p	0.03	1.41	Up
hsa-miR-423-5p	0.03	1.41	Up
hsa-miR-1296-5p	0.05	1.46	Up

Table 4.2: DE miRNAs were identified at 1.4 FC with $p < 0.05$. All the identified DE miRNAs in both sexes were upregulated relative to controls.

4.3.3 Identification of DEI from Human Transcriptome Array 2.0 (HTA 2.0)

Samples used for miRNA profiling were also used for generating gene expression data at the isoform level using HTA 2.0. Of the 42 samples used for the study, two samples did not pass the quality control during the microarray experiments and were removed from further analysis. Therefore, 21 cases and 19 controls remained for further analysis. In males, 1324 DEI (Appendix Table 7.4) were identified at 1.4 FC with $p < 0.05$, of which 1027 were up-regulated and 297 were down-regulated. 43 of the up-regulated DEI and 16 of the down-regulated DEI belonged to sex chromosomes while the remaining (1265) were present in autosomes. In females, 372 DEI (Appendix Table 7.5) were identified at 1.4 FC and $p < 0.05$, with 297 DEI being up-regulated and 75 DEI being down-regulated. Eight up-regulated and five down-regulated DEI were present in

sex chromosomes, and 359 in autosomes, respectively. These results also confirm the literature findings that sexually dimorphic differences exist both at the sex chromosome level and also at the autosome level (22). 52 DEI (~3%) of the total identified showed overlap between the sexes.

In summary, different DEI appear to contribute to CC in a sex-specific manner. The majority of signatures from autosomes are an indication of the contribution of diverse genes in conferring cachexia in males and females by distinct mechanisms.

4.3.4 Identification of canonical pathways for DEI

The identified DEI for males and females were subjected to IPA to understand the implications of putative canonical pathways in CC pathophysiology. In this analysis, I focused on canonical pathways showing $p < 0.05$. The DEI were also used to identify the potential upstream regulators and their downstream target genes. I have also identified the relevant networks to understand the interaction between the genes using IPA.

In males, 73 canonical pathways were identified (Appendix Table 7.6). Many of the top hit pathways have been implicated in skeletal muscle atrophy. These include Protein ubiquitination signaling, glucocorticoid receptor signaling, mTOR signaling, PI3K/AKT signaling, Insulin receptor signaling (23), NFKB1 signaling (24), AMPK signaling (25), MAPK signaling (26), TNFR2 signaling, fatty acid oxidation (27), and IL6 signaling (28). Up to 10% (122 DEI) of the identified DEI were associated with these aforementioned canonical pathways. This may be correlated to the clinical evidence that men lose more skeletal muscle and at a faster rate when compared to females.

In females, 35 canonical pathways were identified at $p < 0.05$ (Appendix Table 7.7). The top hit pathways were associated with inflammation, glutathione mediated detoxification, adipogenesis pathway, lysine degradation and cardiolipin biosynthesis.

Common pathways identified between the sexes included AMPK signaling, PI3K/AKT signaling and Protein Ubiquitination Pathway. Although only a few common pathways were identified between sexes, yet the genes involved in these pathways were predominantly different.

4.3.5 Upstream regulatory analysis and network analysis using IPA

In males, TGFB1 and KLF3 were identified as upstream regulators with TGFB1 being activated (z-score = 2) and KLF3 being inhibited (z-score = -3.6). Z-score value indicates the activation or inhibition of a particular regulator molecule. Based on IPA prediction, a positive z-score indicates the activation of a molecule and a negative z-score indicates the inhibition of that molecule. Recently TGFB1 was shown to have implications in CC pathophysiology (29). KLF3 is a transcriptional factor that is known to regulate muscle specific gene expression. It is predominantly present in the muscle gene promoter region and is found to be up-regulated during muscle differentiation (30). Hence, inhibition of this molecule may have an impact on muscle differentiation. In females, TGFB1 and NFKB complex were identified as potential upstream regulators with both the molecules being activated with a z-score of 2.3 and 2.7, respectively. Although TGFB1 was a common upstream regulator in both the sexes, their downstream targets were predominantly different (Figure 4.1). It could be inferred that the same transcription factor may activate different downstream targets. At the network level analysis, NFKB network was significantly enriched in both sexes (Figure 4.2). It has been known for long that NFKB has a major role in skeletal muscle atrophy and CC pathophysiology (24).

Figure 4.1 Upstream regulatory molecules and downstream targets for males and females

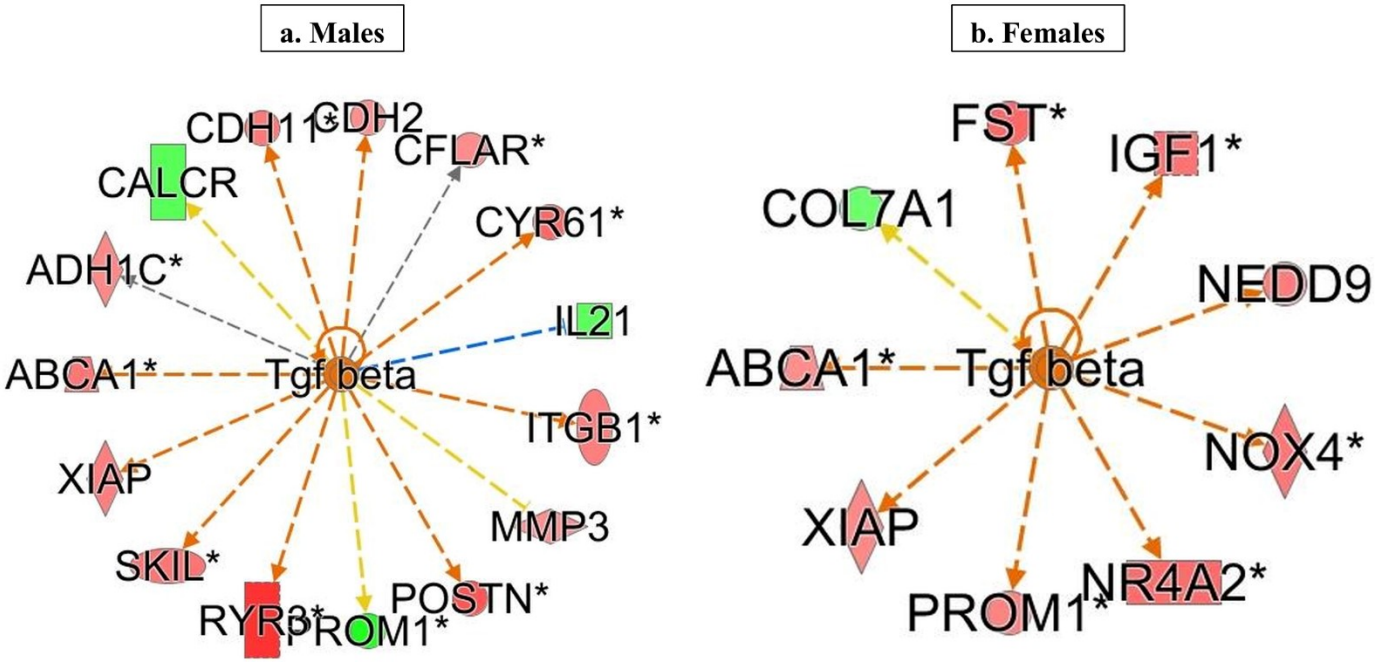


Figure 4.1: Green color indicates down-regulated DEI and red color indicates up-regulated DEI. Intensity of green or red color indicates the degree of down or up-regulation, respectively. Vertical rectangle shape indicates G-protein coupled receptors, horizontal rectangle shape indicates ligand-dependent nuclear receptors, vertical rhombus shape indicates enzymes, horizontal rhombus indicates peptidase, trapezium indicates transporters, horizontal oval shape indicates transcription regulators, vertical oval shape indicates transmembrane receptors, square indicates cytokines and circle indicates other functions. Asterisk indicate that multiple identifiers in the dataset file map to a single gene/ chemical in the Global Molecular Network. Orange lines indicate activation of that molecule, blue lines indicate inhibition of that molecule, and gray lines indicate no set predictions and yellow lines indicate that these molecules could not be fit into a pattern.

Figure 4.2 Network analysis for males and females using IPA

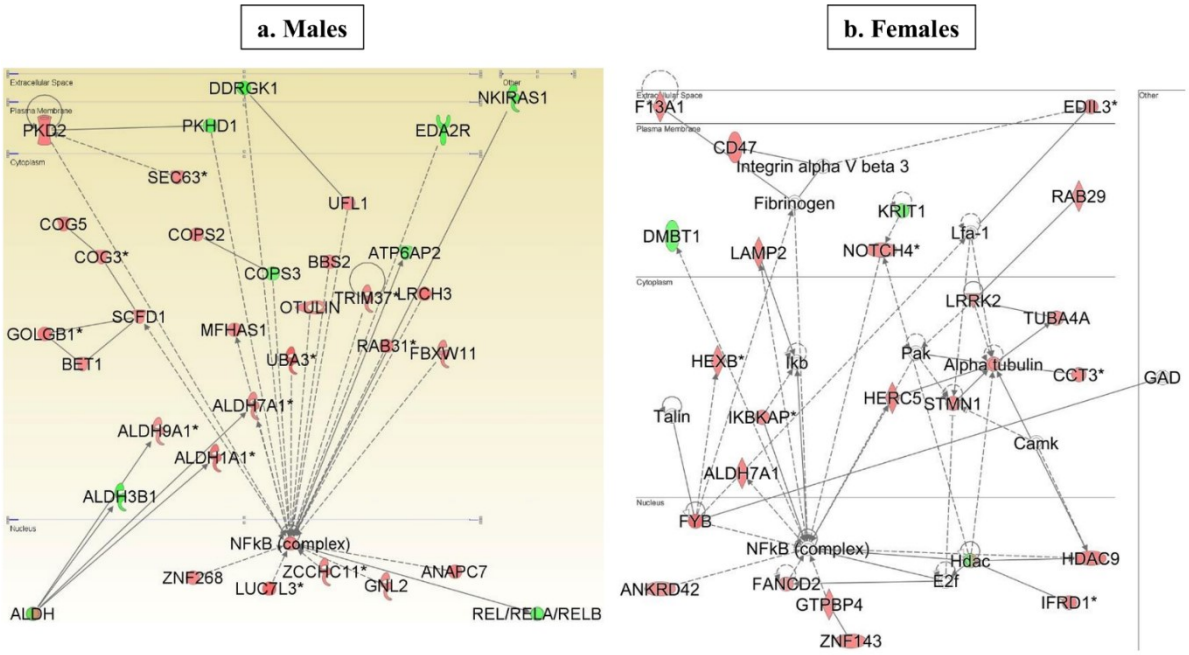


***Figure 4.2*:** NFkB network was highly enriched in both the sexes. However, different DEI were involved in activating the NFkB complex. Red color indicates upregulation of DEI and green color indicates the down-regulation of DEI in our dataset. Dotted lines indicate an indirect relationship between the genes and the bold lines indicate a direct relationship between the genes. Asterisk indicate that multiple identifiers in the dataset file map to a single gene/ chemical in the Global Molecular Network.

4.3.6 Target identification for DE miRNAs

Conventionally, miRNAs bind to the 3' UTR of a gene and bring about translational repression or mRNA degradation. Identifying gene targets regulated by DE miRNAs may aid in identifying the potential pathways that they are involved in, which would help in understanding their role in CC pathophysiology. In the literature, target genes are predominantly identified through in silico predictions using databases such as TargetScan or miRanda. However, one of the potential limitations of such an approach is that the identified targets are not presented in a tissue-specific manner. It has also been a general practice in literature to use the whole gene expression dataset to identify the miRNA targets. It is currently recognized that more than 90% of human genes have

multiple isoforms and are expressed in a tissue specific manner (31). For example, MEF2C- a myocyte enhancer factor, has six isoforms in humans that are generated by alternative exon usage. From the animal studies, it is evident that isoforms of MEF2C are expressed in a tissue-specific manner (31). For instance, in our study, only one isoform (out of six known isoforms) of MEF2C was found to be expressed in muscle tissues at the specified cut-offs. Therefore, identifying isoform specific targets for DE miRNAs could be more accurate than identifying at the whole gene level per se, to understand the underlying pathophysiology. Therefore, our aim was to identify isoform specific targets for DE miRNAs. HTA 2.0, used in the current study, can capture gene expression at an isoform level, hence the use of this profiling platform in the current study. The use of matched datasets and the identification of isoform specific targets are unique to this study and also in literature and a major strength of the study conclusions.

To identify putative targets for DE miRNAs, I only considered inverse relationship, i.e., if a miRNA was up-regulated, then its corresponding target should be down-regulated. In males, 565 down-regulated targets were identified for 10 DE up-regulated miRNAs. The DE miRNAs were found to be involved in pathways such as GABA receptor signaling, PI3K/AKT signaling, ILK signaling and insulin receptor signaling. While Insulin receptor signaling and PI3K/AKT signaling are known to be associated with skeletal muscle atrophy (23), defective ILK signaling is implicated in dystrophic conditions (32) and this is the first study to show the ILK gene in CC.

In females, 29 down-regulated targets were identified for 3 DE up-regulated miRNAs. Adipogenesis and calcium signaling were identified as top pathways, deregulation of which has been associated with CC pathophysiology (33, 34).

Interestingly, adipogenesis and calcium signaling were identified in both male and female canonical pathways. However, the miRNAs and the isoforms associated with these pathways were different for both the sexes. For example, in females, adipogenesis was identified to be regulated by hsa-miR-423-5p and hsa-miR-3184-3p, whereas in males, the same pathway was identified to be regulated by hsa-let-7b-3p. From these observations, it could be surmised that different miRNAs contribute to regulation in a sex-specific manner and in a disease context to activate the same pathways. Examples of

other pathways common to both the sexes but involving different molecules include actin-cytoskeleton pathways and phospholipase C signaling pathways.

A summary of target identification and their pathways are given in Tables 4.3 and Table 4.4 for males and females, respectively. In both the sexes, pleiotropic and redundant nature of the miRNAs were observed.

Table 4.3 Identification of canonical pathways and inverse targets for DE miRNA in males

Canonical pathways	Inverse (downregulated) targets identified from DEG	DE miRNA (upregulated)
GABA receptor signaling	SLC6A11 GABBR1 KCNQ3	hsa-miR-193b-5p hsa-let-7b-3p hsa-miR-92a-3p hsa-miR-320a, hsa-miR-193b-5p, hsa-miR-199a-3p, hsa-let-7b-3p
PI3K/AKT Signaling	SYNJ1 LIMS1 YWHAZ GSK3A	hsa-miR-92a-3p, hsa-miR-532-5p, hsa-miR-199a-3p, hsa-let-7b-5p hsa-miR-320a, hsa-miR-193b-5p, hsa-miR-92a-3p, hsa-miR-532-5p, hsa-let-7b-3p hsa-miR-320a, hsa-miR-92a-3p ,hsa-miR-532-5p, hsa-miR-199a-3p, hsa-let-7b-5p hsa-miR-744-5p
ILK Signaling	VEGFA PTK2 CFL1 LIMS1 GSK3A	hsa-miR-423-3p, hsa-let-7b-3p hsa-miR-92a-3p hsa-let-7b-3p hsa-miR-320a, hsa-miR-193b-5p, hsa-miR-92a-3p, hsa-miR-532-5p, hsa-let-7b-3p hsa-miR-744-5p
Adipogenesis pathway	HDAC8 CTBP2 RBBP7	hsa-let-7b-3p hsa-let-7b-3p, hsa-let-7d-3p, hsa-miR-199a-3p, hsa-miR-532-5p hsa-let-7b-3p, hsa-miR-532-5p
Calcium signaling	HDAC8 PRKAR1B	hsa-let-7b-3p hsa-miR-92a-3p

Table 4.4 Identification of canonical pathways and inverse targets for DE miRNA in females

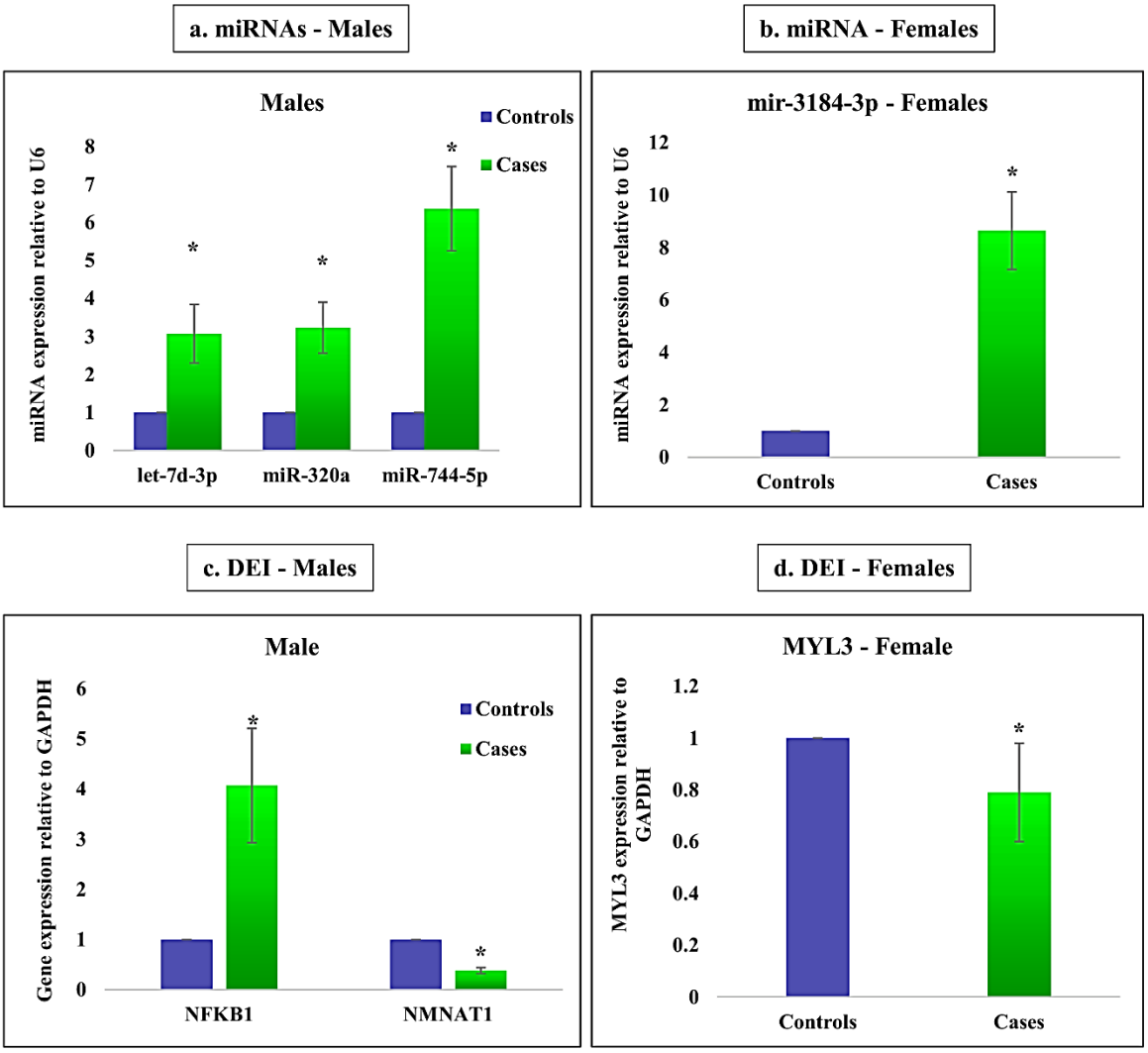
Canonical pathways	Inverse (downregulated) targets identified from DEG	DE miRNA (upregulated)
Adipogenesis pathway	RUNX1T1 HDAC4 DLK1	hsa-miR-3184-3p ,hsa-miR-1296-5p hsa-miR-423-5p hsa-miR-3184-3p , hsa-miR-423-5p
Calcium signaling	HDAC4 MYL3	hsa-miR-423-5p hsa-miR-423-5p
GABA Receptor Signaling	GABBR2	hsa-miR-3184-3p , hsa-miR-423-5p
Glutathione Redox Reactions I	GPX5	hsa-miR-1296-5p

Tables 4.3 and 4.4: Upregulated miRNAs were mapped to downregulated DEI using matched samples. There were no overlapping miRNA between sexes. Although there were common pathways identified between sexes, they are regulated by different miRNAs and DEIs in a sex-specific manner.

4.3.7 Validation of representative signatures using qRT-PCR

Representative miRNAs and DEI selected from male and female analyses were validated in all of the study samples using qRT-PCR. All the three miRNAs in males – hsa-let-7d-3p, hsa-miR-320a and hsa-miR-744-5p showed similar direction of expression in terms of fold change, as observed in NGS (Figure 4.3) and are statistically significant at $p < 0.05$. In females, hsa-miR-3184-3p showed similar direction of expression and statistical significance at $p < 0.05$ (Figure 4.3). At the DEI level, NMNAT1 and NFKB1 in males (Figure 4.3) and MYL3 (Figure 4.3) in females were chosen for validation. qRT-PCR results confirmed the findings from microarray and were significant at $p < 0.05$. None of the miRNAs and the DEI (except NFKB1) validated in this study, were previously shown to be associated with CC.

Figure 4.3 qRT-PCR validation of miRNAs and DEI



* = $p \leq 0.05$

Figure 4.3: Representative DE miRNAs and DEI were validated using qRT-PCR and confirmed the findings from NGS and microarray, respectively. All the DE miRNAs and DEI showed similar direction of expression as observed in NGS and microarray respectively and were statistically significant at $p < 0.05$.

4.4 Discussion

This is the first study to systematically identify and document the molecular differences based on sex in the pathophysiology of CC. 10 DE miRNAs were identified for males and 3 DE miRNAs were identified in females. I found no DE miRNAs to be

overlapping between the two sexes. I have identified 1324 DEI (males) and 372 DEI (females) and yet few of these showed overlap between the sexes. Although I identified common pathways both at the miRNA and at the DEI levels, the molecules involved in those pathways were predominantly different in males and females. Among the males, the top hit pathways were found to be involved in protein ubiquitination, glucocorticoid signaling and muscle atrophy related pathways, among others. These molecular level evidence support the observation from clinical study findings that men lose more muscle than women. In females, adipogenesis and potential pathways that may be implicated in fatty muscle conditions were identified. Although similar upstream regulators and networks were identified from both the sexes, their corresponding downstream targets were very different, suggesting that the overall pathophysiological processes for CC may be different among the sexes. Our study also conforms to the previous findings that sex-specific expression is not restricted to sex chromosomes but also involves the autosomes. With these multiple layers of evidence from the preliminary study, I demonstrated that sex-specific expression plays an important role in CC pathophysiology.

The pleiotropic and redundant nature of miRNAs are well established i.e. the same miRNAs can regulate several isoforms and a single isoform can be regulated by many miRNAs. This was evident from the pathway analysis conducted for miRNA targets identified from males (Table 4.3). For example, miR-92a-3p plays a role in PI3K/AKT signaling by regulating SYNJ1, and GABA receptor signaling by regulating GABBR1. Dysregulation of PI3K/AKT signaling roles in CC are well established (23). hsa-let-7b-3p was involved in ILK signaling and regulates CFL1 and LIMS1. ILK signaling has been involved in cancer progression and deletion of ILK in muscle leads to degenerating muscle fibers (32). Not much has been studied in understanding the role of GABA signaling in the context of skeletal muscle and CC, and may represent a candidate pathway to explore in future studies. The phenomenon of sexual dimorphism has been studied in various physiological and pathological states. While many of the studies have been carried out using model systems for various diseases (3, 4), only a handful of studies have attempted to understand the impact of sexual dimorphism in CC using image and anthropometric analyses (9, 35). However, for CC, no attempt has yet been made to understand sexual dimorphism at the molecular level. Body composition analysis has

revealed differences between the two sexes at tissue level, including bone and skeletal muscle. Since the dimorphic patterns are observed at every level, it is highly plausible that this pattern can also be observed in gene expression. Similarly, if sexual dimorphism can have an influence at the physiological level, it may also be applicable in the disease states, a premise explored for CC in the current study. With CC being more prevalent in males than in females and based on the premise that men lose more skeletal muscle mass at a faster rate, the probability that different mechanisms may be involved in a sex-specific manner to bring about muscle loss is higher.

The differences highlighted in my study (molecular signature, networks and pathways) could have wide therapeutic implications. For instance, one could deepen the concept of personalized medicine based on sex. Generally, drug interventions target certain pathways to ameliorate the condition. This is done under the assumption that they may be metabolized in a similar fashion for all individuals. However, this may not be the case in reality. It is increasingly being realized that dimorphic patterns are observed in adverse drug reactions (36). The effects of adverse drug reactions has been identified in various musculoskeletal conditions such as myositis and rhabdomyolysis (37). However, the effect of sex differences in adverse drug reaction for either musculoskeletal conditions or for CC has not been studied yet. From the current study, it is understood that sex-specific expression differences do exist at the molecular level in CC. Unless the molecular differences are fully understood between sexes in disease specific context, it would be difficult to translate these results from bench to bedside.

The current study has its own share of limitations. To begin with, the findings from my study have to be interpreted with caution owing to the small sample size used and preliminary nature of the findings. While I recognize the importance of sample size in these kinds of studies, it is also important to move the science forward by offering these small but crucial leads, which can eventually be employed in studies with large sample sizes, which has also been emphasized by Fearon et al., from an omics perspective (38). To address this concern, international collaborations have been sought for more muscle biopsies with complete clinical information to validate the current study results. Additionally, the TaqMan primers are designed by using common exon boundaries, where applicable. For example, if there are 4 isoforms of a gene, the exon boundaries

common to all four isoforms demonstrating the highest success rate for assay design and validation would have been selected; these may not be isoform specific primers. However, the fact that the validated isoform has a similar direction of effect in microarray and in qRT-PCR adds confidence to the study findings. In the future, isoform specific validation can be addressed by designing primers that binds to unique regions of the expressed isoforms and the ongoing efforts on the assay design software developments will likely contribute to the validation of isoform signatures associated with sex specific differences in CC.

4.5 References

1. Penaloza C, Estevez B, Orlanski S, Sikorska M, Walker R, Smith C, et al. Sex of the cell dictates its response: differential gene expression and sensitivity to cell death inducing stress in male and female cells. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2009;23(6):1869-79.

2. Yang X, Schadt EE, Wang S, Wang H, Arnold AP, Ingram-Drake L, et al. Tissue-specific expression and regulation of sexually dimorphic genes in mice. Genome research. 2006;16(8):995-1004.

3. Choi M, Choi JW, Chaudhari HN, Aseer KR, Mukherjee R, Yun JW. Gender-dimorphic regulation of skeletal muscle proteins in streptozotocin-induced diabetic rats. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2013;31(2-3):408-20.

4. Grove KL, Fried SK, Greenberg AS, Xiao XQ, Clegg DJ. A microarray analysis of sexual dimorphism of adipose tissues in high-fat-diet-induced obese mice. International journal of obesity. 2010;34(6):989-1000.

5. Marinho AT, Rodrigues PM, Caixas U, Antunes AM, Branco T, Harjivan SG, et al. Differences in nevirapine biotransformation as a factor for its sex-dependent dimorphic profile of adverse drug reactions. The Journal of antimicrobial chemotherapy. 2014;69(2):476-82.

6. Clocchiatti A, Cora E, Zhang Y, Dotto GP. Sexual dimorphism in cancer. Nature reviews Cancer. 2016;16(5):330-9.

7. Cosper PF, Leinwand LA. Cancer causes cardiac atrophy and autophagy in a sexually dimorphic manner. Cancer research. 2011;71(5):1710-20.

8. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology. 2011;12(5):489-95.

9. Stephens NA, Gray C, MacDonald AJ, Tan BH, Gallagher IJ, Skipworth RJ, et al. Sexual dimorphism modulates the impact of cancer cachexia on lower limb muscle mass and function. Clinical nutrition. 2012;31(4):499-505.

10. Wells JCK. Sexual dimorphism of body composition. Best Practice & Research Clinical Endocrinology & Metabolism.21(3):415-30.

11. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. The American journal of clinical nutrition. 2010;91(4):1133S-7S.

12. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281-97.

13. Narasimhan A, Ghosh S, Stretch C, Greiner R, Bathe OF, Baracos V, et al. Small RNAome profiling from human skeletal muscle: novel miRNAs and their targets associated with cancer cachexia. Journal of cachexia, sarcopenia and muscle. 2017.

14. Kornblihtt AR, Schor IE, Allo M, Dujardin G, Petrillo E, Munoz MJ. Alternative splicing: a pivotal step between eukaryotic transcription and translation. Nature reviews Molecular cell biology. 2013;14(3):153-65.

15. Mironov AA, Fickett JW, Gelfand MS. Frequent alternative splicing of human genes. Genome research. 1999;9(12):1288-93.

16. Sharma S, Eghbali M. Influence of sex differences on microRNA gene regulation in disease. Biology of sex differences. 2014;5(1):3.

17. Lindholm ME, Huss M, Solnestam BW, Kjellqvist S, Lundeberg J, Sundberg CJ. The human skeletal muscle transcriptome: sex differences, alternative splicing, and tissue homogeneity assessed with RNA sequencing. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2014;28(10):4571-81.

18. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47.

19. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Seminars in cell & developmental biology. 2016;54:2-10.

20. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods. 2001;25(4):402-8.

21. Esfandiari N, Ghosh S, Prado CM, Martin L, Mazurak V, Baracos VE. Age, Obesity, Sarcopenia, and Proximity to Death Explain Reduced Mean Muscle Attenuation in Patients with Advanced Cancer. The Journal of frailty & aging. 2014;3(1):3-8.

22. Wijchers PJ, Yandim C, Panousopoulou E, Ahmad M, Harker N, Saveliev A, et al. Sexual dimorphism in mammalian autosomal gene regulation is determined not only by Sry but by sex chromosome complement as well. Developmental cell. 2010;19(3):477-84.

23. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nature reviews Cancer. 2014;14(11):754-62.

24. Li H, Malhotra S, Kumar A. Nuclear factor-kappa B signaling in skeletal muscle atrophy. Journal of molecular medicine. 2008;86(10):1113-26.

25. White JP, Puppa MJ, Gao S, Sato S, Welle SL, Carson JA. Muscle mTORC1 suppression by IL-6 during cancer cachexia: a role for AMPK. American journal of physiology Endocrinology and metabolism. 2013;304(10):E1042-52.

26. Puigserver P, Rhee J, Lin J, Wu Z, Yoon JC, Zhang CY, et al. Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARgamma coactivator-1. Molecular cell. 2001;8(5):971-82.

27. Fukawa T, Yan-Jiang BC, Min-Wen JC, Jun-Hao ET, Huang D, Qian CN, et al. Excessive fatty acid oxidation induces muscle atrophy in cancer cachexia. Nature medicine. 2016;22(6):666-71.

28. Carson JA, Baltgalvis KA. Interleukin 6 as a key regulator of muscle mass during cachexia. Exercise And Sport Sciences Reviews. 2010;38(4):168-76.

29. Waning DL, Mohammad KS, Reiken S, Xie W, Andersson DC, John S, et al. Excess TGF-ß mediates muscle weakness associated with bone metastases in mice. Nature medicine. 2015;21(11):1262-71.

30. Himeda CL, Ranish JA, Pearson RC, Crossley M, Hauschka SD. KLF3 regulates muscle-specific gene expression and synergizes with serum response factor on KLF binding sites. Molecular and cellular biology. 2010;30(14):3430-43.

31. Sekiyama Y, Suzuki H, Tsukahara T. Functional gene expression analysis of tissue-specific isoforms of Mef2c. Cellular and molecular neurobiology. 2012;32(1):129-39.

32. Gheyara AL, Vallejo-Illarramendi A, Zang K, Mei L, St-Arnaud R, Dedhar S, et al. Deletion of integrin-linked kinase from skeletal muscles of mice resembles muscular dystrophy due to alpha 7 beta 1-integrin deficiency. The American journal of pathology. 2007;171(6):1966-77.

33. Isaac ST, Tan TC, Polly P. Endoplasmic Reticulum Stress, Calcium Dysregulation and Altered Protein Translation: Intersection of Processes That Contribute to Cancer Cachexia Induced Skeletal Muscle Wasting. Current drug targets. 2016;17(10):1140-6.

34. Ebadi M, Mazurak VC. Evidence and mechanisms of fat depletion in cancer. Nutrients. 2014;6(11):5280-97.

35. Norman K, Stobaus N, Reiss J, Schulzke J, Valentini L, Pirlich M. Effect of sexual dimorphism on muscle strength in cachexia. Journal of cachexia, sarcopenia and muscle. 2012;3(2):111-6.

36. Yu Y, Chen J, Li D, Wang L, Wang W, Liu H. Systematic Analysis of Adverse Event Reports for Sex Differences in Adverse Drug Events. Sci Rep. 2016;6:24955.

37. Golomb BA, Evans MA. Statin adverse effects : a review of the literature and evidence for a mitochondrial mechanism. Am J Cardiovasc Drugs. 2008;8(6):373-418.

38. Gallagher IJ, Jacobi C, Tardif N, Rooyackers O, Fearon K. Omics/systems biology and cancer cachexia. Seminars in cell & developmental biology. 2016;54:92-103.

5 Discussion

In this thesis on human cancer cachexia, I have identified post-transcriptional regulatory molecules i.e. miRNAs and ASGs associated with CC pathophysiology using human skeletal muscle biopsies. Further, I observed that the expression of these post-transcriptional regulatory molecules occurred in a sex-specific manner. The contribution of post-transcriptional regulatory mechanisms has not been explored before for CC using human skeletal muscle biopsies. The key findings from the study are summarized below.

Eight miRNAs were identified as up-regulated in cachectic cases, compared to controls. Although the association of miRNAs with CC has been studied in adipose tissue in rodent models (1, 2), my unique contribution is the study in the context of human skeletal muscle using next generation sequencing, at the whole genome level. None of the DE miRNAs except let-7d-3p, have been reported to be associated with skeletal muscle or its related functions. Studies in the literature have used *in-silico* predicted gene targets to understand the role of miRNAs. However these databases do not predict tissue-specific targets. In my study, I have identified the putative targets of miRNAs using in-house muscle transcriptome dataset, which is one of the major strengths of this work. The DE miRNAs identified have been reported to be associated with myogenesis (hsa-let-7d-3p) (3), IGF-1 signaling (hsa-miR-345-5p) (4) and Wnt/β-catenin signaling (hsa-miR-3184-3p) (5). I observed DE of the above miRs in the context of CC, and therefore are new findings in my thesis. *In vitro* studies have shown that defective IGF-1 signaling is associated with impaired protein synthesis, leading to muscle atrophy, and dysregulated Wnt/β-catenin signaling leads to muscle developmental defects (6). It was also interesting to observe that two DE miRNAs were shown to be associated with lipid biosynthesis (miR-423-5p and miR-3184-3p). It could be surmised that these miRNAs may be associated with fatty infiltration of the muscle. These inferences need to be validated using model systems to confirm if these DE miRNAs are indeed playing these roles in CC pathophysiology. The identified DE miRNAs also showed prognostic and predictive value, even though these were not the primary objectives of the study, merely to indicate that the miRNA signatures indeed harbor information for prognostication or for

predicting the cachectic state of the patient. Therefore, functional characterization of these eight DE miRNAs is warranted to understand its roles in CC pathophysiology.

Alternative splicing is the process of generating multiple isoforms from a single pre-mRNA (7, 8). DASGs identified from this work were found to be involved in myogenesis, inflammation, ubiquitination, circadian rhythm and adipogenesis. I also identified novel DASGs to be associated with CC. Many of the DASGs identified have not been previously reported to be associated with CC or with skeletal muscle. For example, overexpression of DEPDC1 was shown to be associated with bladder cancer (9) but has not been reported to be expressed in skeletal muscle or associated with skeletal muscle diseases. Independent confirmation of the described DASGs by semi-quantitative RT-PCR gives the confidence in the study findings that these are indeed expressed in skeletal muscle and may have a role in CC. Although the DASGs have never before been reported for CC, the signaling pathways in which they play a role have been reported earlier, based on results from model systems. Consistent with earlier findings, I have identified IGF-1 signaling (10), IL-8 signaling (11), CXCR4 signaling (12) and glucocorticoid signaling (13) to be associated with the pathophysiology of human CC. Pathological infiltration of fat in muscle is known as myosteatosis. Myosteatosis is associated with conditions such as cancer and diabetes (14). However, molecules that may be involved in fatty infiltration have never been studied in CC. As cachectic cases have lower muscle radiation attenuation relative to non-cachectic, it likely indicates the presence of fat accumulation in muscle. FABP4 and FAR1 have been reported to play a role in fatty acid transport (15) and β oxidation of fatty acids (16) respectively. Up-regulation of both these DASGs may potentially lead to accumulation of fat in skeletal muscle.

I also identified many splicing factors that play an important role in the regulation AS mechanism. Dysregulation of splicing factors may affect the processing of pre-mRNAs and may lead to defective conditions. SRSF 10, a splicing factor identified in my study is known to play a role in myogenic differentiation. Defective SRSF10 has been reported to impair calcium mechanism in cardiomyocytes (17). Experiments are warranted to understand the role of SRSF 10 and other splicing factors identified in this study in delineating their role in skeletal muscle and CC. In the future, engineered splice

variants or deletions of exons need to be tested in animal or cell line models to confirm the functional relevance of my findings. TGFB1 was identified as an upstream regulator, deregulation of which was shown to be associated with CC pathophysiology and with muscle weakness (18, 19). My findings also bring to fore the pleiotropic roles of TGFB1 and the targets regulated should be studied in detail for possible therapeutic targets.

Sexual dimorphism exists in physiological as well as in pathological states. It has been documented at the organ, tissue and even at the chromosomal level. However, sex-specific expression differences at the molecular level remained unidentified for CC. My work on sexual dimorphism, though preliminary (Chapter 4) highlights the expression of miRNAs and differential expression of genes at the isoform level in a sex-specific manner. Among the males, the top hit pathways were found to be involved in protein ubiquitination, glucocorticoid signaling and muscle atrophy related pathways, among others. These molecular level evidence support the observation from clinical study findings that men lose more muscle than women. In females, adipogenesis and potential pathways that may be implicated in fatty muscle conditions were identified. Although similar upstream regulators and networks were identified from both the sexes, their corresponding downstream targets were very different, suggesting that the overall pathophysiological processes for CC may be different among the sexes. In addition, sex-specific expression differences were predominantly observed in autosomes and were not restricted to sex chromosomes alone. It has been recognized that autosomally expressed transcripts have a role in conferring sexually dimorphic traits including susceptibility to infections, diseases, drug metabolism and overall cellular immunity (20). This study demonstrates the significance of including sex as an important parameter when designing studies for future work on CC. This could also be an eye-opener for future clinical trials as treating with the same drug for both sexes, may not necessarily lead to similar outcomes (21, 22). Continued efforts in this direction may eventually help in identifying potential therapeutic interventions based on sex differences.

5.1 Classification of cachectic patients

One of the important reasons for a limited number of human studies using skeletal muscle biopsies could be attributed to the difficulty in obtaining samples. If obtaining

samples are at one end of the spectrum, procuring detailed clinicopathological characteristics lies at the other end of the spectrum. These details, which are not restricted to anthropometric measurements, are crucial to classify the samples as cases and controls, thus contributing to a thorough study. Many published cachexia studies have predominantly classified patients based on % weight loss alone (1, 23). In this stratification, a single cut point such as weight loss >5% or >10% versus weight loss less than the cutoff value, was used. Although it is a commonplace, some of the equally important hidden parameters might be missed. It is increasingly being recognized that body composition analysis may be a crucial component in classifying patients as cachectic or non-cachectic. For instance, if a cancer patient has lost less than 5% of his/her pre-illness weight, they are considered non-cachectic. However, their body composition analysis may give a different picture. In my study sample classification, a couple of patients were classified as weight stable cancer patients based on physician-documented weight loss. However, when their skeletal muscle mass and fat mass values were estimated, they were found to be extremely cachectic when adjusted for their age and sex. A recent study has shown that cancer patients who had weight loss of less than 5% had a skeletal muscle loss of more than 5% (24). Therefore, I considered both weight information and body composition measurements to classify the samples. I was immensely fortunate to have had access to patient samples with complete clinical annotation along with their body composition measurements, which is one of the major strengths of the study.

5.2 Skeletal muscle biopsies and sample size

Only few studies have been conducted using human skeletal muscle to understand CC pathophysiology and most of the studies have been conducted using animal models. More so, even fewer gene expression studies have been carried out to understand the pathological changes that occur in skeletal muscle at the molecular level. However, conflicting results have been reported between human and animal studies (25). Yet, one of the advantages of using animal models is the feasibility of conducting many time-point studies to understand the spatial and temporal changes that can occur in a disease context. In their recent review, Petruzzelli et al., have stated that the time of muscle sample

collection could also be one of the reasons for the discrepancy in results between human and animal studies. In addition, they have suggested a collection of skeletal muscle samples at multiple time points to make the results comparative between animal and human studies (26). While this may be possible for animal studies, such a study design may not be viable for humans in immediate future. A single muscle biopsy sample during primary tumor resection is an invasive procedure. Acquiring multiple biopsy samples after tumor resection would be considered extremely invasive and it is highly likely that the ethics board may not approve of such a procedure to answer a research question. Nevertheless, until such time an alternative is identified, a single muscle biopsy sample remains as one of the best resources to conduct a molecular study.

Despite the above-mentioned challenges, the current molecular study has used one of the largest reported sample sizes with complete clinical annotation and body composition measurements. Some of the previous gene expression studies in CC have used fewer samples compared to the current study (25, 27). Previous work from our group showed sample size needed for reproducibility of the findings based on a p-value cut-off ($p<10^{-3}$) and cut-offs for fold change may vary in studies reported in the literature. It is customary to adopt lower stringency of FC or p-values ($p<0.05$) in the discovery phase and no set rules exist in these studies. Most genome-wide scans are now conducted with two or more independent datasets. The initial study is frequently referred to as the discovery phase and subsequent stages of study in independent sample sets are referred to as validation sets. There is no single consensus approach in the literature on the sample size needed in the genome-wide scans as these tend to be hypothesis-generating. Instead, the biology-driven studies have considered replication of select gene signatures in independent studies and samples distinct from the discovery phase. Therefore, sample size estimation can be calculated in two ways. One way is to rank the genes based on p-value alone, without considering effect sizes (fold changes in microarray and RNA-sequencing data) (28). The other way to calculate the sample size depends on fold change, along with p-values. Evidence from literature supports that fold change, along with non-stringent p-values remained as a better metric for reproducibility of the microarray (29, 30) and RNA-sequencing data (31). Based on this premise, I considered post-transcriptional regulatory molecules showing 1.4 fold change difference with $p <$

0.05 as differentially expressed. At this cut-off, I required at least 19 samples in each group for my overall study premise. The findings from discovery phase are independently confirmed using RT-PCR to demonstrate that the identified signatures are independent of the platform (NGS vs. RT-PCR) used as observed from the similar direction of effects. Platform specific concordances are the norm in gene expression studies.

As much as the sample size is crucial to association studies or any study, it is equally important to move science forward by constantly addressing these existing gaps in literature to expand our understanding of CC pathophysiology. Independent validation studies are warranted for the findings from my thesis. To achieve this, international collaborations would be one of the best ways to accrue more muscle biopsies. This may also serve as a validation of study findings in different populations, thereby increasing the robustness of the identified molecules.

5.3 References

1. Kulyte A, Lorente-Cebrian S, Gao H, Mejhert N, Agustsson T, Arner P, et al. MicroRNA profiling links miR-378 to enhanced adipocyte lipolysis in human cancer cachexia. American journal of physiology Endocrinology and metabolism. 2014;306(3):E267-74.

2. He WA, Calore F, Londhe P, Canella A, Guttridge DC, Croce CM. Microvesicles containing miRNAs promote muscle cell death in cancer cachexia via TLR7. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(12):4525-9.

3. Drummond MJ, McCarthy JJ, Sinha M, Spratt HM, Volpi E, Esser KA, et al. Aging and microRNA expression in human skeletal muscle: a microarray and bioinformatics analysis. Physiological Genomics. 2011;43(10):595-603.

4. Rommel C, Bodine SC, Clarke BA, Rossman R, Nunez L, Stitt TN, et al. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. Nature cell biology. 2001;3(11):1009-13.

5. Jones AE, Price FD, Le Grand F, Soleimani VD, Dick SA, Megeney LA, et al. Wnt/beta-catenin controls follistatin signalling to regulate satellite cell myogenic potential. Skeletal Muscle. 2015;5:14.

6. Suzuki A, Scruggs A, Iwata J. The temporal specific role of WNT/beta-catenin signaling during myogenesis. J Nat Sci. 2015;1(8):e143.

7. Gamazon ER, Stranger BE. Genomics of alternative splicing: evolution, development and pathophysiology. Human genetics. 2014;133(6):679-87.

8. Boue S, Letunic I, Bork P. Alternative splicing and evolution. Bioessays. 2003;25(11):1031-4.

9. Kanehira M, Harada Y, Takata R, Shuin T, Miki T, Fujioka T, et al. Involvement of upregulation of DEPDC1 (DEP domain containing 1) in bladder carcinogenesis. Oncogene. 2007;26(44):6448-55.

10. Penna F, Bonetto A, Muscaritoli M, Costamagna D, Minero VG, Bonelli G, et al. Muscle atrophy in experimental cancer cachexia: is the IGF-1 signaling pathway involved? Int J Cancer. 2010;127(7):1706-17.

11. Song B, Zhang D, Wang S, Zheng H, Wang X. Association of interleukin-8 with cachexia from patients with low-third gastric cancer. Comp Funct Genomics. 2009:212345.

12. Martinelli GB, Olivari D, Re Cecconi AD, Talamini L, Ottoboni L, Lecker SH, et al. Activation of the SDF1/CXCR4 pathway retards muscle atrophy during cancer cachexia. Oncogene. 2016.

13. Schakman O, Kalista S, Barbe C, Loumaye A, Thissen JP. Glucocorticoid-induced skeletal muscle atrophy. The international journal of biochemistry & cell biology. 2013;45(10):2163-72.

14. Esfandiari N, Ghosh S, Prado CM, Martin L, Mazurak V, Baracos VE. Age, Obesity, Sarcopenia, and Proximity to Death Explain Reduced Mean Muscle Attenuation in Patients with Advanced Cancer. The Journal of frailty & aging. 2014;3(1):3-8.

15. Furuhashi M, Saitoh S, Shimamoto K, Miura T. Fatty Acid-Binding Protein 4 (FABP4): Pathophysiological Insights and Potent Clinical Biomarker of Metabolic and Cardiovascular Diseases. Clinical Medicine InsightsCardiology. 2015;8:23-33.

16. bin Yusof MT, Kershaw MJ, Soanes DM, Talbot NJ. FAR1 and FAR2 regulate the expression of genes associated with lipid metabolism in the rice blast fungus Magnaporthe oryzae. PloS one. 2014;9(6):e99760-e.

17. Wei N, Cheng Y, Wang Z, Liu Y, Luo C, Liu L, et al. SRSF10 Plays a Role in Myoblast Differentiation and Glucose Production via Regulation of Alternative Splicing. Cell reports. 2015;13(8):1647-57.

18. Waning DL, Mohammad KS, Reiken S, Xie W, Andersson DC, John S, et al. Excess TGF-ß mediates muscle weakness associated with bone metastases in mice. Nature medicine. 2015;21(11):1262-71.

19. Guttridge DC. A TGF-ß pathway associated with cancer cachexia. Nature medicine. 2015;21(11):1248-9.

20. Nunn CL, Lindenfors P, Pursall ER, Rolff J. On sexual dimorphism in immune function. Philos Trans R Soc Lond B Biol Sci. 2009;364(1513):61-9.

21. Garcia JM, Friend J, Allen S. Therapeutic potential of anamorelin, a novel, oral ghrelin mimetic, in patients with cancer-related cachexia: a multicenter, randomized, double-blind, crossover, pilot study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2013;21(1):129-37.

22. Smiderle L, Lima LO, Hutz MH, Van der Sand CR, Van der Sand LC, Ferreira ME, et al. Evaluation of sexual dimorphism in the efficacy and safety of simvastatin/atorvastatin therapy in a southern Brazilian cohort. Arq Bras Cardiol. 2014;103(1):33-40.

23. Stephens NA, Skipworth RJ, Gallagher IJ, Greig CA, Guttridge DC, Ross JA, et al. Evaluating potential biomarkers of cachexia and survival in skeletal muscle of upper gastrointestinal cancer patients. Journal of cachexia, sarcopenia and muscle. 2015;6(1):53-61.

24. Roeland EJ, Ma JD, Nelson SH, Seibert T, Heavey S, Revta C, et al. Weight loss versus muscle loss: re-evaluating inclusion criteria for future cancer cachexia interventional trials. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2016.

25. Stephens NA, Gallagher IJ, Rooyackers O, Skipworth RJ, Tan BH, Marstrand T, et al. Using transcriptomics to identify and validate novel biomarkers of human skeletal muscle cancer cachexia. Genome Med. 2010;2(1):1.

26. Petruzzelli M, Wagner EF. Mechanisms of metabolic dysfunction in cancer-associated cachexia. Genes Dev. 2016;30(5):489-501.

27. Gallagher IJ, Stephens NA, MacDonald AJ, Skipworth RJ, Husi H, Greig CA, et al. Suppression of skeletal muscle turnover in cancer cachexia: evidence from the transcriptome in sequential human muscle biopsies. Clinical cancer research : an official journal of the American Association for Cancer Research. 2012;18(10):2817-27.

28. Stretch C, Khan S, Asgarian N, Eisner R, Vaisipour S, Damaraju S, et al. Effects of sample size on differential gene expression, rank order and prediction accuracy of a gene signature. PloS one. 2013;8(6):e65380.

29. Shi L, Jones WD, Jensen RV, Harris SC, Perkins RG, Goodsaid FM, et al. The balance of reproducibility, sensitivity, and specificity of lists of differentially expressed genes in microarray studies. BMC bioinformatics. 2008;9 Suppl 9:S10.

30. Gallagher IJ, Jacobi C, Tardif N, Rooyackers O, Fearon K. Omics/systems biology and cancer cachexia. Seminars in cell & developmental biology. 2016;54:92-103.

31. Robinson DG, Wang JY, Storey JD. A nested parallel experiment demonstrates differences in intensity-dependence between RNA-seq and microarrays. Nucleic acids research. 2015;43(20):e131.

6 Future Directions and Conclusions

6.1 Future Directions

The identified miRNAs should be replicated in independent samples. Cell based assays can be performed to (i) functionally characterize the identified DE miRNAs and (ii) to confirm the binding specificity of DE miRNAs to its target genes, identified from in silico predictions. It is recognized that more than 97% of the human genome consists of non-coding regions. miRNAs is one such fraction that plays an important role in post-transcriptional gene silencing. Recent literature suggests that there are many other small non-coding RNAs including piwi-interacting RNAs (piRNAs) (1), small nucleolar RNAs (snoRNAs) (2) and transfer RNAs (tRNAs) (3), that are also involved in performing various functions in physiological as well as in pathological processes. piRNAs have also been shown to play an important role in stem cell maintenance and regeneration (4). Based on the various roles of piRNAs, it may be surmised that they play an important role in satellite cells differentiation. piRNAs were also shown to regulate gene expression similar to miRNAs (5). Profiling of the other small non-coding RNAs and identifying their corresponding gene targets may give us more insights into the role of these molecules in CC pathophysiology. The advantage of using NGS is that the alignment files generated could be mapped to any of the small non-coding RNAs under study, that may not be possible using microarrays. It may be interesting to explore if piRNAs and miRNAs regulate similar genes and pathways, in addition to the unique genes to understand the converging and diverging mechanisms of these molecules. The role of snoRNAs in gene regulation is slowly emerging and is particularly relevant in epigenetic regulation in addition to their chemical modification roles of rRNA and tRNAs (2). Recent literature has reported that snoRNAs harbor miRNAs and/or piRNAs. The processing of snoRNAs may give rise to miRNAs and/or piRNAs, and may thus indirectly contribute to regulation of gene expression (6).

Recently, another class of non-coding RNAs, called the long non-coding RNAs (lncRNAs), are being extensively studied in various physiological and pathological contexts (7, 8). In particular, lncRNAs have been extensively studied in skeletal muscle

context (9). They have been shown to play an active role in myogenesis as myogenic regulators (10). Recent evidence suggest that dysregulation of lncRNAs contribute to skeletal muscle conditions such as muscular dystrophy and facioscapulohumeral muscular dystrophy (11). However, their roles in CC remain to be explored. The functions of many lncRNAs are slowly being characterized. Interestingly, the total number of lncRNAs in the human genome is now estimated to surpass the number of protein coding genes. They are also known for post-transcriptional regulation of gene expression, similar to small non-coding RNAs (12). Clearly, many more functions of these molecules need to be discerned. As of now, the databases for lncRNAs are rudimentary as different nomenclatures are used. Synchronizing these in the coming years would be a boon to advance our understanding on these molecules.

Replication of DASGs are warranted in independent samples to confirm and add confidence to the current study findings. HTA 2.0 arrays have probes designed to study both coding and non-coding regions of the genome. I studied the coding portions of the genome and not lncRNAs due to ongoing challenges of annotations of these RNAs and evolving informatics to handle the complexity of the datasets for integrative analysis for a comprehensive role of all non-coding classes of RNAs in the pathophysiology of CC. miRNAs also bind to lncRNAs and regulate their expression (13). It is increasingly being recognized that lncRNAs are also alternatively spliced but are not translated. Future studies can be carried out to profile and understand the role of lncRNAs splice variants in CC pathophysiology (14). Profiling and identifying the role of other small non-coding RNAs, lncRNAs and studying the role of lncRNAs splice variants are novel themes that have never been studied for CC pathophysiology.

Through this thesis work, I have also shown that sex-specific molecular differences exist in CC. This theme can also be extrapolated to other RNAs described earlier, including the splice variants for lncRNAs, to understand if sexual dimorphic patterns exist for these RNA molecules as well. Studying these exciting themes may offer us a more comprehensive understanding of the contribution of post-transcriptional regulatory molecules in CC. A thorough understanding of these molecules, their mechanisms, and

various pathways that they regulate may eventually be utilized as targets for possible therapeutic interventions to improve the quality of life for CC patients.

Research conducted for CC using skeletal muscle biopsies are considered fairly invasive. There remains a need to use minimally invasive techniques to accrue bio specimens to conduct the study. One such option is the use of serum or plasma as many of the small non-coding RNAs have been shown to be present in circulation in disease states. Many miRNAs (as well as other classes of non-coding RNAs) have also been identified in serum and plasma. Specific miRNAs were detected for myotonic dystrophy and muscular dystrophy (15, 16). A similar approach can be adopted for CC. Cancer patients are frequently monitored during the course of the disease. If serum and plasma are serially collected alongside the blood draws for various biochemical tests, it could serve as an alternative for muscle biopsies. This way, time point studies may also be carried out to understand the expression of different molecules during the progression of the disease. Whole genome profiling of serum and plasma are challenging at the current point of time as the RNA yield from these bio specimens are so low that they cannot be used for sequencing (17, 18). qRT-PCR panel remains the best way to validate the findings from serum and plasma. There are methods now being developed to optimize the use of serum and plasma for whole-genome profiling.

Many of these above mentioned approaches may help in understanding the mechanisms underlying the disease. There also remains a need to identify CC patients early as the disease trajectory of CC is very severe and the life expectancy of patients with CC is reduced. Study of germline DNA variants such as single nucleotide polymorphisms (19) and other structural variants such as copy number variants (CNVs) may help in identifying individuals who are genetically predisposed to CC, long before its onset (20). Although genetic determinants associated with CC susceptibility have been identified using candidate gene association studies, yet they remain unexplored at the whole genome level. Whole genome analysis and candidate studies have thus pointed out to the fact that genetic susceptibility determinants may indeed play a role in etiology of CC (19, 21-23). Future studies using large sample sizes may help us find more genetic

variants associated with CC, which may help in identifying individuals at higher risk for CC, long before its onset.

6.2 Conclusions

In all, my thesis has laid the foundation in the field of CC by identifying the potential role of post-transcriptional regulatory molecules involved in the pathophysiology of CC using human skeletal muscle. With my larger interests in understanding the post-transcriptional gene regulatory mechanisms (both coding and non-coding) underlying the pathophysiology of CC, I felt compelled to carry out systematic studies first at profiling of these RNA classes in human skeletal muscle biopsies. There was also a need to establish bioinformatics and statistical methodologies pertinent to the study objectives, including integration of miRNA and mRNA/transcripts (isoforms) to study regulation by miRs. Through these attempts, I was able to confirm genes/pathways that are already reported in CC literature and add newer findings, giving me the confidence in the design of the study, approaches used and ensuing interpretations. As the sample size is limited, I initially considered Non-cachectic vs. cachectic as a primary binary for statistical power prior to addressing stratified analysis for sexual dimorphism. This study premise has been recommended in biomarker studies. Following successful demonstration of DE of miRs and DASGs associated with CC, I attempted the stratified analysis based on sex. These initial steps formed the underpinnings of the sex-specific gene regulatory events in CC. I have also shown that post-transcriptional regulatory molecules are expressed in a sex-specific manner (*albeit*, in a small sample size). The identified molecules should be replicated in independent samples and further functional characterization of the identified molecules should be carried out to understand their biological role in CC. Several pathways identified in this study were found to be associated with CC in a sex-specific manner, which needs to be experimentally validated. If the roles of these molecules are ascertained, these pathways could be targeted in future for therapeutic interventions in a sex-specific manner, eventually leading to precision medicine for Cancer Cachexia.

6.3 References

1. Ng KW, Anderson C, Marshall EA, Minatel BC, Enfield KS, Saprunoff HL, et al. Piwi-interacting RNAs in cancer: emerging functions and clinical utility. Mol Cancer. 2016;15:5.

2. Makarova JA, Ivanova SM, Tonevitsky AG, Grigoriev AI. New functions of small nucleolar RNAs. Biochemistry (Mosc). 2013;78(6):638-50.

3. Raina M, Ibba M. tRNAs as regulators of biological processes. Front Genet. 2014;5:171.

4. Samji T. PIWI, piRNAs, and germline stem cells: what's the link? Yale J Biol Med. 2009;82(3):121-4.

5. Hashim A, Rizzo F, Marchese G, Ravo M, Tarallo R, Nassa G, et al. RNA sequencing identifies specific PIWI-interacting small non-coding RNA expression patterns in breast cancer. Oncotarget. 2014;5(20):9901-10.

6. Krishnan P, Ghosh S, Wang B, Heyns M, Graham K, Mackey JR, et al. Profiling of Small Nucleolar RNAs by Next Generation Sequencing: Potential New Players for Breast Cancer Prognosis. PloS one. 2016;11(9):e0162622.

7. Huarte M. The emerging role of lncRNAs in cancer. Nature medicine. 2015;21(11):1253-61.

8. Tripathi V, Shen Z, Chakraborty A, Giri S, Freier SM, Wu X, et al. Long noncoding RNA MALAT1 controls cell cycle progression by regulating the expression of oncogenic transcription factor B-MYB. PLoS Genet. 2013;9(3):e1003368.

9. Neguembor MV, Jothi M, Gabellini D. Long noncoding RNAs, emerging players in muscle differentiation and disease. Skelet Muscle. 2014;4(1):8.

10. Gong C, Li Z, Ramanujan K, Clay I, Zhang Y, Lemire-Brachat S, et al. A long non-coding RNA, LncMyoD, regulates skeletal muscle differentiation by blocking IMP2-mediated mRNA translation. Developmental cell. 2015;34(2):181-91.

11. Erriquez D, Perini G, Ferlini A. Non-coding RNAs in muscle dystrophies. Int J Mol Sci. 2013;14(10):19681-704.

12. Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. Annual review of biochemistry. 2012;81:145-66.

13. Leucci E, Patella F, Waage J, Holmstrom K, Lindow M, Porse B, et al. microRNA-9 targets the long non-coding RNA MALAT1 for degradation in the nucleus. Sci Rep. 2013;3:2535.

14. Gonzalez I, Munita R, Agirre E, Dittmer TA, Gysling K, Misteli T, et al. A lncRNA regulates alternative splicing via establishment of a splicing-specific chromatin signature. Nature structural & molecular biology. 2015;22(5):370-6.

15. Koutsoulidou A, Kyriakides TC, Papadimas GK, Christou Y, Kararizou E, Papanicolaou EZ, et al. Elevated Muscle-Specific miRNAs in Serum of Myotonic Dystrophy Patients Relate to Muscle Disease Progress. PLoS ONE [Electronic Resource]. 2015;10(4):e0125341.

16. Freedman JE, Gerstein M, Mick E, Rozowsky J, Levy D, Kitchen R, et al. Diverse human extracellular RNAs are widely detected in human plasma. Nat Commun. 2016;7:11106.

17. Ichikawa M, Akiyama H. A combination of extraction reagent and DNA microarray that allows for the detection of global miRNA profiles from serum/plasma. Methods Mol Biol. 2013;1024:247-53.

18. Gautam A, Kumar R, Dimitrov G, Hoke A, Hammamieh R, Jett M. Identification of extracellular miRNA in archived serum samples by next-generation sequencing from RNA extracted using multiple methods. Mol Biol Rep. 2016;43(10):1165-78.

19. Tan BH, Fladvad T, Braun TP, Vigano A, Strasser F, Deans DA, et al. P-selectin genotype is associated with the development of cancer cachexia. EMBO molecular medicine. 2012;4(6):462-71.

20. Abstracts of the 2(nd) Cancer Cachexia Conference, Montreal, Canada, 26-28 September 2014. Journal of cachexia, sarcopenia and muscle. 2015;6(1):2-31.

21. Johns N, Tan BH, MacMillan M, Solheim TS, Ross JA, Baracos VE, et al. Genetic basis of interindividual susceptibility to cancer cachexia: selection of potential

candidate gene polymorphisms for association studies. Journal of genetics. 2014;93(3):893-916.

22. Tan BH, Fearon KC. Cytokine gene polymorphisms and susceptibility to cachexia. Current opinion in supportive and palliative care. 2010;4(4):243-8.

23. Johns N, Stretch C, Tan BHL, Solheim TS, Sørhaug S, Stephens NA, et al. New genetic signatures associated with cancer cachexia as defined by low skeletal muscle index and weight loss. Journal of cachexia, sarcopenia and muscle. 2016.

Bibliography

Abstracts of the 2(nd) Cancer Cachexia Conference, Montreal, Canada, 26-28 September 2014. Journal of cachexia, sarcopenia and muscle. 2015;6(1):2-31.

Agarwal V, Bell GW, Nam J-W, Bartel DP. Predicting effective microRNA target sites in mammalian mRNAs. Elife. 2015;4.

Ahn J, Lee H, Jung CH, Jeon TI, Ha TY. MicroRNA-146b promotes adipogenesis by suppressing the SIRT1-FOXO1 cascade. EMBO molecular medicine. 2013;5(10):1602-12.

Arafat H, Lazar M, Salem K, Chipitsyna G, Gong Q, Pan TC, et al. Tumor-specific expression and alternative splicing of the COL6A3 gene in pancreatic cancer. Surgery. 2011;150(2):306-15.

Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nature reviews Cancer. 2014;14(11):754-62.

Argiles JM, Busquets S, Toledo M, Lopez-Soriano FJ. The role of cytokines in cancer cachexia. Current Opinion in Supportive & Palliative Care. 2009;3(4):263-8.

Argiles JM, Busquets S, Toledo M, Lopez-Soriano FJ. The role of cytokines in cancer cachexia. Current opinion in supportive and palliative care. 2009;3(4):263-8.

Argiles JM, Lopez-Soriano FJ. The ubiquitin-dependent proteolytic pathway in skeletal muscle: its role in pathological states. Trends in pharmacological sciences. 1996;17(6):223-6.

Ashwal R, Hemi R, Tirosh A, Gordin R, Yissachar E, Cohen-Dayag A, et al. Differential expression of novel adiponectin receptor-1 transcripts in skeletal muscle of subjects with normal glucose tolerance and type 2 diabetes. Diabetes. 2011;60(3):936-46.

Aversa Z, Pin F, Lucia S, Penna F, Verzaro R, Fazi M, et al. Autophagy is induced in the skeletal muscle of cachectic cancer patients. Sci Rep. 2016;6:30340.

Babiychuk EB, Draeger A. Annexins in Cell Membrane Dynamics: Ca 2+ -Regulated Association of Lipid Microdomains. Rockefeller University Press; 2000. p. 1113.

Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. The American journal of clinical nutrition. 2010;91(4):1133S-7S.

Bartel DP. MicroRNAs. Cell.116(2):281-97.

Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281-97.

bin Yusof MT, Kershaw MJ, Soanes DM, Talbot NJ. FAR1 and FAR2 regulate the expression of genes associated with lipid metabolism in the rice blast fungus Magnaporthe oryzae. PloS one. 2014;9(6):e99760-e.

Bing C, Bao Y, Jenkins J, Sanders P, Manieri M, Cinti S, et al. Zinc-alpha2-glycoprotein, a lipid mobilizing factor, is expressed in adipocytes and is up-regulated in mice with cancer cachexia. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(8):2500-5.

Black DL. Mechanisms of alternative pre-messenger RNA splicing. Annual review of biochemistry. 2003;72:291-336.

Bland CS, Wang ET, Vu A, David MP, Castle JC, Johnson JM, et al. Global regulation of alternative splicing during myogenic differentiation. Nucleic acids research. 2010;38(21):7651-64.

Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L, Clarke BA, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. Science. 2001;294(5547):1704-8.

Bönnemann CG. The collagen VI-related myopathies: muscle meets its matrix. Nature ReviewsNeurology. 2011;7(7):379-90.

Bonnieu A, Carnac G, Vernus B. Myostatin in the Pathophysiology of Skeletal Muscle. Current Genomics. 2007;8(7):415.

Boue S, Letunic I, Bork P. Alternative splicing and evolution. Bioessays. 2003;25(11):1031-4.

Braun TP, Zhu X, Szumowski M, Scott GD, Grossberg AJ, Levasseur PR, et al. Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic-pituitary-adrenal axis. The Journal of experimental medicine. 2011;208(12):2449-63.

Cagliani R, Magri F, Toscano A, Merlini L, Fortunato F, Lamperti C, et al. Mutation finding in patients with dysferlin deficiency and role of the dysferlin interacting proteins annexin A1 and A2 in muscular dystrophies. Human mutation. 2005;26(3):283-.

Cahlin C, Korner A, Axelsson H, Wang W, Lundholm K, Svanberg E. Experimental cancer cachexia: the role of host-derived cytokines interleukin (IL)-6, IL-12, interferon-gamma, and tumor necrosis factor alpha evaluated in gene knockout, tumor-bearing mice on C57 Bl background and eicosanoid-dependent cachexia. Cancer research. 2000;60(19):5488-93.

Carson JA, Baltgalvis KA. Interleukin 6 as a key regulator of muscle mass during cachexia. Exercise And Sport Sciences Reviews. 2010;38(4):168-76.

Castle JC, Zhang C, Shah JK, Kulkarni AV, Kalsotra A, Cooper TA, et al. Expression of 24,426 human alternative splicing events and predicted cis regulation in 48 tissues and cell lines. Nature genetics. 2008;40(12):1416-25.

Chang YC, Liu PH, Lee WJ, Chang TJ, Jiang YD, Li HY, et al. Common variation in the fat mass and obesity-associated (FTO) gene confers risk of obesity and modulates BMI in the Chinese population. Diabetes. 2008;57(8):2245-52.

Chen JF, Mandel EM, Thomson JM, Wu Q, Callis TE, Hammond SM, et al. The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation. Nature genetics. 2006;38(2):228-33.

Chen L, Hou J, Ye L, Chen Y, Cui J, Tian W, et al. MicroRNA-143 regulates adipogenesis by modulating the MAP2K5-ERK5 signaling. Sci Rep. 2014;4:3819.

Choi M, Choi JW, Chaudhari HN, Aseer KR, Mukherjee R, Yun JW. Gender-dimorphic regulation of skeletal muscle proteins in streptozotocin-induced diabetic rats. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2013;31(2-3):408-20.

Clarke PA, te Poele R, Wooster R, Workman P. Gene expression microarray analysis in cancer biology, pharmacology, and drug development: progress and potential. Biochemical pharmacology. 2001;62(10):1311-36.

Clocchiatti A, Cora E, Zhang Y, Dotto GP. Sexual dimorphism in cancer. Nature reviews Cancer. 2016;16(5):330-9.

Cortese A, Plagnol V, Brady S, Simone R, Lashley T, Acevedo-Arozena A, et al. Widespread RNA metabolism impairment in sporadic inclusion body myositis TDP43-proteinopathy. Neurobiol Aging. 2014;35(6):1491-8.

Cosper PF, Leinwand LA. Cancer causes cardiac atrophy and autophagy in a sexually dimorphic manner. Cancer research. 2011;71(5):1710-20.

Das SK, Hoefler G. The role of triglyceride lipases in cancer associated cachexia. Trends in molecular medicine. 2013;19(5):292-301.

Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. American Journal of Medicine. 1980;69(4):491-7.

Dodson S, Baracos VE, Jatoi A, Evans WJ, Cella D, Dalton JT, et al. Muscle wasting in cancer cachexia: clinical implications, diagnosis, and emerging treatment strategies. Annual review of medicine. 2011;62:265-79.

D'Orlando C, Marzetti E, Francois S, Lorenzi M, Conti V, di Stasio E, et al. Gastric cancer does not affect the expression of atrophy-related genes in human skeletal muscle. Muscle Nerve. 2014;49(4):528-33.

Drummond MJ, McCarthy JJ, Sinha M, Spratt HM, Volpi E, Esser KA, et al. Aging and microRNA expression in human skeletal muscle: a microarray and bioinformatics analysis. Physiological Genomics. 2011;43(10):595-603.

Durham WJ, Dillon EL, Sheffield-Moore M. Inflammatory burden and amino acid metabolism in cancer cachexia. Current Opinion in Clinical Nutrition & Metabolic Care. 2009;12(1):72-7 6p.

Dwarkasing JT, Boekschoten MV, Argilès JM, van Dijk M, Busquets S, Penna F, et al. Differences in food intake of tumour-bearing cachectic mice are associated with hypothalamic serotonin signalling. Journal of cachexia, sarcopenia and muscle. 2015;6(1):84-94.

Ebadi M, Mazurak VC. Evidence and mechanisms of fat depletion in cancer. Nutrients. 2014;6(11):5280-97.

Erriquez D, Perini G, Ferlini A. Non-coding RNAs in muscle dystrophies. Int J Mol Sci. 2013;14(10):19681-704.

Esfandiari N, Ghosh S, Prado CM, Martin L, Mazurak V, Baracos VE. Age, Obesity, Sarcopenia, and Proximity to Death Explain Reduced Mean Muscle Attenuation in Patients with Advanced Cancer. The Journal of frailty & aging. 2014;3(1):3-8.

Esfandiari N, Ghosh S, Prado CMM, Martin L, Mazurak V, Baracos VE. Age, Obesity, Sarcopenia, and Proximity to Death Explain Reduced Mean Muscle Attenuation in Patients with Advanced Cancer. The Journal of frailty & aging. 2014;3(1):3-8.

Eswaran J, Horvath A, Godbole S, Reddy SD, Mudvari P, Ohshiro K, et al. RNA sequencing of cancer reveals novel splicing alterations. Nature Publishing Group; 2013.

Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clinical nutrition. 2008;27(6):793-9.

Fan X, Tang L. Aberrant and alternative splicing in skeletal system disease. Gene. 2013;528(1):21-6.

Farkas J, von Haehling S, Kalantar-Zadeh K, Morley JE, Anker SD, Lainscak M. Cachexia as a major public health problem: frequent, costly, and deadly. Journal of cachexia, sarcopenia and muscle. 2013;4(3):173-8.

Faustino NA, Cooper TA. Pre-mRNA splicing and human disease. Genes & development. 2003(4):419.

Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology. 2011;12(5):489-95.

Fearon KC, Baracos VE. Cachexia in pancreatic cancer: new treatment options and measures of success. HPB : the official journal of the International Hepato Pancreato Biliary Association. 2010;12(5):323-4.

Fearon KC, Voss AC, Hustead DS, Cancer Cachexia Study G. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. The American journal of clinical nutrition. 2006;83(6):1345-50.

Fukawa T, Yan-Jiang BC, Min-Wen JC, Jun-Hao ET, Huang D, Qian CN, et al. Excessive fatty acid oxidation induces muscle atrophy in cancer cachexia. Nature medicine. 2016;22(6):666-71.

Furuhashi M, Saitoh S, Shimamoto K, Miura T. Fatty Acid-Binding Protein 4 (FABP4): Pathophysiological Insights and Potent Clinical Biomarker of Metabolic and Cardiovascular Diseases. Clinical Medicine InsightsCardiology. 2015;8:23-33.

Futatsugi A, Kuwajima G, Mikoshiba K. Tissue-specific and developmentally regulated alternative splicing in mouse skeletal muscle ryanodine receptor mRNA. Biochemical Journal. 1995;305(Pt 2):373-8.

Gallagher IJ, Jacobi C, Tardif N, Rooyackers O, Fearon K. Omics/systems biology and cancer cachexia. Seminars in cell & developmental biology. 2016;54:92-103.

Gallagher IJ, Stephens NA, MacDonald AJ, Skipworth RJ, Husi H, Greig CA, et al. Suppression of skeletal muscle turnover in cancer cachexia: evidence from the transcriptome in sequential human muscle biopsies. Clinical cancer research : an official journal of the American Association for Cancer Research. 2012;18(10):2817-27.

Gallagher IJ, Stephens NA, MacDonald AJ, Skipworth RJ, Husi H, Greig CA, et al. Suppression of skeletal muscle turnover in cancer cachexia: evidence from the transcriptome in sequential human muscle biopsies. Clinical Cancer Research. 2012;18(10):2817-27.

Gamazon ER, Stranger BE. Genomics of alternative splicing: evolution, development and pathophysiology. Human genetics. 2014;133(6):679-87.

Gardina PJ, Clark TA, Shimada B, Staples MK, Yang Q, Veitch J, et al. Alternative splicing and differential gene expression in colon cancer detected by a whole genome exon array. BMC genomics. 2006;7:325.

Ge Y, Waldemer RJ, Nalluri R, Nuzzi PD, Chen J. Flt3L is a novel regulator of skeletal myogenesis. Journal of cell science. 2013;126:3370-9.

Gelse K, Pöschl E, Aigner T. Collagens—structure, function, and biosynthesis. Advanced Drug Delivery Reviews. 2003;55(12):1531.

Gheyara AL, Vallejo-Illarramendi A, Zang K, Mei L, St-Arnaud R, Dedhar S, et al. Deletion of integrin-linked kinase from skeletal muscles of mice resembles muscular dystrophy due to alpha 7 beta 1-integrin deficiency. The American journal of pathology. 2007;171(6):1966-77.

Gomes MD, Lecker SH, Jagoe RT, Navon A, Goldberg AL. Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(25):14440-5.

Gong C, Li Z, Ramanujan K, Clay I, Zhang Y, Lemire-Brachat S, et al. A long non-coding RNA, LncMyoD, regulates skeletal muscle differentiation by blocking IMP2-mediated mRNA translation. Developmental cell. 2015;34(2):181-91.

Gonzalez I, Munita R, Agirre E, Dittmer TA, Gysling K, Misteli T, et al. A lncRNA regulates alternative splicing via establishment of a splicing-specific chromatin signature. Nature structural & molecular biology. 2015;22(5):370-6.

Grove KL, Fried SK, Greenberg AS, Xiao XQ, Clegg DJ. A microarray analysis of sexual dimorphism of adipose tissues in high-fat-diet-induced obese mice. International journal of obesity. 2010;34(6):989-1000.

Guillory B, Splenser A, Garcia J. The role of ghrelin in anorexia-cachexia syndromes. Vitamins & Hormones. 2013;92:61-106.

Guller I, Russell AP. MicroRNAs in skeletal muscle: their role and regulation in development, disease and function. Journal of Physiology. 2010;588(Pt 21):4075-87.

Guttridge DC. A TGF-ß pathway associated with cancer cachexia. Nature medicine. 2015;21(11):1248-9.

Haines BP, Wheldon LM, Summerbell D, Heath JK, Rigby PWJ. Regulated expression of FLRT genes implies a functional role in the regulation of FGF signalling during mouse development. Developmental biology. 2006;297:14-25.

Hargreaves M. Skeletal muscle metabolism during exercise in humans. Clin Exp Pharmacol Physiol. 2000;27(3):225-8.

Hashim A, Rizzo F, Marchese G, Ravo M, Tarallo R, Nassa G, et al. RNA sequencing identifies specific PIWI-interacting small non-coding RNA expression patterns in breast cancer. Oncotarget. 2014;5(20):9901-10.

Hasselgren PO, Wray C, Mammen J. Molecular regulation of muscle cachexia: it may be more than the proteasome. Biochemical and biophysical research communications. 2002;290(1):1-10.

He WA, Berardi E, Cardillo VM, Acharyya S, Aulino P, Thomas-Ahner J, et al. NF-kappaB-mediated Pax7 dysregulation in the muscle microenvironment promotes cancer cachexia. Journal of Clinical Investigation. 2013;123(11):4821-35.

He WA, Berardi E, Cardillo VM, Acharyya S, Aulino P, Thomas-Ahner J, et al. NF-kappaB-mediated Pax7 dysregulation in the muscle microenvironment promotes cancer cachexia. The Journal of clinical investigation. 2013;123(11):4821-35.

He WA, Calore F, Londhe P, Canella A, Guttridge DC, Croce CM. Microvesicles containing miRNAs promote muscle cell death in cancer cachexia via TLR7. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(12):4525-9.

Henderson JT, Seniuk NA, Richardson PM, Gauldie J, Roder JC. Systemic administration of ciliary neurotrophic factor induces cachexia in rodents. Journal of Clinical Investigation. 1994;93(6):2632-8.

Himeda CL, Ranish JA, Pearson RC, Crossley M, Hauschka SD. KLF3 regulates muscle-specific gene expression and synergizes with serum response factor on KLF binding sites. Molecular and cellular biology. 2010;30(14):3430-43.

Hu G, Wang X, Saunders DN, Henderson M, Russell AJ, Herring BP, et al. Modulation of Myocardin Function by the Ubiquitin E3 Ligase UBR5. Journal of Biological Chemistry. 2010(16).

Huarte M. The emerging role of lncRNAs in cancer. Nature medicine. 2015;21(11):1253-61.

Inacio Pinto N, Carnier J, Oyama LM, Otoch JP, Alcantara PS, Tokeshi F, et al. Cancer as a Proinflammatory Environment: Metastasis and Cachexia. Mediators Inflamm. 2015;2015:791060.

Inui A, Meguid MM. Cachexia and obesity: two sides of one coin? Current Opinion in Clinical Nutrition & Metabolic Care. 2003;6(4):395-9.

Inui A, Meguid MM. Cachexia and obesity: two sides of one coin? Current opinion in clinical nutrition and metabolic care. 2003;6(4):395-9.

Inui A. Neuropeptide Y: a key molecule in anorexia and cachexia in wasting disorders? Molecular medicine today. 1999;5(2):79-85.

Isaac ST, Tan TC, Polly P. Endoplasmic Reticulum Stress, Calcium Dysregulation and Altered Protein Translation: Intersection of Processes That Contribute to Cancer Cachexia Induced Skeletal Muscle Wasting. Current drug targets. 2016;17(10):1140-6.

Jones AE, Price FD, Le Grand F, Soleimani VD, Dick SA, Megeney LA, et al. Wnt/beta-catenin controls follistatin signalling to regulate satellite cell myogenic potential. Skeletal Muscle. 2015;5:14.

Kanehira M, Harada Y, Takata R, Shuin T, Miki T, Fujioka T, et al. Involvement of upregulation of DEPDC1 (DEP domain containing 1) in bladder carcinogenesis. Oncogene. 2007;26(44):6448-55.

Kapur K, Xing Y, Ouyang Z, Wong WH. Exon arrays provide accurate assessments of gene expression. Genome biology. 2007;8(5):R82.

Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Seminars in cell & developmental biology. 2016;54:2-10.

Kelley DE, Mokan M, Simoneau JA, Mandarino LJ. Interaction between glucose and free fatty acid metabolism in human skeletal muscle. The Journal of clinical investigation. 1993;92(1):91-8.

Keren H, Lev-Maor G, Ast G. Alternative splicing and evolution: diversification, exon definition and function. Nature Reviews Genetics. 2010;11(5):345-55.

Kern KA, Norton JA. Cancer cachexia. Journal of Parenteral and Enteral Nutrition. 1988;12(3):286-98.

Kern KA, Norton JA. Cancer cachexia. JPEN Journal of parenteral and enteral nutrition. 1988;12(3):286-98.

Khal J, Wyke SM, Russell ST, Hine AV, Tisdale MJ. Expression of the ubiquitin-proteasome pathway and muscle loss in experimental cancer cachexia. British journal of cancer. 2005;93(7):774-80.

Kir S, White JP, Kleiner S, Kazak L, Cohen P, Baracos VE, et al. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. Nature. 2014;513(7516):100-4.

Kole R, Leppert BJ. Targeting mRNA splicing as a potential treatment for Duchenne muscular dystrophy. Discovery Medicine. 2012;14(74):59-69.

Kornblihtt AR, Schor IE, Allo M, Dujardin G, Petrillo E, Munoz MJ. Alternative splicing: a pivotal step between eukaryotic transcription and translation. Nature reviews Molecular cell biology. 2013;14(3):153-65.

Koutsoulidou A, Kyriakides TC, Papadimas GK, Christou Y, Kararizou E, Papanicolaou EZ, et al. Elevated Muscle-Specific miRNAs in Serum of Myotonic Dystrophy Patients Relate to Muscle Disease Progress. PLoS ONE [Electronic Resource]. 2015;10(4):e0125341.

Krishnan P, Ghosh S, Graham K, Mackey JR, Kovalchuk O, Damaraju S. Piwi-interacting RNAs and PIWI genes as novel prognostic markers for breast cancer. Oncotarget. 2016.

Krishnan P, Ghosh S, Wang B, Heyns M, Graham K, Mackey JR, et al. Profiling of Small Nucleolar RNAs by Next Generation Sequencing: Potential New Players for Breast Cancer Prognosis. PloS one. 2016;11(9):e0162622.

Krishnan P, Ghosh S, Wang B, Li D, Narasimhan A, Berendt R, et al. Next generation sequencing profiling identifies miR-574-3p and miR-660-5p as potential novel prognostic markers for breast cancer. BMC genomics. 2015;16(1):735.

Krishnan P, Ghosh S, Wang B, Li D, Narasimhan A, Berendt R, et al. Next generation sequencing profiling identifies miR-574-3p and miR-660-5p as potential novel prognostic markers for breast cancer. BMC genomics. 2015;16:735.

Kubrak C, Olson K, Jha N, Scrimger R, Parliament M, McCargar L, et al. Clinical determinants of weight loss in patients receiving radiation and chemoirradiation for head and neck cancer: a prospective longitudinal view. Head & neck. 2013;35(5):695-703.

Kulyte A, Lorente-Cebrian S, Gao H, Mejhert N, Agustsson T, Arner P, et al. MicroRNA profiling links miR-378 to enhanced adipocyte lipolysis in human cancer cachexia. American Journal of Physiology - Endocrinology & Metabolism. 2014;306(3):E267-74.

Kulyte A, Lorente-Cebrian S, Gao H, Mejhert N, Agustsson T, Arner P, et al. MicroRNA profiling links miR-378 to enhanced adipocyte lipolysis in human cancer cachexia. American journal of physiology Endocrinology and metabolism. 2014;306(3):E267-74.

Laguna JC, Alegret M. Regulation of gene expression in atherosclerosis: insights from microarray studies in monocytes/macrophages. Pharmacogenomics. 2012;13(4):477-95.

Lall S, Grun D, Krek A, Chen K, Wang YL, Dewey CN, et al. A genome-wide map of conserved microRNA targets in C. elegans. Current biology : CB. 2006;16(5):460-71.

Lecker SH, Jagoe RT, Gilbert A, Gomes M, Baracos V, Bailey J, et al. Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. The FASEB Journal. 2004;18(1):39-51.

Lee C, Roy M. Analysis of alternative splicing with microarrays: successes and challenges. Genome Biol. 2004;5(7):231.

Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75(5):843-54.

Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell.75(5):843-54.

Li H, Durbin R. Fast and accurate short read alignment with Burrows–Wheeler transform. Bioinformatics. 2009;25(14):1754-60.

Li H, Malhotra S, Kumar A. Nuclear factor-kappa B signaling in skeletal muscle atrophy. Journal of molecular medicine. 2008;86(10):1113-26.

Li X, Li Y, Zhao L, Zhang D, Yao X, Zhang H, et al. Circulating Muscle-specific miRNAs in Duchenne Muscular Dystrophy Patients. Molecular TherapyNucleic Acids. 2014;3:e177.

Liang Y, Ridzon D, Wong L, Chen C. Characterization of microRNA expression profiles in normal human tissues. BMC genomics. 2007;8:166.

Lindholm ME, Huss M, Solnestam BW, Kjellqvist S, Lundeberg J, Sundberg CJ. The human skeletal muscle transcriptome: sex differences, alternative splicing, and tissue homogeneity assessed with RNA sequencing. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2014;28(10):4571-81.

Liu J, Xiao Y, Xiong HM, Li J, Huang B, Zhang HB, et al. Alternative splicing of apoptosis-related genes in imatinib-treated K562 cells identified by exon array analysis. Int J Mol Med. 2012;29(4):690-8.

Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods. 2001;25(4):402-8.

Llorian M, Smith CW. Decoding muscle alternative splicing. Current opinion in genetics & development. 2011;21(4):380-7.

Lu ZX, Jiang P, Xing Y. Genetic variation of pre-mRNA alternative splicing in human populations. Wiley Interdisciplinary Reviews. 2012;3(4):581-92.

MacDonald N, Easson AM, Mazurak VC, Dunn GP, Baracos VE. Understanding and managing cancer cachexia. Journal of the American College of Surgeons. 2003;197(1):143-61.

Mahmoud FA, Rivera NI. The role of C-reactive protein as a prognostic indicator in advanced cancer. Curr Oncol Rep. 2002;4(3):250-5.

Marinho AT, Rodrigues PM, Caixas U, Antunes AM, Branco T, Harjivan SG, et al. Differences in nevirapine biotransformation as a factor for its sex-dependent dimorphic profile of adverse drug reactions. The Journal of antimicrobial chemotherapy. 2014;69(2):476-82.

Marioni JC, Mason CE, Mane SM, Stephens M, Gilad Y. RNA-seq: an assessment of technical reproducibility and comparison with gene expression arrays. Genome research. 2008;18(9):1509-17.

Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47.

Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(1):90-9.

Matsuyama T, Ishikawa T, Okayama T, Oka K, Adachi S, Mizushima K, et al. Tumor inoculation site affects the development of cancer cachexia and muscle wasting. Int J Cancer. 2015;137(11):2558-65.

Meissner B, Kridel R, Lim RS, Rogic S, Tse K, Scott DW, et al. The E3 ubiquitin ligase UBR5 is recurrently mutated in mantle cell lymphoma. Blood. 2013;121(16):3161-4.

Merkestein M, McTaggart JS, Lee S, Kramer HB, McMurray F, Lafond M, et al. Changes in gene expression associated with FTO overexpression in mice. PloS one. 2014;9(5):e97162.

Meyers JR, Planamento J, Ebrom P, Krulewitz N, Wade E, Pownall ME. Sulf1 modulates BMP signaling and is required for somite morphogenesis and development of the horizontal myoseptum. Developmental biology. 2013;378(2):107-21.

Mironov AA, Fickett JW, Gelfand MS. Frequent alternative splicing of human genes. Genome research. 1999;9(12):1288-93.

Mizuno S, Yoda M, Shimoda M, Tohmonda T, Okada Y, Toyama Y, et al. A Disintegrin and Metalloprotease 10 (ADAM10) Is Indispensable for Maintenance of the Muscle Satellite Cell Pool. The Journal of biological chemistry. 2015;290(47):28456-64.

Moldawer LL, Georgieff M, Lundholm K. Interleukin 1, tumour necrosis factor-alpha (cachectin) and the pathogenesis of cancer cachexia. Clinical Physiology. 1987;7(4):263-74.

Momin AA, Park H, Portz BJ, Haynes CA, Shaner RL, Kelly SL, et al. A method for visualization of "omic" datasets for sphingolipid metabolism to predict potentially interesting differences. Journal of lipid research. 2011;52(6):1073-83.

Mortazavi A, Williams BA, McCue K, Schaeffer L, Wold B. Mapping and quantifying mammalian transcriptomes by RNA-Seq. Nat Meth. 2008;5(7):621-8.

Mosthaf L, Grako K, Dull TJ, Coussens L, Ullrich A, McClain DA. Functionally distinct insulin receptors generated by tissue-specific alternative splicing. The EMBO journal. 1990;9(8):2409-13.

Murphy AJ, Kraakman MJ, Kammoun HL, Dragoljevic D, Lee MKS, Lawlor KE, et al. IL-18 Production from the NLRP1 Inflammasome Prevents Obesity and Metabolic Syndrome. Cell Metabolism. 2016;23(1):155-64.

Muscaritoli M, Bossola M, Aversa Z, Bellantone R, Rossi Fanelli F. Prevention and treatment of cancer cachexia: new insights into an old problem. European journal of cancer. 2006;42(1):31-41.

Mutz KO, Heilkenbrinker A, Lonne M, Walter JG, Stahl F. Transcriptome analysis using next-generation sequencing. Curr Opin Biotechnol. 2013;24(1):22-30.

Neguembor MV, Jothi M, Gabellini D. Long noncoding RNAs, emerging players in muscle differentiation and disease. Skelet Muscle. 2014;4(1):8.

Norman K, Stobaus N, Reiss J, Schulzke J, Valentini L, Pirlich M. Effect of sexual dimorphism on muscle strength in cachexia. Journal of cachexia, sarcopenia and muscle. 2012;3(2):111-6.

Onesti JK, Guttridge DC. Inflammation based regulation of cancer cachexia. Biomed Res Int. 2014;2014:168407.

Ortega FJ, Mercader JM, Catalan V, Moreno-Navarrete JM, Pueyo N, Sabater M, et al. Targeting the circulating microRNA signature of obesity. Clinical chemistry. 2013;59(5):781-92.

Penaloza C, Estevez B, Orlanski S, Sikorska M, Walker R, Smith C, et al. Sex of the cell dictates its response: differential gene expression and sensitivity to cell death inducing stress in male and female cells. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2009;23(6):1869-79.

Penna F, Baccino FM, Costelli P. Coming back: autophagy in cachexia. Current opinion in clinical nutrition and metabolic care. 2014;17(3):241-6.

Penna F, Costamagna D, Fanzani A, Bonelli G, Baccino FM, Costelli P. Muscle Wasting and Impaired Myogenesis in Tumor Bearing Mice Are Prevented by ERK Inhibition. PloS one. 2010;5(10):1-11.

Penna F, Costamagna D, Pin F, Camperi A, Fanzani A, Chiarpotto EM, et al. Autophagic degradation contributes to muscle wasting in cancer cachexia. The American journal of pathology. 2013;182(4):1367-78.

Petersen AMW, Penkowa M, Iversen M, Frydelund-Larsen L, Andersen JL, Mortensen J, et al. Elevated levels of IL-18 in plasma and skeletal muscle in chronic obstructive pulmonary disease. Lung. 2007;185(3):161-71.

Petruzzelli M, Wagner EF. Mechanisms of metabolic dysfunction in cancer-associated cachexia. Genes Dev. 2016;30(5):489-501.

Pistoni M, Ghigna C, Gabellini D. Alternative splicing and muscular dystrophy. RNA biology. 2010;7(4):441-52.

Polge C, Leulmi R, Jarzaguet M, Claustre A, Combaret L, Béchet D, et al. UBE2B is implicated in myofibrillar protein loss in catabolic C2C12 myotubes. Journal of cachexia, sarcopenia and muscle. 2016;7(3):377-87.

Potter JD, Robertson SP, Johnson JD. Magnesium and the regulation of muscle contraction. Federation proceedings. 1981;40(12):2653-6.

Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncology. 2008;9(7):629-35 7p.

Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncology. 2008;9(7):629-35.

Puigserver P, Rhee J, Lin J, Wu Z, Yoon JC, Zhang CY, et al. Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARgamma coactivator-1. Molecular cell. 2001;8(5):971-82.

Reece EA, Ji I, Wu YK, Zhao Z. Characterization of differential gene expression profiles in diabetic embryopathy using DNA microarray analysis. Am J Obstet Gynecol. 2006;195(4):1075-80.

Rigmor S, Vigdis A, Hege Thoresen G, Eili Tranheim K, Christian AD, Arild CR, et al. Leptin expression in human primary skeletal muscle cells is reduced during differentiation. Journal of cellular biochemistry. 2005;96(1):89.

Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. Annual review of biochemistry. 2012;81:145-66.

Rodriguez A, Hilvo M, Kytomaki L, Fleming R, Britton R, Bacon B, et al. Effects of iron loading on muscle: genome-wide mRNA expression profiling in the mouse. BMC genomics. 2007;8(1):379.

Roeland EJ, Ma JD, Nelson SH, Seibert T, Heavey S, Revta C, et al. Weight loss versus muscle loss: re-evaluating inclusion criteria for future cancer cachexia interventional trials. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2016.

Romaine SP, Tomaszewski M, Condorelli G, Samani NJ. MicroRNAs in cardiovascular disease: an introduction for clinicians. Heart. 2015;101(12):921-8.

Rommel C, Bodine SC, Clarke BA, Rossman R, Nunez L, Stitt TN, et al. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. Nature cell biology. 2001;3(11):1009-13.

Samji T. PIWI, piRNAs, and germline stem cells: what's the link? Yale J Biol Med. 2009;82(3):121-4.

Sato M, Hiraoka M, Suzuki H, Sakima M, Mamun AA, Yamane Y, et al. Protection of Cardiomyocytes from the Hypoxia-Mediated Injury by a Peptide Targeting the Activator of G-Protein Signaling 8. PloS one. 2014;9(3):1-9.

Schakman O, Kalista S, Barbe C, Loumaye A, Thissen JP. Glucocorticoid-induced skeletal muscle atrophy. The international journal of biochemistry & cell biology. 2013;45(10):2163-72.

Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. Nat Meth. 2012;9(7):671-5.

Schwerk C, Schulze-Osthoff K. Regulation of apoptosis by alternative pre-mRNA splicing. Molecular cell. 2005;19(1):1-13.

Sekiyama Y, Suzuki H, Tsukahara T. Functional gene expression analysis of tissue-specific isoforms of Mef2c. Cellular and molecular neurobiology. 2012;32(1):129-39.

Sharma M, Juvvuna PK, Kukreti H, McFarlane C. Mega roles of microRNAs in regulation of skeletal muscle health and disease. Frontiers in Physiology. 2014;5:239.

Sharma S, Eghbali M. Influence of sex differences on microRNA gene regulation in disease. Biology of sex differences. 2014;5(1):3.

Skipworth RJ, Stewart GD, Dejong CH, Preston T, Fearon KC. Pathophysiology of cancer cachexia: much more than host-tumour interaction? Clinical nutrition. 2007;26(6):667-76.

Smith IJ, Aversa Z, Hasselgren PO, Pacelli F, Rosa F, Doglietto GB, et al. Calpain activity is increased in skeletal muscle from gastric cancer patients with no or minimal weight loss. Muscle Nerve. 2011;43(3):410-4.

Sohn J-W, Elmquist JK, Williams KW. Neuronal circuits that regulate feeding behavior and metabolism. Trends in neurosciences. 2013;36(9):504-12.

Sorsa T, Tjäderhane L, Salo T. Matrix metalloproteinases (MMPs) in oral diseases. Oral diseases. 2004;10(6):311-8.

Steinman J, DeBoer MD. Treatment of cachexia: melanocortin and ghrelin interventions. Vitamins & Hormones. 2013;92:197-242.

Stephens NA, Gallagher IJ, Rooyackers O, Skipworth RJ, Tan BH, Marstrand T, et al. Using transcriptomics to identify and validate novel biomarkers of human skeletal muscle cancer cachexia. Genome Med. 2010;2(1):1.

Stephens NA, Gallagher IJ, Rooyackers O, Skipworth RJ, Tan BH, Marstrand T, et al. Using transcriptomics to identify and validate novel biomarkers of human skeletal muscle cancer cachexia. Genome Medicine. 2010;2(1):1.

Stephens NA, Gray C, MacDonald AJ, Tan BH, Gallagher IJ, Skipworth RJ, et al. Sexual dimorphism modulates the impact of cancer cachexia on lower limb muscle mass and function. Clinical nutrition. 2012;31(4):499-505.

Stretch C, Khan S, Asgarian N, Eisner R, Vaisipour S, Damaraju S, et al. Effects of sample size on differential gene expression, rank order and prediction accuracy of a gene signature. PLoS ONE [Electronic Resource]. 2013;8(6):e65380.

Suchismita C, Tingqing G, Teresa T, Weiping C, Murphy Dennis L, McPherron Alexandra C. Effects of serotonin on skeletal muscle growth. BMC Proceedings. 2012:O3.

Suzuki ASAIJ. The temporal specific role of WNT/β-catenin signaling during myogenesis. Journal of Nature and Science. 2015;1(8).

Tam S, de Borja R, Tsao MS, McPherson JD. Robust global microRNA expression profiling using next-generation sequencing technologies. Laboratory Investigation. 2014;94(3):350-8.

Tan BH, Fearon KC. Cachexia: prevalence and impact in medicine. Current Opinion in Clinical Nutrition & Metabolic Care. 2008;11(4):400-7.

Tan BH, Fladvad T, Braun TP, Vigano A, Strasser F, Deans DA, et al. P-selectin genotype is associated with the development of cancer cachexia. EMBO molecular medicine. 2012;4(6):462-71.

Taub MA, Corrada Bravo H, Irizarry RA. Overcoming bias and systematic errors in next generation sequencing data. Genome Med. 2010;2(12):87.

Thompson MP, Cooper ST, Parry BR, Tuckey JA. Increased expression of the mRNA for hormone-sensitive lipase in adipose tissue of cancer patients. Biochimica et biophysica acta. 1993;1180(3):236-42.

Tisdale MJ. Catabolic mediators of cancer cachexia. Current Opinion in Supportive & Palliative Care. 2008;2(4):256-61.

Tisdale MJ. Mechanisms of cancer cachexia. Physiol Rev. 2009;89(2):381-410.

Tisdale MJ. Mechanisms of cancer cachexia. Physiological reviews. 2009;89(2):381-410.

Todorov PT, Field WN, Tisdale MJ. Role of a proteolysis-inducing factor (PIF) in cachexia induced by a human melanoma (G361). British journal of cancer. 1999;80(11):1734-7.

Tripathi V, Shen Z, Chakraborty A, Giri S, Freier SM, Wu X, et al. Long noncoding RNA MALAT1 controls cell cycle progression by regulating the expression of oncogenic transcription factor B-MYB. PLoS Genet. 2013;9(3):e1003368.

Tsoli M, Schweiger M, Vanniasinghe AS, Painter A, Zechner R, Clarke S, et al. Depletion of White Adipose Tissue in Cancer Cachexia Syndrome Is Associated with Inflammatory Signaling and Disrupted Circadian Regulation. PloS one. 2014;9(3):1-12.

Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can up-regulate translation. Science. 2007;318(5858):1931-4.

Waddell JN, Zhang P, Wen Y, Gupta SK, Yevtodiyenko A, Schmidt JV, et al. Dlk1 is necessary for proper skeletal muscle development and regeneration. PLoS ONE [Electronic Resource]. 2010;5(11):e15055.

Waning DL, Mohammad KS, Reiken S, Xie W, Andersson DC, John S, et al. Excess TGF-beta mediates muscle weakness associated with bone metastases in mice. Nature medicine. 2015;21(11):1262-71.

Waning DL, Mohammad KS, Reiken S, Xie W, Andersson DC, John S, et al. Excess TGF-ß mediates muscle weakness associated with bone metastases in mice. Nature medicine. 2015;21(11):1262-71.

Ward AJ, Cooper TA. The pathobiology of splicing. Journal of Pathology. 2010;220(2):152-63.

Wei N, Cheng Y, Wang Z, Liu Y, Luo C, Liu L, et al. SRSF10 Plays a Role in Myoblast Differentiation and Glucose Production via Regulation of Alternative Splicing. Cell reports. 2015;13(8):1647-57.

Wells JC. Sexual dimorphism of body composition. Best practice & research Clinical endocrinology & metabolism. 2007;21(3):415-30.

White JP, Puppa MJ, Gao S, Sato S, Welle SL, Carson JA. Muscle mTORC1 suppression by IL-6 during cancer cachexia: a role for AMPK. American journal of physiology Endocrinology and metabolism. 2013;304(10):E1042-52.

Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell.75(5):855-62.

Wijchers PJ, Yandim C, Panousopoulou E, Ahmad M, Harker N, Saveliev A, et al. Sexual dimorphism in mammalian autosomal gene regulation is determined not only by Sry but by sex chromosome complement as well. Developmental cell. 2010;19(3):477-84.

Xu W, Seok J, Mindrinos MN, Schweitzer AC, Jiang H, Wilhelmy J, et al. Human transcriptome array for high-throughput clinical studies. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(9):3707-12.

Yang X, Schadt EE, Wang S, Wang H, Arnold AP, Ingram-Drake L, et al. Tissue-specific expression and regulation of sexually dimorphic genes in mice. Genome research. 2006;16(8):995-1004.

Yoshida T, Tabony AM, Galvez S, Mitch WE, Higashi Y, Sukhanov S, et al. Molecular mechanisms and signaling pathways of angiotensin II-induced muscle wasting: potential therapeutic targets for cardiac cachexia. The international journal of biochemistry & cell biology. 2013;45(10):2322-32.

Younossi ZM, Afendy A, Stepanova M, Hossain N, Younossi I, Ankrah K, et al. Gene expression profile associated with superimposed non-alcoholic fatty liver disease and hepatic fibrosis in patients with chronic hepatitis C. Liver Int. 2009;29(9):1403-12.

Zhang X, Azhar G, Wei JY. The expression of microRNA and microRNA clusters in the aging heart. PLoS ONE [Electronic Resource]. 2012;7(4):e34688.

Zhang Z, Pal S, Bi Y, Tchou J, Davuluri RV. Isoform level expression profiles provide better cancer signatures than gene level expression profiles. Genome Medicine. 2013;5(4):1-13.

Zimmers TA, Davies MV, Koniaris LG, Haynes P, Esquela AF, Tomkinson KN, et al. Induction of cachexia in mice by systemically administered myostatin. Science. 2002;296(5572):1486-8.

7 Appendix

Table 7.1 List of Up-regulated DASGs

Probeset ID	RefSeq	Gene Symbol	Fold-change	p-value
PSR01014122.hg.1	ENST00000370153	SLC35A3	1.42	2.36E-02
PSR01001904.hg.1	ENST00000377153	UBE4B	1.53	1.21E-02
PSR01002047.hg.1	ENST00000538557	PGD	1.40	4.34E-02
PSR01014633.hg.1	ENST00000370021	PRPF38B	1.45	1.92E-02
PSR01045980.hg.1	NM_001205228	SORT1	1.46	3.62E-03
PSR01046007.hg.1	NM_001199773	PSMA5	1.61	4.11E-04
PSR01014992.hg.1	NM_006496	GNAI3	1.42	1.99E-03
PSR01033955.hg.1	NM_004958	MTOR	1.41	4.31E-03
PSR01046921.hg.1	ENST00000369541	BCAS2	1.58	1.98E-02
PSR01047006.hg.1	ENST00000353928	AMPD1	1.45	6.42E-03
PSR01047316.hg.1	ENST00000369442	GDAP2	1.73	2.91E-02
PSR01002611.hg.1	NM_015378	VPS13D	1.40	2.33E-02
PSR01018073.hg.1	NM_007259	VPS45	1.46	7.96E-03
PSR01050656.hg.1	NM_001043352	TPM3	1.46	2.98E-02
PSR01050692.hg.1	ENST00000302206	TPM3	1.54	4.80E-02
PSR01052056.hg.1	ENST00000472765	CCT3	1.47	2.72E-02
PSR01022022.hg.1	ENST00000543859	FCGR2C	1.69	2.67E-02
PSR01022023.hg.1	NM_201563	FCGR2C	1.62	2.28E-02
PSR01022477.hg.1	ENST00000367883	LOC100505828	1.71	5.11E-04
PSR01022481.hg.1	ENST00000367884	LOC100505828	1.48	2.13E-03
PSR01022841.hg.1	ENST00000494797	ATP1B1	1.53	3.33E-02
PSR01054473.hg.1	ENST00000303469	METTL18	1.41	1.76E-02
PSR01054515.hg.1	ENST00000367767	KIFAP3	1.48	1.75E-02
PSR01055228.hg.1	NM_004673	ANGPTL1	1.46	7.15E-03
PSR01024516.hg.1	NM_002293	LAMC1	1.51	3.35E-02
PSR01055625.hg.1	NM_001127651	NCF2	1.58	3.36E-02
PSR01055696.hg.1	NM_025191	EDEM3	1.42	1.14E-02
PSR01055802.hg.1	ENST00000392007	IVNS1ABP	1.44	8.89E-03
PSR01055824.hg.1	ENST00000392007	IVNS1ABP	1.42	3.40E-02
PSR01055893.hg.1	ENST00000367478	TPR	1.54	2.28E-02
PSR01055895.hg.1	ENST00000367478	TPR	1.51	2.57E-02
PSR01025108.hg.1	ENST00000432079	TROVE2	1.43	9.99E-03
PSR01025113.hg.1	ENST00000432079	TROVE2	1.50	1.36E-02
PSR01025467.hg.1	ENST00000352140	PTPRC	1.43	2.05E-02
PSR01056971.hg.1	NM_015999	ADIPOR1	1.63	1.53E-02
PSR01035342.hg.1	NM_001161727	PLA2G2A	1.51	1.05E-02
PSR01035344.hg.1	NM_001161727	PLA2G2A	2.07	2.96E-03
PSR01035345.hg.1	NM_001161727	PLA2G2A	1.92	2.36E-02
PSR01035348.hg.1	NM_001161727	PLA2G2A	1.46	1.30E-02
PSR01035349.hg.1	NM_001161727	PLA2G2A	1.92	9.60E-03
PSR01035351.hg.1	NM_001161727	PLA2G2A	1.46	2.40E-02
PSR01026343.hg.1	ENST00000414487	SNRPE	1.71	5.74E-03

PSR01027232.hg.1	ENST00000367053	CR1	1.46	6.21E-04
PSR01058149.hg.1	ENST00000440600	INTS7	1.40	3.67E-03
PSR01058151.hg.1	ENST00000440600	INTS7	1.47	2.54E-02
PSR01027903.hg.1	NM_001136475	VASH2	1.43	3.43E-02
PSR01058477.hg.1	ENST00000366934	GPATCH2	1.65	6.66E-04
PSR01058533.hg.1	ENST00000366923	EPRS	1.49	1.64E-02
PSR01028390.hg.1	ENST00000344441	MIA3	1.57	1.97E-02
PSR01028413.hg.1	ENST00000344441	MIA3	1.91	1.61E-02
PSR01028414.hg.1	ENST00000344441	MIA3	1.47	2.16E-02
PSR01028419.hg.1	ENST00000344441	MIA3	1.40	5.52E-03
PSR01028446.hg.1	ENST00000344441	MIA3	1.46	2.41E-02
PSR01028657.hg.1	ENST00000391877	DEGS1	1.45	1.54E-02
PSR01059262.hg.1	ENST00000284563	ENAH	1.64	1.71E-02
PSR01060240.hg.1	ENST00000430153	PCNXL2	1.44	1.12E-03
PSR01060369.hg.1	ENST00000366606	RBM34	1.65	2.65E-02
PSR01060371.hg.1	ENST00000366606	RBM34	1.49	1.91E-02
PSR01060411.hg.1	NM_016374	ARID4B	1.62	1.40E-02
PSR01060421.hg.1	NM_016374	ARID4B	1.44	3.49E-02
PSR01030057.hg.1	ENST00000282841	GGPS1	1.46	1.88E-02
PSR01060524.hg.1	ENST00000389793	LYST	1.47	3.67E-02
PSR01036023.hg.1	ENST00000478691	HNRNPR	1.41	1.64E-02
PSR01036027.hg.1	ENST00000374616	HNRNPR	1.48	3.19E-03
PSR01030120.hg.1	ENST00000366592	GPR137B	1.52	3.64E-03
PSR01030121.hg.1	ENST00000366592	GPR137B	1.47	1.05E-02
PSR01030697.hg.1	ENST00000355875	SDCCAG8	1.50	2.72E-02
PSR01030702.hg.1	ENST00000476722	SDCCAG8	1.57	2.19E-02
PSR01030846.hg.1	ENST00000366528	COX20	1.61	4.11E-02
PSR01005995.hg.1	NM_006582	GMEB1	1.44	3.55E-02
PSR01037437.hg.1	NM_005626	SRSF4	1.40	9.51E-03
PSR1_gl000191_random000017.hg.1	NM_001191006	SRSF10	1.50	3.08E-03
PSR01007911.hg.1	ENST00000372771	RLF	1.47	2.04E-03
PSR01009701.hg.1	ENST00000402363	NASP	1.55	1.01E-02
PSR01010377.hg.1	ENST00000447887	OSBPL9	1.51	1.04E-02
PSR01010395.hg.1	NM_148909	OSBPL9	1.65	1.61E-02
PSR01041728.hg.1	ENST00000257177	ZCCHC11	1.81	1.37E-02
PSR01041748.hg.1	ENST00000257177	ZCCHC11	1.56	2.29E-02
PSR01041903.hg.1	NM_002370	MAGOH	1.49	8.62E-03
PSR01041904.hg.1	NM_002370	MAGOH	1.47	3.50E-03
PSR01042878.hg.1	ENST00000271002	ITGB3BP	1.42	4.30E-02
PSR01042880.hg.1	ENST00000271002	ITGB3BP	1.42	3.86E-02
PSR01042890.hg.1	ENST00000271002	ITGB3BP	1.45	3.68E-03
PSR01011445.hg.1	ENST00000371086	DLEU2L	1.81	4.37E-05
PSR01011446.hg.1	ENST00000371086	DLEU2L	1.58	2.86E-02
PSR01011449.hg.1	ENST00000371086	DLEU2L	1.71	1.15E-03
PSR01011432.hg.1	NM_032437	EFCAB7	1.60	7.05E-03
PSR01011435.hg.1	NM_032437	EFCAB7	1.66	3.50E-04
PSR01011437.hg.1	NM_032437	EFCAB7	1.91	4.18E-04
PSR01011438.hg.1	NM_032437	EFCAB7	1.92	1.75E-03
PSR01011440.hg.1	NM_032437	EFCAB7	1.51	6.58E-03
PSR01043217.hg.1	NM_001114120	DEPDC1	1.52	5.50E-04

PSR01043257.hg.1	ENST00000370952	LRRC40	1.51	5.88E-03
PSR01001564.hg.1	ENST00000476864	CAMTA1	1.41	5.35E-03
PSR01012603.hg.1	NM_001172309	NEXN	1.72	8.52E-03
PSR01043671.hg.1	ENST00000370768	FUBP1	1.41	4.88E-03
PSR01043850.hg.1	ENST00000370630	CTBS	1.42	1.09E-02
PSR01013024.hg.1	ENST00000451137	CYR61	1.49	9.04E-03
PSR01013026.hg.1	ENST00000451137	CYR61	2.00	3.12E-03
PSR01013027.hg.1	ENST00000451137	CYR61	1.74	1.15E-02
PSR01013029.hg.1	ENST00000451137	CYR61	1.69	4.25E-02
PSR01013031.hg.1	ENST00000451137	CYR61	1.56	3.01E-02
PSR01013033.hg.1	ENST00000451137	CYR61	1.62	4.15E-02
PSR01013035.hg.1	ENST00000451137	CYR61	1.88	1.35E-02
PSR01013036.hg.1	ENST00000451137	CYR61	1.72	3.74E-02
PSR01013039.hg.1	ENST00000451137	CYR61	1.92	1.01E-02
PSR01044190.hg.1	NM_001184766	ODF2L	1.43	1.14E-02
PSR01044195.hg.1	NM_001184766	ODF2L	1.42	3.54E-02
PSR01044201.hg.1	NM_001184766	ODF2L	1.52	6.98E-03
PSR01044204.hg.1	NM_001184766	ODF2L	1.62	5.67E-03
PSR01044207.hg.1	NM_001184766	ODF2L	1.44	4.27E-03
PSR01013155.hg.1	NM_016009	SH3GLB1	1.52	4.98E-02
PSR01044336.hg.1	NM_018284	GBP3	1.67	1.04E-02
PSR01044351.hg.1	NM_018284	GBP3	1.41	9.83E-04
PSR01013329.hg.1	NM_015350	LRRC8B	1.48	1.20E-03
PSR01044791.hg.1	ENST00000370280	TMED5	1.56	2.09E-02
PSR10020453.hg.1	ENST00000407654	ERLIN1	1.42	8.50E-03
PSR10020549.hg.1	ENST00000370372	BLOC1S2	1.44	3.64E-02
PSR10021205.hg.1	ENST00000343289	NT5C2	1.52	4.12E-02
PSR10009311.hg.1	ENST00000369727	SFR1	1.45	2.13E-03
PSR10012137.hg.1	ENST00000381344	IDI1	1.64	1.96E-02
PSR10009596.hg.1	NM_005445	SMC3	1.46	3.22E-02
PSR10009611.hg.1	NM_005445	SMC3	1.42	1.65E-02
PSR10009689.hg.1	NM_001199492	PDCD4	1.63	2.78E-02
PSR10009691.hg.1	NM_001199492	PDCD4	1.48	3.73E-02
PSR10009694.hg.1	NM_001199492	PDCD4	1.47	1.39E-02
PSR10021767.hg.1	ENST00000447005	BBIP1	1.75	5.08E-03
PSR10010089.hg.1	NM_001135051	FAM160B1	1.66	3.51E-02
PSR10022230.hg.1	ENST00000334464	PDZD8	1.47	1.30E-02
PSR10022272.hg.1	NM_022063	FAM204A	1.48	2.30E-03
PSR10022274.hg.1	NM_022063	FAM204A	1.49	1.30E-02
PSR10010522.hg.1	NM_001243194	INPP5F	1.55	3.98E-02
PSR10012938.hg.1	ENST00000491614	NUDT5	1.58	1.92E-02
PSR10011227.hg.1	ENST00000368689	FANK1	1.40	1.80E-04
PSR10001472.hg.1	NM_002438	MRC1	1.45	2.63E-02
PSR10001473.hg.1	NM_002438	MRC1	1.51	2.62E-02
PSR10001481.hg.1	NM_002438	MRC1	1.44	1.38E-02
PSR10001523.hg.1	NM_002438	MRC1	1.45	2.63E-02
PSR10001524.hg.1	NM_002438	MRC1	1.51	2.62E-02
PSR10001532.hg.1	NM_002438	MRC1	1.44	1.38E-02
PSR10001666.hg.1	ENST00000455457	C10orf112	1.43	1.44E-02
PSR10013807.hg.1	ENST00000376980	DNAJC1	1.41	3.09E-02

PSR10013835.hg.1	ENST00000323883	PIP4K2A	1.42	4.10E-02
PSR10002277.hg.1	NM_021252	RAB18	1.51	3.75E-02
PSR10014801.hg.1	ENST00000374742	CUL2	1.49	1.35E-02
PSR10002844.hg.1	ENST00000374660	ANKRD30A	1.59	4.34E-02
PSR10002847.hg.1	ENST00000374660	ANKRD30A	1.46	2.23E-02
PSR10002848.hg.1	ENST00000374660	ANKRD30A	1.44	1.46E-02
PSR10002850.hg.1	ENST00000374660	ANKRD30A	1.59	4.34E-02
PSR10002854.hg.1	ENST00000374660	ANKRD30A	1.46	2.23E-02
PSR10002855.hg.1	ENST00000374660	ANKRD30A	1.44	1.46E-02
PSR10002861.hg.1	ENST00000374660	ANKRD30A	1.46	2.23E-02
PSR10003368.hg.1	NM_001169107	FAM21C	1.53	7.42E-03
PSR10003531.hg.1	ENST00000543972	FAM21C	1.41	1.94E-02
PSR10000478.hg.1	NM_017782	FAM208B	1.77	2.68E-02
PSR10016908.hg.1	ENST00000412272	HERC4	1.49	1.34E-03
PSR10017115.hg.1	ENST00000539557	SLC25A16	1.47	7.27E-03
PSR10004629.hg.1	NM_024045	DDX50	1.41	1.00E-02
PSR10004653.hg.1	NM_004728	DDX21	1.56	4.30E-03
PSR10004662.hg.1	NM_004728	DDX21	1.55	1.10E-02
PSR10004716.hg.1	ENST00000373382	VPS26A	1.49	2.67E-02
PSR10017213.hg.1	ENST00000373241	SAR1A	1.54	1.15E-02
PSR10006701.hg.1	NM_133447	AGAP11	1.70	2.43E-03
PSR10019110.hg.1	ENST00000371697	ANKRD1	2.83	3.35E-02
PSR10007292.hg.1	NM_025235	TNKS2	1.46	3.56E-02
PSR10007343.hg.1	NM_003972	BTAF1	1.42	1.32E-02
PSR10019356.hg.1	NM_145246	FRA10AC1	1.58	1.29E-02
PSR10019419.hg.1	NM_022451	NOC3L	1.55	1.36E-02
PSR10019421.hg.1	NM_022451	NOC3L	1.54	1.06E-02
PSR10019519.hg.1	ENST00000371246	SORBS1	1.49	1.48E-02
PSR10020156.hg.1	NM_001206528	CRTAC1	1.60	3.30E-02
PSR11026567.hg.1	ENST00000348423	TRPC6	1.48	5.19E-03
PSR11011933.hg.1	NM_001377	DYNC2H1	1.42	1.29E-03
PSR11011966.hg.1	NM_001377	DYNC2H1	1.49	9.49E-04
PSR11011977.hg.1	NM_001377	DYNC2H1	1.49	2.63E-03
PSR11027029.hg.1	NM_152434	CWF19L2	1.41	2.05E-02
PSR11027121.hg.1	ENST00000278612	NPAT	1.59	1.83E-02
PSR11012188.hg.1	NM_000051	ATM	1.62	1.09E-02
PSR11027478.hg.1	ENST00000528832	IL18	1.78	1.02E-03
PSR11027479.hg.1	ENST00000528832	IL18	1.41	1.59E-02
PSR11028315.hg.1	ENST00000527673	RPS25	1.67	1.95E-02
PSR11029384.hg.1	ENST00000423662	PRDM10	1.41	2.01E-03
PSR11002764.hg.1	NM_001030273	ARNTL	1.54	6.21E-05
PSR11002779.hg.1	NM_001030273	ARNTL	1.65	2.81E-03
PSR11002780.hg.1	NM_001030273	ARNTL	1.46	6.83E-03
PSR11002782.hg.1	NM_001030273	ARNTL	1.54	6.42E-03
PSR11002791.hg.1	NM_001030273	ARNTL	1.53	3.45E-04
PSR11002820.hg.1	ENST00000354817	FAR1	1.43	8.00E-03
PSR11018020.hg.1	ENST00000534746	RRAS2	1.43	2.16E-02
PSR11015958.hg.1	ENST00000331588	DUSP8	1.42	3.72E-03
PSR11018278.hg.1	ENST00000265970	PIK3C2A	1.41	3.97E-02
PSR11003130.hg.1	NM_000331	SAA1	1.51	1.48E-02

PSR11018530.hg.1	ENST00000438420	HPS5	1.48	2.54E-04
PSR11018793.hg.1	NM_148893	SVIP	1.66	2.32E-03
PSR11003738.hg.1	ENST00000403099	METTL15	1.44	8.39E-03
PSR11019108.hg.1	ENST00000534812	IMMP1L	1.46	3.77E-03
PSR11019267.hg.1	NM_001326	CSTF3	1.47	1.44E-02
PSR11019274.hg.1	ENST00000438862	CSTF3	1.43	2.46E-02
PSR11004469.hg.1	NM_001243747	API5	1.69	8.35E-03
PSR11005340.hg.1	NM_175732	PTPMT1	1.63	1.23E-02
PSR11020521.hg.1	ENST00000378460	NUP160	1.62	3.72E-02
PSR11020546.hg.1	ENST00000530326	NUP160	1.45	2.03E-02
PSR11020548.hg.1	ENST00000530326	NUP160	1.41	2.09E-02
PSR11006007.hg.1	ENST00000532114	MS4A4A	1.45	1.98E-02
PSR11006008.hg.1	ENST00000532114	MS4A4A	1.46	4.89E-02
PSR11006009.hg.1	ENST00000355131	MS4A4A	1.63	1.30E-02
PSR11022071.hg.1	NM_018093	WDR74	1.52	1.88E-03
PSR11022093.hg.1	ENST00000525239	WDR74	1.41	3.75E-02
PSR11007864.hg.1	NM_001048218	SCYL1	1.69	1.12E-02
PSR11010133.hg.1	ENST00000543525	PPME1	1.54	9.29E-03
PSR11010208.hg.1	NM_014752	SPCS2	1.77	2.95E-02
PSR11010210.hg.1	NM_014752	SPCS2	1.44	7.50E-03
PSR11010389.hg.1	ENST00000356136	UVRAG	1.52	8.10E-03
PSR11010410.hg.1	ENST00000356136	UVRAG	1.45	4.81E-03
PSR11025840.hg.1	ENST00000398294	CREBZF	1.48	9.13E-03
PSR11025921.hg.1	NM_001206946	PICALM	1.51	7.29E-03
PSR11026082.hg.1	ENST00000528341	NOX4	1.62	2.75E-03
PSR11026089.hg.1	ENST00000413594	NOX4	1.63	1.23E-02
PSR11026171.hg.1	ENST00000320585	CHORDC1	1.66	1.95E-02
PSR11026172.hg.1	ENST00000320585	CHORDC1	1.50	2.61E-03
PSR11026173.hg.1	ENST00000320585	CHORDC1	1.47	1.79E-02
PSR11026174.hg.1	ENST00000320585	CHORDC1	1.48	1.43E-02
PSR11026175.hg.1	ENST00000320585	CHORDC1	1.46	5.39E-03
PSR11026176.hg.1	ENST00000529726	CHORDC1	1.62	4.27E-03
PSR11026177.hg.1	ENST00000320585	CHORDC1	1.47	9.28E-03
PSR11026178.hg.1	ENST00000529726	CHORDC1	1.50	1.55E-02
PSR11026179.hg.1	ENST00000320585	CHORDC1	1.45	1.11E-02
PSR11026180.hg.1	ENST00000529987	CHORDC1	1.46	2.37E-02
PSR11026182.hg.1	ENST00000530765	CHORDC1	1.70	1.89E-03
PSR11002362.hg.1	ENST00000299606	ZNF143	1.43	1.19E-02
PSR11002373.hg.1	ENST00000299606	ZNF143	1.46	9.01E-03
PSR11026504.hg.1	ENST00000278520	CCDC82	1.42	3.34E-02
PSR11026518.hg.1	ENST00000278520	CCDC82	1.63	5.32E-03
PSR12024672.hg.1	ENST00000337514	IGF1	1.47	2.39E-02
PSR12024673.hg.1	ENST00000337514	IGF1	1.42	3.59E-02
PSR12024868.hg.1	ENST00000240055	NFYB	1.44	1.05E-02
PSR12010578.hg.1	ENST00000550344	C12orf23	1.58	4.09E-02
PSR12025083.hg.1	NM_004075	CRY1	1.45	2.00E-02
PSR12025087.hg.1	NM_004075	CRY1	1.49	7.07E-03
PSR12010835.hg.1	ENST00000377854	ACACB	1.60	2.40E-02
PSR12027329.hg.1	ENST00000336229	ZCCHC8	1.54	1.36E-02
PSR12027568.hg.1	NM_001167856	SBNO1	1.55	9.00E-03

PSR12016684.hg.1	ENST00000281172	EPS8	1.42	1.26E-02
PSR12016738.hg.1	ENST00000537304	LMO3	1.46	8.16E-03
PSR12016740.hg.1	ENST00000537304	LMO3	1.61	7.35E-03
PSR12016741.hg.1	ENST00000537304	LMO3	1.72	4.91E-03
PSR12016744.hg.1	ENST00000534946	LMO3	1.45	2.97E-02
PSR12016746.hg.1	NM_001243613	LMO3	1.52	3.99E-02
PSR12016750.hg.1	ENST00000534946	LMO3	1.83	2.29E-03
PSR12002666.hg.1	NM_001190860	PLEKHA5	1.48	5.66E-04
PSR12014504.hg.1	ENST00000280665	DCP1B	1.42	2.67E-02
PSR12014508.hg.1	ENST00000280665	DCP1B	1.40	2.20E-02
PSR12002870.hg.1	ENST00000545178	PYROXD1	1.40	3.74E-02
PSR12002884.hg.1	NM_024854	PYROXD1	1.46	3.75E-02
PSR12002887.hg.1	NM_024854	PYROXD1	1.40	4.65E-02
PSR12002940.hg.1	ENST00000335148	ETNK1	1.73	3.09E-03
PSR12002943.hg.1	NM_018638	ETNK1	1.41	2.61E-02
PSR12002947.hg.1	NM_018638	ETNK1	1.44	1.94E-02
PSR12003103.hg.1	NM_001164746	RASSF8	1.54	1.76E-02
PSR12017371.hg.1	ENST00000381340	ITPR2	1.46	4.03E-03
PSR12017384.hg.1	ENST00000381340	ITPR2	1.57	2.32E-02
PSR12003163.hg.1	NM_004264	MED21	1.49	5.89E-03
PSR12003257.hg.1	NM_003622	PPFIBP1	1.64	1.36E-02
PSR12003619.hg.1	NM_005690	DNM1L	1.76	2.63E-02
PSR12003621.hg.1	NM_005690	DNM1L	1.79	2.31E-03
PSR12003641.hg.1	NM_032834	ALG10	1.46	1.06E-02
PSR12018001.hg.1	ENST00000331366	CPNE8	1.48	3.89E-02
PSR12018012.hg.1	ENST00000395670	KIF21A	1.44	2.58E-02
PSR12018132.hg.1	NM_001099650	GXYLT1	1.41	3.83E-02
PSR12018271.hg.1	NM_001098614	PUS7L	1.45	3.34E-03
PSR12000590.hg.1	ENST00000179259	C12orf5	1.59	5.20E-03
PSR12000592.hg.1	ENST00000179259	C12orf5	1.61	1.19E-02
PSR12004182.hg.1	ENST00000422737	ARID2	1.57	7.38E-03
PSR12004183.hg.1	ENST00000422737	ARID2	1.48	5.69E-03
PSR12018482.hg.1	NM_018018	SLC38A4	1.64	3.90E-03
PSR12018483.hg.1	ENST00000266579	SLC38A4	1.82	7.98E-03
PSR12018484.hg.1	ENST00000266579	SLC38A4	1.94	1.44E-02
PSR12018485.hg.1	ENST00000266579	SLC38A4	1.70	1.22E-02
PSR12018486.hg.1	ENST00000266579	SLC38A4	1.87	1.39E-02
PSR12018487.hg.1	ENST00000266579	SLC38A4	1.71	1.67E-02
PSR12018488.hg.1	ENST00000266579	SLC38A4	1.47	3.70E-02
PSR12018491.hg.1	ENST00000266579	SLC38A4	1.46	2.95E-02
PSR12018492.hg.1	ENST00000266579	SLC38A4	1.58	2.92E-02
PSR12018493.hg.1	ENST00000266579	SLC38A4	1.61	2.29E-02
PSR12018494.hg.1	ENST00000266579	SLC38A4	1.63	4.33E-02
PSR12018495.hg.1	ENST00000266579	SLC38A4	1.52	4.25E-02
PSR12018496.hg.1	ENST00000266579	SLC38A4	1.79	1.29E-02
PSR12018497.hg.1	ENST00000266579	SLC38A4	1.50	3.19E-02
PSR12018498.hg.1	ENST00000266579	SLC38A4	1.68	2.83E-02
PSR12018499.hg.1	ENST00000266579	SLC38A4	1.44	4.56E-02
PSR12018503.hg.1	ENST00000266579	SLC38A4	1.72	2.02E-02
PSR12019681.hg.1	NM_001174126	SLC11A2	1.52	2.15E-02

PSR12019688.hg.1	ENST00000262052	SLC11A2	1.44	6.05E-03
PSR12019689.hg.1	ENST00000262052	SLC11A2	1.44	3.52E-02
PSR12020288.hg.1	NM_001244705	CSAD	1.41	2.87E-02
PSR12005991.hg.1	ENST00000546500	HNRNPA1	1.42	1.77E-03
PSR12022223.hg.1	ENST00000379141	LRIG3	1.41	4.80E-02
PSR12007591.hg.1	NM_007235	XPOT	1.56	9.28E-03
PSR12007626.hg.1	ENST00000331710	TBK1	1.46	2.50E-02
PSR12007707.hg.1	NM_014319	LEMD3	1.73	1.15E-02
PSR12007708.hg.1	NM_014319	LEMD3	1.73	1.15E-02
PSR12007841.hg.1	NM_018448	CAND1	1.48	1.96E-02
PSR12008050.hg.1	ENST00000544561	MDM2	1.56	3.57E-02
PSR12008038.hg.1	ENST00000545204	MDM2	1.40	2.96E-02
PSR12008081.hg.1	ENST00000456847	CPSF6	1.47	1.18E-02
PSR12008100.hg.1	ENST00000247843	YEATS4	1.52	8.16E-03
PSR12023116.hg.1	ENST00000229214	KRR1	1.54	3.17E-02
PSR12023162.hg.1	NM_139207	NAP1L1	1.53	9.35E-03
PSR12023163.hg.1	NM_139207	NAP1L1	1.63	3.74E-02
PSR12023164.hg.1	NM_139207	NAP1L1	1.48	3.30E-03
PSR12023169.hg.1	ENST00000535020	NAP1L1	1.55	1.00E-02
PSR12023173.hg.1	ENST00000535020	NAP1L1	1.46	2.96E-02
PSR12015476.hg.1	ENST00000541972	CD163	1.41	2.19E-02
PSR12008556.hg.1	ENST00000334822	ZDHHC17	1.48	3.13E-02
PSR12008850.hg.1	ENST00000548324	ACSS3	1.48	6.01E-03
PSR12023621.hg.1	ENST00000547691	CEP290	1.48	1.97E-02
PSR12023624.hg.1	ENST00000547691	CEP290	1.44	1.38E-02
PSR12023625.hg.1	ENST00000547691	CEP290	1.45	6.93E-03
PSR12023633.hg.1	ENST00000547691	CEP290	1.45	2.00E-02
PSR12023638.hg.1	ENST00000547691	CEP290	1.42	6.67E-03
PSR12023639.hg.1	ENST00000547691	CEP290	1.58	8.82E-03
PSR12023645.hg.1	ENST00000547691	CEP290	1.45	3.75E-02
PSR12023647.hg.1	ENST00000547691	CEP290	1.41	1.76E-02
PSR12023649.hg.1	ENST00000397838	CEP290	1.68	6.76E-03
PSR12023668.hg.1	ENST00000397838	CEP290	1.49	2.64E-02
PSR12023679.hg.1	ENST00000552770	CEP290	1.82	9.80E-03
PSR12009033.hg.1	NM_181783	TMTC3	1.43	6.27E-03
PSR12009036.hg.1	NM_181783	TMTC3	1.41	1.61E-02
PSR12023803.hg.1	ENST00000359142	ATP2B1	1.52	4.70E-03
PSR12023913.hg.1	ENST00000322349	EEA1	1.43	9.39E-03
PSR13000177.hg.1	NM_006531	IFT88	1.54	1.76E-02
PSR13000178.hg.1	NM_006531	IFT88	1.41	2.24E-02
PSR13000181.hg.1	NM_006531	IFT88	1.50	2.16E-02
PSR13005300.hg.1	ENST00000382592	LATS2	1.45	3.41E-02
PSR13000319.hg.1	ENST00000537476	SGCG	1.77	1.45E-03
PSR13000944.hg.1	NM_005800	USPL1	1.44	6.42E-03
PSR13001006.hg.1	ENST00000343307	B3GALTL	1.41	8.08E-03
PSR13006405.hg.1	NM_015087	SPG20	1.46	3.91E-03
PSR13006426.hg.1	NM_015087	SPG20	1.52	1.62E-02
PSR13006554.hg.1	ENST00000464744	SUPT20H	1.46	3.60E-02
PSR13001510.hg.1	ENST00000239878	UFM1	1.77	3.45E-02
PSR13001645.hg.1	NM_007187	WBP4	1.47	2.36E-02

PSR13007287.hg.1	ENST00000323076	LCP1	1.45	4.77E-02
PSR13002516.hg.1	ENST00000336617	RNASEH2B	1.53	1.69E-02
PSR13008092.hg.1	NM_016075	VPS36	1.55	4.47E-03
PSR13008384.hg.1	ENST00000377780	DIS3	1.43	1.58E-02
PSR13002996.hg.1	ENST00000377687	KLF5	1.70	3.23E-02
PSR13008644.hg.1	ENST00000360084	MYCBP2	1.51	3.08E-02
PSR13003444.hg.1	NM_005708	GPC6	1.97	3.57E-02
PSR13003717.hg.1	NM_001144072	UBAC2	1.46	2.44E-02
PSR13009333.hg.1	ENST00000340807	GPR18	1.44	2.62E-03
PSR13009345.hg.1	NM_004951	GPR183	1.51	1.60E-02
PSR14009632.hg.1	ENST00000262715	TEP1	1.41	7.97E-03
PSR14011784.hg.1	NM_182648	BAZ1A	1.48	4.75E-02
PSR14002332.hg.1	ENST00000556994	SRP54	1.54	2.75E-02
PSR14002337.hg.1	ENST00000556994	SRP54	1.50	1.52E-02
PSR14012696.hg.1	ENST00000324679	SAV1	1.40	1.03E-02
PSR14003093.hg.1	ENST00000457354	TMX1	1.42	1.81E-02
PSR14012951.hg.1	NM_014584	ERO1L	1.88	6.33E-03
PSR14012953.hg.1	NM_014584	ERO1L	1.48	3.65E-02
PSR14003513.hg.1	ENST00000416613	KTN1	1.46	4.66E-02
PSR14003701.hg.1	ENST00000216455	PSMA3	1.58	1.11E-02
PSR14003703.hg.1	ENST00000216455	PSMA3	1.49	1.97E-02
PSR14003722.hg.1	ENST00000395168	ARID4A	1.67	3.14E-02
PSR14003751.hg.1	NM_002892	ARID4A	1.47	1.60E-02
PSR14003883.hg.1	NM_014992	DAAM1	1.41	2.50E-02
PSR14003975.hg.1	ENST00000406854	PCNXL4	1.55	4.92E-03
PSR14003980.hg.1	NM_022495	PCNXL4	1.46	3.01E-03
PSR14003991.hg.1	ENST00000406854	PCNXL4	1.50	2.10E-03
PSR14004151.hg.1	ENST00000394997	HIF1A	1.42	2.58E-02
PSR14004250.hg.1	ENST00000357395	SYNE2	1.40	2.23E-02
PSR14004252.hg.1	ENST00000357395	SYNE2	1.52	4.06E-02
PSR14004270.hg.1	ENST00000357395	SYNE2	1.44	4.48E-02
PSR14004285.hg.1	ENST00000357395	SYNE2	1.56	4.08E-03
PSR14004289.hg.1	ENST00000357395	SYNE2	1.88	1.09E-02
PSR14004541.hg.1	ENST00000359118	CHURC1	1.58	3.78E-04
PSR14004542.hg.1	ENST00000359118	CHURC1	1.41	3.33E-03
PSR14004547.hg.1	ENST00000359118	CHURC1	1.56	3.03E-02
PSR14004760.hg.1	NM_004094	EIF2S1	1.54	7.84E-03
PSR14004996.hg.1	NM_001252152	SLC39A9	1.42	2.10E-04
PSR14005068.hg.1	NM_006925	SRSF5	1.57	3.90E-03
PSR14005355.hg.1	ENST00000525321	RBM25	1.43	4.74E-03
PSR14005372.hg.1	ENST00000261973	RBM25	1.49	1.91E-02
PSR14006606.hg.1	ENST00000406216	ZC3H14	1.56	4.89E-03
PSR14006614.hg.1	ENST00000406216	ZC3H14	1.48	3.11E-02
PSR14006617.hg.1	ENST00000406216	ZC3H14	1.46	2.20E-02
PSR14006618.hg.1	ENST00000557607	ZC3H14	1.48	2.71E-02
PSR14016160.hg.1	ENST00000267622	TRIP11	1.58	1.84E-02
PSR14016755.hg.1	ENST00000359933	ATG2B	1.68	1.94E-02
PSR14007524.hg.1	ENST00000392990	PAPOLA	1.42	3.42E-02
PSR14007531.hg.1	ENST00000392990	PAPOLA	1.43	5.30E-03
PSR14007532.hg.1	NM_001252007	PAPOLA	1.56	2.42E-02

PSR14007536.hg.1	ENST00000557320	PAPOLA	1.54	4.84E-03
PSR14007537.hg.1	NM_001252007	PAPOLA	1.47	1.32E-02
PSR15018432.hg.1	ENST00000344791	LYSMD4	1.51	4.64E-02
PSR15000221.hg.1	ENST00000450802	GOLGA8I	1.49	1.95E-02
PSR15001006.hg.1	ENST00000341650	GOLGA8J	1.49	1.95E-02
PSR15010785.hg.1	NM_014691	AQR	1.63	2.10E-02
PSR15001632.hg.1	ENST00000491535	FAM98B	1.47	1.03E-02
PSR15011013.hg.1	NM_003134	SRP14	1.40	2.87E-02
PSR15003046.hg.1	ENST00000260327	CTDSPL2	1.48	2.80E-02
PSR15012892.hg.1	NM_004236	COPS2	1.41	9.96E-03
PSR15012978.hg.1	NM_024837	ATP8B4	1.52	2.33E-02
PSR15003708.hg.1	NM_005154	USP8	1.44	2.11E-02
PSR15013062.hg.1	NM_017672	TRPM7	1.44	1.70E-02
PSR15013070.hg.1	NM_017672	TRPM7	1.45	4.67E-02
PSR15013076.hg.1	NM_017672	TRPM7	1.46	3.92E-02
PSR15013090.hg.1	NM_017672	TRPM7	1.46	2.13E-02
PSR15013102.hg.1	NM_017672	TRPM7	1.44	2.00E-02
PSR15003737.hg.1	NM_007347	AP4E1	1.40	6.02E-03
PSR15013986.hg.1	NM_001110	ADAM10	1.51	3.20E-02
PSR15013996.hg.1	NM_001110	ADAM10	1.48	1.88E-02
PSR15013998.hg.1	NM_001110	ADAM10	1.64	5.67E-03
PSR15014018.hg.1	NM_001110	ADAM10	1.40	3.97E-02
PSR15014172.hg.1	ENST00000267859	BNIP2	1.51	2.55E-02
PSR15014316.hg.1	ENST00000249837	VPS13C	1.78	3.51E-02
PSR15014381.hg.1	ENST00000249837	VPS13C	1.52	1.65E-02
PSR15014481.hg.1	ENST00000439025	RPS27L	1.48	1.05E-02
PSR15015085.hg.1	NM_001144823	DENND4A	1.42	2.13E-02
PSR15005182.hg.1	NM_001206804	MAP2K5	1.56	1.34E-02
PSR15005392.hg.1	ENST00000340965	PAQR5	1.41	4.64E-03
PSR15005525.hg.1	NM_001199017	LRRC49	1.44	1.75E-03
PSR15006602.hg.1	ENST00000559554	CHRNA5	1.44	2.04E-02
PSR15006603.hg.1	ENST00000559554	CHRNA5	1.64	3.81E-02
PSR15006604.hg.1	ENST00000559554	CHRNA5	1.44	1.95E-02
PSR15007223.hg.1	ENST00000286760	WHAMM	1.46	1.14E-02
PSR15007496.hg.1	NM_020778	ALPK3	1.44	4.71E-03
PSR15008581.hg.1	NM_001042572	CHD2	1.42	1.20E-02
PSR15008583.hg.1	NM_001042572	CHD2	1.69	1.17E-02
PSR15008586.hg.1	ENST00000420239	LOC100507217	1.49	5.84E-03
PSR15008787.hg.1	NM_183376	ARRDC4	1.54	2.63E-02
PSR16012479.hg.1	NM_004862	LITAF	1.45	2.64E-02
PSR16012481.hg.1	NM_004862	LITAF	1.48	3.07E-02
PSR16002511.hg.1	ENST00000329565	SNN	1.47	3.42E-02
PSR16014118.hg.1	NM_015171	XPO6	1.40	9.21E-04
PSR16015782.hg.1	NM_007006	NUDT21	1.60	4.30E-03
PSR16006569.hg.1	NM_014669	NUP93	1.43	1.77E-02
PSR16007210.hg.1	ENST00000345436	CKLF	1.46	2.00E-03
PSR16007377.hg.1	ENST00000290858	CBFB	1.44	1.30E-02
PSR16002246.hg.1	NM_001142333	RBFOX1	1.49	6.45E-03
PSR16008987.hg.1	NM_001100624	CENPN	1.44	6.96E-03
PSR17002213.hg.1	ENST00000425538	MYOCD	1.44	5.73E-04

PSR17015652.hg.1	ENST00000494511	PMP22	1.44	1.01E-02
PSR17015823.hg.1	NM_001042698	ZSWIM7	1.43	1.11E-02
PSR17015927.hg.1	ENST00000395848	NCOR1	1.51	1.35E-02
PSR17016234.hg.1	ENST00000338854	SREBF1	1.50	4.16E-03
PSR17004175.hg.1	ENST00000261716	TAOK1	1.47	3.41E-02
PSR17017816.hg.1	NM_024683	TEFM	1.43	8.71E-03
PSR17018119.hg.1	ENST00000308377	SLFN11	1.41	6.53E-03
PSR17000357.hg.1	NM_004937	CTNS	1.40	3.02E-02
PSR17018607.hg.1	NM_198836	ACACA	1.60	1.39E-03
PSR17005299.hg.1	NM_133439	TADA2A	1.41	3.67E-02
PSR17013559.hg.1	ENST00000158149	C17orf85	1.40	1.66E-02
PSR17020949.hg.1	ENST00000398389	MPP3	1.41	1.40E-03
PSR17007465.hg.1	ENST00000331493	EFCAB13	1.41	3.00E-03
PSR17008830.hg.1	ENST00000544170	LUC7L3	1.46	4.24E-02
PSR17008854.hg.1	NM_016424	LUC7L3	1.82	2.04E-04
PSR17008869.hg.1	NM_016424	LUC7L3	1.43	2.83E-02
PSR17008984.hg.1	NM_016001	UTP18	1.43	8.21E-03
PSR17000823.hg.1	ENST00000262477	RABEP1	1.52	2.49E-02
PSR17009546.hg.1	ENST00000393021	RPS6KB1	1.42	1.77E-02
PSR17023598.hg.1	NM_020748	INTS2	1.42	1.37E-02
PSR17012774.hg.1	NM_001128159	VPS53	1.42	2.14E-02
PSR17000898.hg.1	NM_019013	FAM64A	1.42	6.76E-03
PSR17024477.hg.1	NM_080283	ABCA9	1.46	5.30E-03
PSR17024479.hg.1	NM_080283	ABCA9	1.54	1.00E-04
PSR17024482.hg.1	NM_080283	ABCA9	1.56	2.61E-03
PSR17024484.hg.1	NM_080283	ABCA9	1.48	1.36E-02
PSR17024486.hg.1	NM_080283	ABCA9	1.44	4.24E-04
PSR17024492.hg.1	NM_080283	ABCA9	1.42	1.26E-03
PSR17024493.hg.1	NM_080283	ABCA9	1.43	8.98E-03
PSR17024497.hg.1	NM_080283	ABCA9	1.40	1.19E-03
PSR17024499.hg.1	NM_080283	ABCA9	1.41	2.49E-03
PSR17024502.hg.1	NM_080283	ABCA9	1.44	3.81E-02
PSR17024503.hg.1	NM_080283	ABCA9	1.41	1.98E-03
PSR17024523.hg.1	NM_080284	ABCA6	1.49	6.68E-03
PSR17024544.hg.1	NM_080284	ABCA6	1.45	2.12E-02
PSR17024548.hg.1	NM_080284	ABCA6	1.50	6.51E-03
PSR17024551.hg.1	NM_080284	ABCA6	1.76	1.56E-02
PSR17024555.hg.1	NM_080284	ABCA6	1.42	3.84E-02
PSR17024556.hg.1	NM_080284	ABCA6	1.42	9.35E-03
PSR17024566.hg.1	NM_080284	ABCA6	1.45	4.13E-02
PSR17024572.hg.1	ENST00000416101	ABCA10	1.60	7.59E-03
PSR17024573.hg.1	ENST00000416101	ABCA10	1.57	1.21E-02
PSR17024602.hg.1	ENST00000416101	ABCA10	1.40	3.90E-03
PSR17024609.hg.1	ENST00000416101	ABCA10	1.40	1.28E-02
PSR17024639.hg.1	ENST00000392676	ABCA5	1.45	1.67E-02
PSR17024641.hg.1	ENST00000392676	ABCA5	1.50	9.93E-03
PSR17024644.hg.1	ENST00000392676	ABCA5	1.56	3.24E-02
PSR17024647.hg.1	ENST00000392676	ABCA5	1.55	1.09E-02
PSR17024679.hg.1	ENST00000392676	ABCA5	1.41	3.10E-02
PSR17001962.hg.1	NM_001025579	NDEL1	1.46	1.37E-02

PSR18003980.hg.1	ENST00000327283	PTPN2	1.44	9.17E-03
PSR18000949.hg.1	NM_001145029	ANKRD30B	1.47	7.07E-03
PSR18004107.hg.1	ENST00000269214	ESCO1	1.47	1.15E-02
PSR18004114.hg.1	ENST00000269214	ESCO1	1.61	1.67E-02
PSR18001030.hg.1	ENST00000261537	MIB1	1.41	3.97E-02
PSR18003214.hg.1	ENST00000261600	THOC1	1.44	3.32E-02
PSR18000106.hg.1	ENST00000261598	SMCHD1	1.57	4.26E-02
PSR18000113.hg.1	ENST00000261598	SMCHD1	1.55	1.93E-02
PSR18003352.hg.1	NM_014646	LPIN2	1.44	2.06E-03
PSR18001494.hg.1	NM_001191324	RNF138	1.49	2.50E-03
PSR18001530.hg.1	ENST00000269197	ASXL3	1.47	7.78E-04
PSR18001691.hg.1	ENST00000423854	ELP2	1.41	8.39E-03
PSR18003554.hg.1	ENST00000284898	L3MBTL4	1.42	2.64E-03
PSR18002572.hg.1	NM_194449	PHLPP1	1.54	3.42E-03
PSR18005811.hg.1	ENST00000356424	SERPINB4	1.40	1.93E-02
PSR18005951.hg.1	ENST00000255674	RTTN	1.41	2.65E-02
PSR18000460.hg.1	NM_001204056	ANKRD12	1.54	1.97E-02
PSR18000463.hg.1	NM_001204056	ANKRD12	1.83	1.74E-02
PSR18000466.hg.1	NM_001204056	ANKRD12	1.52	4.12E-02
PSR18000470.hg.1	NM_001204056	ANKRD12	1.44	4.03E-02
PSR19002782.hg.1	NM_153464	ILF3	1.48	2.67E-02
PSR19019268.hg.1	NM_001166056	PEPD	1.47	4.85E-03
PSR19020094.hg.1	ENST00000531805	ZNF585B	1.54	4.68E-03
PSR19008499.hg.1	NM_198089	ZNF155	1.44	2.42E-02
PSR19024414.hg.1	NM_001102657	ZNF836	1.53	7.11E-03
PSR02010338.hg.1	NM_181453	GCC2	1.57	3.85E-02
PSR02010344.hg.1	NM_181453	GCC2	1.41	2.84E-02
PSR02010362.hg.1	NM_181453	GCC2	1.56	3.32E-02
PSR02010368.hg.1	NM_181453	GCC2	1.62	3.35E-02
PSR02035920.hg.1	ENST00000409573	ZC3H8	1.54	6.64E-03
PSR02010911.hg.1	ENST00000409871	ZC3H6	1.40	1.57E-02
PSR02025471.hg.1	ENST00000401753	ROCK2	1.42	4.42E-03
PSR02036776.hg.1	ENST00000322313	SFT2D3	1.40	2.63E-02
PSR02013227.hg.1	ENST00000280097	HNMT	1.41	2.98E-02
PSR02037868.hg.1	NM_001171653	ZEB2	1.47	4.18E-02
PSR02013455.hg.1	ENST00000241416	ACVR2A	1.55	4.79E-02
PSR02013697.hg.1	NM_018151	RIF1	1.62	2.31E-02
PSR02013698.hg.1	NM_018151	RIF1	1.62	7.79E-03
PSR02013699.hg.1	NM_018151	RIF1	1.46	4.78E-02
PSR02013702.hg.1	NM_018151	RIF1	1.55	6.51E-03
PSR02013705.hg.1	NM_018151	RIF1	1.50	7.64E-03
PSR02013706.hg.1	NM_018151	RIF1	1.42	2.17E-02
PSR02013707.hg.1	NM_018151	RIF1	1.61	2.92E-02
PSR02038309.hg.1	NM_001037174	ARL5A	1.40	1.27E-02
PSR02038316.hg.1	NM_177985	ARL5A	1.42	3.78E-02
PSR02013758.hg.1	NM_052905	FMNL2	1.49	7.64E-03
PSR02013807.hg.1	ENST00000326446	ARL6IP6	1.48	1.88E-02
PSR02013812.hg.1	NM_152522	ARL6IP6	1.44	2.00E-02
PSR02038804.hg.1	ENST00000554112	LY75-CD302	1.41	2.71E-02
PSR02038806.hg.1	NM_001198759	LY75-CD302	1.41	4.71E-02

PSR02038807.hg.1	NM_001198759	LY75-CD302	1.46	3.75E-02
PSR02039231.hg.1	ENST00000543549	GRB14	1.43	4.06E-02
PSR02039460.hg.1	NM_024753	TTC21B	1.41	2.34E-02
PSR02025667.hg.1	ENST00000406434	FAM49A	1.68	2.38E-03
PSR02025674.hg.1	ENST00000406434	FAM49A	1.42	1.79E-02
PSR02025680.hg.1	ENST00000406434	FAM49A	1.45	1.45E-02
PSR02039979.hg.1	ENST00000434911	TLK1	1.48	3.62E-03
PSR02015434.hg.1	NM_007023	RAPGEF4	1.40	2.60E-02
PSR02015443.hg.1	NM_007023	RAPGEF4	1.47	1.50E-03
PSR02015460.hg.1	ENST00000431503	ZAK	1.48	3.08E-03
PSR02015508.hg.1	ENST00000306721	CDCA7	1.42	8.94E-03
PSR02040206.hg.1	ENST00000284719	OLA1	1.43	2.11E-02
PSR02015849.hg.1	ENST00000409888	AGPS	1.71	8.07E-03
PSR02025733.hg.1	NM_001142286	SMC6	1.51	3.09E-02
PSR02025739.hg.1	NM_001142286	SMC6	1.49	2.41E-02
PSR02041415.hg.1	NM_020943	CWC22	1.65	1.64E-02
PSR02016298.hg.1	ENST00000264065	DNAJC10	1.41	4.82E-03
PSR02016321.hg.1	ENST00000264065	DNAJC10	1.44	1.51E-03
PSR02016374.hg.1	ENST00000541912	NUP35	1.40	1.12E-02
PSR02016815.hg.1	ENST00000432292	PMS1	1.48	3.37E-02
PSR02017013.hg.1	ENST00000320717	GLS	1.47	4.36E-02
PSR02017146.hg.1	NM_001254736	NABP1	1.50	2.53E-02
PSR02017457.hg.1	NM_153689	C2orf69	1.58	2.44E-02
PSR02018084.hg.1	NM_015934	NOP58	1.60	4.92E-02
PSR02018085.hg.1	NM_015934	NOP58	1.47	6.25E-03
PSR02018095.hg.1	NM_015934	NOP58	1.45	8.72E-03
PSR02018099.hg.1	NM_015934	NOP58	1.42	1.44E-02
PSR02018100.hg.1	NM_015934	NOP58	1.56	3.94E-02
PSR02018101.hg.1	NM_015934	NOP58	1.48	1.04E-02
PSR02018148.hg.1	NM_001204	BMPR2	1.45	1.27E-02
PSR02043325.hg.1	ENST00000418208	ICA1L	1.51	1.03E-02
PSR02018321.hg.1	ENST00000356079	CYP20A1	1.44	9.76E-03
PSR02018332.hg.1	ENST00000356079	CYP20A1	1.58	3.48E-02
PSR02018846.hg.1	NM_134442	CREB1	1.46	3.91E-02
PSR02018867.hg.1	ENST00000295414	CCNYL1	1.42	3.53E-02
PSR02043993.hg.1	NM_001079526	IKZF2	1.40	8.14E-03
PSR02044016.hg.1	ENST00000260947	BARD1	1.43	2.15E-03
PSR02019375.hg.1	ENST00000540518	ATIC	1.53	4.09E-02
PSR02020015.hg.1	ENST00000273064	RQCD1	1.44	7.45E-03
PSR02021574.hg.1	NM_001080391	SP100	1.54	1.97E-02
PSR02021588.hg.1	NM_001206703	SP100	1.56	3.95E-02
PSR02023022.hg.1	NM_198189	COPS8	1.60	3.40E-02
PSR02023025.hg.1	ENST00000354371	COPS8	1.59	1.56E-02
PSR02023135.hg.1	NM_001137550	LRRFIP1	1.41	3.72E-02
PSR02026156.hg.1	ENST00000238789	ATAD2B	1.45	5.96E-03
PSR02024082.hg.1	ENST00000264042	FARP2	1.42	1.69E-03
PSR02001494.hg.1	ENST00000407625	FAM228B	1.43	1.38E-02
PSR02027723.hg.1	NM_015955	MEMO1	1.60	2.17E-02
PSR02027904.hg.1	NM_003162	STRN	1.47	3.34E-02
PSR02028231.hg.1	ENST00000449105	HNRNPLL	1.52	3.03E-02

PSR02028246.hg.1	ENST00000449105	HNRNPLL	1.40	3.53E-02
PSR02004008.hg.1	ENST00000282406	PLEKHH2	1.42	3.86E-02
PSR02004094.hg.1	NM_001033557	PPM1B	1.69	1.78E-02
PSR02004095.hg.1	ENST00000409432	PPM1B	1.46	1.20E-02
PSR02004097.hg.1	ENST00000378551	PPM1B	1.49	6.11E-03
PSR02004098.hg.1	ENST00000378551	PPM1B	1.41	3.04E-02
PSR02028894.hg.1	NM_001171617	PREPL	1.47	3.00E-03
PSR02028929.hg.1	NM_006036	PREPL	1.45	2.70E-02
PSR02029096.hg.1	ENST00000409105	MCFD2	1.96	1.15E-02
PSR02029211.hg.1	NM_025133	FBXO11	1.45	1.73E-02
PSR02004981.hg.1	ENST00000339012	CCDC104	1.57	2.73E-03
PSR02005295.hg.1	ENST00000357022	AHSA2	1.55	8.23E-03
PSR02030521.hg.1	NM_001005739	VPS54	1.63	1.37E-04
PSR02030532.hg.1	NM_001005739	VPS54	1.42	6.95E-03
PSR02030534.hg.1	NM_001005739	VPS54	1.43	2.71E-02
PSR02030540.hg.1	NM_001005739	VPS54	1.42	2.80E-02
PSR02005919.hg.1	NM_020143	PNO1	1.55	1.82E-04
PSR02031163.hg.1	ENST00000282574	TIA1	2.13	1.57E-02
PSR02031164.hg.1	ENST00000282574	TIA1	1.42	1.80E-02
PSR02031360.hg.1	NM_001004311	FIGLA	1.43	6.61E-03
PSR02006504.hg.1	ENST00000264447	ZNF638-IT1	1.41	1.22E-02
PSR02006527.hg.1	ENST00000264447	ZNF638-IT1	1.48	3.42E-02
PSR02006535.hg.1	ENST00000264447	ZNF638-IT1	1.62	7.34E-03
PSR02006988.hg.1	NM_006636	MTHFD2	1.52	8.34E-03
PSR02032998.hg.1	NM_001198952	RNF103	1.41	4.97E-02
PSR02025092.hg.1	ENST00000473731	KIDINS220	1.77	1.26E-02
PSR02025273.hg.1	ENST00000238081	YWHAQ	1.48	1.64E-02
PSR02009094.hg.1	NM_001164315	ANKRD36	1.45	4.85E-02
PSR02034505.hg.1	NM_015348	TMEM131	1.59	3.60E-02
PSR02009423.hg.1	ENST00000409016	INPP4A	1.42	2.37E-02
PSR02034567.hg.1	NM_001160154	MGAT4A	1.43	1.64E-02
PSR02034584.hg.1	ENST00000264968	MGAT4A	1.41	4.30E-02
PSR02009479.hg.1	NM_145197	LIPT1	1.53	8.15E-03
PSR20009033.hg.1	NM_016649	ESF1	1.43	1.79E-02
PSR20009043.hg.1	NM_016649	ESF1	1.58	8.81E-03
PSR20009047.hg.1	NM_016649	ESF1	1.51	2.07E-02
PSR20009074.hg.1	ENST00000378072	SEL1L2	1.46	4.06E-02
PSR20009101.hg.1	ENST00000341420	FLRT3	1.50	3.91E-02
PSR20009104.hg.1	ENST00000341420	FLRT3	1.78	2.36E-02
PSR20009106.hg.1	NM_198391	FLRT3	1.61	1.66E-02
PSR20009107.hg.1	ENST00000341420	FLRT3	1.44	1.49E-02
PSR20001736.hg.1	NM_181528	NAA20	1.41	7.07E-03
PSR20001773.hg.1	ENST00000377306	C20orf26	1.44	1.35E-02
PSR20001777.hg.1	ENST00000389656	C20orf26	1.65	3.36E-02
PSR20009480.hg.1	ENST00000202677	RALGAPA2	1.59	1.40E-02
PSR20001968.hg.1	ENST00000377051	GZF1	1.44	1.73E-02
PSR20002909.hg.1	ENST00000344201	CBFA2T2	1.41	2.03E-02
PSR20011275.hg.1	ENST00000262878	SAMHD1	1.40	1.74E-02
PSR20004424.hg.1	NM_006275	SRSF6	1.49	1.53E-02
PSR20011778.hg.1	ENST00000372970	OSER1	1.42	7.99E-03

PSR20011780.hg.1	ENST00000372970	OSER1	1.85	9.69E-03
PSR20004873.hg.1	ENST00000396731	STK4	1.50	3.25E-02
PSR20011946.hg.1	NM_003064	SLPI	1.60	1.37E-02
PSR20005944.hg.1	NM_001033521	CSTF1	1.41	1.33E-02
PSR20008702.hg.1	ENST00000379019	GPCPD1	1.47	2.35E-02
PSR20013543.hg.1	NM_001256403	SLMO2	1.55	6.55E-03
PSR21000229.hg.1	ENST00000306618	CXADR	1.54	3.11E-02
PSR21003980.hg.1	ENST00000389194	LTN1	1.46	9.78E-03
PSR21004013.hg.1	ENST00000389194	LTN1	1.47	3.13E-02
PSR21000532.hg.1	ENST00000535828	USP16	1.50	1.69E-02
PSR21000533.hg.1	ENST00000535828	USP16	1.44	1.18E-02
PSR21000570.hg.1	ENST00000399934	MAP3K7CL	1.43	3.25E-02
PSR21000576.hg.1	ENST00000399947	MAP3K7CL	1.67	3.38E-02
PSR21000577.hg.1	ENST00000399947	MAP3K7CL	1.47	1.75E-02
PSR21000578.hg.1	ENST00000399947	MAP3K7CL	1.65	1.90E-02
PSR21000579.hg.1	ENST00000399947	MAP3K7CL	1.52	1.43E-02
PSR21000612.hg.1	ENST00000286800	GRIK1-AS2	1.46	4.86E-02
PSR21000615.hg.1	ENST00000286800	GRIK1-AS2	1.47	3.36E-02
PSR21004512.hg.1	NM_001160302	SYNJ1	1.42	4.03E-03
PSR21004531.hg.1	NM_016631	PAXBP1	1.43	9.27E-03
PSR21004540.hg.1	ENST00000290178	PAXBP1	1.43	8.26E-03
PSR21004544.hg.1	ENST00000290178	PAXBP1	1.68	4.91E-04
PSR21000866.hg.1	ENST00000404220	IFNAR2	1.68	1.79E-02
PSR21004668.hg.1	ENST00000381839	GART	1.41	2.14E-02
PSR21004674.hg.1	ENST00000543717	GART	1.43	3.01E-03
PSR21005172.hg.1	ENST00000309117	DSCR3	1.42	1.73E-02
PSR21001528.hg.1	ENST00000451934	DYRK1A	1.47	1.85E-02
PSR21001548.hg.1	NM_130438	DYRK1A	1.42	2.22E-02
PSR21005332.hg.1	ENST00000380900	PSMG1	1.57	8.62E-03
PSR21005333.hg.1	ENST00000380900	PSMG1	1.41	3.77E-02
PSR21005340.hg.1	ENST00000380900	PSMG1	1.45	6.97E-03
PSR21006118.hg.1	ENST00000270162	SIK1	1.60	4.54E-02
PSR21006362.hg.1	NM_182688	UBE2G2	1.42	1.79E-02
PSR21002848.hg.1	NM_015834	ADARB1	1.42	6.25E-03
PSR22000258.hg.1	NM_017414	USP18	1.41	1.98E-02
PSR22009515.hg.1	ENST00000454608	USP41	1.45	6.38E-03
PSR22012281.hg.1	NM_001082577	RBFOX2	2.05	1.56E-02
PSR22013866.hg.1	NM_003932	ST13	1.60	2.83E-02
PSR22006574.hg.1	NM_001469	XRCC6	1.45	1.60E-02
PSR03001199.hg.1	NM_001018115	FANCD2	1.41	5.16E-03
PSR03029323.hg.1	ENST00000405772	CBLB	1.63	2.29E-03
PSR03009971.hg.1	ENST00000325805	BBX	1.41	1.31E-02
PSR03029393.hg.1	NM_198793	CD47	1.46	5.54E-03
PSR03010466.hg.1	NM_014170	GTPBP8	1.67	1.68E-02
PSR03029845.hg.1	ENST00000314400	C3orf17	1.42	2.67E-02
PSR03029925.hg.1	NM_001164496	WDR52	1.43	1.16E-02
PSR03030298.hg.1	ENST00000393765	B4GALT4	1.45	4.31E-02
PSR03020236.hg.1	ENST00000287814	TIMP4	1.41	2.65E-02
PSR03020249.hg.1	NM_002880	RAF1	1.50	2.68E-02
PSR03032189.hg.1	ENST00000426664	TMCC1	1.41	2.36E-02

PSR03012922.hg.1	NM_198329	UBA5	1.47	4.00E-02
PSR03032478.hg.1	ENST00000337331	NPHP3	1.43	4.43E-02
PSR03013048.hg.1	ENST00000431519	CDV3	1.73	1.35E-02
PSR03032832.hg.1	NM_005862	STAG1	1.66	8.88E-03
PSR03032833.hg.1	NM_005862	STAG1	1.46	1.15E-03
PSR03032860.hg.1	NM_005862	STAG1	1.52	8.31E-03
PSR03033398.hg.1	ENST00000264951	XRN1	1.46	8.97E-03
PSR03014174.hg.1	NM_001080415	U2SURP	1.50	1.42E-02
PSR03033605.hg.1	NM_173653	SLC9A9	1.76	5.27E-03
PSR03033615.hg.1	NM_173653	SLC9A9	1.44	2.74E-02
PSR03014419.hg.1	ENST00000345003	GYG1	1.55	2.92E-03
PSR03034159.hg.1	ENST00000461930	PFN2	1.92	9.64E-03
PSR03014578.hg.1	NM_014779	TSC22D2	1.41	2.62E-02
PSR03020582.hg.1	ENST00000253686	MRPS25	1.52	5.95E-03
PSR03034337.hg.1	NM_001081455	P2RY14	1.51	4.05E-04
PSR03015540.hg.1	ENST00000357388	SMC4	1.44	1.02E-02
PSR03015542.hg.1	ENST00000469762	SMC4	1.48	1.63E-02
PSR03015562.hg.1	ENST00000357388	SMC4	1.68	1.44E-02
PSR03015582.hg.1	ENST00000357388	SMC4	1.46	6.21E-03
PSR03015585.hg.1	ENST00000357388	SMC4	1.42	2.11E-03
PSR03015587.hg.1	ENST00000357388	SMC4	1.49	9.17E-03
PSR03015590.hg.1	ENST00000357388	SMC4	1.45	6.16E-03
PSR03015591.hg.1	ENST00000357388	SMC4	1.45	4.37E-02
PSR03015593.hg.1	ENST00000357388	SMC4	1.44	8.35E-03
PSR03015600.hg.1	ENST00000357388	SMC4	1.44	2.93E-02
PSR03015604.hg.1	ENST00000357388	SMC4	1.48	7.19E-03
PSR03002129.hg.1	ENST00000339732	GALNT15	1.40	1.17E-02
PSR03002131.hg.1	ENST00000339732	GALNT15	1.46	4.77E-03
PSR03035314.hg.1	ENST00000453925	WDR49	1.47	1.24E-04
PSR03035771.hg.1	ENST00000340989	PLD1	1.45	1.64E-03
PSR03016130.hg.1	NM_022763	FNDC3B	1.42	3.04E-03
PSR03016235.hg.1	ENST00000545397	NLGN1	1.45	1.54E-02
PSR03016401.hg.1	ENST00000326361	ZNF639	1.55	1.90E-02
PSR03016482.hg.1	NM_177989	ACTL6A	1.46	1.39E-02
PSR03016708.hg.1	ENST00000468861	FXR1	1.43	4.04E-02
PSR03016812.hg.1	ENST00000323116	ATP11B	1.48	7.02E-03
PSR03016829.hg.1	NM_014616	ATP11B	1.44	1.37E-02
PSR03016837.hg.1	NM_014616	ATP11B	1.43	1.70E-02
PSR03036334.hg.1	NM_020166	MCCC1	1.61	4.61E-02
PSR03016889.hg.1	ENST00000465010	B3GNT5	1.57	4.65E-02
PSR03036416.hg.1	ENST00000414362	MCF2L2	1.62	6.52E-03
PSR03036906.hg.1	ENST00000537818	ETV5	1.46	5.51E-03
PSR03037221.hg.1	NM_001130845	BCL6	1.49	5.79E-03
PSR03037222.hg.1	NM_001130845	BCL6	1.55	2.85E-03
PSR03018453.hg.1	NM_198485	TPRG1	1.74	2.29E-02
PSR03037291.hg.1	ENST00000295522	CLDN1	1.42	4.61E-02
PSR03018688.hg.1	NM_015560	OPA1	1.45	1.95E-02
PSR03037818.hg.1	ENST00000326793	ACAP2	1.47	4.64E-02
PSR03037877.hg.1	NM_001647	APOD	1.85	1.43E-03
PSR03018999.hg.1	ENST00000314118	PIGX	1.45	2.62E-02

PSR03019038.hg.1	ENST00000323460	SENP5	1.54	1.09E-02
PSR03038425.hg.1	ENST00000450955	DLG1	1.41	1.33E-02
PSR03019102.hg.1	NM_001011537	FYTTD1	1.44	1.21E-02
PSR03019132.hg.1	ENST00000441090	LRCH3	1.60	9.15E-03
PSR03021343.hg.1	NM_001068	TOP2B	1.49	1.74E-02
PSR03002719.hg.1	ENST00000359013	TGFBR2	1.43	4.77E-02
PSR03002740.hg.1	ENST00000295770	STT3B	1.44	2.99E-02
PSR03000204.hg.1	ENST00000280591	TRNT1	1.65	1.99E-02
PSR03002870.hg.1	ENST00000538368	CNOT10	1.48	6.83E-03
PSR03003058.hg.1	ENST00000307296	PDCD6IP	1.54	4.88E-02
PSR03003065.hg.1	ENST00000307296	PDCD6IP	1.49	3.42E-03
PSR03003066.hg.1	ENST00000307296	PDCD6IP	1.53	1.75E-02
PSR03003072.hg.1	ENST00000307296	PDCD6IP	1.51	1.50E-02
PSR03003084.hg.1	ENST00000307296	PDCD6IP	1.45	2.42E-04
PSR03003105.hg.1	ENST00000307296	PDCD6IP	1.53	2.59E-02
PSR03003107.hg.1	ENST00000307296	PDCD6IP	1.53	8.22E-03
PSR03022007.hg.1	NM_014831	TRANK1	1.54	5.63E-03
PSR03000029.hg.1	NM_001253388	CHL1	1.44	1.76E-02
PSR03004820.hg.1	ENST00000383745	ZNF197	1.47	2.26E-02
PSR03022930.hg.1	NM_020696	KIAA1143	1.40	1.73E-02
PSR03023055.hg.1	ENST00000296135	LZTFL1	1.41	3.15E-02
PSR03005534.hg.1	ENST00000446256	DHX30	1.70	1.79E-02
PSR03005944.hg.1	ENST00000451634	CCDC36	1.69	3.45E-02
PSR03026410.hg.1	ENST00000394830	PBRM1	1.52	3.77E-02
PSR03007513.hg.1	NM_206826	GNL3	1.41	3.22E-03
PSR03026786.hg.1	ENST00000294241	DCP1A	1.45	1.70E-03
PSR03026787.hg.1	ENST00000294241	DCP1A	1.44	3.50E-02
PSR03007925.hg.1	ENST00000394672	CCDC66	1.41	1.23E-02
PSR03008047.hg.1	ENST00000383718	SLMAP	1.65	6.94E-04
PSR03008363.hg.1	ENST00000474889	PTPRG	1.46	1.77E-03
PSR03008629.hg.1	NM_032505	KBTBD8	1.53	2.59E-02
PSR03028008.hg.1	ENST00000543976	TMF1	1.49	2.62E-02
PSR03028020.hg.1	ENST00000543976	TMF1	1.42	4.18E-02
PSR03028054.hg.1	ENST00000415609	UBA3	1.45	4.42E-02
PSR03008738.hg.1	ENST00000394351	MITF	1.41	4.80E-02
PSR03009128.hg.1	NM_001174150	ARL13B	1.41	1.75E-02
PSR03028744.hg.1	NM_032778	MINA	1.45	3.79E-02
PSR03028745.hg.1	NM_032778	MINA	1.44	1.25E-02
PSR04019651.hg.1	NM_000667	ADH1A	1.41	1.31E-02
PSR04019657.hg.1	NM_000667	ADH1A	1.42	1.44E-02
PSR04019674.hg.1	ENST00000305046	ADH1B	1.74	3.81E-03
PSR04019675.hg.1	ENST00000305046	ADH1B	1.62	1.09E-02
PSR04019676.hg.1	ENST00000305046	ADH1B	1.52	1.33E-02
PSR04019677.hg.1	ENST00000305046	ADH1B	1.78	2.72E-03
PSR04019678.hg.1	ENST00000305046	ADH1B	1.50	1.09E-02
PSR04019679.hg.1	ENST00000305046	ADH1B	1.41	2.26E-02
PSR04019684.hg.1	ENST00000305046	ADH1B	1.48	1.68E-02
PSR04019685.hg.1	ENST00000305046	ADH1B	1.45	2.40E-02
PSR04019688.hg.1	ENST00000305046	ADH1B	1.44	2.73E-02
PSR04019696.hg.1	NM_000669	ADH1C	1.48	5.86E-03

PSR04019701.hg.1	NM_000669	ADH1C	1.41	1.85E-02
PSR04019704.hg.1	NM_000669	ADH1C	1.44	1.75E-02
PSR04019948.hg.1	NM_001135146	SLC39A8	1.45	1.84E-03
PSR04008209.hg.1	ENST00000399100	SEC24B	1.42	4.23E-02
PSR04020847.hg.1	ENST00000394634	CFI	1.53	8.22E-03
PSR04008443.hg.1	NM_025144	ALPK1	1.55	9.39E-03
PSR04008445.hg.1	NM_025144	ALPK1	1.46	2.02E-02
PSR04008464.hg.1	NM_025144	ALPK1	1.42	2.25E-03
PSR04021044.hg.1	NM_172115	CAMK2D	1.57	1.44E-02
PSR04008746.hg.1	ENST00000388822	METTL14	1.60	3.47E-02
PSR04008752.hg.1	ENST00000388822	METTL14	1.40	2.01E-02
PSR04008801.hg.1	NM_016599	MYOZ2	1.54	3.98E-02
PSR04021481.hg.1	ENST00000296511	ANXA5	1.58	1.94E-02
PSR04009302.hg.1	ENST00000296464	HSPA4L	1.45	2.21E-02
PSR04021690.hg.1	ENST00000296468	MFSD8	1.52	1.65E-02
PSR04021790.hg.1	NM_144643	SCLT1	1.44	4.35E-02
PSR04014284.hg.1	ENST00000288723	RAB28	1.56	6.71E-03
PSR04009688.hg.1	NM_057175	NAA15	1.46	2.77E-03
PSR04009691.hg.1	NM_057175	NAA15	1.84	1.20E-02
PSR04009778.hg.1	ENST00000506322	SCOC	1.54	1.59E-02
PSR04022300.hg.1	ENST00000506217	INPP4B	1.54	2.23E-02
PSR04022305.hg.1	ENST00000506217	INPP4B	1.43	2.00E-02
PSR04022316.hg.1	ENST00000507861	INPP4B	1.46	3.47E-02
PSR04022319.hg.1	ENST00000507861	INPP4B	1.41	2.22E-02
PSR04022976.hg.1	ENST00000393956	FBXW7	1.46	2.97E-02
PSR04014425.hg.1	NM_001193535	FBXL5	1.65	2.20E-02
PSR04023665.hg.1	NM_017631	DDX60	1.40	2.01E-02
PSR04023668.hg.1	NM_017631	DDX60	1.49	2.52E-02
PSR04023718.hg.1	NM_001012967	DDX60L	1.78	5.69E-03
PSR04023719.hg.1	NM_001012967	DDX60L	1.40	2.75E-02
PSR04011542.hg.1	ENST00000335742	PALLD	1.51	1.25E-02
PSR04011544.hg.1	ENST00000335742	PALLD	1.43	3.21E-02
PSR04011546.hg.1	ENST00000335742	PALLD	1.42	2.26E-02
PSR04011554.hg.1	ENST00000335742	PALLD	1.40	2.31E-02
PSR04011560.hg.1	ENST00000335742	PALLD	1.51	1.24E-02
PSR04011562.hg.1	ENST00000333488	PALLD	1.52	4.73E-02
PSR04011596.hg.1	ENST00000335742	PALLD	1.58	2.60E-02
PSR04023920.hg.1	ENST00000393381	C4orf27	1.46	4.47E-02
PSR04023982.hg.1	ENST00000353187	AADAT	1.50	2.72E-02
PSR04012140.hg.1	ENST00000504169	CDKN2AIP	1.52	4.76E-02
PSR04012178.hg.1	NM_199053	TRAPPC11	1.42	1.94E-02
PSR04012185.hg.1	NM_199053	TRAPPC11	1.44	4.46E-02
PSR04012371.hg.1	ENST00000335174	ANKRD37	1.45	3.07E-02
PSR04014826.hg.1	ENST00000508133	GPR125	1.49	3.49E-02
PSR04014835.hg.1	ENST00000508133	GPR125	1.53	2.22E-03
PSR04002905.hg.1	NM_005349	RBPJ	1.49	1.03E-02
PSR04001103.hg.1	NM_002111	HTT	1.46	9.20E-03
PSR04003358.hg.1	NM_025132	WDR19	1.50	4.54E-03
PSR04015595.hg.1	ENST00000503396	PDS5A	1.45	1.26E-02
PSR04016193.hg.1	ENST00000537810	FRYL	1.42	2.08E-02

PSR04016195.hg.1	ENST00000537810	FRYL	1.44	4.01E-03
PSR04016245.hg.1	ENST00000507711	FRYL	1.69	1.99E-02
PSR04016262.hg.1	ENST00000507711	FRYL	1.42	2.49E-02
PSR04016475.hg.1	ENST00000263921	CHIC2	1.75	4.84E-02
PSR04004530.hg.1	ENST00000506198	TMEM165	1.61	4.32E-02
PSR04016582.hg.1	ENST00000381322	CLOCK	1.83	3.66E-02
PSR04017001.hg.1	ENST00000322244	UBA6	1.44	4.77E-02
PSR04017314.hg.1	ENST00000254801	IGJ	1.50	1.10E-02
PSR04005691.hg.1	ENST00000331145	MTHFD2L	1.44	4.14E-02
PSR04005804.hg.1	ENST00000502620	THAP6	1.46	2.02E-02
PSR04005810.hg.1	ENST00000311638	THAP6	1.43	3.76E-02
PSR04005850.hg.1	ENST00000514213	USO1	1.41	3.85E-02
PSR04017843.hg.1	NM_018115	SDAD1	1.44	8.11E-03
PSR04005913.hg.1	ENST00000355810	ART3	1.43	7.77E-03
PSR04005927.hg.1	ENST00000355810	ART3	1.61	3.68E-02
PSR04005932.hg.1	ENST00000355810	ART3	1.56	5.51E-03
PSR04006482.hg.1	NM_001201	BMP3	1.40	2.18E-02
PSR04018264.hg.1	ENST00000335927	RASGEF1B	1.45	2.26E-02
PSR04018266.hg.1	ENST00000335927	RASGEF1B	1.49	1.06E-02
PSR04018878.hg.1	NM_014991	WDFY3	1.49	2.71E-02
PSR04019037.hg.1	ENST00000273963	KLHL8	1.40	5.25E-03
PSR04006933.hg.1	NM_001251830	SPP1	1.46	4.68E-02
PSR04006934.hg.1	NM_001251830	SPP1	1.53	3.71E-02
PSR04019336.hg.1	ENST00000345009	SNCA	1.58	1.78E-02
PSR04007330.hg.1	ENST00000512274	PDLIM5	1.42	3.17E-02
PSR05022361.hg.1	ENST00000508629	GIN1	1.43	3.97E-02
PSR05022374.hg.1	ENST00000508629	GIN1	1.40	1.75E-02
PSR05007072.hg.1	ENST00000438717	FER	1.44	2.28E-02
PSR05007530.hg.1	NM_022828	YTHDC2	1.45	5.44E-03
PSR05007618.hg.1	NM_001284	AP3S1	1.45	2.08E-02
PSR05023641.hg.1	ENST00000507093	RAPGEF6	1.45	2.98E-02
PSR05008995.hg.1	ENST00000304858	HSPA4	1.44	1.08E-02
PSR05008999.hg.1	ENST00000304858	HSPA4	1.55	4.54E-03
PSR05024312.hg.1	ENST00000481195	PPP2CA	1.42	9.27E-03
PSR05024313.hg.1	ENST00000481195	PPP2CA	1.47	9.68E-03
PSR05024314.hg.1	ENST00000481195	PPP2CA	1.43	3.10E-02
PSR05009135.hg.1	NM_003337	UBE2B	1.43	1.54E-02
PSR05009217.hg.1	NM_021982	SEC24A	1.48	3.87E-02
PSR05009326.hg.1	ENST00000546290	TXNDC15	1.93	4.07E-02
PSR05025273.hg.1	ENST00000302060	DNAJC18	1.42	1.87E-02
PSR05011385.hg.1	NM_001112724	STK32A	1.48	2.85E-04
PSR05012132.hg.1	ENST00000429484	SLC36A1	1.73	2.89E-02
PSR05012808.hg.1	ENST00000296786	UBLCP1	1.48	1.79E-02
PSR05012809.hg.1	ENST00000296786	UBLCP1	1.40	3.63E-02
PSR05016878.hg.1	NM_019000	FAM134B	1.53	9.34E-03
PSR05016879.hg.1	NM_019000	FAM134B	1.43	3.92E-02
PSR05016890.hg.1	ENST00000399793	FAM134B	1.43	2.80E-02
PSR05016892.hg.1	NM_019000	FAM134B	1.40	4.62E-02
PSR05028223.hg.1	ENST00000046794	LCP2	1.40	2.93E-02
PSR05015215.hg.1	ENST00000393438	RUFY1	1.65	2.95E-03

PSR05015218.hg.1	ENST00000393438	RUFY1	1.50	3.26E-02
PSR05029724.hg.1	ENST00000356731	HNRNPH1	1.40	6.07E-03
PSR05029732.hg.1	ENST00000356731	HNRNPH1	1.46	4.95E-02
PSR05029744.hg.1	ENST00000442819	HNRNPH1	1.66	4.99E-03
PSR05029798.hg.1	ENST00000442819	HNRNPH1	1.58	1.31E-02
PSR05017265.hg.1	ENST00000442743	DROSHA	1.44	3.19E-02
PSR05017673.hg.1	NM_000949	PRLR	1.55	2.66E-03
PSR05001721.hg.1	ENST00000356031	SPEF2	1.40	1.49E-02
PSR05001916.hg.1	NM_133433	NIPBL	1.53	4.22E-03
PSR05001919.hg.1	NM_133433	NIPBL	1.46	8.08E-03
PSR05001940.hg.1	NM_133433	NIPBL	1.52	3.42E-02
PSR05001949.hg.1	ENST00000282516	NIPBL	1.45	1.25E-02
PSR05001950.hg.1	ENST00000282516	NIPBL	1.46	2.43E-03
PSR05017989.hg.1	NM_199231	GDNF	2.14	2.94E-02
PSR05017995.hg.1	NM_199231	GDNF	1.59	3.86E-02
PSR05018145.hg.1	NM_199335	FYB	1.59	2.53E-02
PSR05018249.hg.1	NM_001343	DAB2	1.46	3.12E-02
PSR05018612.hg.1	ENST00000512085	C5orf28	1.50	2.58E-02
PSR05018677.hg.1	NM_182789	PAIP1	1.41	4.38E-02
PSR05018784.hg.1	ENST00000303221	EMB	1.42	4.06E-02
PSR05002731.hg.1	ENST00000256759	FST	1.52	5.14E-03
PSR05002738.hg.1	ENST00000256759	FST	1.76	1.55E-03
PSR05002742.hg.1	ENST00000256759	FST	1.71	1.26E-03
PSR05002866.hg.1	ENST00000230640	SKIV2L2	1.54	3.25E-03
PSR05002868.hg.1	ENST00000230640	SKIV2L2	1.56	1.42E-02
PSR05019068.hg.1	ENST00000515629	SLC38A9	1.41	2.02E-02
PSR05019357.hg.1	ENST00000317118	PDE4D	1.66	1.94E-03
PSR05003391.hg.1	ENST00000381070	CWC27	1.42	4.67E-02
PSR05003787.hg.1	NM_181523	PIK3R1	1.53	2.07E-02
PSR05003834.hg.1	NM_181504	PIK3R1	1.48	1.73E-02
PSR05003851.hg.1	NM_024055	SLC30A5	1.46	2.00E-02
PSR05020059.hg.1	ENST00000274400	GTF2H2	1.48	1.19E-02
PSR05004486.hg.1	ENST00000358731	BDP1	1.44	3.81E-02
PSR05004689.hg.1	ENST00000506351	TNPO1	1.47	5.56E-03
PSR05004711.hg.1	ENST00000341845	FCHO2	1.56	2.28E-02
PSR05004744.hg.1	NM_001146032	FCHO2	1.56	2.51E-02
PSR05004747.hg.1	NM_001146032	FCHO2	1.41	1.16E-02
PSR05004828.hg.1	ENST00000296792	UTP15	1.48	1.48E-02
PSR05004829.hg.1	ENST00000296792	UTP15	1.44	3.06E-02
PSR05004840.hg.1	ENST00000296792	UTP15	1.51	7.03E-03
PSR05004943.hg.1	NM_000521	HEXB	1.50	2.56E-03
PSR05004945.hg.1	NM_000521	HEXB	1.40	1.00E-02
PSR05004946.hg.1	NM_000521	HEXB	1.40	2.89E-02
PSR05004948.hg.1	NM_000521	HEXB	1.42	2.49E-02
PSR05004975.hg.1	NM_014886	NSA2	1.61	7.17E-03
PSR05005070.hg.1	ENST00000380481	POLK	1.41	2.73E-02
PSR05005157.hg.1	ENST00000379730	IQGAP2	1.63	2.24E-03
PSR05005163.hg.1	ENST00000379730	IQGAP2	1.49	4.03E-02
PSR05005164.hg.1	ENST00000379730	IQGAP2	1.52	2.55E-02
PSR05005180.hg.1	ENST00000379730	IQGAP2	1.42	1.25E-02

PSR05005351.hg.1	NM_001029854	PDE8B	1.41	4.90E-02
PSR05020742.hg.1	ENST00000519295	AP3B1	1.67	8.32E-03
PSR05020743.hg.1	ENST00000519295	AP3B1	1.40	9.49E-03
PSR05016463.hg.1	ENST00000264669	FASTKD3	1.52	1.27E-02
PSR05005649.hg.1	NM_001105251	ZFYVE16	1.43	3.42E-02
PSR05021085.hg.1	NM_012446	SSBP2	1.44	3.67E-02
PSR05005843.hg.1	ENST00000458350	ATG10	1.47	3.31E-02
PSR05021305.hg.1	ENST00000504878	CCNH	1.41	2.21E-02
PSR05021483.hg.1	NM_001193347	MEF2C	1.44	3.81E-02
PSR05006405.hg.1	ENST00000265140	ANKRD32	1.58	8.79E-04
PSR05022135.hg.1	ENST00000283109	RIOK2	1.50	1.43E-02
PSR05022138.hg.1	ENST00000283109	RIOK2	1.54	2.27E-03
PSR05022177.hg.1	ENST00000284049	CHD1	1.58	1.99E-03
PSR06024363.hg.1	ENST00000369208	SIM1	1.52	4.64E-02
PSR06000674.hg.1	NM_145649	GCNT2	1.46	4.19E-02
PSR06010473.hg.1	NM_032194	RPF2	1.44	4.31E-02
PSR06015248.hg.1	ENST00000379433	NEDD9	1.61	5.26E-03
PSR06025313.hg.1	ENST00000368658	TUBE1	1.51	6.24E-03
PSR06025485.hg.1	ENST00000368632	HDAC2	1.40	1.38E-02
PSR06010745.hg.1	NM_001080976	DSE	1.41	2.62E-03
PSR06010798.hg.1	NM_001007464	RWDD1	1.44	1.42E-02
PSR06025598.hg.1	ENST00000368576	ZUFSP	1.46	9.21E-03
PSR06025610.hg.1	ENST00000530250	GPRC6A	1.54	1.06E-02
PSR06010915.hg.1	ENST00000368494	NUS1	1.53	3.96E-03
PSR06010920.hg.1	ENST00000368494	NUS1	1.52	1.43E-02
PSR06010923.hg.1	ENST00000368494	NUS1	1.47	2.58E-03
PSR06025825.hg.1	NM_005907	MAN1A1	1.57	1.95E-02
PSR06025826.hg.1	NM_005907	MAN1A1	1.45	2.65E-02
PSR06011358.hg.1	NM_001242846	RNF146	1.47	4.64E-02
PSR06026835.hg.1	ENST00000367822	HBS1L	1.61	3.98E-02
PSR06026877.hg.1	NM_001134831	AHI1	1.47	1.83E-03
PSR06026880.hg.1	NM_001134831	AHI1	1.58	3.01E-03
PSR06026882.hg.1	NM_001134831	AHI1	1.49	5.40E-03
PSR06026884.hg.1	NM_001134831	AHI1	1.40	2.19E-02
PSR06026890.hg.1	NM_001134831	AHI1	1.50	6.36E-03
PSR06015386.hg.1	ENST00000539980	RANBP9	1.55	2.33E-02
PSR06026972.hg.1	NM_001077440	BCLAF1	1.41	2.56E-03
PSR06026974.hg.1	NM_001077440	BCLAF1	1.74	3.40E-02
PSR06012254.hg.1	ENST00000367609	GPR126	1.78	1.39E-03
PSR06027528.hg.1	ENST00000275233	SHPRH	1.51	6.75E-03
PSR06027529.hg.1	ENST00000275233	SHPRH	1.44	6.51E-03
PSR06027692.hg.1	ENST00000253329	PPIL4	1.42	4.79E-02
PSR06028105.hg.1	ENST00000495090	SYNE1	1.41	4.42E-02
PSR06028418.hg.1	ENST00000367088	DYNLT1	1.60	3.24E-04
PSR06013726.hg.1	NM_000876	IGF2R	1.45	4.08E-03
PSR06013954.hg.1	NM_206853	QKI	1.58	8.88E-03
PSR06028877.hg.1	ENST00000361731	SFT2D1	1.41	7.81E-03
PSR06001434.hg.1	NM_020662	MRS2	1.56	3.19E-02
PSR06016302.hg.1	NM_007149	ZNF184	1.46	3.50E-02
PSR06005791.hg.1	ENST00000373715	SRSF3	1.48	4.24E-03

PSR06000322.hg.1	NM_003913	PRPF4B	1.62	1.86E-02
PSR06021543.hg.1	NM_001190986	CRISP3	1.56	2.47E-02
PSR06022262.hg.1	ENST00000421834	DST	1.49	1.19E-02
PSR06022495.hg.1	ENST00000370577	LMBRD1	1.46	2.12E-02
PSR06008425.hg.1	ENST00000322773	COL19A1	1.79	1.76E-02
PSR06008480.hg.1	NM_001858	COL19A1	1.51	2.93E-02
PSR06008712.hg.1	ENST00000370392	KCNQ5	1.61	1.38E-02
PSR06008716.hg.1	NM_001160132	KCNQ5	1.51	5.79E-03
PSR06008720.hg.1	NM_019842	KCNQ5	1.48	2.37E-02
PSR06000525.hg.1	ENST00000379834	RIOK1	1.41	2.34E-02
PSR06023528.hg.1	NM_001159675	SYNCRIP	1.46	5.12E-03
PSR06023538.hg.1	ENST00000355238	SYNCRIP	1.47	1.16E-02
PSR06009496.hg.1	NM_001197259	ORC3	1.41	1.97E-02
PSR06009509.hg.1	NM_001197259	ORC3	1.40	2.29E-02
PSR06023718.hg.1	ENST00000452027	SRSF12	1.40	4.28E-03
PSR06024253.hg.1	ENST00000327681	USP45	1.41	2.77E-02
PSR06024264.hg.1	ENST00000327681	USP45	1.45	2.44E-02
PSR6_dbb_hap3000459.hg.1	NM_001025091	ABCF1	1.42	2.98E-02
PSR07010537.hg.1	ENST00000334914	KMT2E	1.42	1.80E-02
PSR07010540.hg.1	ENST00000334914	KMT2E	1.45	3.94E-02
PSR07010544.hg.1	ENST00000334914	KMT2E	1.85	3.17E-03
PSR07010549.hg.1	ENST00000334914	KMT2E	1.43	2.10E-02
PSR07010560.hg.1	ENST00000334914	KMT2E	1.54	6.75E-03
PSR07010565.hg.1	ENST00000334914	KMT2E	1.44	3.27E-02
PSR07026997.hg.1	ENST00000011473	SYPL1	1.51	4.24E-02
PSR07010876.hg.1	ENST00000465919	BCAP29	1.44	8.27E-03
PSR07027430.hg.1	NM_182529	THAP5	1.40	2.96E-02
PSR07011030.hg.1	NM_012328	DNAJB9	1.42	1.55E-02
PSR07011122.hg.1	NM_001197079	IFRD1	1.63	1.30E-02
PSR07011124.hg.1	NM_001197079	IFRD1	1.51	1.70E-02
PSR07011128.hg.1	ENST00000429071	IFRD1	1.51	4.02E-02
PSR07011131.hg.1	NM_001197079	IFRD1	1.77	7.30E-03
PSR07011135.hg.1	NM_001197079	IFRD1	1.50	4.66E-02
PSR07011138.hg.1	NM_001197079	IFRD1	1.53	3.27E-02
PSR07011147.hg.1	NM_001197079	IFRD1	1.50	2.41E-02
PSR07011149.hg.1	NM_001197079	IFRD1	1.50	2.99E-02
PSR07011150.hg.1	NM_001197079	IFRD1	1.72	1.98E-02
PSR07011151.hg.1	NM_001197079	IFRD1	1.76	4.23E-02
PSR07011152.hg.1	NM_001197079	IFRD1	1.50	3.42E-02
PSR07011889.hg.1	ENST00000540573	ASB15	1.80	2.18E-02
PSR07012881.hg.1	ENST00000437945	MEST	1.75	2.93E-02
PSR07012925.hg.1	ENST00000352689	MKLN1	1.44	1.19E-02
PSR07012940.hg.1	ENST00000352689	MKLN1	1.45	2.88E-03
PSR07013186.hg.1	ENST00000361675	CALD1	1.40	4.79E-02
PSR07013301.hg.1	ENST00000285968	NUP205	1.42	3.33E-02
PSR07013353.hg.1	ENST00000285968	NUP205	1.49	8.91E-03
PSR07013907.hg.1	ENST00000465582	SSBP1	1.43	2.38E-02
PSR07030458.hg.1	ENST00000378115	ARHGEF35	1.45	1.87E-02
PSR07016371.hg.1	NM_018051	WDR60	1.51	1.52E-02
PSR07001743.hg.1	NM_001621	AHR	1.43	2.81E-02

PSR07001924.hg.1	ENST00000222573	ITGB8	1.46	1.96E-02
PSR07018756.hg.1	NM_013293	TRA2A	1.48	2.26E-03
PSR07002776.hg.1	NM_182898	CREB5	1.79	2.72E-03
PSR07002780.hg.1	NM_182898	CREB5	1.62	3.47E-02
PSR07002806.hg.1	NM_182898	CREB5	1.56	3.45E-02
PSR07002946.hg.1	ENST00000409123	WIPF3	1.64	1.11E-02
PSR07003048.hg.1	ENST00000389266	GARS	1.48	5.19E-03
PSR07020004.hg.1	ENST00000258749	AOAH	1.41	9.61E-03
PSR07021940.hg.1	ENST00000331162	ZNF479	1.42	1.30E-03
PSR07017626.hg.1	ENST00000404360	ZNF12	1.50	2.08E-02
PSR07005668.hg.1	NM_001127231	AUTS2	1.70	8.05E-04
PSR07005680.hg.1	NM_001127231	AUTS2	1.64	3.28E-03
PSR07005688.hg.1	NM_001127231	AUTS2	2.02	8.34E-04
PSR07005699.hg.1	NM_001127231	AUTS2	1.58	1.13E-03
PSR07006905.hg.1	ENST00000443097	UPK3B	1.46	4.84E-02
PSR07023307.hg.1	ENST00000430584	GSAP	1.65	1.78E-02
PSR07006989.hg.1	ENST00000248594	PTPN12	1.46	3.25E-02
PSR07007032.hg.1	ENST00000248594	PTPN12	1.46	2.50E-02
PSR07007042.hg.1	NM_198467	RSBN1L	1.52	2.55E-02
PSR07007088.hg.1	NM_001127359	PHTF2	1.52	1.72E-02
PSR07007633.hg.1	NM_152999	STEAP2	1.44	1.00E-02
PSR07024136.hg.1	NM_004912	KRIT1	1.44	2.25E-02
PSR07008490.hg.1	NM_014916	LMTK2	1.47	1.62E-02
PSR07008544.hg.1	NM_003496	TRRAP	1.43	1.48E-02
PSR08019360.hg.1	ENST00000395956	YWHAZ	1.50	1.64E-02
PSR08019388.hg.1	ENST00000395956	YWHAZ	1.53	6.96E-03
PSR08019641.hg.1	ENST00000518205	UBR5	1.63	7.14E-03
PSR08019725.hg.1	ENST00000347770	AZIN1	1.43	3.60E-03
PSR08019738.hg.1	ENST00000347770	AZIN1	1.42	9.41E-04
PSR08019746.hg.1	ENST00000347770	AZIN1	1.49	1.21E-03
PSR08019750.hg.1	ENST00000347770	AZIN1	1.48	1.85E-02
PSR08008727.hg.1	ENST00000518738	ATP6V1C1	1.63	3.91E-03
PSR08019918.hg.1	ENST00000311955	ABRA	1.78	1.74E-02
PSR08009171.hg.1	ENST00000378402	PKHD1L1	1.54	1.82E-04
PSR08020538.hg.1	ENST00000378164	TAF2	1.46	4.74E-02
PSR08020966.hg.1	NM_014751	MTSS1	1.52	2.37E-02
PSR08021219.hg.1	ENST00000519540	FAM49B	1.45	4.74E-02
PSR08021223.hg.1	ENST00000519540	FAM49B	1.51	3.68E-02
PSR08012541.hg.1	ENST00000511869	DLC1	1.59	6.50E-03
PSR08010180.hg.1	ENST00000519656	EFR3A	1.49	3.70E-02
PSR08021528.hg.1	ENST00000377901	TMEM71	1.44	2.38E-02
PSR08022170.hg.1	ENST00000340930	PTK2	1.57	1.35E-02
PSR08001080.hg.1	NM_006765	TUSC3	1.46	5.92E-03
PSR08001186.hg.1	ENST00000324849	VPS37A	1.40	9.02E-03
PSR08002628.hg.1	ENST00000276440	DOCK5	1.41	1.46E-02
PSR08002644.hg.1	ENST00000276440	DOCK5	1.49	4.82E-03
PSR08002657.hg.1	ENST00000276440	DOCK5	1.62	2.77E-03
PSR08002661.hg.1	ENST00000276440	DOCK5	1.42	2.00E-02
PSR08002846.hg.1	ENST00000518611	BNIP3L	1.43	1.21E-02
PSR08014980.hg.1	ENST00000220772	SFRP1	1.43	4.58E-02

PSR08004838.hg.1	NM_032410	HOOK3	1.48	9.82E-03
PSR08004854.hg.1	NM_032410	HOOK3	1.75	2.63E-02
PSR08015625.hg.1	NM_001083617	RB1CC1	1.45	2.98E-02
PSR08015647.hg.1	NM_001083617	RB1CC1	1.63	1.66E-02
PSR08005458.hg.1	NM_002350	LYN	1.46	2.68E-02
PSR08006093.hg.1	ENST00000320270	RRS1	1.55	4.48E-04
PSR08006263.hg.1	NM_170709	SGK3	1.41	3.52E-02
PSR08017155.hg.1	NM_014393	STAU2	1.41	1.21E-02
PSR08006985.hg.1	ENST00000455036	ZBTB10	1.53	2.10E-03
PSR08006986.hg.1	ENST00000455036	ZBTB10	1.43	1.21E-02
PSR08006987.hg.1	ENST00000430430	ZBTB10	1.40	6.29E-03
PSR08017599.hg.1	ENST00000256104	FABP4	1.98	3.59E-02
PSR08017600.hg.1	NM_001442	FABP4	1.86	4.76E-02
PSR08017674.hg.1	ENST00000220669	ZFAND1	1.69	2.03E-02
PSR08000555.hg.1	NM_153332	ERI1	1.69	6.70E-03
PSR08018379.hg.1	NM_001198679	RUNX1T1	1.48	3.61E-02
PSR08000614.hg.1	ENST00000522110	TNKS	1.48	5.03E-04
PSR08018659.hg.1	ENST00000421249	KIAA1429	1.45	2.30E-02
PSR08007953.hg.1	ENST00000523731	INTS8	1.50	1.56E-03
PSR09005523.hg.1	ENST00000330847	NR4A3	1.90	4.84E-02
PSR09017664.hg.1	NM_015051	ERP44	1.61	1.65E-02
PSR09005630.hg.1	NM_003692	TMEFF1	1.41	3.59E-02
PSR09017837.hg.1	NM_005502	ABCA1	1.48	6.33E-03
PSR09017838.hg.1	NM_005502	ABCA1	1.44	2.63E-03
PSR09017840.hg.1	NM_005502	ABCA1	1.47	1.17E-02
PSR09017841.hg.1	NM_005502	ABCA1	1.44	4.08E-03
PSR09017842.hg.1	NM_005502	ABCA1	1.42	9.43E-04
PSR09017846.hg.1	NM_005502	ABCA1	1.44	6.29E-03
PSR09017857.hg.1	NM_005502	ABCA1	1.40	6.74E-03
PSR09017862.hg.1	NM_005502	ABCA1	1.40	2.22E-03
PSR09005944.hg.1	NM_006731	FKTN	1.45	1.92E-03
PSR09018035.hg.1	ENST00000325580	CTNNAL1	1.44	1.78E-02
PSR09018136.hg.1	NM_002829	PTPN3	1.40	6.04E-03
PSR09018161.hg.1	NM_002829	PTPN3	1.51	2.20E-02
PSR09018484.hg.1	ENST00000374255	PTBP3	1.46	1.14E-02
PSR09018496.hg.1	ENST00000374255	PTBP3	1.54	4.43E-02
PSR09019297.hg.1	NM_005047	PSMD5	1.45	3.81E-02
PSR09019314.hg.1	NM_005047	PSMD5	1.41	1.27E-03
PSR09007568.hg.1	NM_001134778	PBX3	1.42	4.12E-02
PSR09020077.hg.1	ENST00000361436	RPL12	1.64	2.60E-02
PSR09008758.hg.1	NM_015354	NUP188	1.45	4.58E-03
PSR09021303.hg.1	ENST00000224140	SETX	1.51	3.42E-02
PSR09000954.hg.1	ENST00000425824	CNTLN	1.58	1.77E-02
PSR09000977.hg.1	ENST00000425824	CNTLN	1.48	3.85E-02
PSR09001180.hg.1	NM_017794	FOCAD	1.41	3.11E-02
PSR09012712.hg.1	ENST00000359039	KLHL9	1.48	2.90E-02
PSR09001587.hg.1	NM_147134	NFX1	1.41	2.01E-03
PSR09001619.hg.1	ENST00000290943	ANKRD18B	1.57	1.75E-02
PSR09001632.hg.1	ENST00000290943	ANKRD18B	1.53	4.69E-02
PSR09013992.hg.1	ENST00000396757	CD72	1.78	1.99E-02

PSR09014528.hg.1	NM_147195	ANKRD18A	1.62	7.99E-03
PSR09011751.hg.1	ENST00000381895	SPATA6L	1.40	1.35E-03
PSR09000384.hg.1	ENST00000381858	CDC37L1	1.59	1.26E-02
PSR09000438.hg.1	ENST00000539801	JAK2	1.74	5.36E-03
PSR09000440.hg.1	ENST00000539801	JAK2	1.62	1.05E-02
PSR09000441.hg.1	ENST00000539801	JAK2	1.48	1.78E-02
PSR09000442.hg.1	ENST00000539801	JAK2	1.49	2.71E-02
PSR09000446.hg.1	ENST00000539801	JAK2	1.46	2.16E-02
PSR09000447.hg.1	ENST00000539801	JAK2	1.44	3.62E-02
PSR09000449.hg.1	ENST00000539801	JAK2	1.40	3.52E-02
PSR09000450.hg.1	ENST00000539801	JAK2	1.42	2.33E-02
PSR09000455.hg.1	ENST00000539801	JAK2	1.58	3.04E-02
PSR09000456.hg.1	ENST00000539801	JAK2	1.47	1.31E-02
PSR09000460.hg.1	ENST00000539801	JAK2	1.43	1.32E-02
PSR09015021.hg.1	ENST00000377449	CBWD6	1.58	2.69E-02
PSR09015057.hg.1	ENST00000377449	CBWD6	1.44	1.61E-02
PSR09015078.hg.1	ENST00000377439	CBWD6	1.51	2.34E-02
PSR09015193.hg.1	ENST00000377384	LOC101060578	1.46	1.59E-02
PSR09003150.hg.1	ENST00000377342	LOC101060578	1.44	1.20E-02
PSR09003421.hg.1	ENST00000361138	SMC5	1.48	1.95E-02
PSR09003510.hg.1	NM_004293	GDA	1.73	4.47E-02
PSR09015566.hg.1	NM_001177311	TRPM6	1.50	3.17E-02
PSR09003641.hg.1	NM_012383	OSTF1	1.46	4.96E-02
PSR09015770.hg.1	ENST00000286548	GNAQ	1.43	2.66E-02
PSR09016238.hg.1	ENST00000375963	ZCCHC6	1.42	1.27E-02
PSR09016590.hg.1	NM_013417	IARS	1.41	5.61E-03
PSR09016995.hg.1	ENST00000289081	FANCC	1.46	1.16E-02
PSR09017184.hg.1	NM_033331	CDC14B	1.65	3.78E-03
PSR09017185.hg.1	NM_033331	CDC14B	1.44	2.14E-02
PSR0X016813.hg.1	ENST00000451301	MORF4L2	1.57	1.15E-02
PSR0X016822.hg.1	ENST00000423833	MORF4L2	1.40	4.32E-02
PSR0X007340.hg.1	NM_001168385	ALG13	1.51	4.54E-03
PSR0X007493.hg.1	ENST00000420625	PLS3	1.42	2.67E-02
PSR0X007602.hg.1	NM_144658	DOCK11	1.50	3.09E-02
PSR0X007617.hg.1	NM_144658	DOCK11	1.42	4.14E-02
PSR0X007683.hg.1	ENST00000304778	LONRF3	1.48	1.43E-02
PSR0X007687.hg.1	ENST00000304778	LONRF3	1.44	1.64E-02
PSR0X007756.hg.1	NM_181777	UBE2A	1.46	2.21E-02
PSR0X017682.hg.1	NM_080632	UPF3B	1.41	4.08E-02
PSR0X017770.hg.1	NM_001122606	LAMP2	1.40	2.27E-02
PSR0X017990.hg.1	NM_001081550	THOC2	1.74	1.02E-02
PSR0X007941.hg.1	NM_001167	XIAP	1.54	9.91E-03
PSR0X008081.hg.1	ENST00000357121	OCRL	1.41	4.37E-03
PSR0X018225.hg.1	ENST00000370978	ZNF280C	1.41	2.31E-02
PSR0X018230.hg.1	ENST00000370978	ZNF280C	1.49	1.10E-02
PSR0X018284.hg.1	NM_182314	ENOX2	1.46	6.69E-03
PSR0X018407.hg.1	NM_133486	MBNL3	1.49	1.58E-02
PSR0X018443.hg.1	ENST00000370836	HS6ST2	1.43	3.33E-02
PSR0X018516.hg.1	ENST00000394299	GPC3	1.40	3.30E-02
PSR0X008612.hg.1	ENST00000370695	SLC9A6	1.48	1.21E-02

PSR0X011564.hg.1	ENST00000316715	GPM6B	1.50	9.01E-03
PSR0X011579.hg.1	ENST00000316715	GPM6B	1.43	3.41E-02
PSR0X019002.hg.1	ENST00000327569	ATP11C	1.41	1.89E-02
PSR0X019003.hg.1	ENST00000327569	ATP11C	1.47	1.89E-02
PSR0X000906.hg.1	ENST00000482354	MOSPD2	1.53	3.32E-03
PSR0X000909.hg.1	ENST00000482354	MOSPD2	1.41	1.35E-02
PSR0X000915.hg.1	ENST00000482354	MOSPD2	1.43	2.76E-02
PSR0X009405.hg.1	NM_001017980	VMA21	1.45	7.95E-03
PSR0X009715.hg.1	ENST00000421401	ZNF275	1.43	2.06E-03
PSR0X010720.hg.1	NM_005840	SPRY3	1.52	1.25E-03
PSR0X011795.hg.1	ENST00000545766	AP1S2	1.67	2.12E-02
PSR0X012318.hg.1	ENST00000540702	RPS6KA3	1.58	1.01E-02
PSR0X001289.hg.1	NM_014927	CNKSR2	1.86	8.31E-03
PSR0X012348.hg.1	NM_153270	KLHL34	1.53	4.56E-02
PSR0X001464.hg.1	ENST00000379251	SAT1	1.63	4.46E-02
PSR0X001588.hg.1	NM_001142386	PDK3	1.45	8.36E-03
PSR0X001689.hg.1	ENST00000378993	IL1RAPL1	1.51	2.59E-02
PSR0X001762.hg.1	NM_203391	GK	1.42	3.38E-02
PSR0X001795.hg.1	NM_203391	GK	1.43	2.33E-02
PSR0X001994.hg.1	NM_000397	CYBB	1.69	4.30E-02
PSR0X012728.hg.1	ENST00000432389	DYNLT3	1.41	2.88E-02
PSR0X012774.hg.1	ENST00000378505	RPGR	1.44	1.01E-02
PSR0X012777.hg.1	ENST00000339363	RPGR	1.42	2.15E-02
PSR0X002710.hg.1	NM_004651	USP11	1.47	3.68E-02
PSR0X014469.hg.1	ENST00000262854	HUWE1	2.20	2.42E-02
PSR0X005274.hg.1	ENST00000449580	TAF1	1.40	1.10E-02
PSR0X016096.hg.1	ENST00000537751	CHM	1.40	2.35E-02

Table 7.2 List of Down-regulated DASGs

Probeset ID	RefSeq	Gene Symbol	Fold-change	p-value
PSR01000415.hg.1	NM_153339	PUSL1	-1.59	0.01
PSR01018127.hg.1	ENST00000369111	CA14	-1.41	0.00
PSR01051099.hg.1	NM_001204294	MUC1	-1.44	0.00
PSR01051129.hg.1	NM_001018016	MUC1	-1.45	0.00
PSR01003017.hg.1	ENST00000375998	FHAD1	-1.45	0.01
PSR01053120.hg.1	NM_015726	DCAF8	-1.51	0.00
PSR01022558.hg.1	ENST00000537173	POGK	-1.49	0.02
PSR01023315.hg.1	ENST00000460397	C1orf105	-1.45	0.02
PSR01055476.hg.1	ENST00000339526	GLUL	-1.61	0.00
PSR01027416.hg.1	ENST00000400959	TRAF3IP3	-1.68	0.01
PSR01035564.hg.1	ENST00000312239	HP1BP3	-1.50	0.05
PSR01027858.hg.1	ENST00000366966	VASH2	-1.73	0.00
PSR01029769.hg.1	NM_001004342	TRIM67	-1.46	0.00
PSR01004649.hg.1	NM_198174	GRHL3	-1.70	0.00
PSR01032673.hg.1	ENST00000401094	TTC34	-1.55	0.02
PSR01036844.hg.1	ENST00000357089	UBXN11	-1.54	0.00
PSR01037132.hg.1	ENST00000374025	CD164L2	-1.45	0.00
PSR01038594.hg.1	ENST00000373347	DLGAP3	-1.42	0.00
PSR01033394.hg.1	NM_001561	TNFRSF9	-1.58	0.00
PSR01001791.hg.1	ENST00000377376	TMEM201	-1.44	0.02
PSR01045227.hg.1	ENST00000306031	DPYD	-1.43	0.01
PSR10012152.hg.1	ENST00000381344	IDI1	-1.45	0.02
PSR10009660.hg.1	NM_014456	PDCD4	-1.43	0.02
PSR10022069.hg.1	NM_001003408	ABLIM1	-1.80	0.00
PSR10022082.hg.1	NM_002313	ABLIM1	-1.43	0.01
PSR10022083.hg.1	NM_002313	ABLIM1	-1.47	0.02
PSR10010139.hg.1	ENST00000355044	ATRNL1	-1.64	0.04
PSR10023380.hg.1	NM_173575	STK32C	-1.49	0.01
PSR10011814.hg.1	NM_207128	PAOX	-1.42	0.01
PSR10001301.hg.1	NM_183005	RPP38	-1.42	0.03
PSR11012125.hg.1	ENST00000320578	RAB39A	-1.53	0.03
PSR11019245.hg.1	NM_001008391	CCDC73	-1.47	0.01
PSR11019973.hg.1	NM_001101802	PHF21A	-1.50	0.04
PSR11006890.hg.1	ENST00000544661	SLC22A10	-1.44	0.01
PSR11007995.hg.1	ENST00000394224	SIPA1	-1.49	0.00
PSR11008336.hg.1	NM_030981	RAB1B	-1.48	0.05
PSR11008710.hg.1	ENST00000308831	RHOD	-1.43	0.03
PSR11008712.hg.1	ENST00000308831	RHOD	-1.48	0.03
PSR11023769.hg.1	ENST00000312438	CLCF1	-1.45	0.01
PSR11009611.hg.1	NM_021046	KRTAP5-8	-1.48	0.02
PSR11010558.hg.1	ENST00000278559	CAPN5	-1.53	0.04
PSR11026380.hg.1	NM_016403	CWC15	-1.41	0.00
PSR11011632.hg.1	NM_015036	ENDOD1	-1.42	0.03
PSR12024643.hg.1	ENST00000240079	CCDC53	-1.56	0.01
PSR12027456.hg.1	ENST00000280562	PITPNM2	-1.47	0.00
PSR12000300.hg.1	NM_001167625	CACNA1C	-1.44	0.01

PSR12018284.hg.1	NM_001098614	PUS7L	-1.41	0.00
PSR12006563.hg.1	NM_002475	MYL6B	-1.50	0.00
PSR12006565.hg.1	NM_002475	MYL6B	-1.44	0.03
PSR12006566.hg.1	NM_002475	MYL6B	-1.49	0.04
PSR12006572.hg.1	NM_002475	MYL6B	-1.41	0.04
PSR12007094.hg.1	NM_004984	KIF5A	-1.41	0.00
PSR13004353.hg.1	NM_001113513	ARHGEF7	-1.53	0.01
PSR13000090.hg.1	NM_003453	ZMYM2	-1.43	0.02
PSR13006383.hg.1	NM_001144983	CCDC169	-1.54	0.00
PSR13006446.hg.1	NM_001142294	SPG20	-1.46	0.01
PSR14000189.hg.1	ENST00000250416	PARP2	-1.42	0.03
PSR14011114.hg.1	ENST00000554411	CIDEB	-1.54	0.03
PSR14011615.hg.1	ENST00000543095	HEATR5A	-1.42	0.02
PSR15009736.hg.1	ENST00000331837	NDN	-1.57	0.02
PSR15015663.hg.1	NM_001206797	PKM	-1.41	0.02
PSR16002869.hg.1	NM_004996	ABCC1	-1.49	0.04
PSR16003166.hg.1	NM_001199022	CCP110	-1.43	0.00
PSR16004128.hg.1	NM_015202	KIAA0556	-1.57	0.02
PSR16006974.hg.1	NM_001204911	USB1	-1.44	0.03
PSR16007416.hg.1	ENST00000521920	FBXL8	-1.52	0.00
PSR16016498.hg.1	ENST00000258201	FHOD1	-1.44	0.00
PSR16007965.hg.1	ENST00000413021	PLA2G15	-1.42	0.04
PSR16010801.hg.1	NM_016541	GNG13	-1.47	0.01
PSR17013016.hg.1	ENST00000421807	INPP5K	-1.41	0.03
PSR17000320.hg.1	NM_001100398	RAP1GAP2	-1.50	0.02
PSR17004917.hg.1	ENST00000378526	LIG3	-1.44	0.02
PSR17019732.hg.1	NM_033188	KRTAP4-5	-1.61	0.01
PSR17023326.hg.1	ENST00000389934	TEX14	-1.55	0.03
PSR17025408.hg.1	NM_001256124	TRIM65	-1.49	0.02
PSR17012379.hg.1	ENST00000333383	NPB	-1.58	0.00
PSR18005053.hg.1	NM_013305	ST8SIA5	-1.42	0.00
PSR19017412.hg.1	ENST00000396969	DNAJB1	-1.41	0.02
PSR19022221.hg.1	ENST00000245925	EML2	-1.51	0.03
PSR19009675.hg.1	ENST00000344846	SYNGR4	-2.00	0.01
PSR19010541.hg.1	NM_030973	MED25	-1.42	0.04
PSR19014699.hg.1	ENST00000372412	PTPRS	-1.60	0.01
PSR19024332.hg.1	ENST00000354957	ZNF649	-1.52	0.00
PSR19025017.hg.1	ENST00000391746	LILRB2	-1.42	0.03
PSR19025452.hg.1	ENST00000424985	FAM71E2	-1.41	0.00
PSR02016551.hg.1	NM_016315	GULP1	-1.40	0.03
PSR02016876.hg.1	NM_002194	INPP1	-1.47	0.02
PSR02019446.hg.1	ENST00000392132	XRCC5	-1.41	0.01
PSR02044956.hg.1	ENST00000265316	ABCB6	-1.51	0.02
PSR02045085.hg.1	ENST00000392089	GLB1L	-1.50	0.02
PSR02045204.hg.1	NM_012100	DNPEP	-1.64	0.01
PSR02003901.hg.1	ENST00000405592	MTA3	-1.41	0.00
PSR02008394.hg.1	NM_001244676	THNSL2	-1.49	0.01
PSR02009044.hg.1	ENST00000305510	CNNM3	-1.59	0.01
PSR20008290.hg.1	ENST00000380201	DDRGK1	-1.46	0.00
PSR20004071.hg.1	ENST00000262879	RALGAPB	-1.41	0.04

PSR20005926.hg.1	NM_001324	CSTF1	-1.47	0.04
PSR20007238.hg.1	ENST00000422202	COL20A1	-1.41	0.01
PSR21005362.hg.1	ENST00000333229	BRWD1	-1.83	0.01
PSR21002909.hg.1	ENST00000355480	COL18A1	-1.68	0.01
PSR22003691.hg.1	ENST00000403435	NF2	-1.67	0.00
PSR22003845.hg.1	ENST00000404390	INPP5J	-1.41	0.00
PSR22012350.hg.1	ENST00000328429	APOL4	-1.48	0.04
PSR22007337.hg.1	ENST00000441876	FAM118A	-1.47	0.03
PSR03030931.hg.1	ENST00000451055	SEMA5B	-1.44	0.03
PSR03015130.hg.1	ENST00000470811	LEKR1	-1.44	0.00
PSR03015131.hg.1	ENST00000470811	LEKR1	-1.42	0.01
PSR03015870.hg.1	ENST00000337002	SEC62	-1.43	0.01
PSR03021023.hg.1	NM_001134380	TBC1D5	-1.48	0.03
PSR03017006.hg.1	NM_182537	HTR3D	-1.45	0.02
PSR03017013.hg.1	NM_182537	HTR3D	-1.46	0.05
PSR03037941.hg.1	NM_018406	MUC4	-1.43	0.01
PSR03021235.hg.1	ENST00000421515	NKIRAS1	-1.60	0.00
PSR03021734.hg.1	NM_016141	DYNC1LI1	-1.51	0.04
PSR03007772.hg.1	ENST00000415676	CACNA2D3	-1.45	0.01
PSR03028071.hg.1	ENST00000349511	UBA3	-1.47	0.03
PSR04022320.hg.1	ENST00000262992	INPP4B	-1.90	0.00
PSR04013188.hg.1	NM_001174070	FAM53A	-1.41	0.03
PSR04024477.hg.1	ENST00000438320	DCTD	-1.45	0.00
PSR04000253.hg.1	ENST00000505477	MYL5	-1.57	0.00
PSR04006515.hg.1	NM_024672	THAP9	-1.56	0.02
PSR04018904.hg.1	ENST00000395161	MAPK10	-1.46	0.01
PSR04018938.hg.1	ENST00000395161	MAPK10	-1.47	0.00
PSR05007985.hg.1	NM_152546	SRFBP1	-1.42	0.05
PSR05028004.hg.1	ENST00000517901	GABRB2	-1.41	0.03
PSR05013283.hg.1	ENST00000521089	WWC1	-1.50	0.00
PSR05013639.hg.1	ENST00000519385	GABRP	-1.41	0.00
PSR05014811.hg.1	NM_002082	GRK6	-1.41	0.00
PSR05029874.hg.1	NM_001164444	CBY3	-1.46	0.03
PSR05019923.hg.1	NM_016283	TAF9	-1.48	0.04
PSR05021918.hg.1	ENST00000358746	TTC37	-1.81	0.01
PSR06015230.hg.1	ENST00000542862	ERVFRD-1	-1.42	0.01
PSR06012408.hg.1	NM_001013623	ZC2HC1B	-1.54	0.03
PSR06001717.hg.1	NM_003542	HIST1H4C	-1.53	0.03
PSR06014463.hg.1	ENST00000274643	MYLK4	-1.66	0.04
PSR06014466.hg.1	ENST00000274643	MYLK4	-1.49	0.03
PSR06014467.hg.1	ENST00000274643	MYLK4	-1.46	0.03
PSR06014469.hg.1	ENST00000274643	MYLK4	-1.71	0.05
PSR06016995.hg.1	NM_001164239	DHX16	-1.49	0.02
PSR06017815.hg.1	ENST00000375686	VWA7	-1.54	0.01
PSR06008778.hg.1	ENST00000415954	MTO1	-1.46	0.00
PSR06009078.hg.1	NM_003318	TTK	-1.64	0.00
PSR07010174.hg.1	ENST00000536178	SH2B2	-1.55	0.01
PSR07010313.hg.1	NM_001031618	SPDYE2	-1.41	0.01
PSR07002374.hg.1	ENST00000354639	STK31	-1.47	0.01
PSR07024212.hg.1	NM_194455	KRIT1	-1.41	0.00

PSR07016499.hg.1	NM_006869	ADAP1	-1.43	0.05
PSR07009399.hg.1	ENST00000452089	PILRB	-1.48	0.01
PSR08009690.hg.1	ENST00000518448	FAM83A	-1.40	0.01
PSR08012552.hg.1	NM_024767	DLC1	-1.56	0.01
PSR08001704.hg.1	ENST00000518533	FGF17	-1.42	0.00
PSR08004249.hg.1	NM_145004	ADAM32	-1.50	0.00
PSR08005211.hg.1	ENST00000517663	C8orf22	-1.45	0.02
PSR08005212.hg.1	ENST00000517663	C8orf22	-1.45	0.02
PSR08018385.hg.1	NM_001198679	RUNX1T1	-1.41	0.04
PSR09005246.hg.1	ENST00000357054	CCDC180	-1.48	0.05
PSR09007376.hg.1	ENST00000373580	OLFML2A	-1.44	0.04
PSR09016192.hg.1	NM_177937	GOLM1	-1.42	0.04
PSR0X006811.hg.1	NM_017416	IL1RAPL2	-1.44	0.02
PSR0X007914.hg.1	ENST00000434753	XIAP	-1.46	0.01
PSR0X003389.hg.1	NM_001032384	PQBP1	-1.53	0.00
PSR0X014340.hg.1	NM_001111125	IQSEC2	-1.45	0.01
PSR0X015030.hg.1	NM_001199687	EDA2R	-1.57	0.01
PSR0X005570.hg.1	ENST00000481445	COX7B	-1.52	0.01

Table 7.3 List of significant (p<0.05) canonical pathways identified using IPA for DASGs.

Canonical Ingenuity Pathways	z-score	p-value	Molecules
Rac Signaling	3.61	2.40E-03	PTK2,RPS6KB1,RAF1,IQGAP2,NOX4,RRAS2,PIK3C2A,PIK3R1,NCF2,CYBB,PIP4K2A,PLD1,ATM
Melanocyte Development and Pigmentation Signaling	3.16	3.89E-03	RPS6KB1,RAF1,RRAS2,PIK3C2A,MITF,PIK3R1,CREB1,SH2B2,RPS6KA3,CREB5,ATM
FLT3 Signaling in Hematopoietic Progenitor Cells	3.16	3.98E-03	RPS6KB1,RAF1,MTOR,RRAS2,PIK3C2A,PIK3R1,CREB1,RPS6KA3,CREB5,ATM
fMLP Signaling in Neutrophils	3.16	2.09E-02	GNAI3,RAF1,NOX4,RRAS2,PIK3C2A,ITPR2,PIK3R1,NCF2,CYBB,GNG13,ATM
Glioma Signaling	3.16	2.69E-02	RAF1,MTOR,RRAS2,CAMK2D,IGF1,PIK3C2A,PIK3R1,MDM2,IGF2R,ATM
CNTF Signaling	3.00	1.48E-03	RPS6KB1,RAF1,MTOR,RRAS2,PIK3C2A,PIK3R1,RPS6KA3,JAK2,ATM
IGF-1 Signaling	3.00	3.24E-03	YWHAQ,PTK2,RPS6KB1,RAF1,RRAS2,IGF1,PIK3C2A,PIK3R1,YWHAZ,JAK2,CYR61,ATM
IL-8 Signaling	3.00	8.51E-03	RPS6KB1,RAF1,NOX4,PIK3C2A,PIK3R1,GNG13,PLD1,ROCK2,PTK2,GNAI3,MTOR,RRAS2,RHOD,NCF2,MAPK10,CYBB,ATM
B Cell Receptor Signaling	2.98	8.71E-05	FCGR2C,RPS6KB1,RAF1,PIK3C2A,PIK3R1,CREB5,BCL6,OCRL,PTPRC,PTK2,MTOR,RRAS2,CAMK2D,SYNJ1,INPP5J,INPP5F,CREB1,LYN,MEF2C,INPP5K,ATM
p70S6K Signaling	2.89	2.45E-03	RPS6KB1,RAF1,PIK3C2A,PPP2CA,PIK3R1,GNAQ,YWHAZ,PLD1,YWHAQ,GNAI3,MTOR,RRAS2,LYN,ATM
ERK5 Signaling	2.83	5.25E-04	YWHAQ,RPS6KB1,RRAS2,CREB1,YWHAZ,RPS6KA3,GNAQ,MEF2C,CREB5,MAP2K5
GM-CSF Signaling	2.83	1.78E-02	RAF1,RRAS2,CAMK2D,PIK3C2A,PIK3R1,LYN,JAK2,ATM
Neurotrophin/TRK Signaling	2.83	2.19E-02	RAF1,RRAS2,PIK3C2A,PIK3R1,CREB1,CREB5,MAP2K5,ATM
JAK/Stat Signaling	2.83	3.55E-02	RAF1,MTOR,RRAS2,PIK3C2A,PIK3R1,GNAQ,JAK2,ATM
VEGF Signaling	2.83	3.89E-02	ROCK2,PTK2,RAF1,RRAS2,PIK3C2A,PIK3R1,HIF1A,EIF2S1,ATM
GNRH Signaling	2.71	3.02E-02	PTK2,GNAI3,RAF1,RRAS2,CAMK2D,ITPR2,CREB1,MAPK10,GNAQ,DNM1L,CREB5
EGF Signaling	2.65	3.47E-02	RPS6KB1,RAF1,MTOR,PIK3C2A,ITPR2,PIK3R1,ATM
Chemokine Signaling	2.65	3.47E-02	ROCK2,PTK2,GNAI3,RAF1,RRAS2,CAMK2D,GNAQ
NGF Signaling	2.53	1.70E-02	ROCK2,RPS6KB1,RAF1,RRAS2,PIK3C2A,PIK3R1,CREB1,MAPK10,RPS6KA3,CREB5,ATM
Thrombin Signaling	2.50	1.02E-02	RPS6KB1,RAF1,PIK3C2A,ITPR2,PIK3R1,MYL5,GNAQ,GN

			G13,MYL6B,ROCK2,PTK2,GNAI3,RRAS2,CAMK2D,RHOD,CREB1,ATM
Aldosterone Signaling in Epithelial Cells	2.45	3.89E-02	RAF1,PIK3C2A,ITPR2,PIK3R1,DNAJC10,DNAJC1,DNAJB9,HSPA4,DNAJC18,DNAJB1,PIP4K2A,ATM,HSPA4L
Role of NFAT in Cardiac Hypertrophy	2.14	2.63E-02	RAF1,PIK3C2A,HDAC2,ITPR2,PIK3R1,GNAQ,GNG13,TGFBR2,GNAI3,RRAS2,CAMK2D,IGF1,MAPK10,MEF2C,ATM
GDNF Family Ligand-Receptor Interactions	2.12	7.59E-03	RAF1,RRAS2,GDNF,PIK3C2A,ITPR2,PIK3R1,CREB1,MAPK10,ATM
p38 MAPK Signaling	2.12	4.07E-02	TGFBR2,RPS6KB1,IL18,IL1RAPL2,CREB1,RPS6KA3,MEF2C,IL1RAPL1,CREB5,PLA2G2A
Regulation of eIF4 and p70S6K Signaling	2.12	4.90E-02	RPS6KB1,RAF1,MTOR,RRAS2,PIK3C2A,PPP2CA,PIK3R1,PAIP1,RPS27L,RPS25,EIF2S1,ATM
PDGF Signaling	2.11	2.57E-03	RAF1,RRAS2,INPP5J,SYNJ1,INPP5F,PIK3C2A,PIK3R1,INPP5K,JAK2,OCRL,ATM
Role of IL-17F in Allergic Inflammatory Airway Diseases	2.00	3.72E-02	RAF1,IGF1,CREB1,RPS6KA3,CREB5
RhoA Signaling	1.90	4.79E-02	ROCK2,PTK2,IGF1,MYL5,PFN2,RAPGEF6,MYL6B,PIP4K2A,PLD1,KTN1
UVB-Induced MAPK Signaling	1.89	3.02E-02	RPS6KB1,MTOR,PIK3C2A,PIK3R1,MAPK10,RPS6KA3,ATM
PTEN Signaling	-1.73	3.02E-03	PTK2,TGFBR2,RAF1,RPS6KB1,RRAS2,INPP5F,SYNJ1,INPP5J,PIK3R1,BMPR2,INPP5K,OCRL,IGF2R
UVA-Induced MAPK Signaling	1.67	6.31E-03	RPS6KB1,MTOR,TNKS,RRAS2,PIK3C2A,PIK3R1,PARP2,MAPK10,RPS6KA3,TNKS2,ATM
FcγRIIB Signaling in B Lymphocytes	1.63	3.24E-02	RRAS2,PIK3C2A,PIK3R1,MAPK10,LYN,ATM
Cardiac Hypertrophy Signaling	1.61	4.79E-03	RPS6KB1,RAF1,PIK3C2A,PIK3R1,MYL5,GNAQ,GNG13,CACNA1C,MYL6B,TGFBR2,ROCK2,GNAI3,MTOR,RRAS2,IGF1,RHOD,CREB1,MAPK10,MEF2C,ATM
Fc Epsilon RI Signaling	1.60	1.05E-03	RAF1,PIK3C2A,PIK3R1,OCRL,PLA2G2A,RRAS2,INPP5F,INPP5J,SYNJ1,MAPK10,LYN,INPP5K,LCP2,ATM
CXCR4 Signaling	1.60	3.39E-03	RAF1,PIK3C2A,ITPR2,PIK3R1,MYL5,GNAQ,GNG13,MYL6B,ROCK2,PTK2,GNAI3,RRAS2,RHOD,LYN,MAPK10,ATM
Insulin Receptor Signaling	1.60	3.98E-03	RPS6KB1,RAF1,PIK3C2A,PIK3R1,JAK2,OCRL,MTOR,RRAS2,INPP5F,INPP5J,SYNJ1,SH2B2,INPP5K,ATM
Gα12/13 Signaling	1.51	3.55E-02	ROCK2,PTK2,RAF1,RRAS2,PIK3C2A,PIK3R1,MYL5,MAPK10,MEF2C,MYL6B,ATM
Signaling by Rho Family GTPases	1.50	1.78E-02	RAF1,NOX4,PIK3C2A,PIK3R1,ARHGEF7,MYL5,GNAQ,GNG13,MYL6B,PLD1,ROCK2,PTK2,GNAI3,RHOD,NCF2,MAPK10,CYBB,PIP4K2A,ATM
STAT3 Pathway	1.41	1.78E-02	TGFBR2,RAF1,RRAS2,PTPN2,MAPK10,BMPR2,JAK2,IGF2R
Phospholipase C Signaling	1.39	9.55E-03	FCGR2C,RAF1,HDAC2,ITPR2,ARHGEF7,MYL5,GNAQ,RPS6KA3,GNG13,MYL6B,CREB5,PLD1,PLA2G2A,RRAS2,RHOD,CREB1,LYN,MEF2C,LCP2
Hypoxia Signaling in	1.34	7.59E-03	UBE2G2,UBE2A,UBE2B,CREB1,MDM2,HIF1A,CREB5,AT

the Cardiovascular System			M
Protein Kinase A Signaling	1.28	3.63E-02	RAF1,DUSP8,PTPN2,MYL5,GNG13,MYL6B,PTPN12,PTPRC,ROCK2,YWHAQ,PTK2,TGFBR2,CAMK2D,CREB1,PDE4D,PTPRG,ITPR2,YWHAZ,GNAQ,PTPN3,CREB5,GNAI3,CDC14B,PTPRS,PDE8B
Glioma Invasiveness Signaling	1.13	3.98E-02	PTK2,TIMP4,RRAS2,PIK3C2A,RHOD,PIK3R1,ATM
Role of JAK1, JAK2 and TYK2 in Interferon Signaling	1.00	2.19E-02	RAF1,PTPN2,JAK2,IFNAR2
PPARα/RXRα Activation	-0.91	3.80E-03	RAF1,IL1RAPL2,GNAQ,BMPR2,JAK2,ADIPOR1,ABCA1,TGFBR2,CAND1,RRAS2,GK,CLOCK,MEF2C,NCOR1,IL1RAPL1,ACVR2A
PI3K/AKT Signaling	0.78	4.37E-04	RPS6KB1,RAF1,PPP2CA,PIK3R1,YWHAZ,MDM2,JAK2,OCRL,YWHAQ,MTOR,RRAS2,SYNJ1,INPP5J,INPP5F,INPP5K
ATM Signaling	-0.71	5.13E-03	SMC3,FANCD2,CREB1,MAPK10,MDM2,TLK1,CREB5,ATM
PAK Signaling	0.63	1.58E-02	PTK2,RAF1,RRAS2,PIK3C2A,ARHGEF7,PIK3R1,MYL5,MAPK10,MYL6B,ATM
ILK Signaling	0.50	1.48E-02	PIK3C2A,PPP2CA,PIK3R1,MUC1,MYL5,MYL6B,ITGB8,HIF1A,CREB5,PTK2,MTOR,RHOD,SH2B2,CREB1,MAPK10,ATM
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	-0.45	2.34E-02	YWHAQ,TOP2B,PTPMT1,YWHAZ,MDM2,ATM
HIPPO signaling	-0.38	1.51E-02	YWHAQ,DLG1,STK4,SAV1,WWC1,PPP2CA,YWHAZ,NF2,LATS2
AMPK Signaling	0.30	4.90E-02	PBRM1,RPS6KB1,ACACB,PIK3C2A,PPP2CA,PIK3R1,ARID2,CREB5,MTOR,PPM1B,CREB1,ACACA,CHRNA5,ATM
D-myo-inositol (1,4,5)-trisphosphate Degradation	NaN	1.02E-04	INPP1,INPP5J,SYNJ1,INPP5F,INPP5K,OCRL
Telomere Extension by Telomerase	NaN	3.98E-04	TNKS,HNRNPA1,XRCC6,TNKS2,XRCC5
IL-4 Signaling	NaN	4.07E-04	RPS6KB1,MTOR,RRAS2,INPP5J,SYNJ1,INPP5F,PIK3C2A,PIK3R1,INPP5K,JAK2,OCRL,ATM
Protein Ubiquitination Pathway	NaN	6.17E-04	USP18,USP45,USP41,UBE2A,UBE4B,USP11,PSMD5,FBXW7,DNAJC10,DNAJC1,MDM2,DNAJB9,USO1,UBE2G2,HSPA4,USP8,UBE2B,CUL2,USP16,PSMA5,DNAJC18,PSMA3,DNAJB1,HSPA4L
Superpathway of D-myo-inositol (1,4,5)-trisphosphate Metabolism	NaN	7.41E-04	INPP1,INPP5J,SYNJ1,INPP5F,INPP5K,OCRL
Tetrahydrofolate Salvage from 5,10-methenyltetrahydrofolate	NaN	8.71E-04	MTHFD2,MTHFD2L,GART

Cleavage and Polyadenylation of Pre-mRNA	NaN	1.58E-03	PAPOLA,CPSF6,NUDT21,CSTF3
1D-myo-inositol Hexakisphosphate Biosynthesis II (Mammalian)	NaN	1.70E-03	INPP5J,SYNJ1,INPP5F,INPP5K,OCRL
D-myo-inositol (1,3,4)-trisphosphate Biosynthesis	NaN	1.70E-03	INPP5J,SYNJ1,INPP5F,INPP5K,OCRL
DNA Double-Strand Break Repair by Non-Homologous End Joining	NaN	2.95E-03	XRCC6,XRCC5,ATM,LIG3
Biotin-carboxyl Carrier Protein Assembly	NaN	6.03E-03	ACACB,ACACA
Cholecystokinin/Gastrin-mediated Signaling	NaN	6.31E-03	ROCK2,PTK2,RAF1,IL18,RRAS2,RHOD,ITPR2,MAPK10,GNAQ,MEF2C,MAP2K5
3-phosphoinositide Degradation	NaN	1.10E-02	PTPRC,INPP4A,NUDT5,DUSP8,INPP5F,SYNJ1,INPP5J,PTPN2,PTPMT1,INPP5K,OCRL,PTPN12,UBLCP1
Spermine and Spermidine Degradation I	NaN	1.17E-02	PAOX,SAT1
Melanoma Signaling	NaN	1.20E-02	RAF1,RRAS2,PIK3C2A,MITF,PIK3R1,MDM2,ATM
Huntington's Disease Signaling	NaN	1.29E-02	CAPN5,PIK3C2A,HDAC2,GLS,PIK3R1,GNAQ,GNG13,CREB5,ZDHHC17,HSPA4,MTOR,IGF1,CREB1,HTT,NCOR1,DNAJB1,DNM1L,SNCA,ATM
Myc Mediated Apoptosis Signaling	NaN	1.41E-02	YWHAQ,RRAS2,IGF1,PIK3C2A,PIK3R1,YWHAZ,MAPK10,ATM
Circadian Rhythm Signaling	NaN	1.58E-02	ARNTL,CREB1,CLOCK,CRY1,CREB5
Adipogenesis pathway	NaN	1.74E-02	RPS6KB1,ARNTL,CCNH,HDAC2,SREBF1,KLF5,CLOCK,BMPR2,GTF2H2,FBXW7,FABP4,HIF1A
Role of Tissue Factor in Cancer	NaN	2.00E-02	RPS6KB1,MTOR,RRAS2,PIK3C2A,PIK3R1,RPS6KA3,LYN,GNAQ,JAK2,CYR61,ATM
Glucocorticoid Receptor Signaling	NaN	2.04E-02	PBRM1,RAF1,TAF9,CCNH,PIK3C2A,PIK3R1,SLPI,GTF2H2,ARID2,JAK2,CD163,TGFBR2,HSPA4,TAF1,RRAS2,CREB1,MAPK10,NCOR1,TAF2,ATM,CREBZF
Natural Killer Cell Signaling	NaN	2.09E-02	RAF1,RRAS2,INPP5J,SYNJ1,INPP5F,PIK3C2A,PIK3R1,INPP5K,OCRL,LCP2,ATM
autophagy	NaN	2.29E-02	MTOR,LAMP2,WDFY3,ATG10,RB1CC1
Prostate Cancer Signaling	NaN	2.40E-02	RAF1,MTOR,RRAS2,PIK3C2A,PIK3R1,CREB1,MDM2,CREB5,ATM
Estrogen Receptor Signaling	NaN	3.24E-02	TAF9,RAF1,CCNH,TAF1,RRAS2,TRRAP,MED21,GTF2H2,NCOR1,RBFOX2,TAF2
TR/RXR Activation	NaN	3.47E-02	MTOR,PIK3C2A,SREBF1,PIK3R1,NCOR1,ACACA,MDM2,HIF1A,ATM
phagosome maturation	NaN	4.27E-02	DYNC1LI1,LAMP2,NOX4,ATP6V1C1,NCF2,CYBB,DYNC2H1,VPS37A,DYNLT1,EEA1

Renin-Angiotensin Signaling	NaN	4.57E-02	PTK2,RAF1,RRAS2,PIK3C2A,ITPR2,PIK3R1,MAPK10,GNAQ,JAK2,ATM
Glutamine Biosynthesis I	NaN	4.57E-02	GLUL
Lipoate Salvage and Modification	NaN	4.57E-02	LIPT1
Histidine Degradation III	NaN	4.79E-02	MTHFD2,MTHFD2L

Positive z-scores= Predicted pathway activation

Negative Z-scores= Predicted pathway inhibition

NaN= No prediction

Table 7.4 List of DEI in males

Probeset ID	RefSeq	Gene Symbol	Fold-Change	p-value
PSR01001878.hg.1	NM_022787	NMNAT1	-2.36	1.88E-02
PSR01014113.hg.1	ENST00000370153	SLC35A3	1.53	4.99E-02
PSR01014121.hg.1	ENST00000370153	SLC35A3	1.40	4.10E-02
PSR01014122.hg.1	ENST00000370153	SLC35A3	1.72	1.78E-02
PSR01014216.hg.1	NM_003672	CDC14A	1.42	1.57E-02
PSR01014218.hg.1	NM_003672	CDC14A	1.46	4.04E-02
PSR01001904.hg.1	ENST00000377153	UBE4B	1.61	1.92E-02
PSR01045418.hg.1	NM_015958	DPH5	1.44	2.43E-03
PSR01014347.hg.1	ENST00000524631	RNPC3	1.71	4.33E-02
PSR01014373.hg.1	BC010697	RNPC3	1.89	5.59E-03
PSR01045724.hg.1	ENST00000264128	SLC25A24	-1.44	3.03E-02
PSR01045725.hg.1	ENST00000264128	SLC25A24	-1.70	2.99E-02
PSR01045737.hg.1	NM_001143989	NBPF4	1.42	4.75E-02
PSR01014572.hg.1	ENST00000357046	NBPF5P	1.42	4.75E-02
PSR01014635.hg.1	ENST00000467302	PRPF38B	1.53	1.75E-02
PSR01045956.hg.1	NM_001205228	SORT1	1.54	1.51E-02
PSR01045976.hg.1	NM_001205228	SORT1	1.43	2.08E-02
PSR01045980.hg.1	NM_001205228	SORT1	1.56	3.61E-02
PSR01046007.hg.1	NM_001199773	PSMA5	1.69	3.03E-02
PSR01015464.hg.1	BC032610	CEPT1	1.41	4.62E-02
PSR01015743.hg.1	BC000144	CAPZA1	1.45	4.04E-02
PSR01047059.hg.1	NM_001102396	SIKE1	1.59	2.13E-02
PSR01047063.hg.1	BC005934	SIKE1	3.66	1.42E-02
PSR01047071.hg.1	ENST00000506320	SIKE1	1.63	2.81E-02
PSR01016557.hg.1	BC137546	FAM72B	1.89	3.39E-03
PSR01002611.hg.1	NM_015378	VPS13D	1.72	8.21E-03
PSR01034142.hg.1	ENST00000331684	PRAMEF11	1.49	2.30E-02
PSR01031931.hg.1	NM_017900	AURKAIP1	-1.42	1.24E-02
PSR01031930.hg.1	ENST00000338338	AURKAIP1	-1.40	1.53E-02
PSR01017102.hg.1	ENST00000369339	LOC101060684	1.44	1.39E-02
PSR01017103.hg.1	ENST00000369339	LOC101060684	1.49	4.04E-03
PSR01048610.hg.1	ENST00000369202	LOC101060226	1.55	5.72E-03
PSR01048617.hg.1	ENST00000369202	LOC101060226	1.41	1.64E-03
PSR01048640.hg.1	ENST00000369202	LOC101060226	1.41	1.64E-03
PSR01048655.hg.1	ENST00000369202	LOC101060226	1.41	1.64E-03
PSR01048665.hg.1	ENST00000369202	LOC101060226	1.41	1.64E-03
PSR01017777.hg.1	NM_001102663	NBPF16	1.49	2.26E-03
PSR01018073.hg.1	NM_007259	VPS45	1.61	2.53E-02
PSR01049049.hg.1	NM_030920	ANP32E	1.48	4.07E-02
PSR01049050.hg.1	ENST00000436748	ANP32E	1.76	6.32E-04
PSR01049060.hg.1	ENST00000436748	ANP32E	1.51	2.03E-02
PSR01049258.hg.1	NM_001199739	CTSS	1.41	1.73E-02
PSR01018724.hg.1	ENST00000290541	PSMB4	-2.39	1.74E-03
PSR01050001.hg.1	ENST00000489410	THEM4	1.55	4.30E-02
PSR01019180.hg.1	ENST00000368698	S100A1	-1.47	4.55E-02

PSR01019181.hg.1	ENST00000368698	S100A1	-1.63	2.84E-02
PSR01019182.hg.1	ENST00000368696	S100A1	-1.81	1.29E-02
PSR01019183.hg.1	ENST00000368698	S100A1	-1.58	1.86E-02
PSR01019184.hg.1	ENST00000368698	S100A1	-1.51	2.11E-02
PSR01050542.hg.1	ENST00000537590	SLC39A1	-2.00	4.41E-02
PSR01050649.hg.1	NM_001043351	TPM3	1.42	4.34E-02
PSR01050650.hg.1	NM_001043351	TPM3	1.56	9.32E-03
PSR01050656.hg.1	NM_001043352	TPM3	1.74	1.16E-02
PSR01034267.hg.1	ENST00000376005	C1orf195	-1.42	3.55E-02
PSR01051516.hg.1	ENST00000405763	YY1AP1	1.51	1.21E-02
PSR01003130.hg.1	BC047363	DNAJC16	1.53	2.81E-02
PSR01053120.hg.1	NM_015726	DCAF8	-1.66	2.62E-02
PSR01003228.hg.1	ENST00000489568	SLC25A34	-1.56	5.24E-03
PSR01003305.hg.1	NM_015001	SPEN	1.41	2.54E-02
PSR01053963.hg.1	NM_000696	ALDH9A1	1.42	5.95E-03
PSR01053974.hg.1	ENST00000461664	ALDH9A1	1.42	4.73E-02
PSR01022571.hg.1	ENST00000537173	POGK	1.43	4.28E-02
PSR01034596.hg.1	ENST00000392963	NBPF1	1.48	3.34E-02
PSR01054473.hg.1	ENST00000303469	METTL18	1.66	1.36E-02
PSR01023186.hg.1	ENST00000392080	PRRC2C	1.40	1.05E-02
PSR01023188.hg.1	ENST00000392080	PRRC2C	1.43	2.80E-02
PSR01023279.hg.1	ENST00000367731	DNM3	1.50	1.85E-02
PSR01023381.hg.1	ENST00000340385	PRDX6	-1.46	7.55E-03
PSR01023487.hg.1	ENST00000367692	RABGAP1L	1.72	9.91E-03
PSR01023510.hg.1	ENST00000251507	RABGAP1L	1.49	3.56E-02
PSR01034886.hg.1	ENST00000375436	RCC2	1.46	1.82E-02
PSR01023784.hg.1	NM_001170724	TEX35	1.42	1.70E-02
PSR01055230.hg.1	BC050640	ANGPTL1	1.58	3.89E-02
PSR01055232.hg.1	BC050640	ANGPTL1	1.56	1.25E-02
PSR01055233.hg.1	BC050640	ANGPTL1	1.53	1.59E-02
PSR01055234.hg.1	ENST00000415564	ANGPTL1	1.49	2.46E-02
PSR01055239.hg.1	ENST00000415564	ANGPTL1	1.59	1.79E-02
PSR01055240.hg.1	ENST00000415564	ANGPTL1	1.69	4.01E-02
PSR01024159.hg.1	NM_004736	XPR1	1.68	3.67E-02
PSR01055503.hg.1	BC090934	RNASEL	-1.50	1.53E-02
PSR01055787.hg.1	ENST00000367504	TRMT1L	1.55	2.18E-02
PSR01055790.hg.1	ENST00000367504	TRMT1L	1.52	1.93E-02
PSR01024889.hg.1	NM_005807	PRG4	1.83	1.89E-02
PSR01055870.hg.1	ENST00000367478	TPR	1.43	4.25E-02
PSR01055886.hg.1	ENST00000367478	TPR	1.42	1.09E-02
PSR01055895.hg.1	ENST00000367478	TPR	1.75	2.89E-02
PSR01055899.hg.1	ENST00000367478	TPR	1.43	3.61E-02
PSR01055900.hg.1	ENST00000367478	TPR	1.45	1.42E-02
PSR01055903.hg.1	ENST00000367478	TPR	1.52	2.39E-02
PSR01055905.hg.1	ENST00000367478	TPR	1.42	4.41E-02
PSR01055926.hg.1	ENST00000367472	TPR	1.53	4.14E-02
PSR01055927.hg.1	ENST00000367472	TPR	1.43	3.64E-02
PSR01055928.hg.1	ENST00000367472	TPR	1.42	2.64E-02
PSR01055929.hg.1	ENST00000367472	TPR	1.61	4.09E-02
PSR01055930.hg.1	ENST00000367472	TPR	1.84	2.97E-02

PSR01055931.hg.1	ENST00000367472	TPR	1.51	3.36E-02
PSR01025103.hg.1	ENST00000432079	TROVE2	1.59	5.63E-03
PSR01025108.hg.1	ENST00000432079	TROVE2	1.53	2.33E-02
PSR01056110.hg.1	ENST00000294725	KCNT2	1.51	2.78E-02
PSR01025208.hg.1	NM_001201551	CFHR4	-1.40	1.38E-02
PSR01056187.hg.1	BC132818	ZBTB41	1.52	2.36E-02
PSR01056194.hg.1	BC132818	ZBTB41	1.76	4.63E-03
PSR01056383.hg.1	BC041801	DDX59	-1.65	1.57E-02
PSR01056632.hg.1	ENST00000367313	LAD1	-1.61	1.76E-03
PSR01025810.hg.1	ENST00000482943	TIMM17A	1.73	4.01E-03
PSR01025811.hg.1	ENST00000482943	TIMM17A	1.76	8.83E-04
PSR01035342.hg.1	NM_001161727	PLA2G2A	1.51	1.89E-02
PSR01026343.hg.1	ENST00000414487	SNRPE	2.11	2.03E-02
PSR01026347.hg.1	ENST00000367208	SNRPE	1.46	1.53E-02
PSR01057402.hg.1	NM_001193272	RBBP5	1.55	1.25E-02
PSR01057405.hg.1	NM_001193272	RBBP5	1.49	3.20E-02
PSR01057675.hg.1	ENST00000469540	C1orf186	1.45	1.30E-02
PSR01027136.hg.1	ENST00000367062	CD55	1.61	2.37E-02
PSR01027232.hg.1	ENST00000367053	CR1	1.43	1.14E-02
PSR01058149.hg.1	ENST00000440600	INTS7	1.40	1.96E-02
PSR01058156.hg.1	ENST00000440600	INTS7	1.45	4.99E-02
PSR01035610.hg.1	ENST00000374935	EIF4G3	1.63	2.37E-02
PSR01027732.hg.1	BC110883	PPP2R5A	1.49	1.06E-02
PSR01027742.hg.1	BC110883	PPP2R5A	1.64	2.98E-02
PSR01027744.hg.1	NM_006243	PPP2R5A	1.48	3.55E-02
PSR01027853.hg.1	NM_014053	FLVCR1	1.47	2.80E-02
PSR01027858.hg.1	ENST00000366966	VASH2	-1.63	2.43E-02
PSR01027874.hg.1	ENST00000366964	VASH2	-1.50	9.52E-03
PSR01058259.hg.1	BC047469	ANGEL2	1.80	9.86E-03
PSR01004180.hg.1	ENST00000318220	LOC101060684	1.50	4.43E-03
PSR01028389.hg.1	ENST00000344441	MIA3	1.42	1.65E-02
PSR01028415.hg.1	ENST00000344441	MIA3	1.56	1.59E-02
PSR01058828.hg.1	ENST00000474863	AIDA	1.43	4.03E-03
PSR01058830.hg.1	ENST00000340020	AIDA	1.54	5.44E-03
PSR01028689.hg.1	ENST00000366857	CNIH4	1.42	5.07E-03
PSR01029126.hg.1	NM_178549	ZNF678	1.46	2.00E-02
PSR01059791.hg.1	ENST00000366687	CCSAP	1.52	8.19E-03
PSR01059967.hg.1	ENST00000523410	C1orf198	1.47	4.51E-02
PSR01060015.hg.1	ENST00000366662	TTC13	1.56	8.08E-03
PSR01029772.hg.1	NM_014236	GNPAT	-1.66	7.57E-03
PSR01060145.hg.1	NM_020808	SIPA1L2	1.49	2.43E-02
PSR01060164.hg.1	ENST00000344698	PCNXL2	-1.53	5.02E-03
PSR01060371.hg.1	ENST00000366606	RBM34	1.55	3.44E-02
PSR01060428.hg.1	NM_016374	ARID4B	1.49	3.90E-03
PSR01060433.hg.1	NM_016374	ARID4B	1.47	2.31E-02
PSR01030083.hg.1	BC008654	TBCE	1.58	9.47E-04
PSR01060475.hg.1	ENST00000366599	B3GALNT2	-1.54	2.02E-02
PSR01030438.hg.1	ENST00000450451	LOC100130331	-1.50	3.06E-05
PSR01061086.hg.1	ENST00000366535	ADSS	1.48	2.56E-02
PSR01061089.hg.1	ENST00000449326	ADSS	1.43	6.63E-03

PSR01061095.hg.1	ENST00000449326	ADSS	1.55	3.99E-02
PSR01061096.hg.1	ENST00000449326	ADSS	1.41	1.73E-02
PSR01061264.hg.1	ENST00000326225	AHCTF1	1.41	9.98E-03
PSR01061489.hg.1	ENST00000317965	OR2M7	1.71	2.90E-02
PSR01036817.hg.1	BC038106	UBXN11	-1.47	2.84E-02
PSR01005669.hg.1	NM_001143912	FAM76A	1.46	1.41E-02
PSR01037447.hg.1	ENST00000373795	SRSF4	1.41	1.12E-02
PSR01037645.hg.1	ENST00000423018	PUM1	1.44	3.59E-02
PSR01006642.hg.1	ENST00000373510	ZBTB8A	1.66	1.22E-02
PSR01006750.hg.1	ENST00000531123	S100PBP	1.83	7.45E-03
PSR01001124.hg.1	ENST00000378295	TP73	-1.53	6.83E-03
PSR01007189.hg.1	ENST00000471099	AGO3	1.45	2.77E-02
PSR01039034.hg.1	ENST00000373104	CSF3R	-1.58	7.59E-03
PSR01039155.hg.1	ENST00000545489	GNL2	1.52	3.23E-02
PSR01007547.hg.1	ENST00000317713	MACF1	1.41	7.22E-03
PSR01007570.hg.1	ENST00000317713	MACF1	1.43	3.09E-02
PSR01007585.hg.1	ENST00000476350	MACF1	1.48	1.83E-02
PSR01007586.hg.1	ENST00000476350	MACF1	1.72	5.89E-03
PSR01007612.hg.1	ENST00000476350	MACF1	1.46	1.20E-02
PSR01039660.hg.1	ENST00000316891	TRIT1	1.50	2.12E-02
PSR01008522.hg.1	NM_001195831	WDR65	-1.50	1.09E-02
PSR01009698.hg.1	ENST00000402363	NASP	1.79	2.33E-02
PSR01009704.hg.1	ENST00000402363	NASP	1.50	6.21E-04
PSR01009712.hg.1	ENST00000530073	NASP	1.41	3.83E-02
PSR01041425.hg.1	NM_001159969	EPS15	1.41	1.65E-02
PSR01010377.hg.1	ENST00000447887	OSBPL9	1.58	1.11E-02
PSR01010380.hg.1	NM_148909	OSBPL9	1.47	4.27E-03
PSR01010483.hg.1	NM_032864	PRPF38A	1.44	3.97E-02
PSR01041757.hg.1	ENST00000257177	ZCCHC11	1.55	2.96E-02
PSR01041758.hg.1	ENST00000257177	ZCCHC11	1.49	1.71E-02
PSR01041905.hg.1	ENST00000462941	MAGOH	1.63	2.10E-02
PSR01010670.hg.1	BC029566	DMRTB1	-1.51	3.46E-03
PSR01042495.hg.1	ENST00000469854	OMA1	1.64	1.95E-02
PSR01042496.hg.1	ENST00000469854	OMA1	1.73	4.42E-02
PSR01042501.hg.1	ENST00000469854	OMA1	1.61	9.36E-03
PSR01011318.hg.1	NM_003368	USP1	1.40	2.55E-02
PSR01011323.hg.1	NM_003368	USP1	1.51	2.24E-02
PSR01011435.hg.1	NM_032437	EFCAB7	1.76	4.32E-02
PSR01011437.hg.1	NM_032437	EFCAB7	2.05	3.18E-02
PSR01011439.hg.1	ENST00000461039	EFCAB7	1.74	4.58E-02
PSR01001413.hg.1	ENST00000437392	TAS1R1	-1.42	2.97E-02
PSR01001462.hg.1	ENST00000545645	ZBTB48	-1.49	7.39E-04
PSR01011743.hg.1	ENST00000480109	PDE4B	2.36	1.52E-03
PSR01011862.hg.1	ENST00000355356	MIER1	1.49	2.19E-02
PSR01011870.hg.1	BC125218	MIER1	1.53	1.10E-03
PSR01011872.hg.1	BC125218	MIER1	1.47	1.37E-02
PSR01011873.hg.1	BC125218	MIER1	1.45	2.15E-02
PSR01011885.hg.1	NM_020948	MIER1	1.44	1.90E-02
PSR01043219.hg.1	ENST00000370964	DEPDC1	1.59	9.64E-03
PSR01043257.hg.1	ENST00000370952	LRRC40	1.56	7.45E-03

PSR01043321.hg.1	ENST00000477096	ZRANB2	1.53	3.04E-02
PSR01043323.hg.1	ENST00000477096	ZRANB2	1.43	9.50E-03
PSR01043328.hg.1	ENST00000477096	ZRANB2	1.45	2.48E-02
PSR01043337.hg.1	BC039814	ZRANB2	1.52	4.91E-03
PSR01000084.hg.1	ENST00000443772	LOC100287934	1.42	1.60E-03
PSR01043479.hg.1	ENST00000370859	SLC44A5	-2.56	9.90E-03
PSR01043480.hg.1	NM_001130058	SLC44A5	-2.41	2.39E-02
PSR01043481.hg.1	ENST00000370855	SLC44A5	-2.05	1.15E-02
PSR01043484.hg.1	ENST00000370855	SLC44A5	-1.82	1.15E-02
PSR01043485.hg.1	NM_001130058	SLC44A5	-2.90	4.19E-02
PSR01043487.hg.1	NM_001130058	SLC44A5	-1.98	2.05E-02
PSR01043488.hg.1	NM_001130058	SLC44A5	-2.29	1.52E-02
PSR01043489.hg.1	NM_001130058	SLC44A5	-1.57	2.61E-02
PSR01043490.hg.1	NM_001130058	SLC44A5	-2.55	9.19E-03
PSR01043491.hg.1	NM_001130058	SLC44A5	-3.49	1.40E-02
PSR01043492.hg.1	NM_001130058	SLC44A5	-3.07	1.84E-02
PSR01043493.hg.1	NM_001130058	SLC44A5	-2.67	2.94E-02
PSR01043494.hg.1	NM_001130058	SLC44A5	-3.81	1.62E-02
PSR01043495.hg.1	NM_001130058	SLC44A5	-3.17	3.48E-02
PSR01043496.hg.1	NM_001130058	SLC44A5	-2.74	1.69E-02
PSR01043497.hg.1	NM_001130058	SLC44A5	-3.21	9.63E-03
PSR01043498.hg.1	NM_001130058	SLC44A5	-2.58	3.00E-02
PSR01043499.hg.1	NM_001130058	SLC44A5	-3.14	2.70E-02
PSR01043500.hg.1	NM_001130058	SLC44A5	-3.13	3.73E-02
PSR01043501.hg.1	NM_001130058	SLC44A5	-1.99	3.90E-02
PSR01043502.hg.1	NM_001130058	SLC44A5	-2.44	1.91E-02
PSR01043504.hg.1	NM_001130058	SLC44A5	-3.18	1.73E-02
PSR01043506.hg.1	NM_001130058	SLC44A5	-2.60	2.19E-02
PSR01043608.hg.1	ENST00000370794	USP33	1.69	3.83E-02
PSR01043661.hg.1	ENST00000489495	FUBP1	1.57	7.01E-03
PSR01043665.hg.1	ENST00000489495	FUBP1	1.60	4.44E-03
PSR01043666.hg.1	ENST00000489495	FUBP1	1.60	1.65E-02
PSR01043667.hg.1	NM_003902	FUBP1	1.42	4.06E-02
PSR01043671.hg.1	ENST00000370768	FUBP1	1.65	8.03E-03
PSR01043687.hg.1	BC017247	FUBP1	1.42	1.51E-02
PSR01043695.hg.1	BC017247	FUBP1	1.41	8.19E-03
PSR01043698.hg.1	BC017247	FUBP1	1.43	8.41E-03
PSR01012724.hg.1	ENST00000370747	IFI44	1.53	2.19E-02
PSR01013026.hg.1	ENST00000451137	CYR61	1.87	3.37E-02
PSR01013027.hg.1	ENST00000451137	CYR61	1.69	5.00E-02
PSR01013035.hg.1	ENST00000451137	CYR61	1.96	4.39E-02
PSR01044062.hg.1	BC110898	ZNHIT6	1.67	3.74E-02
PSR01044067.hg.1	BC110898	ZNHIT6	1.44	1.50E-02
PSR01044181.hg.1	NM_001184766	ODF2L	1.74	2.66E-02
PSR01044188.hg.1	NM_001184766	ODF2L	1.60	3.12E-02
PSR01044190.hg.1	NM_001184766	ODF2L	1.76	2.06E-02
PSR01044201.hg.1	NM_001184766	ODF2L	1.74	1.81E-03
PSR01044207.hg.1	NM_001184766	ODF2L	1.44	3.50E-02
PSR01013323.hg.1	BC030607	LRRC8B	1.80	4.50E-03
PSR01013329.hg.1	NM_015350	LRRC8B	1.51	3.37E-02

PSR01001728.hg.1	ENST00000377443	CA6	-1.44	1.43E-02
PSR01013547.hg.1	NM_024813	RPAP2	-1.76	3.74E-03
PSR01044791.hg.1	ENST00000370280	TMED5	1.60	1.83E-02
PSR01013798.hg.1	ENST00000536817	ABCD3	1.44	1.23E-02
PSR01013810.hg.1	ENST00000536817	ABCD3	1.46	3.24E-02
PSR01013880.hg.1	NM_001199679	TMEM56	1.47	4.25E-02
PSR01013887.hg.1	NM_001199679	TMEM56	1.66	2.10E-02
PSR10020362.hg.1	NM_078470	COX15	1.49	1.02E-02
PSR10020365.hg.1	NM_078470	COX15	1.43	2.94E-02
PSR10020471.hg.1	BC092514	CHUK	1.58	9.58E-04
PSR10020482.hg.1	BC092514	CHUK	1.65	3.79E-03
PSR10020487.hg.1	BC092514	CHUK	1.61	4.73E-03
PSR10020488.hg.1	BC092514	CHUK	1.63	1.25E-02
PSR10020492.hg.1	BC092514	CHUK	1.47	5.64E-03
PSR10008515.hg.1	ENST00000457585	SEMA4G	-1.59	1.80E-02
PSR10008639.hg.1	NM_030929	KAZALD1	-1.52	1.04E-02
PSR10021226.hg.1	BC001595	NT5C2	1.65	3.00E-02
PSR10021231.hg.1	BC001595	NT5C2	1.48	1.22E-02
PSR10009275.hg.1	NM_014720	SLK	1.42	1.53E-02
PSR10009276.hg.1	NM_014720	SLK	1.48	4.16E-02
PSR10009285.hg.1	NM_014720	SLK	1.49	1.67E-02
PSR10009292.hg.1	NM_014720	SLK	1.42	1.11E-02
PSR10009296.hg.1	NM_014720	SLK	1.40	2.39E-02
PSR10012137.hg.1	ENST00000381344	IDI1	2.04	4.73E-02
PSR10012140.hg.1	ENST00000381344	IDI1	1.44	3.46E-02
PSR10012141.hg.1	ENST00000381344	IDI1	1.53	2.43E-02
PSR10009597.hg.1	NM_005445	SMC3	1.50	1.49E-02
PSR10009598.hg.1	NM_005445	SMC3	1.41	2.24E-02
PSR10009636.hg.1	ENST00000539821	RBM20	1.84	2.24E-02
PSR10000846.hg.1	ENST00000417956	CELF2	1.47	2.49E-02
PSR10000860.hg.1	ENST00000417956	CELF2	1.41	2.31E-02
PSR10000865.hg.1	ENST00000417956	CELF2	1.59	1.72E-03
PSR10000866.hg.1	NM_001025077	CELF2	1.62	1.43E-02
PSR10021828.hg.1	ENST00000480130	GPAM	1.53	2.68E-02
PSR10021923.hg.1	ENST00000369360	NRAP	1.41	5.39E-03
PSR10022056.hg.1	ENST00000369263	ABLIM1	-1.48	3.02E-02
PSR10022064.hg.1	ENST00000369263	ABLIM1	-1.58	4.27E-02
PSR10022069.hg.1	NM_001003408	ABLIM1	-2.09	2.11E-02
PSR10022085.hg.1	ENST00000369256	ABLIM1	-1.54	4.28E-02
PSR10010107.hg.1	BC030601	TRUB1	1.42	4.83E-02
PSR10022230.hg.1	ENST00000334464	PDZD8	1.68	2.90E-02
PSR10022252.hg.1	NM_014904	RAB11FIP2	1.49	8.02E-03
PSR10022256.hg.1	BC075074	RAB11FIP2	1.44	2.27E-02
PSR10022272.hg.1	NM_022063	FAM204A	1.60	9.00E-03
PSR10022274.hg.1	NM_022063	FAM204A	1.65	4.41E-02
PSR10022276.hg.1	NM_022063	FAM204A	1.44	1.97E-02
PSR10022279.hg.1	ENST00000469758	FAM204A	1.45	9.73E-03
PSR10022366.hg.1	ENST00000369144	EIF3A	1.50	1.98E-02
PSR10022376.hg.1	ENST00000462527	EIF3A	1.45	4.70E-02
PSR10010516.hg.1	NM_014937	INPP5F	1.42	1.72E-03

PSR10010520.hg.1	ENST00000490818	INPP5F	1.44	8.79E-04
PSR10022979.hg.1	NM_022802	CTBP2	-1.73	1.46E-02
PSR10011290.hg.1	BC146857	DOCK1	2.14	1.93E-02
PSR10001060.hg.1	BC032762	OPTN	-1.46	3.03E-02
PSR10001146.hg.1	NM_003675	PRPF18	1.42	2.79E-02
PSR10013550.hg.1	NM_004412	TRDMT1	1.44	4.33E-02
PSR10013720.hg.1	NM_006393	NEBL	-1.44	5.01E-03
PSR10014101.hg.1	NM_001253866	YME1L1	1.43	1.36E-02
PSR10000023.hg.1	ENST00000381607	ZMYND11	1.51	2.23E-03
PSR10000035.hg.1	ENST00000381607	ZMYND11	1.48	6.84E-03
PSR10012249.hg.1	ENST00000380989	PITRM1	1.47	3.50E-02
PSR10014568.hg.1	BC126281	KIF5B	1.45	2.71E-02
PSR10014642.hg.1	NM_033668	ITGB1	1.66	2.96E-02
PSR10014651.hg.1	ENST00000423113	ITGB1	1.48	2.21E-02
PSR10014652.hg.1	ENST00000423113	ITGB1	1.50	1.01E-02
PSR10014653.hg.1	ENST00000423113	ITGB1	1.43	1.69E-02
PSR10002703.hg.1	NM_182772	CREM	1.44	2.06E-02
PSR10014882.hg.1	ENST00000395867	ZNF248	1.56	1.48E-02
PSR10014888.hg.1	ENST00000395867	ZNF248	1.49	9.80E-03
PSR10003099.hg.1	ENST00000374466	CSGALNACT2	1.53	2.63E-02
PSR10015289.hg.1	ENST00000335258	ZFAND4	1.48	4.21E-02
PSR10000312.hg.1	ENST00000532248	AKR1E2	1.66	5.50E-03
PSR10015901.hg.1	ENST00000542458	ERCC6	1.43	4.57E-02
PSR10000633.hg.1	ENST00000444592	PFKFB3	-2.13	2.66E-02
PSR10016726.hg.1	ENST00000395265	RTKN2	-1.42	9.02E-04
PSR10004373.hg.1	ENST00000438249	REEP3	1.69	4.64E-03
PSR10004435.hg.1	BC012499	SIRT1	1.46	8.56E-04
PSR10004437.hg.1	BC012499	SIRT1	1.67	6.90E-03
PSR10004516.hg.1	NM_021644	HNRNPH3	1.51	3.80E-02
PSR10017115.hg.1	ENST00000539557	SLC25A16	1.61	2.78E-02
PSR10004653.hg.1	NM_004728	DDX21	1.62	2.33E-02
PSR10004660.hg.1	NM_004728	DDX21	1.42	3.17E-02
PSR10004662.hg.1	NM_004728	DDX21	1.83	2.45E-02
PSR10004707.hg.1	ENST00000395098	VPS26A	1.44	1.37E-02
PSR10004944.hg.1	ENST00000520133	COL13A1	-1.63	2.83E-02
PSR10017856.hg.1	ENST00000497106	USP54	1.66	2.52E-02
PSR10017858.hg.1	ENST00000497106	USP54	1.81	1.80E-02
PSR10005806.hg.1	NM_001184783	VDAC2	1.49	4.32E-02
PSR10012726.hg.1	ENST00000471320	KIN	1.66	2.22E-02
PSR10006484.hg.1	BC011349	RGR	-1.44	1.56E-02
PSR10018699.hg.1	ENST00000484070	WAPAL	1.51	9.48E-03
PSR10018702.hg.1	ENST00000372075	WAPAL	1.64	1.53E-03
PSR10006639.hg.1	NM_004329	BMPR1A	1.44	5.85E-03
PSR10006650.hg.1	NM_004329	BMPR1A	1.51	7.94E-03
PSR10006701.hg.1	NM_133447	AGAP11	1.64	3.05E-02
PSR10007156.hg.1	ENST00000487998	RPP30	1.48	2.28E-02
PSR10019106.hg.1	ENST00000371697	ANKRD1	3.00	4.77E-02
PSR10007188.hg.1	ENST00000543648	PCGF5	-1.85	4.53E-03
PSR10019126.hg.1	NM_005398	PPP1R3C	1.47	3.43E-02
PSR10019128.hg.1	NM_005398	PPP1R3C	1.66	1.58E-03

PSR10019129.hg.1	NM_005398	PPP1R3C	1.78	9.78E-04
PSR10007291.hg.1	ENST00000371627	TNKS2	1.59	1.01E-02
PSR10007292.hg.1	NM_025235	TNKS2	1.77	1.73E-02
PSR10019185.hg.1	ENST00000265986	IDE	1.58	4.28E-02
PSR10019214.hg.1	BC096337	IDE	1.41	2.62E-02
PSR10019283.hg.1	BC052617	MYOF	1.51	2.21E-02
PSR10007619.hg.1	NM_015188	TBC1D12	1.41	4.56E-02
PSR10007633.hg.1	NM_015188	TBC1D12	1.72	2.79E-03
PSR10007708.hg.1	ENST00000476630	CYP2C18	-1.54	3.14E-02
PSR10019519.hg.1	ENST00000371246	SORBS1	1.83	7.00E-03
PSR10019773.hg.1	BC136788	TM9SF3	1.44	1.82E-02
PSR10019778.hg.1	BC136788	TM9SF3	1.48	2.47E-02
PSR10019782.hg.1	BC136788	TM9SF3	1.72	4.24E-02
PSR10019808.hg.1	ENST00000371110	PIK3AP1	1.46	3.08E-03
PSR10008088.hg.1	ENST00000455090	ANKRD2	1.73	2.56E-02
PSR10008089.hg.1	ENST00000455090	ANKRD2	1.87	4.11E-02
PSR10008090.hg.1	ENST00000455090	ANKRD2	2.29	3.23E-02
PSR10008091.hg.1	ENST00000455090	ANKRD2	2.22	3.53E-02
PSR10008092.hg.1	ENST00000455090	ANKRD2	2.33	3.75E-02
PSR10008094.hg.1	ENST00000455090	ANKRD2	2.01	4.79E-02
PSR10020156.hg.1	NM_001206528	CRTAC1	2.34	2.66E-02
PSR11011785.hg.1	NM_032021	TMEM133	1.50	4.45E-02
PSR11026708.hg.1	ENST00000299855	MMP3	1.44	1.33E-02
PSR11026835.hg.1	ENST00000532510	LOC643733	1.44	4.66E-02
PSR11012143.hg.1	ENST00000393094	CUL5	1.44	8.88E-03
PSR11027121.hg.1	ENST00000278612	NPAT	1.83	2.47E-02
PSR11027125.hg.1	BC136270	NPAT	1.47	4.65E-02
PSR11027138.hg.1	BC136270	NPAT	1.50	2.86E-02
PSR11027145.hg.1	BC136270	NPAT	1.72	2.19E-02
PSR11027184.hg.1	ENST00000375648	KDELC2	1.49	5.17E-03
PSR11027186.hg.1	ENST00000375648	KDELC2	1.67	1.36E-02
PSR11012541.hg.1	NM_018195	C11orf57	1.68	2.82E-02
PSR11027478.hg.1	ENST00000528832	IL18	1.69	1.20E-02
PSR11012580.hg.1	ENST00000530752	TEX12	1.53	4.30E-02
PSR11013481.hg.1	ENST00000361465	PHLDB1	-1.50	4.16E-02
PSR11028376.hg.1	ENST00000404233	HYOU1	-1.71	3.58E-05
PSR11002577.hg.1	ENST00000535588	USP47	1.45	2.02E-02
PSR11002580.hg.1	ENST00000535588	USP47	1.60	1.19E-02
PSR11002581.hg.1	ENST00000535588	USP47	1.43	1.36E-02
PSR11002590.hg.1	ENST00000535588	USP47	1.53	3.54E-02
PSR11002591.hg.1	ENST00000535588	USP47	1.45	2.41E-02
PSR11002592.hg.1	ENST00000535588	USP47	1.57	7.90E-03
PSR11002593.hg.1	ENST00000535588	USP47	1.70	3.37E-03
PSR11002594.hg.1	ENST00000535588	USP47	1.42	4.70E-02
PSR11002605.hg.1	ENST00000399455	USP47	1.51	2.19E-02
PSR11002607.hg.1	ENST00000399455	USP47	1.49	1.00E-03
PSR11028756.hg.1	ENST00000299333	SCN3B	1.71	4.55E-02
PSR11028757.hg.1	ENST00000299333	SCN3B	1.83	3.42E-03
PSR11029408.hg.1	ENST00000357899	ZBTB44	1.40	4.76E-02
PSR11018052.hg.1	NM_001144061	COPB1	1.48	9.12E-03

PSR11018214.hg.1	BC071599	PLEKHA7	-1.74	2.12E-03
PSR11018530.hg.1	ENST00000438420	HPS5	1.47	3.45E-03
PSR11003167.hg.1	ENST00000265963	GTF2H1	1.41	1.28E-02
PSR11018793.hg.1	NM_148893	SVIP	1.69	1.96E-02
PSR11016349.hg.1	BC022090	NAP1L4	1.45	1.94E-02
PSR11019262.hg.1	NM_001326	CSTF3	1.55	2.58E-02
PSR11019267.hg.1	NM_001326	CSTF3	1.70	3.80E-02
PSR11019274.hg.1	ENST00000438862	CSTF3	1.61	2.42E-02
PSR11004058.hg.1	ENST00000379016	HIPK3	1.42	4.16E-03
PSR11004320.hg.1	BC013166	TRIM44	1.43	4.17E-02
PSR11004322.hg.1	BC013166	TRIM44	1.48	3.41E-02
PSR11016548.hg.1	NM_020402	CHRNA10	-1.41	2.26E-02
PSR11001544.hg.1	ENST00000423050	RRM1	1.42	4.21E-02
PSR11004535.hg.1	ENST00000278353	HSD17B12	1.49	1.28E-02
PSR11004536.hg.1	ENST00000278353	HSD17B12	1.46	3.81E-02
PSR11005011.hg.1	ENST00000526508	ATG13	1.41	3.60E-02
PSR11001596.hg.1	NM_152430	OR51E1	1.67	1.22E-02
PSR11020070.hg.1	BC120869	CKAP5	1.51	1.61E-03
PSR11020073.hg.1	BC120869	CKAP5	1.46	2.83E-03
PSR11020536.hg.1	ENST00000530326	NUP160	1.58	2.76E-02
PSR11020557.hg.1	ENST00000530326	NUP160	1.46	4.62E-02
PSR11020567.hg.1	ENST00000530326	NUP160	1.48	2.15E-02
PSR11020747.hg.1	NM_003146	SSRP1	1.42	2.68E-02
PSR11005946.hg.1	NM_004177	STX3	1.54	3.23E-03
PSR11006067.hg.1	NM_023945	MS4A5	1.46	2.71E-03
PSR11022326.hg.1	NM_015459	ATL3	1.64	3.65E-02
PSR11006955.hg.1	ENST00000538995	RTN3	1.49	4.35E-02
PSR11007106.hg.1	ENST00000246841	FLRT1	-1.51	1.29E-03
PSR11023011.hg.1	NM_138456	BATF2	-1.41	1.17E-02
PSR11023325.hg.1	ENST00000527344	CFL1	-1.44	2.34E-03
PSR11008570.hg.1	NM_001198836	RBM14	-1.55	3.61E-02
PSR11009117.hg.1	ENST00000530046	ALDH3B1	-1.78	2.78E-02
PSR11009469.hg.1	BC034046	PPFIA1	1.47	1.16E-02
PSR11009471.hg.1	BC034046	PPFIA1	1.46	1.07E-02
PSR11024478.hg.1	ENST00000536544	NUMA1	-1.57	3.31E-02
PSR11010248.hg.1	ENST00000529024	NEU3	1.48	1.91E-02
PSR11010317.hg.1	ENST00000278572	RPS3	-1.52	4.13E-02
PSR11010389.hg.1	ENST00000356136	UVRAG	1.80	1.03E-02
PSR11010391.hg.1	ENST00000525872	UVRAG	1.44	3.28E-02
PSR11010393.hg.1	ENST00000356136	UVRAG	1.50	2.92E-02
PSR11010410.hg.1	ENST00000356136	UVRAG	1.53	2.11E-02
PSR11025231.hg.1	NM_004705	PRKRIR	1.42	1.34E-02
PSR11010857.hg.1	BC146778	PCF11	2.26	2.57E-02
PSR11025718.hg.1	ENST00000529031	LOC100506282	1.65	1.15E-02
PSR11010956.hg.1	BC007875	TMEM126A	1.46	2.95E-02
PSR11025840.hg.1	ENST00000398294	CREBZF	1.51	3.21E-02
PSR11025841.hg.1	ENST00000398294	CREBZF	1.45	2.72E-02
PSR11026129.hg.1	NM_020358	TRIM49	1.45	3.81E-02
PSR11026149.hg.1	NM_001105522	TRIM49D2P	1.53	2.51E-04
PSR11011229.hg.1	NM_001195234	TRIM49C	1.45	3.81E-02

PSR11011367.hg.1	NM_033395	KIAA1731	1.73	2.63E-02
PSR11011386.hg.1	NM_033395	KIAA1731	1.57	4.53E-02
PSR11026346.hg.1	ENST00000323929	MRE11A	-1.67	7.45E-03
PSR11002349.hg.1	ENST00000299606	ZNF143	1.56	4.13E-02
PSR11002372.hg.1	ENST00000299606	ZNF143	1.44	2.42E-02
PSR12009861.hg.1	ENST00000392977	ANO4	-1.48	2.81E-02
PSR12024643.hg.1	ENST00000240079	CCDC53	-1.60	4.09E-02
PSR12024868.hg.1	ENST00000240055	NFYB	1.50	3.07E-02
PSR12025036.hg.1	ENST00000552828	CKAP4	-1.49	2.82E-02
PSR12010571.hg.1	ENST00000551813	C12orf23	1.47	1.26E-02
PSR12025236.hg.1	ENST00000420959	CORO1C	1.43	1.71E-02
PSR12025239.hg.1	ENST00000420959	CORO1C	1.52	4.99E-02
PSR12011056.hg.1	NM_032300	TCHP	1.45	6.39E-03
PSR12025530.hg.1	ENST00000547199	ANAPC7	1.57	1.68E-02
PSR12025636.hg.1	NM_139283	PPTC7	1.56	4.52E-02
PSR12025679.hg.1	ENST00000551676	PPP1CC	1.57	1.96E-02
PSR12025818.hg.1	NM_006768	BRAP	1.51	1.21E-03
PSR12011572.hg.1	NM_002834	PTPN11	1.54	2.20E-03
PSR12011577.hg.1	NM_002834	PTPN11	1.55	1.38E-02
PSR12011578.hg.1	NM_002834	PTPN11	1.51	2.24E-02
PSR12011581.hg.1	NM_002834	PTPN11	1.54	7.25E-03
PSR12011588.hg.1	NM_002834	PTPN11	1.41	1.22E-03
PSR12011700.hg.1	ENST00000228928	OAS3	1.47	4.18E-02
PSR12026301.hg.1	ENST00000281928	MED13L	-1.44	3.23E-02
PSR12012124.hg.1	ENST00000229328	PRKAB1	-1.42	2.05E-03
PSR12027271.hg.1	ENST00000302528	CLIP1	1.43	9.04E-03
PSR12027273.hg.1	ENST00000302528	CLIP1	1.44	3.39E-02
PSR12027274.hg.1	ENST00000302528	CLIP1	1.44	5.18E-03
PSR12027285.hg.1	ENST00000302528	CLIP1	1.46	3.26E-02
PSR12027291.hg.1	ENST00000302528	CLIP1	1.46	1.22E-02
PSR12027296.hg.1	ENST00000302528	CLIP1	1.50	1.53E-02
PSR12027297.hg.1	ENST00000302528	CLIP1	1.47	5.28E-03
PSR12027305.hg.1	ENST00000302528	CLIP1	1.51	2.76E-02
PSR12012812.hg.1	ENST00000455982	DENR	1.41	2.40E-02
PSR12027564.hg.1	NM_001167856	SBNO1	1.52	6.89E-03
PSR12027568.hg.1	NM_001167856	SBNO1	2.02	7.53E-03
PSR12013304.hg.1	BC051696	ZNF664	1.58	5.48E-03
PSR12013595.hg.1	ENST00000245255	PIWIL1	1.58	2.84E-03
PSR12013645.hg.1	ENST00000541630	RAN	1.47	2.87E-02
PSR12013650.hg.1	ENST00000541630	RAN	1.54	1.06E-02
PSR12014097.hg.1	NM_001127372	ZNF84	1.51	7.66E-03
PSR12014100.hg.1	NM_001127372	ZNF84	1.41	1.26E-02
PSR12014104.hg.1	NM_001127372	ZNF84	1.47	4.30E-02
PSR12028371.hg.1	ENST00000537226	ZNF891	1.52	2.47E-02
PSR12014148.hg.1	BC024182	ZNF10	1.48	1.56E-02
PSR12014186.hg.1	NM_001165883	ZNF268	1.50	7.16E-03
PSR12016485.hg.1	ENST00000531049	C12orf36	1.59	3.87E-02
PSR12002419.hg.1	ENST00000543189	ATF7IP	1.59	3.95E-02
PSR12016744.hg.1	ENST00000534946	LMO3	1.56	2.41E-02
PSR12016750.hg.1	ENST00000534946	LMO3	1.71	2.03E-02

PSR12016810.hg.1	ENST00000538330	PLCZ1	1.51	4.55E-03
PSR12016828.hg.1	BC125067	PLCZ1	1.41	3.97E-02
PSR12002695.hg.1	ENST00000542828	PLEKHA5	1.89	3.11E-02
PSR12016917.hg.1	NM_002907	RECQL	1.63	6.76E-03
PSR12002940.hg.1	ENST00000335148	ETNK1	1.72	3.23E-02
PSR12017257.hg.1	ENST00000311936	KRAS	1.63	2.38E-02
PSR12017276.hg.1	ENST00000458174	IFLTD1	1.48	3.55E-02
PSR12017371.hg.1	ENST00000381340	ITPR2	1.52	2.80E-02
PSR12017384.hg.1	ENST00000381340	ITPR2	1.96	9.27E-03
PSR12003163.hg.1	NM_004264	MED21	1.64	2.05E-03
PSR12003317.hg.1	BC137116	KLHL42	1.58	6.51E-03
PSR12017671.hg.1	NM_006390	IPO8	1.41	1.22E-02
PSR12017677.hg.1	NM_006390	IPO8	1.45	1.23E-02
PSR12017681.hg.1	NM_001190995	IPO8	1.42	2.36E-02
PSR12017692.hg.1	NM_006390	IPO8	1.46	1.87E-02
PSR12017728.hg.1	ENST00000308433	CAPRIN2	1.59	1.65E-03
PSR12017848.hg.1	ENST00000389082	DENND5B	-1.43	1.45E-02
PSR12003613.hg.1	ENST00000549701	DNM1L	1.45	9.43E-03
PSR12003621.hg.1	NM_005690	DNM1L	1.93	1.95E-02
PSR12003640.hg.1	NM_032834	ALG10	1.45	4.00E-02
PSR12018012.hg.1	ENST00000395670	KIF21A	1.68	4.76E-02
PSR12018015.hg.1	ENST00000395670	KIF21A	1.54	1.11E-03
PSR12018045.hg.1	ENST00000361418	KIF21A	1.43	4.81E-02
PSR12018051.hg.1	ENST00000361418	KIF21A	1.43	2.88E-02
PSR12018052.hg.1	ENST00000361418	KIF21A	1.42	2.91E-02
PSR12018056.hg.1	ENST00000361418	KIF21A	1.76	1.82E-02
PSR12018057.hg.1	ENST00000361418	KIF21A	1.54	1.44E-02
PSR12018058.hg.1	ENST00000361418	KIF21A	1.60	1.42E-04
PSR12018131.hg.1	NM_001099650	GXYLT1	1.40	3.12E-02
PSR12018134.hg.1	NM_001099650	GXYLT1	1.54	2.53E-02
PSR12018157.hg.1	NM_001190977	YAF2	-1.48	1.15E-02
PSR12000592.hg.1	ENST00000179259	C12orf5	2.08	1.93E-02
PSR12000593.hg.1	ENST00000179259	C12orf5	1.62	2.27E-02
PSR12004138.hg.1	ENST00000426898	ANO6	1.69	3.04E-03
PSR12004179.hg.1	ENST00000422737	ARID2	1.43	8.55E-03
PSR12004181.hg.1	ENST00000422737	ARID2	1.50	1.16E-02
PSR12004182.hg.1	ENST00000422737	ARID2	1.76	8.27E-03
PSR12004183.hg.1	ENST00000422737	ARID2	1.55	1.38E-02
PSR12018408.hg.1	ENST00000395453	SCAF11	1.59	1.20E-02
PSR12018410.hg.1	ENST00000395453	SCAF11	1.53	8.78E-03
PSR12018476.hg.1	ENST00000256689	SLC38A2	-1.48	1.36E-02
PSR12018483.hg.1	ENST00000266579	SLC38A4	1.68	3.48E-02
PSR12018487.hg.1	ENST00000266579	SLC38A4	1.67	2.84E-02
PSR12004433.hg.1	NM_001206915	CACNB3	-1.46	3.72E-03
PSR12004904.hg.1	ENST00000518444	LARP4	1.59	2.85E-02
PSR12004928.hg.1	ENST00000518444	LARP4	1.51	4.19E-02
PSR12019678.hg.1	ENST00000262051	SLC11A2	-1.45	3.20E-02
PSR12019754.hg.1	ENST00000549867	TFCP2	1.60	4.49E-02
PSR12005881.hg.1	NM_004503	HOXC6	1.50	2.42E-02
PSR12020741.hg.1	ENST00000209875	CBX5	1.44	4.45E-02

PSR12021595.hg.1	BC003005	PTGES3	1.48	2.25E-02
PSR12007085.hg.1	NM_004984	KIF5A	-1.40	2.83E-02
PSR12022228.hg.1	ENST00000379141	LRIG3	1.44	1.47E-02
PSR12007611.hg.1	ENST00000331710	TBK1	1.47	1.14E-02
PSR12007612.hg.1	ENST00000331710	TBK1	1.63	3.61E-02
PSR12007625.hg.1	ENST00000331710	TBK1	1.42	4.86E-02
PSR12014921.hg.1	ENST00000355479	VAMP1	1.59	4.64E-03
PSR12007841.hg.1	NM_018448	CAND1	1.60	4.12E-02
PSR12007851.hg.1	BC050341	CAND1	1.42	3.33E-02
PSR12022672.hg.1	NM_001205028	MDM1	1.80	3.34E-03
PSR12022727.hg.1	BC022276	CPM	1.53	3.19E-02
PSR12022730.hg.1	BC022276	CPM	1.66	4.62E-02
PSR12022731.hg.1	BC022276	CPM	1.54	2.12E-02
PSR12008118.hg.1	NM_001042555	FRS2	1.43	2.86E-03
PSR12008240.hg.1	ENST00000548230	CNOT2	1.45	7.17E-03
PSR12008273.hg.1	ENST00000549359	LOC100507330	-1.46	7.63E-03
PSR12008287.hg.1	ENST00000546836	LOC100507330	-1.47	1.83E-03
PSR12022966.hg.1	ENST00000549407	ZFC3H1	1.53	3.31E-03
PSR12023162.hg.1	NM_139207	NAP1L1	1.61	3.55E-02
PSR12023169.hg.1	ENST00000535020	NAP1L1	1.68	2.55E-02
PSR12023175.hg.1	ENST00000535020	NAP1L1	1.47	1.33E-02
PSR12023187.hg.1	ENST00000547993	NAP1L1	1.46	9.11E-03
PSR12015479.hg.1	NM_203416	CD163	-1.55	2.61E-02
PSR12023244.hg.1	ENST00000438913	OSBPL8	1.55	1.84E-02
PSR12008724.hg.1	NM_173591	OTOGL	-1.47	3.05E-04
PSR12023622.hg.1	ENST00000547691	CEP290	1.42	2.75E-02
PSR12023638.hg.1	ENST00000547691	CEP290	1.48	1.81E-02
PSR12023668.hg.1	ENST00000397838	CEP290	1.67	1.66E-02
PSR12023679.hg.1	ENST00000552770	CEP290	2.34	1.04E-02
PSR12009033.hg.1	NM_181783	TMTC3	1.53	1.94E-02
PSR12009036.hg.1	NM_181783	TMTC3	1.64	1.55E-02
PSR12001749.hg.1	ENST00000299698	A2ML1	-1.49	2.29E-02
PSR12023800.hg.1	NM_001682	ATP2B1	1.40	1.76E-02
PSR12023801.hg.1	NM_001682	ATP2B1	1.51	1.34E-02
PSR12023802.hg.1	NM_001682	ATP2B1	1.44	9.89E-03
PSR12023803.hg.1	ENST00000359142	ATP2B1	2.08	1.58E-03
PSR12023910.hg.1	ENST00000322349	EEA1	1.43	2.40E-02
PSR12023911.hg.1	ENST00000322349	EEA1	1.49	1.22E-02
PSR12023938.hg.1	ENST00000540777	EEA1	1.44	2.77E-02
PSR12024085.hg.1	NM_001127362	NR2C1	1.48	2.88E-03
PSR12024342.hg.1	ENST00000548760	TMPO-AS1	-1.46	2.40E-02
PSR13009633.hg.1	BC050434	ARGLU1	1.66	4.75E-03
PSR13009683.hg.1	ENST00000405925	LIG4	1.44	1.39E-02
PSR13004136.hg.1	NM_001198950	MYO16	-1.42	3.13E-02
PSR13004353.hg.1	NM_001113513	ARHGEF7	-1.56	1.14E-02
PSR13000170.hg.1	NM_006531	IFT88	1.42	2.71E-02
PSR13000173.hg.1	NM_006531	IFT88	1.65	9.41E-03
PSR13000174.hg.1	NM_006531	IFT88	1.45	1.33E-02
PSR13000175.hg.1	NM_006531	IFT88	1.64	3.12E-02
PSR13000178.hg.1	NM_006531	IFT88	1.55	4.96E-02

PSR13000201.hg.1	NM_006531	IFT88	1.45	2.54E-02
PSR13005240.hg.1	ENST00000473438	N6AMT2	-1.43	4.45E-02
PSR13005250.hg.1	BC113573	XPO4	1.77	4.39E-02
PSR13000585.hg.1	ENST00000463407	NUPL1	1.43	3.99E-02
PSR13000592.hg.1	ENST00000463407	NUPL1	1.50	9.38E-03
PSR13000593.hg.1	ENST00000463407	NUPL1	1.52	3.13E-02
PSR13005680.hg.1	NM_183044	RNF6	-1.43	4.58E-02
PSR13005775.hg.1	BC036755	LNX2	1.41	7.24E-03
PSR13006015.hg.1	NM_002128	HMGB1	1.46	1.24E-02
PSR13006044.hg.1	ENST00000468384	HMGB1	1.89	3.17E-02
PSR13001312.hg.1	ENST00000402346	NBEA	1.60	3.49E-02
PSR13006446.hg.1	NM_001142294	SPG20	-1.70	2.93E-02
PSR13006626.hg.1	ENST00000538347	POSTN	2.20	2.69E-02
PSR13006628.hg.1	ENST00000538347	POSTN	1.73	3.24E-02
PSR13001521.hg.1	ENST00000280481	FREM2	1.44	4.43E-02
PSR13001532.hg.1	ENST00000280481	FREM2	1.55	4.46E-04
PSR13001535.hg.1	ENST00000280481	FREM2	1.40	3.07E-02
PSR13001542.hg.1	ENST00000280481	FREM2	1.44	1.40E-02
PSR13001544.hg.1	ENST00000280481	FREM2	1.43	3.02E-02
PSR13001645.hg.1	NM_007187	WBP4	1.70	1.65E-02
PSR13001648.hg.1	ENST00000379487	WBP4	1.51	4.86E-02
PSR13007044.hg.1	BC000868	SMIM2	1.52	6.91E-04
PSR13002049.hg.1	ENST00000465942	COG3	1.49	2.92E-02
PSR13002062.hg.1	ENST00000349995	COG3	1.40	1.35E-02
PSR13007311.hg.1	ENST00000323076	LCP1	1.50	1.32E-02
PSR13007468.hg.1	ENST00000378594	MED4	1.42	2.24E-02
PSR13007472.hg.1	ENST00000378594	MED4	1.44	3.00E-02
PSR13007473.hg.1	ENST00000378594	MED4	1.42	3.99E-02
PSR13007474.hg.1	ENST00000378594	MED4	1.45	4.11E-02
PSR13002182.hg.1	BC040540	RB1	1.63	1.11E-02
PSR13007533.hg.1	ENST00000544492	RCBTB2	1.53	2.52E-02
PSR13007552.hg.1	NM_001268	RCBTB2	1.77	1.23E-02
PSR13002501.hg.1	ENST00000336617	RNASEH2B	-1.43	4.82E-03
PSR13007835.hg.1	BC039829	INTS6	1.51	1.13E-02
PSR13002585.hg.1	ENST00000298125	WDFY2	1.42	1.87E-02
PSR13008355.hg.1	ENST00000377818	MZT1	1.40	2.11E-02
PSR13002988.hg.1	ENST00000377687	KLF5	1.48	2.51E-03
PSR13002996.hg.1	ENST00000377687	KLF5	2.37	3.86E-02
PSR13003070.hg.1	ENST00000357063	LMO7	1.76	2.75E-02
PSR13003078.hg.1	ENST00000357063	LMO7	1.44	4.70E-02
PSR13003101.hg.1	ENST00000357063	LMO7	1.54	2.21E-02
PSR13008600.hg.1	ENST00000360084	MYCBP2	1.44	2.45E-02
PSR13003217.hg.1	NM_001242871	SLAIN1	1.43	2.59E-02
PSR13008704.hg.1	ENST00000282003	RNF219	1.41	4.41E-02
PSR13008715.hg.1	ENST00000484573	RBM26	1.63	3.32E-02
PSR13008756.hg.1	ENST00000438737	RBM26	1.46	3.60E-02
PSR13008758.hg.1	ENST00000438737	RBM26	1.47	2.16E-02
PSR13003489.hg.1	BC047936	DNAJC3	1.50	1.21E-02
PSR13003493.hg.1	BC047936	DNAJC3	1.55	1.50E-02
PSR13003716.hg.1	NM_001144072	UBAC2	1.59	3.89E-02

PSR14016888.hg.1	BC063598	DEGS2	-1.85	6.34E-03
PSR14007992.hg.1	ENST00000554852	MEG8	1.43	4.20E-02
PSR14008002.hg.1	ENST00000554323	MEG8	1.50	1.92E-02
PSR14008268.hg.1	ENST00000556260	PPP2R5C	1.41	1.84E-02
PSR14020852.hg.1	ENST00000390605	IGHV1-18	1.49	7.82E-04
PSR14022342.hg.1	ENST00000454421	IGHV3-64	1.54	3.55E-02
PSR14000096.hg.1	ENST00000431094	LOC100506303	1.62	1.32E-03
PSR14009432.hg.1	ENST00000400192	LOC101060483	1.60	8.88E-04
PSR14009493.hg.1	ENST00000344684	POTEM	1.44	3.81E-02
PSR14009495.hg.1	ENST00000344684	POTEM	1.84	2.96E-03
PSR14000370.hg.1	NM_002934	RNASE2	1.40	2.38E-02
PSR14009983.hg.1	ENST00000538230	SUPT16H	1.47	6.54E-03
PSR14011114.hg.1	ENST00000554411	CIDEB	-2.06	4.74E-02
PSR14002103.hg.1	ENST00000458591	SCFD1	1.52	3.89E-02
PSR14011691.hg.1	NM_138288	SPTSSA	1.56	1.94E-02
PSR14011765.hg.1	ENST00000543083	BAZ1A	1.42	1.78E-02
PSR14011772.hg.1	ENST00000543083	BAZ1A	1.67	4.68E-03
PSR14011785.hg.1	NM_182648	BAZ1A	1.40	2.98E-02
PSR14011787.hg.1	NM_182648	BAZ1A	1.49	1.25E-02
PSR14002337.hg.1	ENST00000556994	SRP54	1.57	4.11E-02
PSR14011880.hg.1	BC150596	RALGAPA1	1.85	2.51E-02
PSR14002437.hg.1	BC006250	BRMS1L	1.59	3.19E-02
PSR14002444.hg.1	BC006250	BRMS1L	1.59	1.18E-03
PSR14012083.hg.1	ENST00000536508	SEC23A	1.64	3.12E-02
PSR14012107.hg.1	ENST00000536508	SEC23A	1.42	3.20E-02
PSR14002644.hg.1	NM_002687	PNN	1.44	2.54E-02
PSR14002645.hg.1	NM_002687	PNN	1.50	4.84E-02
PSR14002646.hg.1	NM_002687	PNN	1.42	2.37E-02
PSR14002650.hg.1	NM_002687	PNN	1.67	1.04E-02
PSR14002940.hg.1	ENST00000504161	MGAT2	1.67	4.27E-02
PSR14012402.hg.1	ENST00000556672	NEMF	1.43	2.18E-02
PSR14003007.hg.1	NM_015684	ATP5S	1.70	2.68E-02
PSR14012655.hg.1	ENST00000555033	MAP4K5	1.46	7.05E-03
PSR14012664.hg.1	ENST00000555033	MAP4K5	1.44	4.80E-03
PSR14012696.hg.1	ENST00000324679	SAV1	1.58	1.54E-02
PSR14012702.hg.1	ENST00000324679	SAV1	1.49	4.70E-02
PSR14012720.hg.1	ENST00000389868	NIN	1.47	1.13E-02
PSR14012746.hg.1	ENST00000389868	NIN	1.73	2.05E-02
PSR14003204.hg.1	NM_016039	C14orf166	1.55	1.16E-04
PSR14012946.hg.1	NM_014584	ERO1L	1.56	1.77E-02
PSR14012948.hg.1	NM_014584	ERO1L	1.41	1.86E-02
PSR14012949.hg.1	NM_014584	ERO1L	1.49	3.23E-02
PSR14012951.hg.1	NM_014584	ERO1L	2.26	4.14E-03
PSR14012953.hg.1	NM_014584	ERO1L	1.82	1.24E-02
PSR14012954.hg.1	NM_014584	ERO1L	1.45	3.55E-03
PSR14012955.hg.1	NM_014584	ERO1L	1.47	1.44E-03
PSR14012956.hg.1	NM_014584	ERO1L	1.46	1.26E-03
PSR14012957.hg.1	NM_014584	ERO1L	1.41	1.64E-02
PSR14013151.hg.1	BC063041	WDHD1	1.44	1.71E-02
PSR14013160.hg.1	BC063041	WDHD1	1.53	4.60E-02

PSR14003499.hg.1	ENST00000416613	KTN1	1.46	2.60E-02
PSR14003503.hg.1	ENST00000416613	KTN1	1.44	2.43E-02
PSR14003513.hg.1	ENST00000416613	KTN1	2.02	1.14E-02
PSR14003516.hg.1	ENST00000416613	KTN1	1.46	4.68E-02
PSR14013390.hg.1	ENST00000556002	FLJ31306	1.57	1.29E-02
PSR14013398.hg.1	ENST00000557660	FLJ31306	1.90	1.59E-02
PSR14003729.hg.1	ENST00000395168	ARID4A	1.59	2.95E-02
PSR14003777.hg.1	ENST00000354386	KIAA0586	1.60	9.43E-03
PSR14003778.hg.1	ENST00000556134	KIAA0586	1.44	1.45E-02
PSR14003975.hg.1	ENST00000406854	PCNXL4	1.64	4.25E-02
PSR14003979.hg.1	ENST00000406854	PCNXL4	1.48	4.42E-03
PSR14003980.hg.1	NM_022495	PCNXL4	1.50	1.52E-02
PSR14003981.hg.1	NM_022495	PCNXL4	1.47	2.85E-02
PSR14013618.hg.1	NM_174978	C14orf39	1.50	4.40E-02
PSR14013638.hg.1	ENST00000555955	SIX1	-1.53	1.27E-03
PSR14004247.hg.1	ENST00000357395	SYNE2	1.40	3.70E-02
PSR14004251.hg.1	ENST00000357395	SYNE2	1.43	3.83E-02
PSR14004277.hg.1	ENST00000357395	SYNE2	1.44	1.68E-02
PSR14004285.hg.1	ENST00000357395	SYNE2	1.51	4.38E-02
PSR14004541.hg.1	ENST00000359118	CHURC1	1.62	5.13E-03
PSR14004542.hg.1	ENST00000359118	CHURC1	1.43	3.56E-02
PSR14004582.hg.1	ENST00000553633	LOC100506321	-1.53	7.89E-03
PSR14004612.hg.1	NM_178155	FUT8	1.42	1.91E-02
PSR14004619.hg.1	NM_178155	FUT8	1.81	1.88E-02
PSR14004763.hg.1	NM_004094	EIF2S1	1.45	7.03E-03
PSR14004764.hg.1	NM_004094	EIF2S1	1.57	5.30E-03
PSR14005061.hg.1	NM_006925	SRSF5	1.41	9.81E-04
PSR14005064.hg.1	NM_006925	SRSF5	1.41	1.11E-03
PSR14005068.hg.1	NM_006925	SRSF5	1.74	4.21E-02
PSR14005346.hg.1	ENST00000261973	RBM25	1.47	2.18E-02
PSR14005355.hg.1	ENST00000525321	RBM25	1.54	1.03E-02
PSR14005366.hg.1	ENST00000261973	RBM25	1.63	8.56E-03
PSR14005370.hg.1	ENST00000261973	RBM25	1.42	2.07E-02
PSR14005372.hg.1	ENST00000261973	RBM25	1.68	3.80E-02
PSR14005962.hg.1	NM_015072	TTLL5	1.59	2.37E-03
PSR14005969.hg.1	ENST00000557636	TTLL5	1.51	4.57E-03
PSR14006339.hg.1	NM_138970	NRXN3	-1.53	4.48E-02
PSR14015565.hg.1	ENST00000336735	SEL1L	1.52	2.88E-02
PSR14006614.hg.1	ENST00000406216	ZC3H14	1.85	1.05E-02
PSR14006727.hg.1	NM_002802	PSMC1	1.64	3.82E-02
PSR14006988.hg.1	ENST00000439315	GOLGA5	1.44	2.05E-02
PSR14016379.hg.1	ENST00000298896	BTBD7	1.51	2.65E-02
PSR14007524.hg.1	ENST00000392990	PAPOLA	1.55	4.42E-02
PSR14007526.hg.1	ENST00000392990	PAPOLA	1.41	1.85E-02
PSR14007531.hg.1	ENST00000392990	PAPOLA	1.50	2.23E-02
PSR15018677.hg.1	ENST00000428002	TM2D3	1.48	4.47E-02
PSR15009873.hg.1	BC012097	OCA2	-1.50	4.07E-02
PSR15001356.hg.1	ENST00000361728	RYR3	2.74	3.88E-02
PSR15001358.hg.1	ENST00000361728	RYR3	3.51	1.58E-02
PSR15001359.hg.1	ENST00000361728	RYR3	2.62	4.49E-02

PSR15001362.hg.1	ENST00000361728	RYR3	2.34	4.42E-02
PSR15001365.hg.1	ENST00000361728	RYR3	2.28	3.58E-02
PSR15001366.hg.1	ENST00000361728	RYR3	2.99	3.02E-02
PSR15001371.hg.1	ENST00000361728	RYR3	1.76	3.43E-02
PSR15001372.hg.1	ENST00000361728	RYR3	2.59	2.49E-02
PSR15001374.hg.1	ENST00000361728	RYR3	2.31	4.01E-02
PSR15001376.hg.1	ENST00000361728	RYR3	2.08	4.78E-02
PSR15001392.hg.1	ENST00000361728	RYR3	2.49	1.28E-02
PSR15001393.hg.1	ENST00000361728	RYR3	1.91	3.01E-02
PSR15001396.hg.1	ENST00000361728	RYR3	2.34	2.28E-02
PSR15001400.hg.1	ENST00000361728	RYR3	2.65	4.46E-02
PSR15001403.hg.1	ENST00000361728	RYR3	2.78	3.91E-02
PSR15001404.hg.1	ENST00000361728	RYR3	2.06	1.37E-02
PSR15001405.hg.1	ENST00000361728	RYR3	1.66	3.29E-02
PSR15001407.hg.1	ENST00000361728	RYR3	1.67	2.27E-02
PSR15001409.hg.1	ENST00000361728	RYR3	2.30	2.16E-02
PSR15001413.hg.1	ENST00000361728	RYR3	2.65	3.56E-02
PSR15001414.hg.1	ENST00000361728	RYR3	1.94	4.96E-02
PSR15001415.hg.1	ENST00000361728	RYR3	2.26	2.70E-02
PSR15001416.hg.1	ENST00000361728	RYR3	1.69	4.69E-02
PSR15001421.hg.1	ENST00000361728	RYR3	1.76	4.44E-02
PSR15001422.hg.1	ENST00000361728	RYR3	2.49	3.80E-02
PSR15001428.hg.1	ENST00000361728	RYR3	2.81	3.62E-02
PSR15001434.hg.1	ENST00000361728	RYR3	2.11	4.64E-02
PSR15001438.hg.1	ENST00000361728	RYR3	2.18	4.01E-02
PSR15001440.hg.1	ENST00000361728	RYR3	1.95	4.34E-02
PSR15001443.hg.1	ENST00000361728	RYR3	1.99	4.48E-02
PSR15001444.hg.1	ENST00000361728	RYR3	1.92	4.95E-02
PSR15001447.hg.1	ENST00000361728	RYR3	1.76	4.84E-02
PSR15001449.hg.1	ENST00000361728	RYR3	2.08	4.64E-02
PSR15001450.hg.1	ENST00000361728	RYR3	2.71	2.24E-02
PSR15001451.hg.1	ENST00000361728	RYR3	2.28	4.12E-02
PSR15001452.hg.1	ENST00000361728	RYR3	3.02	3.45E-02
PSR15001453.hg.1	ENST00000361728	RYR3	2.50	4.66E-02
PSR15001457.hg.1	ENST00000361728	RYR3	2.79	3.35E-02
PSR15001459.hg.1	ENST00000361728	RYR3	2.10	3.97E-02
PSR15001460.hg.1	ENST00000361728	RYR3	2.84	2.87E-02
PSR15001705.hg.1	ENST00000260356	THBS1	1.73	1.01E-02
PSR15001717.hg.1	ENST00000260356	THBS1	1.67	1.76E-02
PSR15001718.hg.1	ENST00000260356	THBS1	2.22	9.40E-03
PSR15001742.hg.1	ENST00000263791	EIF2AK4	1.48	1.17E-02
PSR15001757.hg.1	ENST00000263791	EIF2AK4	1.43	4.92E-02
PSR15001771.hg.1	ENST00000263791	EIF2AK4	1.47	4.65E-02
PSR15011012.hg.1	NM_003134	SRP14	1.53	1.81E-02
PSR15011013.hg.1	NM_003134	SRP14	1.45	4.02E-02
PSR15011306.hg.1	ENST00000361937	INO80	-1.43	3.87E-02
PSR15002698.hg.1	NM_012142	CCNDBP1	1.46	3.36E-02
PSR15012119.hg.1	BC064387	CATSPER2	1.61	2.98E-02
PSR15003048.hg.1	ENST00000260327	CTDSPL2	1.80	1.12E-02
PSR15012403.hg.1	BC153879	SPG11	1.42	2.08E-02

PSR15012405.hg.1	BC153879	SPG11	1.62	3.20E-03
PSR15012407.hg.1	BC153879	SPG11	1.43	4.83E-02
PSR15012412.hg.1	BC153879	SPG11	1.46	1.83E-02
PSR15003489.hg.1	NM_001025248	DUT	-1.41	3.34E-02
PSR15012844.hg.1	ENST00000332408	SHC4	1.43	4.10E-02
PSR15012892.hg.1	NM_004236	COPS2	1.50	3.99E-02
PSR15003596.hg.1	NM_002009	FGF7	1.83	4.97E-02
PSR15012978.hg.1	NM_024837	ATP8B4	2.02	3.38E-02
PSR15013062.hg.1	NM_017672	TRPM7	1.54	2.78E-02
PSR15013069.hg.1	NM_017672	TRPM7	1.55	2.32E-02
PSR15013070.hg.1	NM_017672	TRPM7	1.62	3.77E-02
PSR15013486.hg.1	NM_000259	MYO5A	1.53	2.32E-02
PSR15003932.hg.1	ENST00000545554	UNC13C	1.70	6.25E-03
PSR15003944.hg.1	ENST00000537900	UNC13C	1.49	2.44E-02
PSR15003991.hg.1	ENST00000537232	TEX9	1.73	3.55E-02
PSR15003992.hg.1	ENST00000558127	TEX9	1.42	1.66E-02
PSR15003993.hg.1	ENST00000537232	TEX9	1.46	4.99E-02
PSR15003997.hg.1	ENST00000560582	TEX9	1.80	1.29E-03
PSR15014017.hg.1	NM_001110	ADAM10	1.55	3.36E-02
PSR15014079.hg.1	NM_024755	SLTM	1.58	3.65E-03
PSR15004300.hg.1	ENST00000288228	FAM81A	-1.49	2.63E-03
PSR15004511.hg.1	ENST00000561311	TLN2	1.41	4.01E-02
PSR15004711.hg.1	BC018113	USP3	1.71	1.30E-02
PSR15015277.hg.1	ENST00000558725	AAGAB	1.56	2.07E-02
PSR15015278.hg.1	ENST00000558725	AAGAB	1.53	3.24E-03
PSR15015279.hg.1	ENST00000558725	AAGAB	1.69	3.64E-03
PSR15015459.hg.1	ENST00000558201	TLE3	1.67	2.32E-03
PSR15005730.hg.1	NM_001172623	NEO1	1.67	4.73E-02
PSR15015869.hg.1	NM_001039614	C15orf59	-1.82	2.06E-02
PSR15016135.hg.1	ENST00000457294	FAM219B	-1.49	5.17E-03
PSR15016141.hg.1	ENST00000357635	FAM219B	-1.52	3.62E-04
PSR15006279.hg.1	BC020204	FBXO22	1.45	3.75E-02
PSR15006538.hg.1	NM_004136	IREB2	1.45	3.00E-03
PSR15006575.hg.1	ENST00000559906	PSMA4	1.49	4.76E-02
PSR15006598.hg.1	BC093069	PSMA4	2.81	4.26E-02
PSR15006631.hg.1	NM_006791	MORF4L1	1.45	3.33E-02
PSR15006642.hg.1	NM_006791	MORF4L1	1.57	5.55E-03
PSR15016989.hg.1	ENST00000268206	EFTUD1	1.43	1.21E-02
PSR15017243.hg.1	NM_001007122	FSD2	1.46	4.20E-02
PSR15017253.hg.1	NM_001007122	FSD2	1.46	3.16E-02
PSR15007220.hg.1	ENST00000286760	WHAMM	1.45	2.40E-02
PSR15007748.hg.1	ENST00000306072	ISG20	-1.69	1.11E-03
PSR15008586.hg.1	ENST00000420239	LOC100507217	1.59	4.91E-02
PSR15018248.hg.1	ENST00000558246	LOC100507325	1.48	3.01E-02
PSR15008778.hg.1	BC028704	ARRDC4	1.92	1.43E-02
PSR15008787.hg.1	NM_183376	ARRDC4	1.61	1.89E-02
PSR15018393.hg.1	NM_001040655	TTC23	1.46	3.34E-02
PSR15018402.hg.1	NM_001040655	TTC23	1.44	4.94E-03
PSR15018403.hg.1	NM_001040655	TTC23	1.88	3.86E-02
PSR16012479.hg.1	NM_004862	LITAF	1.69	6.26E-03

PSR16012481.hg.1	NM_004862	LITAF	1.57	3.06E-02
PSR16012642.hg.1	ENST00000539279	PARN	1.42	8.27E-03
PSR16012918.hg.1	BC131732	ABCC6	-1.42	2.15E-03
PSR16013107.hg.1	BC105273	RPS15A	-1.43	8.56E-03
PSR16003166.hg.1	NM_001199022	CCP110	-1.42	2.21E-02
PSR16013321.hg.1	ENST00000219151	ACSM1	-1.46	1.43E-02
PSR16013465.hg.1	BC096305	ZP2	-1.41	3.85E-03
PSR16015032.hg.1	ENST00000247470	PYCARD	-1.41	9.38E-03
PSR16015779.hg.1	NM_007006	NUDT21	1.49	1.62E-02
PSR16015782.hg.1	NM_007006	NUDT21	1.79	3.95E-02
PSR16015812.hg.1	NM_031885	BBS2	1.50	2.49E-02
PSR16016084.hg.1	ENST00000422872	CNOT1	1.44	1.69E-02
PSR16016166.hg.1	BC013609	CDH11	1.72	2.61E-02
PSR16016167.hg.1	BC013609	CDH11	1.46	4.22E-02
PSR16016172.hg.1	BC013609	CDH11	1.48	3.51E-02
PSR16007192.hg.1	ENST00000536005	BEAN1	-1.45	2.10E-03
PSR16016379.hg.1	NM_016062	FAM96B	-1.52	5.39E-03
PSR16007416.hg.1	ENST00000521920	FBXL8	-1.46	4.95E-02
PSR16017419.hg.1	BC036283	AP1G1	1.46	1.18E-02
PSR16017560.hg.1	ENST00000397992	ZFHX3	-1.41	2.83E-02
PSR16009029.hg.1	BC044840	GAN	1.57	1.40E-03
PSR16009035.hg.1	ENST00000248272	GAN	1.52	5.87E-04
PSR16009193.hg.1	NM_019065	NECAB2	-1.50	4.90E-03
PSR16010046.hg.1	BC111030	SPIRE2	-1.42	1.04E-02
PSR17015472.hg.1	NM_002470	MYH3	1.98	1.91E-02
PSR17015476.hg.1	NM_002470	MYH3	1.90	3.10E-02
PSR17015484.hg.1	NM_002470	MYH3	1.74	4.68E-02
PSR17015488.hg.1	NM_002470	MYH3	1.81	2.28E-02
PSR17015489.hg.1	NM_002470	MYH3	1.88	1.21E-02
PSR17002236.hg.1	ENST00000544416	ARHGAP44	-1.53	3.31E-02
PSR17015652.hg.1	ENST00000494511	PMP22	1.72	2.91E-02
PSR17015656.hg.1	ENST00000494511	PMP22	1.45	1.49E-02
PSR17015658.hg.1	ENST00000494511	PMP22	1.46	3.79E-02
PSR17015659.hg.1	BC091499	PMP22	1.50	1.89E-02
PSR17013073.hg.1	ENST00000263071	SCARF1	-1.41	5.20E-03
PSR17002644.hg.1	ENST00000399273	CCDC144A	2.43	5.00E-02
PSR17016146.hg.1	BC001891	COPS3	-1.42	4.21E-02
PSR17013255.hg.1	BC126110	TSR1	-1.58	2.55E-02
PSR17000258.hg.1	BC064638	PAFAH1B1	1.48	4.32E-02
PSR17000272.hg.1	BC064638	PAFAH1B1	1.42	2.63E-02
PSR17004165.hg.1	NM_005208	CRYBA1	1.57	1.05E-02
PSR17004441.hg.1	ENST00000321990	ATAD5	1.49	2.56E-02
PSR17004600.hg.1	ENST00000498569	NF1	1.40	2.98E-03
PSR17005176.hg.1	BC017931	ZNHIT3	1.51	8.18E-03
PSR17005195.hg.1	BC137491	GGNBP2	1.80	1.63E-03
PSR17005197.hg.1	BC137491	GGNBP2	1.44	1.10E-02
PSR17018607.hg.1	NM_198836	ACACA	1.73	7.75E-03
PSR17005761.hg.1	BC109197	GSDMA	-1.41	8.05E-03
PSR17019641.hg.1	NM_182497	KRT40	1.45	2.37E-02
PSR17020257.hg.1	NM_001144766	DNAJC7	1.72	2.15E-02

PSR17020504.hg.1	BC008849	PTRF	-1.40	9.91E-03
PSR17006375.hg.1	ENST00000225927	NAGLU	-1.51	4.04E-03
PSR17006599.hg.1	BC136369	G6PC	-1.42	2.65E-02
PSR17020942.hg.1	NM_004090	DUSP3	-1.42	9.05E-03
PSR17007460.hg.1	ENST00000331493	EFCAB13	1.63	1.47E-02
PSR17008825.hg.1	ENST00000544170	LUC7L3	1.70	3.01E-03
PSR17008826.hg.1	ENST00000544170	LUC7L3	1.55	2.27E-02
PSR17008833.hg.1	ENST00000544170	LUC7L3	1.44	4.52E-02
PSR17008844.hg.1	ENST00000544170	LUC7L3	1.50	3.58E-02
PSR17008850.hg.1	ENST00000544170	LUC7L3	1.50	1.22E-02
PSR17008851.hg.1	ENST00000544170	LUC7L3	1.47	4.16E-02
PSR17008854.hg.1	NM_016424	LUC7L3	1.93	6.62E-03
PSR17008856.hg.1	ENST00000544170	LUC7L3	1.47	5.22E-03
PSR17008865.hg.1	NM_016424	LUC7L3	1.42	2.47E-03
PSR17008976.hg.1	NM_016001	UTP18	1.49	9.62E-03
PSR17014050.hg.1	NM_032530	ZNF594	1.43	2.50E-02
PSR17014071.hg.1	ENST00000389222	ZNF594	1.44	1.56E-02
PSR17009238.hg.1	ENST00000442934	MSI2	1.47	2.55E-02
PSR17023084.hg.1	BC033785	SRSF1	1.57	2.98E-02
PSR17023349.hg.1	ENST00000262294	TRIM37	1.47	2.67E-02
PSR17023351.hg.1	ENST00000262294	TRIM37	1.48	2.03E-02
PSR17023355.hg.1	ENST00000262294	TRIM37	1.55	2.58E-03
PSR17023358.hg.1	ENST00000262294	TRIM37	1.43	3.40E-02
PSR17009419.hg.1	NM_024612	DHX40	-1.52	3.31E-02
PSR17009488.hg.1	ENST00000393043	CLTC	1.48	1.11E-02
PSR17009489.hg.1	ENST00000393043	CLTC	1.43	4.64E-02
PSR17023781.hg.1	ENST00000403162	CCDC47	1.48	2.74E-03
PSR17010088.hg.1	ENST00000375812	PSMC5	1.45	3.27E-02
PSR17010089.hg.1	ENST00000375812	PSMC5	1.42	1.76E-02
PSR17024272.hg.1	BC094881	HELZ	1.58	1.00E-02
PSR17010339.hg.1	NM_004459	BPTF	1.48	3.57E-02
PSR17024357.hg.1	NM_001174166	SLC16A6	1.70	3.93E-02
PSR17024358.hg.1	BC064832	SLC16A6	1.44	1.55E-02
PSR17024359.hg.1	BC064832	SLC16A6	1.49	3.07E-03
PSR17024360.hg.1	BC064832	SLC16A6	1.79	2.64E-02
PSR17024362.hg.1	BC064832	SLC16A6	1.47	2.07E-02
PSR17010448.hg.1	ENST00000536854	PRKAR1A	1.45	1.93E-02
PSR17024523.hg.1	NM_080284	ABCA6	1.55	1.77E-02
PSR17024543.hg.1	NM_080284	ABCA6	1.43	1.01E-02
PSR17024547.hg.1	NM_080284	ABCA6	1.44	1.38E-02
PSR17024548.hg.1	NM_080284	ABCA6	1.49	3.27E-02
PSR17024639.hg.1	ENST00000392676	ABCA5	1.51	3.49E-02
PSR17024641.hg.1	ENST00000392676	ABCA5	1.46	4.68E-02
PSR17024647.hg.1	ENST00000392676	ABCA5	1.58	3.81E-02
PSR17024648.hg.1	ENST00000392676	ABCA5	1.44	1.56E-02
PSR17024650.hg.1	ENST00000392676	ABCA5	1.47	3.93E-02
PSR17024651.hg.1	ENST00000392676	ABCA5	1.44	2.22E-02
PSR17024652.hg.1	ENST00000392676	ABCA5	1.53	1.41E-02
PSR17024657.hg.1	ENST00000392676	ABCA5	1.51	2.91E-02
PSR17024671.hg.1	ENST00000392676	ABCA5	1.42	3.12E-02

PSR17024673.hg.1	ENST00000392676	ABCA5	1.41	3.02E-02
PSR17012804.hg.1	ENST00000301328	GLOD4	1.47	3.26E-02
PSR17001213.hg.1	NM_003985	TNK1	-1.58	3.15E-03
PSR17025083.hg.1	ENST00000476258	HN1	1.41	1.90E-02
PSR17025096.hg.1	ENST00000476258	HN1	1.42	2.17E-02
PSR17001269.hg.1	BC011371	CHRNB1	1.42	4.24E-02
PSR17001580.hg.1	ENST00000360606	DNAH2	-1.47	4.43E-03
PSR17025992.hg.1	NM_173628	DNAH17	-1.42	1.09E-03
PSR17001620.hg.1	ENST00000360606	DNAH2	-1.47	4.48E-03
PSR17012199.hg.1	NM_001080519	BAHCC1	-1.42	1.59E-03
PSR17012379.hg.1	ENST00000333383	NPB	-1.89	9.98E-04
PSR17026916.hg.1	ENST00000545909	FASN	1.66	5.48E-03
PSR17027115.hg.1	NM_006822	RAB40B	1.50	3.07E-02
PSR17001924.hg.1	NM_025014	ARHGEF15	-1.51	3.46E-02
PSR17012836.hg.1	NM_022463	NXN	-1.47	1.97E-02
PSR17_ctg5_hap1000003.hg.1	NM_016632	ARL17A	1.42	2.70E-02
PSR18000566.hg.1	ENST00000542979	NAPG	1.44	4.67E-03
PSR18000577.hg.1	ENST00000542979	NAPG	1.45	3.52E-02
PSR18003747.hg.1	NM_022068	PIEZO2	1.59	8.90E-03
PSR18003963.hg.1	ENST00000262127	CEP76	-1.50	2.71E-02
PSR18003971.hg.1	ENST00000327283	PTPN2	1.41	3.23E-02
PSR18003976.hg.1	ENST00000327283	PTPN2	1.43	3.96E-02
PSR18003980.hg.1	ENST00000327283	PTPN2	1.68	1.02E-02
PSR18000926.hg.1	NM_001145029	ANKRD30B	2.44	5.91E-03
PSR18000949.hg.1	NM_001145029	ANKRD30B	1.67	2.45E-02
PSR18001019.hg.1	ENST00000261537	MIB1	1.56	3.53E-02
PSR18001023.hg.1	ENST00000261537	MIB1	1.50	2.50E-02
PSR18001252.hg.1	ENST00000317571	TTC39C	1.45	2.34E-02
PSR18004391.hg.1	ENST00000399380	CDH2	1.43	1.99E-03
PSR18004504.hg.1	NM_001034172	SLC25A52	1.64	3.03E-02
PSR18004639.hg.1	NM_001112734	ZSCAN30	1.53	9.97E-03
PSR18004644.hg.1	ENST00000360932	ZSCAN30	1.41	9.65E-03
PSR18001691.hg.1	ENST00000423854	ELP2	1.49	3.24E-02
PSR18000221.hg.1	NM_173211	TGIF1	1.41	9.51E-03
PSR18005313.hg.1	ENST00000356732	MYO5B	-1.42	4.84E-02
PSR18005488.hg.1	NM_001243234	TCF4	1.63	2.51E-02
PSR18003528.hg.1	ENST00000341928	EPB41L3	-1.47	4.74E-02
PSR18002535.hg.1	BC137435	ZCCHC2	1.81	8.23E-04
PSR18002536.hg.1	BC137435	ZCCHC2	1.45	2.62E-02
PSR18002544.hg.1	BC137435	ZCCHC2	1.48	1.43E-02
PSR18002547.hg.1	BC137435	ZCCHC2	1.60	3.31E-02
PSR18002552.hg.1	ENST00000269499	ZCCHC2	1.58	3.81E-02
PSR18002553.hg.1	ENST00000269499	ZCCHC2	1.63	1.16E-02
PSR18003554.hg.1	ENST00000284898	L3MBTL4	1.88	2.27E-03
PSR18005789.hg.1	ENST00000238497	VPS4B	1.71	1.43E-03
PSR18000460.hg.1	NM_001204056	ANKRD12	1.59	3.62E-02
PSR18000466.hg.1	NM_001204056	ANKRD12	1.66	4.86E-02
PSR18000469.hg.1	NM_001204056	ANKRD12	1.59	2.26E-02
PSR18000470.hg.1	NM_001204056	ANKRD12	1.73	2.11E-02
PSR18000473.hg.1	NM_001204056	ANKRD12	1.45	3.67E-02

PSR18000475.hg.1	NM_001204056	ANKRD12	1.43	8.86E-03
PSR18000501.hg.1	BC013126	RALBP1	1.46	1.98E-02
PSR18000514.hg.1	ENST00000435762	RAB31	1.63	2.71E-02
PSR18000515.hg.1	ENST00000435762	RAB31	1.62	3.80E-02
PSR19016088.hg.1	BC144093	DNMT1	1.48	3.00E-02
PSR19016244.hg.1	NM_012289	KEAP1	-1.48	1.72E-02
PSR19003272.hg.1	NM_003437	ZNF136	1.41	1.74E-02
PSR19003277.hg.1	ENST00000343979	ZNF136	1.58	7.15E-03
PSR19016991.hg.1	BC012443	HOOK2	1.47	4.48E-03
PSR19005155.hg.1	ENST00000418063	ZNF90	1.42	2.35E-02
PSR19005373.hg.1	ENST00000334589	ZNF726	1.42	4.24E-02
PSR19014136.hg.1	ENST00000341064	ZNF77	-1.61	7.24E-06
PSR19019104.hg.1	ENST00000392276	C19orf12	-1.50	3.49E-02
PSR19005729.hg.1	NM_001114093	LSM14A	1.68	5.36E-03
PSR19005733.hg.1	NM_001114093	LSM14A	1.45	2.59E-02
PSR19006851.hg.1	NM_032453	ZNF527	1.64	3.84E-02
PSR19006863.hg.1	NM_144694	ZNF570	1.53	3.46E-02
PSR19006865.hg.1	ENST00000542455	ZNF793	-1.46	1.89E-02
PSR19007008.hg.1	ENST00000410018	CATSPERG	-1.41	4.03E-02
PSR19007252.hg.1	NM_001243116	NFKBIB	-1.42	5.11E-03
PSR19007253.hg.1	NM_002503	NFKBIB	-1.40	3.83E-02
PSR19021388.hg.1	BC051865	GSK3A	-1.61	1.02E-02
PSR19008466.hg.1	NM_181845	ZNF283	1.56	4.79E-02
PSR19008546.hg.1	NM_013362	ZNF225	1.47	3.73E-03
PSR19008554.hg.1	ENST00000544184	ZNF225	1.81	2.09E-02
PSR19008561.hg.1	NM_001144824	ZNF234	1.51	2.80E-03
PSR19008572.hg.1	NM_001144824	ZNF234	1.45	1.09E-02
PSR19021911.hg.1	ENST00000391957	ZNF235	1.58	1.98E-02
PSR19008680.hg.1	NM_001039213	CEACAM16	1.42	2.38E-03
PSR19008769.hg.1	NM_001042724	PVRL2	-1.44	2.89E-02
PSR19008911.hg.1	NM_006509	RELB	-1.42	4.93E-03
PSR19008987.hg.1	NM_031417	MARK4	-1.48	1.20E-02
PSR19009009.hg.1	ENST00000538583	MARK4	-1.59	2.74E-02
PSR19000025.hg.1	ENST00000215637	MADCAM1	-1.41	2.62E-02
PSR19010434.hg.1	NM_001101340	ADM5	-1.42	1.41E-02
PSR19010776.hg.1	ENST00000376930	POLD1	-1.42	9.82E-03
PSR19023815.hg.1	ENST00000535879	LRRC4B	-1.44	2.60E-02
PSR19024332.hg.1	ENST00000354957	ZNF649	-1.59	3.18E-02
PSR19024498.hg.1	NM_006969	ZNF28	1.41	3.14E-02
PSR19011660.hg.1	NM_004542	NDUFA3	-1.51	1.00E-02
PSR19025117.hg.1	NM_021706	LAIR1	-1.57	2.58E-02
PSR19012216.hg.1	NM_012314	KIR2DS4	-1.43	9.53E-03
PSR19014742.hg.1	ENST00000415313	SAFB2	1.44	4.94E-03
PSR19014746.hg.1	ENST00000415313	SAFB2	1.42	1.14E-02
PSR19012741.hg.1	BC136762	ZNF470	1.57	3.59E-03
PSR19013215.hg.1	ENST00000413518	ERVK3-1	-1.48	1.07E-02
PSR19014986.hg.1	BC085004	KHSRP	2.03	2.35E-02
PSR02009734.hg.1	ENST00000425019	MAP4K4	1.43	2.31E-02
PSR02009836.hg.1	BC067507	IL1R1	1.78	2.05E-02
PSR02009837.hg.1	BC067507	IL1R1	1.56	9.79E-03

PSR02010165.hg.1	NM_032411	C2orf40	-1.81	1.27E-03
PSR02025364.hg.1	BC005125	NOL10	1.76	1.11E-02
PSR02010257.hg.1	ENST00000540517	SLC5A7	-1.56	3.04E-02
PSR02010337.hg.1	ENST00000309863	GCC2	1.65	2.53E-02
PSR02010340.hg.1	NM_181453	GCC2	1.47	2.49E-02
PSR02010344.hg.1	NM_181453	GCC2	1.54	4.24E-02
PSR02010362.hg.1	NM_181453	GCC2	1.75	3.79E-02
PSR02010385.hg.1	NM_181453	GCC2	1.40	5.36E-03
PSR02010389.hg.1	NM_181453	GCC2	1.52	9.71E-03
PSR02010392.hg.1	NM_001193483	LIMS1	-1.45	1.52E-02
PSR02010563.hg.1	NM_005054	RGPD5	1.55	4.56E-03
PSR02010565.hg.1	NM_005054	RGPD5	1.49	2.03E-02
PSR02035709.hg.1	NM_005054	RGPD5	1.45	2.62E-02
PSR02035920.hg.1	ENST00000409573	ZC3H8	1.58	4.53E-02
PSR02035933.hg.1	NM_032494	ZC3H8	1.52	3.94E-02
PSR02035956.hg.1	NM_001164463	RGPD8	1.42	2.46E-03
PSR02035976.hg.1	NM_005054	RGPD5	1.45	2.62E-02
PSR02035988.hg.1	NM_005054	RGPD5	1.57	4.25E-02
PSR02036118.hg.1	ENST00000446595	LOC100653336	1.53	9.16E-03
PSR02036146.hg.1	ENST00000416673	RPL23AP7	1.46	8.29E-03
PSR02036198.hg.1	ENST00000409342	SLC35F5	1.43	1.31E-02
PSR02000886.hg.1	ENST00000417473	LINC00570	-1.46	5.07E-03
PSR02001015.hg.1	ENST00000435175	LOC100506405	-1.44	4.07E-02
PSR02011561.hg.1	ENST00000474694	DDX18	1.41	7.41E-03
PSR02011573.hg.1	ENST00000474694	DDX18	1.64	2.06E-02
PSR02011585.hg.1	BC024739	DDX18	1.53	2.65E-03
PSR02036668.hg.1	ENST00000433551	IWS1	1.43	4.40E-02
PSR02036692.hg.1	BC110537	IWS1	1.44	2.79E-03
PSR02012948.hg.1	ENST00000283054	ACMSD	-1.45	2.67E-02
PSR02013044.hg.1	ENST00000409478	R3HDM1	1.49	1.56E-03
PSR02013052.hg.1	ENST00000409478	R3HDM1	1.41	1.14E-02
PSR02037469.hg.1	ENST00000264162	LCT	-1.49	3.27E-02
PSR02013227.hg.1	ENST00000280097	HNMT	1.68	2.54E-02
PSR02037779.hg.1	NM_001171653	ZEB2	1.58	9.80E-03
PSR02037784.hg.1	NM_001171653	ZEB2	1.52	3.72E-02
PSR02037810.hg.1	ENST00000303660	ZEB2	1.42	3.59E-02
PSR02013692.hg.1	NM_018151	RIF1	1.43	3.40E-02
PSR02013693.hg.1	NM_018151	RIF1	1.52	4.41E-03
PSR02013696.hg.1	NM_018151	RIF1	1.63	7.48E-03
PSR02013698.hg.1	NM_018151	RIF1	1.90	2.64E-02
PSR02013702.hg.1	NM_018151	RIF1	1.61	4.58E-02
PSR02013704.hg.1	NM_018151	RIF1	1.55	1.53E-02
PSR02013705.hg.1	NM_018151	RIF1	1.65	2.17E-02
PSR02013713.hg.1	NM_018151	RIF1	1.52	1.71E-02
PSR02038093.hg.1	ENST00000409198	NEB	1.47	9.97E-03
PSR02038109.hg.1	ENST00000409198	NEB	1.67	4.25E-02
PSR02038315.hg.1	NM_177985	ARL5A	1.50	1.22E-02
PSR02013758.hg.1	NM_052905	FMNL2	1.47	4.36E-02
PSR02038413.hg.1	ENST00000356402	PRPF40A	1.40	4.35E-02
PSR02038424.hg.1	ENST00000356402	PRPF40A	1.43	4.11E-03

PSR02013884.hg.1	ENST00000540309	GPD2	-1.44	2.37E-02
PSR02038852.hg.1	NM_001198759	LY75-CD302	-1.40	3.37E-03
PSR02014437.hg.1	NM_021007	SCN2A	1.50	4.15E-03
PSR02025681.hg.1	ENST00000355549	FAM49A	1.48	2.88E-02
PSR02025682.hg.1	ENST00000406434	FAM49A	1.55	3.71E-03
PSR02014504.hg.1	ENST00000409756	XIRP2	1.43	1.21E-02
PSR02014514.hg.1	ENST00000409756	XIRP2	1.42	3.66E-02
PSR02014515.hg.1	ENST00000409756	XIRP2	1.42	4.43E-02
PSR02014538.hg.1	NM_001256126	CERS6	1.42	4.23E-02
PSR02014540.hg.1	NM_001256126	CERS6	1.40	1.88E-02
PSR02014549.hg.1	NM_203463	CERS6	1.57	3.49E-02
PSR02039665.hg.1	ENST00000425636	CERS6-AS1	1.54	8.33E-03
PSR02014719.hg.1	ENST00000482772	PPIG	1.55	3.45E-02
PSR02014724.hg.1	ENST00000462903	PPIG	1.54	1.48E-02
PSR02014733.hg.1	ENST00000260970	PPIG	1.50	7.92E-03
PSR02014812.hg.1	BC020818	SSB	1.60	1.78E-02
PSR02014816.hg.1	BC020818	SSB	1.58	4.11E-02
PSR02014869.hg.1	ENST00000465630	UBR3	1.64	1.14E-02
PSR02039963.hg.1	ENST00000356075	TLK1	1.43	1.73E-02
PSR02039979.hg.1	ENST00000434911	TLK1	1.47	2.03E-02
PSR02039987.hg.1	ENST00000434911	TLK1	1.50	3.75E-02
PSR02040024.hg.1	NM_024770	METTL8	1.41	3.78E-02
PSR02015309.hg.1	ENST00000375221	ITGA6	1.48	4.36E-02
PSR02015314.hg.1	ENST00000375221	ITGA6	1.58	1.94E-02
PSR02015466.hg.1	ENST00000480606	ZAK	1.45	8.62E-03
PSR02015470.hg.1	ENST00000480606	ZAK	1.44	6.78E-03
PSR02015472.hg.1	ENST00000539448	ZAK	1.43	7.41E-04
PSR02015479.hg.1	ENST00000338983	ZAK	1.42	8.31E-03
PSR02040195.hg.1	ENST00000455789	SP3	-1.43	4.85E-02
PSR02040206.hg.1	ENST00000284719	OLA1	2.15	1.45E-03
PSR02040407.hg.1	NM_001206602	CHN1	1.59	2.33E-02
PSR02015783.hg.1	ENST00000420139	HNRNPA3	1.43	1.54E-02
PSR02015794.hg.1	ENST00000420139	HNRNPA3	1.58	8.41E-03
PSR02015827.hg.1	ENST00000536686	AGPS	1.40	4.45E-02
PSR02015833.hg.1	ENST00000536686	AGPS	1.54	3.70E-03
PSR02015896.hg.1	NM_001201481	OSBPL6	1.41	1.76E-02
PSR02015903.hg.1	NM_032523	OSBPL6	1.65	1.59E-02
PSR02025738.hg.1	NM_001142286	SMC6	1.51	2.82E-03
PSR02015920.hg.1	NM_001201481	OSBPL6	1.49	2.40E-02
PSR02015921.hg.1	NM_001201481	OSBPL6	1.53	4.96E-02
PSR02015927.hg.1	NM_001201481	OSBPL6	1.41	3.29E-02
PSR02041330.hg.1	ENST00000428443	SESTD1	1.42	2.96E-02
PSR02041503.hg.1	BC009046	NEUROD1	-1.49	5.42E-04
PSR02016374.hg.1	ENST00000541912	NUP35	1.63	2.71E-02
PSR02016447.hg.1	ENST00000536434	ZC3H15	1.46	2.51E-02
PSR02017013.hg.1	ENST00000320717	GLS	1.70	3.22E-02
PSR02017197.hg.1	NM_001127257	SLC39A10	-1.40	3.09E-02
PSR02042499.hg.1	NM_012433	SF3B1	1.44	3.14E-02
PSR02017370.hg.1	NM_199482	MOB4	1.48	2.69E-02
PSR02017375.hg.1	NM_199482	MOB4	1.48	5.90E-03

PSR02017453.hg.1	NM_153689	C2orf69	-1.49	2.36E-02
PSR02017681.hg.1	NM_001207069	BZW1	1.43	1.09E-02
PSR02017691.hg.1	NM_001207069	BZW1	1.41	2.20E-03
PSR02017699.hg.1	NM_001207069	BZW1	1.42	2.27E-02
PSR02017704.hg.1	NM_001207069	BZW1	1.55	1.70E-02
PSR02017708.hg.1	NM_001207069	BZW1	1.55	2.71E-02
PSR02017712.hg.1	NM_001207069	BZW1	1.44	4.89E-02
PSR02017714.hg.1	NM_001207069	BZW1	1.59	2.69E-02
PSR02017836.hg.1	ENST00000457277	CFLAR	1.42	5.40E-03
PSR02017846.hg.1	NM_001202517	CFLAR	1.48	9.19E-04
PSR02018085.hg.1	NM_015934	NOP58	1.73	1.10E-02
PSR02018087.hg.1	NM_015934	NOP58	1.51	2.71E-02
PSR02018094.hg.1	NM_015934	NOP58	1.53	3.30E-02
PSR02018095.hg.1	NM_015934	NOP58	1.62	1.99E-02
PSR02018099.hg.1	NM_015934	NOP58	1.60	2.75E-02
PSR02018100.hg.1	NM_015934	NOP58	1.93	4.58E-02
PSR02018101.hg.1	NM_015934	NOP58	1.64	3.94E-02
PSR02018103.hg.1	NM_015934	NOP58	1.49	2.84E-02
PSR02018105.hg.1	NM_015934	NOP58	1.42	2.68E-02
PSR02018112.hg.1	NM_015934	NOP58	1.48	2.77E-02
PSR02043548.hg.1	BC033509	MDH1B	1.48	1.99E-02
PSR02043850.hg.1	NM_001608	ACADL	1.46	1.24E-02
PSR02044017.hg.1	ENST00000260947	BARD1	1.43	4.58E-02
PSR02045401.hg.1	ENST00000350526	PAX3	1.53	8.64E-03
PSR02045453.hg.1	ENST00000536361	FARSB	1.41	3.88E-04
PSR02021339.hg.1	ENST00000409315	AGFG1	1.49	3.74E-02
PSR02045924.hg.1	ENST00000341772	DNER	-1.44	1.48E-02
PSR02021712.hg.1	ENST00000424440	SPATA3	-1.48	1.36E-02
PSR02021768.hg.1	BC114434	PSMD1	1.45	4.90E-02
PSR02046187.hg.1	BC006494	NCL	1.43	4.85E-03
PSR02021914.hg.1	BC071647	PTMA	1.59	4.35E-02
PSR02022339.hg.1	ENST00000409451	GIGYF2	1.42	1.67E-02
PSR02046391.hg.1	ENST00000450966	USP40	1.41	8.74E-04
PSR02046408.hg.1	ENST00000450966	USP40	1.41	2.96E-02
PSR02046636.hg.1	ENST00000392004	COL6A3	-1.42	4.46E-02
PSR02023144.hg.1	NM_001137550	LRRFIP1	1.55	1.07E-02
PSR02023197.hg.1	NM_005855	RAMP1	-1.46	3.30E-02
PSR02026154.hg.1	ENST00000238789	ATAD2B	1.52	1.44E-02
PSR02026155.hg.1	ENST00000238789	ATAD2B	1.47	2.49E-02
PSR02026156.hg.1	ENST00000238789	ATAD2B	1.52	3.54E-02
PSR02047388.hg.1	NM_005336	HDLBP	1.41	3.95E-02
PSR02047426.hg.1	NM_005336	HDLBP	1.63	4.74E-02
PSR02001485.hg.1	ENST00000407625	FAM228B	1.52	2.34E-02
PSR02002188.hg.1	NM_173650	DNAJC5G	-1.88	5.30E-03
PSR02002427.hg.1	BC093041	ZNF512	1.58	4.70E-02
PSR02002993.hg.1	ENST00000315285	SPAST	1.47	3.32E-02
PSR02028103.hg.1	ENST00000295324	CDC42EP3	1.59	2.15E-02
PSR02028140.hg.1	ENST00000260630	CYP1B1	1.69	3.25E-02
PSR02028492.hg.1	ENST00000437545	MAP4K3	1.41	4.37E-02
PSR02003862.hg.1	BC146799	EML4	2.44	2.20E-03

PSR02029096.hg.1	ENST00000409105	MCFD2	2.67	8.48E-03
PSR02029098.hg.1	ENST00000409105	MCFD2	1.53	7.47E-03
PSR02029103.hg.1	BC037845	MCFD2	1.48	8.50E-03
PSR02029218.hg.1	NM_025133	FBXO11	1.42	5.00E-02
PSR02029219.hg.1	NM_025133	FBXO11	1.51	1.54E-02
PSR02004683.hg.1	ENST00000430487	GTF2A1L	-1.55	3.67E-03
PSR02029594.hg.1	NM_007008	RTN4	1.42	7.70E-03
PSR02029608.hg.1	ENST00000404909	RTN4	1.49	2.16E-02
PSR02029797.hg.1	BC060855	SMEK2	1.52	3.78E-02
PSR02029805.hg.1	BC060855	SMEK2	1.42	2.18E-02
PSR02005052.hg.1	ENST00000412104	VRK2	1.53	2.44E-02
PSR02005053.hg.1	ENST00000440705	VRK2	1.61	4.48E-02
PSR02030202.hg.1	ENST00000263989	USP34	1.50	2.03E-02
PSR02030233.hg.1	ENST00000398571	USP34	1.45	2.84E-03
PSR02005572.hg.1	NM_001001521	UGP2	1.60	8.07E-03
PSR02005811.hg.1	ENST00000398506	MEIS1	1.59	3.00E-02
PSR02005905.hg.1	BC040001	ETAA1	1.61	3.91E-02
PSR02031155.hg.1	ENST00000282574	TIA1	1.48	2.91E-02
PSR02031339.hg.1	NM_001185055	ADD2	-1.66	5.39E-04
PSR02006426.hg.1	BC126389	MPHOSPH10	1.59	1.09E-03
PSR02006429.hg.1	ENST00000425650	MPHOSPH10	1.72	8.44E-03
PSR02006514.hg.1	ENST00000264447	ZNF638-IT1	1.44	1.48E-02
PSR02006551.hg.1	ENST00000264447	ZNF638-IT1	1.45	1.73E-02
PSR02007013.hg.1	ENST00000461531	WDR54	-1.48	1.85E-02
PSR02007357.hg.1	ENST00000409174	HK2	1.63	3.60E-02
PSR02007363.hg.1	ENST00000290573	HK2	1.82	1.59E-02
PSR02007365.hg.1	ENST00000290573	HK2	1.76	4.60E-02
PSR02007541.hg.1	ENST00000402739	CTNNA2	-1.51	1.08E-04
PSR02033606.hg.1	ENST00000482769	IGKV2-28	1.40	3.66E-02
PSR02033636.hg.1	ENST00000465170	IGKV1-37	1.50	3.44E-03
PSR02025123.hg.1	ENST00000473731	KIDINS220	1.40	4.81E-02
PSR02009033.hg.1	ENST00000540067	CNNM4	-1.54	1.06E-02
PSR02034513.hg.1	NM_015348	TMEM131	1.48	7.02E-03
PSR02034567.hg.1	NM_001160154	MGAT4A	1.58	4.58E-02
PSR02034581.hg.1	ENST00000264968	MGAT4A	1.49	1.98E-03
PSR02034589.hg.1	ENST00000264968	MGAT4A	1.67	3.14E-02
PSR02009479.hg.1	NM_145197	LIPT1	1.55	2.35E-02
PSR02000642.hg.1	ENST00000404869	TAF1B	1.55	3.39E-02
PSR20001189.hg.1	NM_001009608	SLX4IP	1.40	2.67E-02
PSR20009035.hg.1	NM_016649	ESF1	1.46	3.41E-02
PSR20009043.hg.1	NM_016649	ESF1	1.89	8.59E-03
PSR20009044.hg.1	NM_016649	ESF1	1.47	3.74E-02
PSR20009045.hg.1	NM_016649	ESF1	1.52	2.70E-02
PSR20009046.hg.1	NM_016649	ESF1	1.47	4.31E-02
PSR20009047.hg.1	NM_016649	ESF1	1.65	4.56E-02
PSR20001388.hg.1	ENST00000448536	MACROD2-IT1	-1.43	1.60E-02
PSR20009261.hg.1	ENST00000483485	SNX5	1.43	4.02E-02
PSR20001773.hg.1	ENST00000377306	C20orf26	1.45	3.42E-02
PSR20001777.hg.1	ENST00000389656	C20orf26	1.91	3.25E-02
PSR20001793.hg.1	ENST00000497372	C20orf26	2.17	4.86E-02

PSR20001807.hg.1	ENST00000377297	C20orf26	1.64	3.39E-02
PSR20001809.hg.1	BC028708	C20orf26	2.07	2.85E-02
PSR20001810.hg.1	BC028708	C20orf26	1.54	6.63E-03
PSR20001811.hg.1	BC028708	C20orf26	1.84	1.84E-02
PSR20001813.hg.1	BC028708	C20orf26	1.99	2.51E-02
PSR20009521.hg.1	ENST00000424490	RALGAPA2	1.46	4.74E-02
PSR20000547.hg.1	BC115400	GNRH2	-1.55	2.22E-02
PSR20008290.hg.1	ENST00000380201	DDRGK1	-1.83	1.97E-02
PSR20010910.hg.1	NM_006047	RBM12	1.43	1.67E-02
PSR20011275.hg.1	ENST00000262878	SAMHD1	1.48	3.00E-02
PSR20004425.hg.1	NM_006275	SRSF6	1.43	2.73E-02
PSR20004764.hg.1	ENST00000372861	KCNK15	-1.52	3.00E-02
PSR20004786.hg.1	ENST00000479421	YWHAB	1.47	3.03E-02
PSR20011946.hg.1	NM_003064	SLPI	1.43	2.56E-02
PSR20012065.hg.1	BC062670	WFDC11	1.76	1.33E-02
PSR20005129.hg.1	ENST00000344780	SNX21	-1.42	1.59E-02
PSR20012912.hg.1	ENST00000327979	FAM65C	-1.42	3.91E-02
PSR20005837.hg.1	ENST00000559286	TSHZ2	1.96	3.43E-02
PSR20006020.hg.1	ENST00000544508	TFAP2C	-1.41	7.58E-03
PSR20006282.hg.1	BC073876	STX16	1.40	3.86E-02
PSR20013543.hg.1	NM_001256403	SLMO2	1.93	2.52E-03
PSR20013545.hg.1	NM_001256403	SLMO2	1.41	4.99E-02
PSR20008755.hg.1	BC027720	LRRN4	-1.40	4.00E-02
PSR20007282.hg.1	ENST00000370179	PPDPF	-1.49	5.75E-03
PSR20001114.hg.1	NM_000933	PLCB4	1.76	2.74E-02
PSR20001116.hg.1	NM_000933	PLCB4	1.55	2.20E-02
PSR21000229.hg.1	ENST00000306618	CXADR	1.89	2.49E-02
PSR21003699.hg.1	ENST00000419299	LINC00320	1.51	1.82E-02
PSR21003891.hg.1	ENST00000400043	CYYR1	1.42	2.20E-02
PSR21000511.hg.1	NM_001032410	USP16	1.55	1.44E-02
PSR21000567.hg.1	ENST00000339024	MAP3K7CL	1.49	4.52E-02
PSR21000570.hg.1	ENST00000399934	MAP3K7CL	1.59	4.97E-02
PSR21000572.hg.1	ENST00000399934	MAP3K7CL	1.92	4.46E-02
PSR21000577.hg.1	ENST00000399947	MAP3K7CL	1.66	3.39E-02
PSR21000579.hg.1	ENST00000399947	MAP3K7CL	1.67	4.37E-02
PSR21000614.hg.1	ENST00000286800	GRIK1-AS2	1.50	4.54E-02
PSR21004539.hg.1	ENST00000290178	PAXBP1	1.45	4.93E-02
PSR21004544.hg.1	ENST00000290178	PAXBP1	1.77	1.25E-02
PSR21004545.hg.1	ENST00000290178	PAXBP1	1.50	6.90E-03
PSR21004551.hg.1	ENST00000290178	PAXBP1	1.59	2.24E-02
PSR21004555.hg.1	ENST00000290178	PAXBP1	1.47	3.86E-03
PSR21004829.hg.1	ENST00000381540	CRYZL1	1.44	3.32E-02
PSR21001087.hg.1	BC117560	ITSN1	1.66	8.14E-03
PSR21004886.hg.1	NM_001697	ATP5O	-1.40	1.62E-02
PSR21001168.hg.1	BC093892	KCNE2	1.46	1.42E-02
PSR21001225.hg.1	ENST00000466328	CBR1	-1.57	8.28E-03
PSR21001346.hg.1	ENST00000314103	CHAF1B	1.41	4.81E-02
PSR21001518.hg.1	NM_130436	DYRK1A	1.43	2.90E-02
PSR21001528.hg.1	ENST00000451934	DYRK1A	1.73	6.00E-03
PSR21001544.hg.1	NM_101395	DYRK1A	1.81	2.88E-03

PSR21001549.hg.1	NM_130438	DYRK1A	1.43	1.39E-02
PSR21005353.hg.1	ENST00000342449	BRWD1	1.56	8.64E-03
PSR21005371.hg.1	ENST00000333229	BRWD1	1.65	1.68E-02
PSR21005372.hg.1	ENST00000333229	BRWD1	1.43	3.77E-02
PSR21005373.hg.1	ENST00000333229	BRWD1	1.51	2.72E-02
PSR21005449.hg.1	ENST00000361263	HMGN1	1.52	2.65E-02
PSR21001690.hg.1	ENST00000380637	SH3BGR	1.47	9.14E-03
PSR21001699.hg.1	ENST00000380637	SH3BGR	1.59	9.68E-03
PSR21001702.hg.1	ENST00000380637	SH3BGR	1.51	3.75E-03
PSR21001703.hg.1	ENST00000380637	SH3BGR	1.49	1.70E-02
PSR21005634.hg.1	ENST00000441268	LINC00323	-1.40	2.17E-02
PSR21002244.hg.1	ENST00000342757	LINC00319	-1.45	3.84E-03
PSR21002848.hg.1	NM_015834	ADARB1	1.55	3.48E-02
PSR21002997.hg.1	ENST00000449640	PCBP3	-1.41	4.57E-02
PSR21003151.hg.1	ENST00000397701	YBEY	1.50	1.78E-02
PSR22003148.hg.1	ENST00000536101	MYO18B	1.41	4.74E-02
PSR22003150.hg.1	ENST00000536101	MYO18B	1.57	3.48E-04
PSR22004340.hg.1	ENST00000432498	SFI1	-1.49	4.18E-02
PSR22004346.hg.1	ENST00000414585	SFI1	-1.48	3.80E-03
PSR22011980.hg.1	NM_001159545	RFPL2	-1.44	4.25E-02
PSR22013769.hg.1	ENST00000463769	MKL1	2.20	4.29E-02
PSR22014419.hg.1	NM_014570	ARFGAP3	1.41	3.99E-03
PSR22007287.hg.1	ENST00000425733	NUP50	1.51	1.51E-02
PSR22007337.hg.1	ENST00000441876	FAM118A	-1.81	6.38E-03
PSR22015093.hg.1	BC047508	BRD1	-1.44	2.11E-02
PSR22007945.hg.1	ENST00000354853	MOV10L1	-1.45	1.19E-03
PSR22015682.hg.1	ENST00000438960	ODF3B	-1.84	7.52E-03
PSR22015832.hg.1	BC014210	ARSA	-1.41	4.95E-02
PSR03029323.hg.1	ENST00000405772	CBLB	1.81	1.41E-02
PSR03029325.hg.1	ENST00000545639	CBLB	1.44	7.87E-04
PSR03009929.hg.1	ENST00000406780	BBX	1.45	2.22E-02
PSR03001350.hg.1	NM_014229	SLC6A11	-1.41	4.56E-02
PSR03010416.hg.1	BC005207	SLC35A5	1.75	1.74E-02
PSR03029933.hg.1	NM_018338	WDR52	1.43	4.78E-02
PSR03010629.hg.1	ENST00000545842	ATP6V1A	1.45	1.42E-02
PSR03030244.hg.1	ENST00000354673	IGSF11	1.52	2.76E-02
PSR03030249.hg.1	ENST00000354673	IGSF11	1.44	1.49E-02
PSR03030255.hg.1	ENST00000354673	IGSF11	1.60	5.08E-03
PSR03030323.hg.1	ENST00000393765	B4GALT4	-1.41	4.17E-02
PSR03030707.hg.1	ENST00000426235	GOLGB1	1.42	3.59E-02
PSR03030721.hg.1	ENST00000426235	GOLGB1	1.64	3.95E-02
PSR03011312.hg.1	ENST00000393627	CD86	1.44	2.61E-02
PSR03030818.hg.1	ENST00000466923	KPNA1	1.41	4.06E-02
PSR03031015.hg.1	BC049369	PTPLB	1.60	3.33E-02
PSR03031018.hg.1	BC049369	PTPLB	1.66	2.88E-02
PSR03031022.hg.1	BC060839	PTPLB	1.86	2.05E-02
PSR03001531.hg.1	ENST00000309576	PPARG	-1.41	2.58E-02
PSR03031412.hg.1	ENST00000536067	SNX4	1.52	7.25E-03
PSR03001621.hg.1	ENST00000170447	MKRN2	1.43	4.51E-04
PSR03020297.hg.1	ENST00000435575	TMEM40	-1.41	2.13E-02

PSR03032092.hg.1	ENST00000507208	MBD4	1.46	2.05E-03
PSR03032094.hg.1	ENST00000507208	MBD4	1.43	1.66E-03
PSR03032189.hg.1	ENST00000426664	TMCC1	1.48	3.21E-02
PSR03032259.hg.1	BC127106	PIK3R4	1.66	1.95E-02
PSR03012810.hg.1	ENST00000486798	DNAJC13	1.42	3.11E-02
PSR03012823.hg.1	ENST00000486798	DNAJC13	1.67	1.39E-02
PSR03012921.hg.1	NM_198329	UBA5	1.68	1.49E-02
PSR03012938.hg.1	NM_198329	UBA5	1.52	3.54E-02
PSR03012996.hg.1	BC000568	TMEM108	1.63	1.76E-02
PSR03013047.hg.1	ENST00000431519	CDV3	1.55	6.27E-04
PSR03013048.hg.1	ENST00000431519	CDV3	1.94	3.84E-02
PSR03013049.hg.1	ENST00000431519	CDV3	1.44	5.93E-04
PSR03032685.hg.1	ENST00000296084	RYK	1.55	4.51E-02
PSR03013175.hg.1	ENST00000383229	CEP63	1.56	1.69E-02
PSR03013251.hg.1	BC065531	PPP2R3A	1.44	3.60E-02
PSR03032833.hg.1	NM_005862	STAG1	1.60	6.07E-03
PSR03032850.hg.1	NM_005862	STAG1	1.56	2.80E-02
PSR03032865.hg.1	NM_005862	STAG1	1.40	1.23E-02
PSR03032866.hg.1	ENST00000480733	STAG1	1.41	4.98E-02
PSR03013328.hg.1	ENST00000472200	SLC35G2	-1.47	1.46E-02
PSR03013499.hg.1	ENST00000469044	ARMC8	1.41	1.29E-02
PSR03013500.hg.1	ENST00000469044	ARMC8	1.48	4.14E-02
PSR03033004.hg.1	ENST00000481834	CEP70	1.46	2.20E-02
PSR03013975.hg.1	ENST00000264952	GRK7	1.45	6.05E-03
PSR03013991.hg.1	ENST00000539728	ATP1B3	1.41	2.65E-02
PSR03033450.hg.1	ENST00000463916	XRN1	1.46	4.60E-02
PSR03014165.hg.1	NM_001080415	U2SURP	1.46	9.50E-03
PSR03014173.hg.1	NM_001080415	U2SURP	1.47	3.28E-02
PSR03014182.hg.1	ENST00000473835	U2SURP	1.52	2.57E-03
PSR03001895.hg.1	ENST00000383794	CCDC174	1.45	3.61E-02
PSR03014440.hg.1	NM_032383	HPS3	1.40	1.98E-02
PSR03034140.hg.1	BC043646	PFN2	1.45	6.15E-03
PSR03034158.hg.1	ENST00000481275	PFN2	1.42	1.60E-02
PSR03034159.hg.1	ENST00000461930	PFN2	2.56	1.16E-02
PSR03034160.hg.1	ENST00000461930	PFN2	1.56	6.53E-03
PSR03020582.hg.1	ENST00000253686	MRPS25	1.55	2.03E-02
PSR03034444.hg.1	ENST00000479270	ARHGEF26-AS1	-1.43	6.26E-03
PSR03014998.hg.1	ENST00000460393	MME	1.67	2.06E-02
PSR03015046.hg.1	ENST00000496455	GMPS	1.51	1.04E-02
PSR03015128.hg.1	ENST00000498839	LEKR1	-1.47	2.13E-03
PSR03015129.hg.1	ENST00000470811	LEKR1	-1.49	1.39E-02
PSR03015130.hg.1	ENST00000470811	LEKR1	-1.55	1.60E-02
PSR03015131.hg.1	ENST00000470811	LEKR1	-1.55	3.46E-02
PSR03015132.hg.1	ENST00000477399	LEKR1	-1.66	2.50E-02
PSR03015141.hg.1	ENST00000477399	LEKR1	-1.56	2.34E-02
PSR03034654.hg.1	BC067812	CCNL1	1.57	2.54E-02
PSR03020799.hg.1	NM_015199	ANKRD28	1.60	1.41E-02
PSR03034840.hg.1	ENST00000462663	RARRES1	1.40	2.37E-02
PSR03034847.hg.1	BC029640	RARRES1	1.62	3.29E-03
PSR03002131.hg.1	ENST00000339732	GALNT15	1.47	8.33E-03

PSR03002132.hg.1	ENST00000339732	GALNT15	1.61	3.42E-02
PSR03035314.hg.1	ENST00000453925	WDR49	1.43	1.16E-02
PSR03035434.hg.1	NM_005241	MECOM	1.47	3.73E-02
PSR03015907.hg.1	ENST00000355897	GPR160	-1.49	1.10E-02
PSR03035558.hg.1	ENST00000494943	PHC3	1.43	2.56E-03
PSR03015993.hg.1	ENST00000490989	SKIL	1.79	1.00E-02
PSR03016009.hg.1	BC059386	SKIL	1.57	2.01E-02
PSR03035766.hg.1	NM_001130081	PLD1	1.43	5.59E-03
PSR03020972.hg.1	ENST00000429383	TBC1D5	1.44	3.82E-03
PSR03020984.hg.1	ENST00000429924	TBC1D5	1.43	1.66E-03
PSR03016617.hg.1	NM_133462	TTC14	1.41	3.16E-02
PSR03016636.hg.1	NM_001042601	TTC14	1.50	4.04E-02
PSR03016638.hg.1	NM_001042601	TTC14	1.48	2.01E-02
PSR03016641.hg.1	NM_133462	TTC14	1.51	4.83E-02
PSR03016648.hg.1	ENST00000382584	TTC14	1.56	4.02E-03
PSR03016692.hg.1	ENST00000468861	FXR1	1.43	4.66E-02
PSR03016812.hg.1	ENST00000323116	ATP11B	1.53	2.72E-02
PSR03016817.hg.1	ENST00000482794	ATP11B	1.50	1.33E-02
PSR03016825.hg.1	NM_014616	ATP11B	1.62	2.35E-02
PSR03016828.hg.1	NM_014616	ATP11B	1.44	4.33E-03
PSR03016829.hg.1	NM_014616	ATP11B	1.66	3.35E-02
PSR03016831.hg.1	NM_014616	ATP11B	1.48	8.26E-03
PSR03016837.hg.1	NM_014616	ATP11B	1.52	3.82E-02
PSR03017072.hg.1	ENST00000498831	EIF2B5	-1.61	8.59E-03
PSR03021082.hg.1	ENST00000493952	SATB1	-1.45	1.38E-02
PSR03037028.hg.1	ENST00000307944	CRYGS	1.49	2.84E-02
PSR03018378.hg.1	ENST00000471917	LPP	1.44	3.26E-02
PSR03018453.hg.1	NM_198485	TPRG1	2.06	6.87E-03
PSR03018454.hg.1	NM_198485	TPRG1	1.59	7.72E-03
PSR03018576.hg.1	ENST00000392456	CCDC50	1.47	1.66E-02
PSR03018688.hg.1	NM_015560	OPA1	1.78	2.31E-02
PSR03037803.hg.1	ENST00000326793	ACAP2	1.44	4.88E-02
PSR03037813.hg.1	ENST00000326793	ACAP2	1.82	1.73E-03
PSR03037877.hg.1	NM_001647	APOD	2.05	2.15E-02
PSR03037878.hg.1	NM_001647	APOD	1.44	3.04E-02
PSR03018999.hg.1	ENST00000314118	PIGX	1.52	4.80E-02
PSR03019066.hg.1	ENST00000446695	MFI2-AS1	-1.45	3.14E-02
PSR03038401.hg.1	ENST00000450955	DLG1	1.42	4.49E-02
PSR03038407.hg.1	ENST00000450955	DLG1	1.53	2.65E-02
PSR03038447.hg.1	NM_001204386	DLG1	1.54	2.28E-02
PSR03019105.hg.1	NM_001011537	FYTTD1	1.47	2.23E-02
PSR03019109.hg.1	NM_001011537	FYTTD1	1.54	2.91E-02
PSR03019110.hg.1	NM_001011537	FYTTD1	1.48	2.59E-02
PSR03019112.hg.1	NM_001011537	FYTTD1	1.51	6.78E-03
PSR03019132.hg.1	ENST00000441090	LRCH3	1.75	1.12E-02
PSR03021235.hg.1	ENST00000421515	NKIRAS1	-1.71	1.47E-02
PSR03021308.hg.1	NM_001068	TOP2B	1.42	3.28E-02
PSR03021309.hg.1	NM_001068	TOP2B	1.45	1.84E-02
PSR03021314.hg.1	NM_001068	TOP2B	1.47	2.45E-02
PSR03021322.hg.1	NM_001068	TOP2B	1.41	8.66E-03

PSR03021332.hg.1	NM_001068	TOP2B	1.48	3.35E-02
PSR03021337.hg.1	NM_001068	TOP2B	1.52	1.57E-03
PSR03021340.hg.1	NM_001068	TOP2B	1.49	1.26E-02
PSR03021343.hg.1	NM_001068	TOP2B	1.73	1.30E-02
PSR03021381.hg.1	BC017220	NGLY1	1.50	3.83E-02
PSR03002740.hg.1	ENST00000295770	STT3B	1.62	4.66E-02
PSR03002746.hg.1	ENST00000295770	STT3B	1.41	3.60E-03
PSR03019360.hg.1	NM_001173482	CRBN	1.47	8.52E-03
PSR03021704.hg.1	NM_016141	DYNC1LI1	1.54	4.64E-02
PSR03021716.hg.1	ENST00000432458	DYNC1LI1	1.49	1.88E-02
PSR03021822.hg.1	ENST00000447368	UBP1	1.65	8.04E-03
PSR03021835.hg.1	ENST00000447368	UBP1	1.44	3.43E-02
PSR03003060.hg.1	ENST00000307296	PDCD6IP	1.66	7.76E-03
PSR03003063.hg.1	ENST00000307296	PDCD6IP	1.52	7.96E-03
PSR03003065.hg.1	ENST00000307296	PDCD6IP	1.56	3.41E-02
PSR03003068.hg.1	ENST00000307296	PDCD6IP	1.43	5.87E-03
PSR03003082.hg.1	ENST00000307296	PDCD6IP	1.49	3.45E-02
PSR03003084.hg.1	ENST00000307296	PDCD6IP	1.54	9.66E-03
PSR03003103.hg.1	ENST00000307296	PDCD6IP	1.45	2.62E-03
PSR03003107.hg.1	ENST00000307296	PDCD6IP	1.63	2.84E-02
PSR03004115.hg.1	ENST00000301825	ENTPD3	-1.61	6.67E-03
PSR03022830.hg.1	ENST00000414522	ANO10	1.44	1.93E-02
PSR03004688.hg.1	ENST00000458276	ABHD5	1.54	2.38E-02
PSR03022930.hg.1	NM_020696	KIAA1143	1.67	2.09E-02
PSR03022931.hg.1	ENST00000484437	KIAA1143	1.45	1.12E-02
PSR03023133.hg.1	ENST00000296140	CCR1	-1.67	1.79E-02
PSR03023318.hg.1	ENST00000447340	PRSS42	1.43	4.89E-02
PSR03005535.hg.1	ENST00000446256	DHX30	1.40	4.09E-02
PSR03005909.hg.1	NM_173546	KLHDC8B	-1.52	3.95E-02
PSR03006224.hg.1	NM_005777	RBM6	1.40	3.66E-03
PSR03025935.hg.1	NM_145071	CISH	-1.62	1.06E-02
PSR03006724.hg.1	ENST00000266037	DOCK3	1.58	6.94E-03
PSR03007071.hg.1	NM_144641	PPM1M	-1.40	3.05E-02
PSR03007075.hg.1	ENST00000296487	PPM1M	-1.69	1.03E-02
PSR03026399.hg.1	ENST00000394830	PBRM1	1.49	1.59E-02
PSR03007925.hg.1	ENST00000394672	CCDC66	1.49	1.91E-02
PSR03007931.hg.1	ENST00000394672	CCDC66	1.44	3.39E-02
PSR03008237.hg.1	BC014479	PXK	1.42	4.39E-02
PSR03008239.hg.1	BC014479	PXK	1.40	2.25E-02
PSR03008363.hg.1	ENST00000474889	PTPRG	1.72	6.75E-03
PSR03027757.hg.1	ENST00000467257	ADAMTS9	1.65	2.30E-02
PSR03028051.hg.1	ENST00000415609	UBA3	2.06	2.90E-02
PSR03028052.hg.1	ENST00000415609	UBA3	1.50	2.53E-02
PSR03008817.hg.1	ENST00000356692	PPP4R2	1.53	4.09E-02
PSR03009116.hg.1	NM_001174150	ARL13B	1.51	3.00E-02
PSR03000590.hg.1	BC010421	THUMPD3	1.46	1.55E-03
PSR03000591.hg.1	BC010421	THUMPD3	1.41	3.20E-02
PSR03000672.hg.1	ENST00000488236	SETD5	1.47	2.23E-02
PSR03000996.hg.1	NM_032492	JAGN1	-2.41	4.67E-03

PSR04019696.hg.1	NM_000669	ADH1C	1.52	2.30E-02
PSR04019704.hg.1	NM_000669	ADH1C	1.42	3.48E-02
PSR04019788.hg.1	BC022248	DNAJB14	1.44	2.34E-02
PSR04019790.hg.1	BC022248	DNAJB14	1.45	4.66E-02
PSR04019843.hg.1	BC013592	DDIT4L	-1.72	1.80E-02
PSR04019845.hg.1	BC013592	DDIT4L	-1.60	3.15E-02
PSR04007743.hg.1	NM_003998	NFKB1	1.43	3.19E-03
PSR04007751.hg.1	NM_003998	NFKB1	1.55	3.89E-02
PSR04007926.hg.1	ENST00000512262	ARHGEF38-IT1	-1.45	2.40E-03
PSR04008194.hg.1	ENST00000399100	SEC24B	-1.50	2.62E-03
PSR04008248.hg.1	NM_018983	GAR1	-1.80	1.25E-03
PSR04008445.hg.1	NM_025144	ALPK1	1.73	2.36E-02
PSR04020994.hg.1	NM_018392	C4orf21	1.63	4.33E-02
PSR04021037.hg.1	NM_172128	CAMK2D	1.45	1.95E-02
PSR04021039.hg.1	NM_172128	CAMK2D	1.48	3.87E-03
PSR04021040.hg.1	ENST00000394526	CAMK2D	1.42	4.69E-02
PSR04021066.hg.1	NM_172128	CAMK2D	1.44	2.81E-02
PSR04021072.hg.1	ENST00000515496	CAMK2D	1.56	6.99E-04
PSR04021206.hg.1	BC035761	SEC24D	1.75	1.67E-02
PSR04021214.hg.1	BC035761	SEC24D	1.43	1.39E-02
PSR04021238.hg.1	ENST00000280551	SEC24D	1.41	3.60E-02
PSR04021256.hg.1	NM_001170330	C4orf3	1.49	3.93E-02
PSR04021260.hg.1	NM_001170330	C4orf3	1.46	1.10E-02
PSR04021492.hg.1	ENST00000296511	ANXA5	1.46	2.95E-02
PSR04021611.hg.1	NM_021803	IL21	-1.52	1.20E-03
PSR04009248.hg.1	ENST00000512995	INTU	-1.49	2.24E-02
PSR04009406.hg.1	NM_032239	LARP1B	1.56	3.42E-02
PSR04014337.hg.1	ENST00000040738	BOD1L1	1.46	4.14E-02
PSR04009684.hg.1	BC104806	NAA15	1.49	2.64E-02
PSR04009687.hg.1	NM_057175	NAA15	1.42	5.48E-03
PSR04009688.hg.1	NM_057175	NAA15	1.65	1.37E-02
PSR04009689.hg.1	NM_057175	NAA15	1.61	8.40E-03
PSR04009698.hg.1	ENST00000398947	NAA15	1.51	9.97E-03
PSR04009829.hg.1	BC004421	ZNF330	1.47	1.42E-02
PSR04010023.hg.1	ENST00000296575	HHIP	1.80	4.52E-03
PSR04022821.hg.1	ENST00000535741	LRBA	1.81	2.01E-02
PSR04022863.hg.1	ENST00000424281	SH3D19	1.48	3.18E-03
PSR04014405.hg.1	NM_001193535	FBXL5	1.42	2.53E-02
PSR04014425.hg.1	NM_001193535	FBXL5	1.99	3.03E-02
PSR04023307.hg.1	ENST00000504672	PDGFC	1.75	3.75E-02
PSR04014486.hg.1	NM_001145852	PROM1	-2.30	7.49E-03
PSR04014494.hg.1	NM_001145852	PROM1	-1.69	3.19E-02
PSR04011395.hg.1	ENST00000506761	KLHL2	1.45	2.81E-02
PSR04011396.hg.1	BC022503	KLHL2	1.49	2.89E-02
PSR04011406.hg.1	BC022503	KLHL2	1.58	1.18E-02
PSR04011410.hg.1	BC022503	KLHL2	1.46	1.99E-02
PSR04013194.hg.1	ENST00000318386	SLBP	1.46	3.73E-02
PSR04011577.hg.1	ENST00000335742	PALLD	1.57	2.59E-02
PSR04011586.hg.1	ENST00000335742	PALLD	1.42	1.43E-02

PSR04011587.hg.1	ENST00000335742	PALLD	1.42	2.89E-02
PSR04011591.hg.1	NM_001166108	PALLD	1.42	4.07E-02
PSR04011595.hg.1	ENST00000335742	PALLD	1.41	1.96E-02
PSR04011849.hg.1	ENST00000296519	CEP44	1.49	2.24E-02
PSR04024164.hg.1	ENST00000296521	HPGD	1.50	4.69E-02
PSR04024301.hg.1	NM_080874	ASB5	1.42	4.69E-02
PSR04011976.hg.1	BC047290	SPCS3	1.71	1.29E-02
PSR04011978.hg.1	ENST00000507001	SPCS3	1.44	1.80E-03
PSR04011982.hg.1	BC047290	SPCS3	1.74	3.36E-03
PSR04014732.hg.1	NM_153686	LCORL	1.41	4.16E-02
PSR04014733.hg.1	BC037322	LCORL	1.66	1.59E-02
PSR04014738.hg.1	ENST00000382224	LCORL	1.47	6.84E-03
PSR04014745.hg.1	BC037322	LCORL	1.52	1.77E-03
PSR04024477.hg.1	ENST00000438320	DCTD	-1.66	1.94E-03
PSR04012086.hg.1	ENST00000448232	WWC2	1.43	3.06E-02
PSR04012103.hg.1	ENST00000506225	WWC2	1.42	2.73E-02
PSR04024506.hg.1	BC107432	RWDD4	1.50	4.26E-02
PSR04012185.hg.1	NM_199053	TRAPPC11	1.81	3.15E-02
PSR04024735.hg.1	ENST00000296775	KIAA1430	1.45	3.69E-02
PSR04024863.hg.1	NM_014476	PDLIM3	1.53	1.87E-02
PSR04012608.hg.1	ENST00000332517	TRIML1	1.99	3.25E-02
PSR04000755.hg.1	ENST00000409248	C4orf48	-1.41	1.25E-02
PSR04014835.hg.1	ENST00000508133	GPR125	1.71	2.11E-02
PSR04013459.hg.1	ENST00000515312	ZFYVE28	-1.44	5.91E-03
PSR04002727.hg.1	BC059383	ANAPC4	2.19	8.08E-03
PSR04002739.hg.1	BC059383	ANAPC4	1.64	1.40E-02
PSR04002812.hg.1	ENST00000515764	SMIM20	-1.45	7.41E-03
PSR04002869.hg.1	ENST00000504907	RBPJ	1.49	1.74E-02
PSR04002885.hg.1	ENST00000345843	RBPJ	1.65	9.48E-03
PSR04002905.hg.1	NM_005349	RBPJ	1.67	2.69E-02
PSR04001128.hg.1	NM_002111	HTT	1.41	4.17E-02
PSR04003307.hg.1	ENST00000359687	KLHL5	1.60	3.46E-03
PSR04015400.hg.1	BC035297	RFC1	1.56	4.66E-02
PSR04015589.hg.1	ENST00000503396	PDS5A	1.43	3.08E-02
PSR04003783.hg.1	BC000948	TMEM33	1.43	4.38E-02
PSR04012752.hg.1	ENST00000506646	ZNF721	1.41	2.05E-03
PSR04004023.hg.1	BC040993	SLAIN2	1.40	1.91E-02
PSR04016261.hg.1	ENST00000507711	FRYL	1.42	1.28E-02
PSR04001458.hg.1	NM_002448	MSX1	-1.44	2.25E-02
PSR04016400.hg.1	NM_022832	USP46	-1.44	2.52E-02
PSR04004556.hg.1	BC094751	EXOC1	1.43	2.41E-02
PSR04004563.hg.1	BC094751	EXOC1	1.61	8.41E-04
PSR04004583.hg.1	BC094751	EXOC1	1.73	1.12E-03
PSR04017075.hg.1	ENST00000502496	TMPRSS11GP	-1.43	2.75E-02
PSR04017308.hg.1	BC038982	IGJ	1.46	4.82E-02
PSR04017843.hg.1	NM_018115	SDAD1	1.53	2.49E-02
PSR04017849.hg.1	NM_018115	SDAD1	1.48	3.46E-02
PSR04017852.hg.1	NM_018115	SDAD1	1.56	3.52E-02
PSR04017853.hg.1	NM_018115	SDAD1	1.47	3.35E-02
PSR04017867.hg.1	NM_018115	SDAD1	1.46	3.09E-02

PSR04005931.hg.1	ENST00000355810	ART3	2.30	2.01E-02
PSR04017931.hg.1	ENST00000264883	NUP54	1.46	2.97E-02
PSR04006323.hg.1	BC036021	BMP2K	1.45	5.09E-03
PSR04006482.hg.1	NM_001201	BMP3	1.47	8.09E-03
PSR04018460.hg.1	ENST00000508479	SEC31A	1.42	2.27E-02
PSR04018483.hg.1	NM_014933	SEC31A	1.52	6.30E-03
PSR04018487.hg.1	NM_014933	SEC31A	1.55	9.70E-03
PSR04018594.hg.1	ENST00000446851	LIN54	1.64	3.67E-02
PSR04019098.hg.1	BC008650	HSD17B11	1.63	4.29E-02
PSR04006965.hg.1	ENST00000508588	PKD2	1.64	3.01E-02
PSR04019320.hg.1	ENST00000509094	FAM13A	-1.63	9.13E-03
PSR04007297.hg.1	NM_001128430	SMARCAD1	1.44	4.52E-02
PSR04007307.hg.1	NM_001128430	SMARCAD1	1.43	1.57E-02
PSR04007308.hg.1	NM_001128430	SMARCAD1	1.42	2.14E-02
PSR04007364.hg.1	NM_001011516	PDLIM5	1.40	1.14E-02
PSR04019444.hg.1	ENST00000506482	STPG2	1.52	5.09E-03
PSR04019508.hg.1	NM_001130679	EIF4E	1.43	1.95E-02
PSR05022350.hg.1	ENST00000510145	LINC00491	1.50	8.40E-03
PSR05022452.hg.1	ENST00000510359	EFNA5	1.79	8.99E-03
PSR05022455.hg.1	ENST00000509503	EFNA5	1.71	8.71E-03
PSR05007071.hg.1	ENST00000438717	FER	1.43	4.85E-02
PSR05007082.hg.1	ENST00000438717	FER	1.46	1.69E-02
PSR05007086.hg.1	ENST00000438717	FER	1.42	2.04E-02
PSR05007242.hg.1	ENST00000505303	WDR36	1.50	6.02E-03
PSR05007530.hg.1	NM_022828	YTHDC2	1.75	3.42E-03
PSR05022915.hg.1	ENST00000379611	CCDC112	-1.42	4.45E-02
PSR05022960.hg.1	ENST00000502631	CDO1	1.67	1.87E-02
PSR05022962.hg.1	ENST00000502631	CDO1	1.41	2.01E-02
PSR05022986.hg.1	NM_004707	ATG12	1.47	1.90E-02
PSR05007631.hg.1	ENST00000379578	AQPEP	1.50	8.96E-03
PSR05007788.hg.1	NM_005509	DMXL1	1.51	3.35E-02
PSR05007882.hg.1	ENST00000414835	HSD17B4	1.79	2.82E-02
PSR05007885.hg.1	ENST00000414835	HSD17B4	1.43	3.75E-02
PSR05007917.hg.1	ENST00000414835	HSD17B4	1.98	3.13E-02
PSR05008069.hg.1	BC040552	SNCAIP	-1.43	9.40E-04
PSR05008094.hg.1	ENST00000510372	SNX2	1.59	5.96E-03
PSR05023229.hg.1	ENST00000306467	CEP120	1.48	2.72E-02
PSR05023336.hg.1	ENST00000553117	ALDH7A1	1.59	1.21E-02
PSR05023354.hg.1	ENST00000553117	ALDH7A1	1.47	6.83E-03
PSR05023355.hg.1	ENST00000553117	ALDH7A1	1.49	1.34E-02
PSR05023453.hg.1	ENST00000501702	FLJ33630	1.54	2.76E-03
PSR05008643.hg.1	ENST00000510516	LYRM7	1.41	3.50E-02
PSR05023643.hg.1	ENST00000507093	RAPGEF6	1.64	3.50E-03
PSR05023661.hg.1	ENST00000507093	RAPGEF6	1.58	1.76E-02
PSR05008826.hg.1	BC136436	RAD50	1.68	4.36E-02
PSR05008852.hg.1	BC136436	RAD50	1.59	4.85E-02
PSR05008858.hg.1	BC136436	RAD50	1.64	3.54E-02
PSR05024005.hg.1	BC045542	KIF3A	1.55	2.23E-02
PSR05008969.hg.1	BC126124	HSPA4	1.46	6.96E-03
PSR05008970.hg.1	BC126124	HSPA4	1.45	1.69E-02

PSR05008977.hg.1	BC126124	HSPA4	1.44	2.46E-02
PSR05008980.hg.1	ENST00000304858	HSPA4	1.48	1.74E-02
PSR05024204.hg.1	BC024300	FSTL4	-1.51	1.90E-02
PSR05009135.hg.1	NM_003337	UBE2B	1.56	1.68E-02
PSR05009375.hg.1	BC101692	CATSPER3	-1.51	1.47E-03
PSR05024772.hg.1	NM_001101801	FAM13B	1.60	5.93E-03
PSR05025129.hg.1	NM_022464	SIL1	1.40	1.98E-02
PSR05010094.hg.1	NM_199189	MATR3	1.44	2.02E-02
PSR05025631.hg.1	ENST00000504366	HARS	1.61	3.99E-03
PSR05026064.hg.1	NM_001024094	NR3C1	1.45	2.33E-02
PSR05026305.hg.1	NM_181675	PPP2R2B	1.78	1.49E-02
PSR05001042.hg.1	NM_138348	FAM105B	1.49	3.94E-02
PSR05011405.hg.1	ENST00000504320	SCGB3A2	1.49	2.63E-02
PSR05011558.hg.1	ENST00000340253	FBXO38	1.58	1.05E-02
PSR05012075.hg.1	ENST00000517973	GPX3	1.63	2.75E-02
PSR05013121.hg.1	ENST00000518731	MAT2B	2.24	7.50E-03
PSR05028286.hg.1	ENST00000518172	MIR4454	1.41	3.14E-02
PSR05028313.hg.1	ENST00000522891	FBXW11	1.53	9.69E-04
PSR05014636.hg.1	ENST00000511258	NSD1	-1.43	1.87E-02
PSR05015008.hg.1	ENST00000511511	FAM153C	1.97	1.96E-02
PSR05015173.hg.1	ENST00000444149	ZNF879	1.43	4.09E-02
PSR05029724.hg.1	ENST00000356731	HNRNPH1	1.55	1.95E-02
PSR05029744.hg.1	ENST00000442819	HNRNPH1	1.80	2.12E-02
PSR05029798.hg.1	ENST00000442819	HNRNPH1	1.88	1.79E-02
PSR05017220.hg.1	ENST00000442743	DROSHA	1.42	4.96E-03
PSR05017221.hg.1	ENST00000442743	DROSHA	1.50	1.33E-02
PSR05017265.hg.1	ENST00000442743	DROSHA	1.57	3.08E-02
PSR05017395.hg.1	ENST00000265069	ZFR	1.44	5.09E-03
PSR05001425.hg.1	BC009610	SUB1	1.62	4.81E-02
PSR05001427.hg.1	BC009610	SUB1	2.05	7.32E-03
PSR05001721.hg.1	ENST00000356031	SPEF2	1.63	9.69E-03
PSR05001916.hg.1	NM_133433	NIPBL	1.72	2.13E-02
PSR05001917.hg.1	NM_133433	NIPBL	1.41	3.95E-02
PSR05001920.hg.1	NM_133433	NIPBL	1.45	7.19E-03
PSR05001921.hg.1	NM_133433	NIPBL	1.46	4.02E-02
PSR05001922.hg.1	NM_133433	NIPBL	1.61	3.24E-02
PSR05001923.hg.1	NM_133433	NIPBL	1.44	4.24E-02
PSR05001924.hg.1	NM_133433	NIPBL	1.51	1.72E-02
PSR05001940.hg.1	NM_133433	NIPBL	1.67	4.25E-02
PSR05018101.hg.1	BC137163	RICTOR	1.45	4.72E-02
PSR05018113.hg.1	BC137163	RICTOR	1.89	1.38E-02
PSR05018114.hg.1	BC137163	RICTOR	1.68	3.13E-02
PSR05018139.hg.1	BC137163	RICTOR	1.50	2.60E-02
PSR05002171.hg.1	BC063851	C7	1.64	4.40E-02
PSR05002173.hg.1	ENST00000515157	C7	1.46	4.16E-02
PSR05018616.hg.1	ENST00000510130	C5orf28	1.64	1.81E-03
PSR05002416.hg.1	NM_012343	NNT	1.56	1.55E-02
PSR05002454.hg.1	NM_012343	NNT	1.51	4.50E-02
PSR05000450.hg.1	ENST00000536857	ADAMTS16	1.42	7.95E-03
PSR05000478.hg.1	ENST00000296564	KIAA0947	2.23	2.44E-02

PSR05000483.hg.1	ENST00000296564	KIAA0947	1.45	7.82E-04
PSR05002851.hg.1	ENST00000504388	SKIV2L2	1.56	7.70E-03
PSR05002859.hg.1	ENST00000230640	SKIV2L2	1.49	2.86E-02
PSR05002866.hg.1	ENST00000230640	SKIV2L2	1.61	1.90E-02
PSR05002872.hg.1	ENST00000230640	SKIV2L2	1.53	2.09E-02
PSR05002875.hg.1	ENST00000230640	SKIV2L2	1.41	4.97E-02
PSR05002882.hg.1	ENST00000230640	SKIV2L2	1.46	2.35E-02
PSR05019110.hg.1	NM_001190981	IL6ST	1.49	4.10E-03
PSR05003080.hg.1	NM_001127235	GPBP1	1.44	2.03E-02
PSR05019357.hg.1	ENST00000317118	PDE4D	1.73	2.64E-02
PSR05003314.hg.1	ENST00000448151	LRRC70	-1.51	3.55E-02
PSR05019692.hg.1	ENST00000506282	CENPK	-1.43	1.60E-02
PSR05019732.hg.1	BC022510	TRIM23	1.45	3.69E-02
PSR05003609.hg.1	BC067770	SREK1	1.53	1.04E-02
PSR05003611.hg.1	BC067770	SREK1	1.48	1.36E-02
PSR05003616.hg.1	ENST00000284041	SREK1	1.54	3.22E-02
PSR05003681.hg.1	BC033215	MAST4	-1.70	4.33E-02
PSR05019891.hg.1	ENST00000380822	TAF9	1.42	1.55E-02
PSR05004483.hg.1	ENST00000358731	BDP1	1.50	1.42E-02
PSR05004488.hg.1	ENST00000358731	BDP1	1.40	3.66E-02
PSR05004667.hg.1	ENST00000506351	TNPO1	1.43	4.58E-02
PSR05004689.hg.1	ENST00000506351	TNPO1	1.80	2.40E-02
PSR05004873.hg.1	ENST00000437974	ARHGEF28	1.43	3.96E-02
PSR05004943.hg.1	NM_000521	HEXB	1.56	1.72E-02
PSR05020476.hg.1	NM_005713	COL4A3BP	1.40	1.45E-03
PSR05005269.hg.1	ENST00000312916	AGGF1	1.48	3.90E-02
PSR05005284.hg.1	BC032844	AGGF1	1.41	1.47E-02
PSR05020740.hg.1	ENST00000519295	AP3B1	1.40	4.87E-02
PSR05020742.hg.1	ENST00000519295	AP3B1	1.83	4.78E-02
PSR05020743.hg.1	ENST00000519295	AP3B1	1.51	3.54E-02
PSR05020752.hg.1	ENST00000519295	AP3B1	1.42	4.18E-02
PSR05005405.hg.1	ENST00000509998	SCAMP1	1.86	2.17E-02
PSR05005406.hg.1	NM_004866	SCAMP1	1.42	4.34E-02
PSR05005500.hg.1	ENST00000502269	PAPD4	1.50	4.79E-02
PSR05000690.hg.1	BC109216	MTRR	2.17	8.71E-03
PSR05005635.hg.1	NM_001105251	ZFYVE16	1.61	1.28E-02
PSR05005637.hg.1	NM_001105251	ZFYVE16	1.81	2.41E-02
PSR05005639.hg.1	NM_001105251	ZFYVE16	1.45	3.54E-02
PSR05005649.hg.1	NM_001105251	ZFYVE16	1.77	1.38E-02
PSR05005654.hg.1	NM_001105251	ZFYVE16	1.69	1.81E-02
PSR05021192.hg.1	ENST00000511450	TMEM167A	1.63	2.07E-02
PSR05005900.hg.1	ENST00000282268	XRCC4	-1.52	2.62E-03
PSR05021305.hg.1	ENST00000504878	CCNH	1.55	3.66E-02
PSR05021307.hg.1	ENST00000504878	CCNH	1.40	4.13E-02
PSR05021453.hg.1	NM_001193347	MEF2C	1.45	4.66E-03
PSR05021483.hg.1	NM_001193347	MEF2C	1.78	2.55E-02
PSR05021492.hg.1	NM_001193350	MEF2C	1.56	1.68E-02
PSR05021583.hg.1	NM_198273	LYSMD3	1.47	3.21E-02
PSR05021589.hg.1	NM_198273	LYSMD3	1.54	1.20E-02
PSR05006540.hg.1	NM_014899	RHOBTB3	1.54	3.84E-02

PSR05006694.hg.1	ENST00000341926	CAST	1.41	7.55E-03
PSR05006726.hg.1	BC065240	ERAP2	1.84	3.39E-02
PSR05006729.hg.1	BC065240	ERAP2	1.91	8.79E-03
PSR05006736.hg.1	BC065240	ERAP2	1.87	2.41E-02
PSR05006746.hg.1	BC065240	ERAP2	1.68	3.40E-02
PSR05006752.hg.1	BC065240	ERAP2	1.41	9.32E-03
PSR05006755.hg.1	BC065240	ERAP2	1.52	7.42E-04
PSR05006758.hg.1	BC065240	ERAP2	1.94	1.58E-02
PSR05022125.hg.1	BC000953	RIOK2	1.52	5.49E-03
PSR05022133.hg.1	BC000953	RIOK2	1.51	8.35E-03
PSR05022138.hg.1	ENST00000283109	RIOK2	1.68	2.10E-02
PSR05022177.hg.1	ENST00000284049	CHD1	1.62	3.35E-02
PSR05022207.hg.1	ENST00000284049	CHD1	1.65	1.59E-02
PSR05022209.hg.1	BC117134	CHD1	1.42	1.55E-02
PSR05022224.hg.1	BC117134	CHD1	1.67	6.40E-03
PSR06024325.hg.1	ENST00000518714	CCNC	1.50	4.75E-02
PSR06024707.hg.1	BC048287	SEC63	1.40	4.50E-02
PSR06024715.hg.1	ENST00000437345	SEC63	1.43	3.58E-02
PSR06024720.hg.1	ENST00000437345	SEC63	1.51	2.81E-02
PSR06024728.hg.1	BC048287	SEC63	1.44	2.83E-02
PSR06024736.hg.1	BC048287	SEC63	1.43	2.71E-02
PSR06010312.hg.1	ENST00000453496	LOC100996634	1.42	3.94E-02
PSR06000842.hg.1	ENST00000456616	ELOVL2-AS1	-1.45	7.00E-04
PSR06010415.hg.1	ENST00000439165	CDC40	1.60	2.42E-02
PSR06000856.hg.1	ENST00000416247	SMIM13	1.45	2.67E-02
PSR06025165.hg.1	ENST00000543871	REV3L	1.61	2.95E-02
PSR06025485.hg.1	ENST00000368632	HDAC2	1.44	3.52E-02
PSR06010745.hg.1	NM_001080976	DSE	1.61	2.55E-02
PSR06010747.hg.1	NM_001080976	DSE	1.51	3.03E-02
PSR06025598.hg.1	ENST00000368576	ZUFSP	1.57	3.89E-02
PSR06010839.hg.1	ENST00000368564	KPNA5	1.44	1.28E-02
PSR06025825.hg.1	NM_005907	MAN1A1	1.75	2.53E-02
PSR06025904.hg.1	NM_020755	SERINC1	1.62	9.29E-03
PSR06011356.hg.1	NM_001242846	RNF146	1.48	6.93E-03
PSR06011365.hg.1	NM_001242846	RNF146	1.45	1.75E-02
PSR06026085.hg.1	NM_001139510	ECHDC1	1.48	2.26E-02
PSR06026185.hg.1	BC144513	PTPRK	1.64	7.72E-07
PSR06026195.hg.1	BC144513	PTPRK	1.43	2.51E-02
PSR06026242.hg.1	ENST00000368227	PTPRK	1.41	3.23E-03
PSR06011440.hg.1	ENST00000443169	LAMA2	1.80	1.28E-02
PSR06011446.hg.1	ENST00000443169	LAMA2	1.48	4.85E-02
PSR06011447.hg.1	ENST00000443169	LAMA2	1.67	7.13E-03
PSR06011448.hg.1	ENST00000443169	LAMA2	1.43	2.57E-02
PSR06011450.hg.1	ENST00000443169	LAMA2	1.47	1.75E-02
PSR06011452.hg.1	ENST00000443169	LAMA2	1.42	2.11E-02
PSR06011453.hg.1	ENST00000443169	LAMA2	1.43	3.72E-02
PSR06011456.hg.1	ENST00000443169	LAMA2	1.65	2.92E-02
PSR06011461.hg.1	ENST00000498257	LAMA2	1.59	1.93E-02
PSR06011468.hg.1	ENST00000443169	LAMA2	1.48	4.89E-03
PSR06026434.hg.1	ENST00000479213	MED23	1.57	4.90E-03

PSR06026477.hg.1	ENST00000368058	MED23	1.57	1.65E-02
PSR06026484.hg.1	ENST00000368058	MED23	1.56	4.34E-02
PSR06011770.hg.1	BC041063	EYA4	1.59	4.46E-02
PSR06011791.hg.1	BC041063	EYA4	1.45	2.11E-02
PSR06011792.hg.1	ENST00000431403	EYA4	1.51	9.32E-03
PSR06026849.hg.1	NM_001145158	HBS1L	-1.43	2.79E-02
PSR06001013.hg.1	ENST00000474485	NOL7	1.43	2.80E-02
PSR06026972.hg.1	NM_001077440	BCLAF1	1.48	1.18E-03
PSR06026977.hg.1	NM_001077440	BCLAF1	1.40	3.33E-02
PSR06026986.hg.1	ENST00000529917	BCLAF1	1.48	8.77E-03
PSR06026988.hg.1	NM_001077440	BCLAF1	1.45	1.63E-02
PSR06026989.hg.1	NM_001077440	BCLAF1	1.50	2.01E-03
PSR06026994.hg.1	NM_001077440	BCLAF1	1.43	2.73E-02
PSR06026997.hg.1	NM_001077440	BCLAF1	1.62	7.07E-03
PSR06026999.hg.1	NM_001077440	BCLAF1	1.59	1.29E-02
PSR06001026.hg.1	NM_001165034	RNF182	-1.46	3.55E-03
PSR06012213.hg.1	ENST00000427932	VTA1	1.44	3.62E-02
PSR06012257.hg.1	ENST00000367609	GPR126	1.46	9.62E-03
PSR06012261.hg.1	ENST00000367609	GPR126	1.44	1.12E-02
PSR06012274.hg.1	ENST00000367609	GPR126	1.49	2.02E-04
PSR06027568.hg.1	ENST00000275233	SHPRH	1.41	3.12E-02
PSR06027576.hg.1	ENST00000275233	SHPRH	1.83	4.31E-02
PSR06027725.hg.1	NM_007044	KATNA1	-1.57	2.90E-02
PSR06012842.hg.1	BC007501	PCMT1	1.54	3.58E-02
PSR06027895.hg.1	ENST00000491268	RMND1	-1.47	1.86E-02
PSR06013027.hg.1	BC011348	C6orf211	1.50	4.70E-02
PSR06013032.hg.1	BC011348	C6orf211	1.69	1.45E-02
PSR06028254.hg.1	ENST00000422970	IPCEF1	-1.57	8.09E-05
PSR06028418.hg.1	ENST00000367088	DYNLT1	1.43	1.76E-02
PSR06013701.hg.1	NM_000876	IGF2R	1.45	1.44E-02
PSR06013714.hg.1	NM_000876	IGF2R	1.42	2.57E-02
PSR06013726.hg.1	NM_000876	IGF2R	1.69	2.31E-02
PSR06013733.hg.1	NM_000876	IGF2R	1.42	2.80E-02
PSR06013734.hg.1	NM_000876	IGF2R	1.44	3.96E-02
PSR06013757.hg.1	NM_000876	IGF2R	1.46	1.36E-02
PSR06013788.hg.1	ENST00000392145	SLC22A3	1.90	7.84E-03
PSR06013789.hg.1	ENST00000392145	SLC22A3	1.75	4.68E-02
PSR06013790.hg.1	ENST00000392145	SLC22A3	2.02	1.74E-02
PSR06013791.hg.1	ENST00000392145	SLC22A3	2.21	2.69E-02
PSR06013792.hg.1	ENST00000392145	SLC22A3	2.27	3.81E-02
PSR06013793.hg.1	ENST00000392145	SLC22A3	1.98	9.04E-03
PSR06013795.hg.1	ENST00000392145	SLC22A3	1.97	3.79E-02
PSR06013796.hg.1	ENST00000392145	SLC22A3	1.85	1.16E-02
PSR06013797.hg.1	ENST00000392145	SLC22A3	2.01	2.38E-02
PSR06013798.hg.1	ENST00000392145	SLC22A3	1.52	2.98E-02
PSR06013799.hg.1	ENST00000392145	SLC22A3	1.95	1.53E-02
PSR06013954.hg.1	NM_206853	QKI	2.02	2.08E-02
PSR06013946.hg.1	NM_206853	QKI	1.63	4.59E-03
PSR06013948.hg.1	NM_206853	QKI	1.42	1.20E-02
PSR06013949.hg.1	NM_206853	QKI	1.51	1.59E-02

PSR06001292.hg.1	NM_001546	ID4	1.68	2.57E-02
PSR06015879.hg.1	ENST00000545780	TDP2	1.45	2.92E-02
PSR06016219.hg.1	BC050425	ZNF322	1.45	8.44E-03
PSR06016224.hg.1	NM_001242798	ZNF322	1.42	2.77E-02
PSR06016299.hg.1	NM_007149	ZNF184	1.41	1.22E-02
PSR06016305.hg.1	NM_007149	ZNF184	1.53	2.24E-02
PSR06016398.hg.1	ENST00000356796	ZKSCAN4	1.52	1.88E-03
PSR06016561.hg.1	BC013580	TRIM27	1.44	1.91E-02
PSR06016787.hg.1	BC017017	TRIM31	-1.43	3.67E-03
PSR06016805.hg.1	BC017017	TRIM31	-1.44	1.18E-02
PSR06003361.hg.1	NM_080870	DPCR1	-1.47	3.80E-03
PSR06017365.hg.1	ENST00000412585	HLA-B	-1.54	2.36E-02
PSR06003534.hg.1	ENST00000454783	LTA	-1.57	1.70E-02
PSR06004938.hg.1	ENST00000374606	PFDN6	-1.51	7.10E-03
PSR06004939.hg.1	ENST00000374606	PFDN6	-1.58	6.64E-03
PSR06004940.hg.1	NM_014260	PFDN6	-1.63	1.88E-02
PSR06019871.hg.1	NM_138718	SLC26A8	-1.51	2.08E-03
PSR06005752.hg.1	ENST00000536757	PI16	1.47	4.60E-02
PSR06020009.hg.1	BC003048	PPIL1	1.51	2.45E-02
PSR06020087.hg.1	ENST00000445172	LOC100505550	1.46	6.80E-03
PSR06006051.hg.1	ENST00000373391	ZFAND3	-1.50	1.12E-02
PSR06006052.hg.1	ENST00000373391	ZFAND3	-1.50	2.81E-02
PSR06020175.hg.1	BC015934	GLO1	1.58	2.36E-02
PSR06000316.hg.1	BC034969	PRPF4B	1.69	7.75E-03
PSR06020412.hg.1	ENST00000479950	OARD1	-1.68	4.48E-02
PSR06006669.hg.1	ENST00000493763	RPL7L1	1.49	3.07E-02
PSR06006671.hg.1	ENST00000493763	RPL7L1	1.47	1.23E-02
PSR06006672.hg.1	ENST00000493763	RPL7L1	1.53	3.96E-02
PSR06006698.hg.1	ENST00000446507	PTCRA	-1.44	5.04E-03
PSR06007054.hg.1	ENST00000304139	TTBK1	-1.41	4.20E-02
PSR06021027.hg.1	ENST00000265351	XPO5	1.41	3.21E-02
PSR06021048.hg.1	ENST00000439465	XPO5	1.44	4.79E-02
PSR06021055.hg.1	ENST00000265351	XPO5	1.42	1.65E-02
PSR06021406.hg.1	ENST00000371253	GPR110	-1.48	3.56E-03
PSR06014377.hg.1	ENST00000230449	EXOC2	1.56	4.79E-02
PSR06021672.hg.1	ENST00000371117	PKHD1	-1.63	2.62E-03
PSR06021810.hg.1	BC020619	GSTA3	-1.80	3.76E-02
PSR06022147.hg.1	ENST00000421834	DST	1.47	4.87E-03
PSR06022205.hg.1	ENST00000421834	DST	1.52	1.16E-02
PSR06022240.hg.1	ENST00000421834	DST	1.41	6.44E-03
PSR06022262.hg.1	ENST00000421834	DST	1.71	1.64E-02
PSR06022272.hg.1	ENST00000421834	DST	1.40	1.55E-02
PSR06014790.hg.1	BC027963	F13A1	1.48	4.89E-02
PSR06014396.hg.1	ENST00000230449	EXOC2	1.40	3.80E-02
PSR06008305.hg.1	ENST00000370651	PTP4A1	1.42	3.74E-02
PSR06008310.hg.1	ENST00000370651	PTP4A1	1.42	3.70E-03
PSR06008519.hg.1	ENST00000457062	FAM135A	1.50	2.79E-02
PSR06014853.hg.1	NM_003144	SSR1	1.55	2.09E-02
PSR06014862.hg.1	ENST00000479485	SSR1	1.64	2.86E-02
PSR06014865.hg.1	ENST00000479485	SSR1	1.43	1.35E-02

PSR06000525.hg.1	ENST00000379834	RIOK1	1.48	3.38E-02
PSR06022976.hg.1	NM_001563	IMPG1	-1.42	1.33E-02
PSR06023012.hg.1	ENST00000479165	PHIP	1.41	3.80E-02
PSR06023016.hg.1	ENST00000479165	PHIP	1.41	3.82E-02
PSR06023022.hg.1	ENST00000275034	PHIP	1.48	3.61E-02
PSR06009184.hg.1	ENST00000369739	DOPEY1	1.41	2.26E-02
PSR06009192.hg.1	ENST00000369739	DOPEY1	1.42	2.23E-02
PSR06023217.hg.1	NM_001199919	PGM3	1.44	9.14E-03
PSR06023220.hg.1	ENST00000513973	PGM3	1.48	3.69E-02
PSR06023232.hg.1	NM_001199919	PGM3	1.67	3.10E-02
PSR06009240.hg.1	NM_033411	RWDD2A	-1.51	3.32E-02
PSR06014997.hg.1	ENST00000426876	SLC35B3	1.48	5.66E-03
PSR06023406.hg.1	ENST00000257766	KIAA1009	1.63	2.43E-03
PSR06023432.hg.1	ENST00000369663	TBX18	1.47	1.72E-02
PSR06023528.hg.1	NM_001159675	SYNCRIP	1.56	3.30E-02
PSR06023535.hg.1	ENST00000355238	SYNCRIP	1.47	5.68E-03
PSR06023537.hg.1	ENST00000355238	SYNCRIP	1.40	8.92E-04
PSR06023538.hg.1	ENST00000355238	SYNCRIP	1.70	2.85E-02
PSR06023609.hg.1	BC057813	GJB7	1.41	1.48E-02
PSR06023701.hg.1	BC019954	RNGTT	1.45	2.81E-02
PSR06009645.hg.1	BC132828	CASP8AP2	1.55	1.18E-02
PSR06009647.hg.1	BC132828	CASP8AP2	1.43	2.59E-02
PSR06009648.hg.1	BC132828	CASP8AP2	1.98	2.25E-02
PSR06023991.hg.1	ENST00000479630	MAP3K7	1.73	1.34E-02
PSR06023994.hg.1	NM_145331	MAP3K7	1.44	3.45E-02
PSR06009762.hg.1	BC028608	UFL1	1.49	4.26E-02
PSR06024215.hg.1	ENST00000369239	PNISR	1.53	3.74E-02
PSR6_apd_hap1000921.hg.1	NM_007028	TRIM31	-1.44	1.18E-02
PSR6_apd_hap1000754.hg.1	BC013580	TRIM27	1.44	1.91E-02
PSR6_cox_hap2002263.hg.1	BC017017	TRIM31	-1.54	1.19E-02
PSR6_cox_hap2002051.hg.1	BC013580	TRIM27	1.44	1.91E-02
PSR6_dbb_hap3002176.hg.1	BC017017	TRIM31	-1.43	3.67E-03
PSR6_dbb_hap3002193.hg.1	BC017017	TRIM31	-1.44	1.18E-02
PSR6_dbb_hap3000756.hg.1	NM_080870	DPCR1	-1.62	1.31E-03
PSR6_dbb_hap3001687.hg.1	NM_005155	PPT2	-1.59	2.95E-02
PSR6_dbb_hap3003603.hg.1	BC012106	HLA-DQB1	-2.32	8.24E-04
PSR6_dbb_hap3002093.hg.1	NM_001470	GABBR1	-1.43	1.15E-02
PSR6_mann_hap4001766.hg.1	BC017017	TRIM31	-1.43	3.67E-03
PSR6_mann_hap4001783.hg.1	NM_007028	TRIM31	-1.44	1.18E-02
PSR6_mann_hap4002247.hg.1	NM_005514	HLA-B	-1.54	2.36E-02
PSR6_mann_hap4002252.hg.1	NM_005514	HLA-B	-1.49	3.48E-02
PSR6_mcf_hap5001984.hg.1	BC017017	TRIM31	-1.44	1.18E-02
PSR6_mcf_hap5001410.hg.1	NM_001204103	PPT2	-1.59	2.95E-02
PSR6_mcf_hap5001898.hg.1	NM_001470	GABBR1	-1.43	1.15E-02
PSR6_qbl_hap6002033.hg.1	BC013580	TRIM27	1.44	1.91E-02
PSR6_qbl_hap6001563.hg.1	NM_001002029	C4B	-1.54	1.21E-02
PSR6_ssto_hap7002020.hg.1	BC017017	TRIM31	-1.43	3.67E-03
PSR6_ssto_hap7002037.hg.1	BC017017	TRIM31	-1.44	1.18E-02
PSR6_ssto_hap7002388.hg.1	NM_005514	HLA-B	-1.54	2.36E-02
PSR6_ssto_hap7002393.hg.1	NM_005514	HLA-B	-1.49	3.48E-02

PSR07025800.hg.1	ENST00000544242	TFR2	-2.03	3.21E-04
PSR07009970.hg.1	ENST00000467414	MUC12	-1.53	2.50E-02
PSR07026259.hg.1	NM_006234	POLR2J	-2.05	2.95E-02
PSR07026366.hg.1	NM_001097615	POLR2J3	-1.95	4.19E-03
PSR07026611.hg.1	ENST00000249270	DNAJC2	1.58	3.24E-02
PSR07026614.hg.1	ENST00000249270	DNAJC2	1.53	3.10E-02
PSR07026795.hg.1	ENST00000433514	LHFPL3-AS1	-1.54	7.43E-04
PSR07026816.hg.1	ENST00000434579	LHFPL3-AS1	-1.52	1.34E-02
PSR07010528.hg.1	ENST00000334914	KMT2E	1.50	1.18E-02
PSR07010540.hg.1	ENST00000334914	KMT2E	1.65	4.70E-02
PSR07010544.hg.1	ENST00000334914	KMT2E	1.93	2.72E-02
PSR07010565.hg.1	ENST00000334914	KMT2E	1.84	4.54E-02
PSR07010708.hg.1	NM_002649	PIK3CG	1.54	1.02E-02
PSR07010734.hg.1	ENST00000265717	PRKAR2B	1.57	4.53E-02
PSR07010737.hg.1	BC075800	PRKAR2B	1.65	3.80E-02
PSR07027108.hg.1	NM_181733	COG5	1.60	4.82E-02
PSR07010876.hg.1	ENST00000465919	BCAP29	1.67	6.62E-03
PSR07010883.hg.1	NM_018844	BCAP29	1.48	1.71E-02
PSR07010993.hg.1	ENST00000437604	DLD	1.47	1.37E-02
PSR07027170.hg.1	BC113455	LAMB1	1.63	4.79E-02
PSR07027430.hg.1	NM_182529	THAP5	1.52	4.45E-02
PSR07011030.hg.1	NM_012328	DNAJB9	1.48	1.84E-02
PSR07027471.hg.1	ENST00000489381	IMMP2L	1.55	2.31E-02
PSR07011131.hg.1	NM_001197079	IFRD1	1.90	2.64E-02
PSR07027927.hg.1	BC106000	CTTNBP2	-1.47	3.38E-02
PSR07027979.hg.1	BC024200	FAM3C	1.45	4.77E-03
PSR07028184.hg.1	ENST00000324698	IQUB	1.42	1.61E-03
PSR07028282.hg.1	NM_003941	WASL	-1.48	1.84E-02
PSR07012225.hg.1	NM_018396	METTL2B	1.44	9.22E-03
PSR07012344.hg.1	ENST00000487361	CCDC136	-1.43	1.61E-02
PSR07012624.hg.1	NM_001134336	STRIP2	1.44	1.12E-02
PSR07012867.hg.1	ENST00000223215	MEST	1.59	2.18E-02
PSR07012878.hg.1	ENST00000437945	MEST	1.80	1.47E-02
PSR07012897.hg.1	ENST00000437945	MEST	1.82	3.26E-02
PSR07012926.hg.1	ENST00000352689	MKLN1	1.41	2.59E-02
PSR07012932.hg.1	ENST00000352689	MKLN1	1.57	5.39E-03
PSR07012939.hg.1	ENST00000352689	MKLN1	1.48	1.47E-02
PSR07012940.hg.1	ENST00000352689	MKLN1	1.64	6.35E-03
PSR07012946.hg.1	ENST00000352689	MKLN1	1.49	7.02E-04
PSR07012956.hg.1	ENST00000352689	MKLN1	1.65	1.01E-03
PSR07013303.hg.1	ENST00000285968	NUP205	1.45	2.80E-03
PSR07031159.hg.1	NM_003078	SMARCD3	-1.46	3.37E-04
PSR07031284.hg.1	NM_001040633	PRKAG2	1.58	3.23E-02
PSR07016212.hg.1	ENST00000348165	UBE3C	1.47	6.23E-03
PSR07018575.hg.1	ENST00000401957	RAPGEF5	-1.56	2.19E-02
PSR07002272.hg.1	ENST00000381990	GPNMB	1.64	4.32E-02
PSR07002281.hg.1	ENST00000381990	GPNMB	1.49	4.63E-02
PSR07002284.hg.1	ENST00000381990	GPNMB	1.57	1.81E-02
PSR07002720.hg.1	ENST00000409980	TAX1BP1	1.46	2.88E-02
PSR07002721.hg.1	ENST00000409980	TAX1BP1	1.51	1.11E-02

PSR07002723.hg.1	ENST00000409980	TAX1BP1	1.49	2.17E-02
PSR07002724.hg.1	ENST00000409980	TAX1BP1	1.41	3.12E-02
PSR07002735.hg.1	ENST00000409980	TAX1BP1	1.41	1.17E-02
PSR07002747.hg.1	ENST00000409980	TAX1BP1	1.40	3.79E-02
PSR07002752.hg.1	NM_001206901	TAX1BP1	1.46	2.03E-02
PSR07002753.hg.1	NM_001206901	TAX1BP1	1.57	4.77E-02
PSR07000578.hg.1	ENST00000489665	AMZ1	-1.48	6.11E-03
PSR07002996.hg.1	ENST00000324489	C7orf41	1.41	1.20E-02
PSR07003001.hg.1	ENST00000324489	C7orf41	1.41	2.54E-02
PSR07020158.hg.1	ENST00000390341	TRGV10	-1.46	2.86E-02
PSR07003967.hg.1	ENST00000496564	MRPL32	-1.53	6.24E-03
PSR07004043.hg.1	ENST00000319357	STK17A	1.47	3.44E-03
PSR07020473.hg.1	ENST00000310564	COA1	1.49	1.47E-03
PSR07020548.hg.1	ENST00000336086	URGCP	1.41	2.70E-02
PSR07021317.hg.1	ENST00000258774	HUS1	1.42	7.58E-03
PSR07021940.hg.1	ENST00000331162	ZNF479	1.58	1.08E-03
PSR07017440.hg.1	ENST00000199389	EIF2AK1	1.41	4.57E-02
PSR07017464.hg.1	ENST00000199389	EIF2AK1	1.52	2.93E-02
PSR07005215.hg.1	ENST00000395391	ZNF107	1.43	3.50E-02
PSR07022038.hg.1	BC066990	LOC441242	1.53	5.84E-03
PSR07017583.hg.1	BC012994	KDELR2	-1.46	2.64E-02
PSR07017589.hg.1	ENST00000258739	KDELR2	-1.48	3.08E-02
PSR07017624.hg.1	ENST00000404360	ZNF12	1.47	1.66E-02
PSR07017641.hg.1	ENST00000330442	ZNF12	1.46	1.63E-02
PSR07005688.hg.1	NM_001127231	AUTS2	1.78	2.43E-02
PSR07005699.hg.1	NM_001127231	AUTS2	1.49	2.08E-02
PSR07001269.hg.1	ENST00000223122	C1GALT1	1.45	4.25E-02
PSR07006905.hg.1	ENST00000443097	UPK3B	1.80	4.58E-02
PSR07016470.hg.1	NM_001164760	PRKAR1B	-1.46	4.88E-03
PSR07023307.hg.1	ENST00000430584	GSAP	2.01	1.63E-02
PSR07006988.hg.1	ENST00000248594	PTPN12	1.46	3.20E-03
PSR07023518.hg.1	ENST00000356860	CACNA2D1	1.41	1.81E-02
PSR07023750.hg.1	ENST00000444627	KIAA1324L	1.51	1.02E-02
PSR07023852.hg.1	NM_000443	ABCB4	1.40	2.65E-02
PSR07007895.hg.1	ENST00000491695	AKAP9	1.68	1.70E-02
PSR07007896.hg.1	ENST00000491695	AKAP9	1.63	2.72E-02
PSR07024160.hg.1	NM_004912	KRIT1	1.53	1.91E-02
PSR07024183.hg.1	NM_004912	KRIT1	1.43	1.86E-02
PSR07008007.hg.1	BC031091	GATAD1	-1.57	2.32E-02
PSR07024424.hg.1	NM_001164737	CALCR	-1.57	7.22E-03
PSR07024452.hg.1	NM_005868	BET1	1.44	1.89E-02
PSR08008470.hg.1	NM_152564	VPS13B	1.41	1.35E-02
PSR08008483.hg.1	NM_152564	VPS13B	1.47	1.86E-02
PSR08019462.hg.1	ENST00000517844	ZNF706	1.45	1.09E-02
PSR08019576.hg.1	ENST00000251810	RRM2B	1.46	1.58E-02
PSR08019725.hg.1	ENST00000347770	AZIN1	1.47	4.05E-02
PSR08019728.hg.1	ENST00000347770	AZIN1	1.56	4.56E-03
PSR08019733.hg.1	ENST00000347770	AZIN1	1.45	4.33E-02
PSR08019738.hg.1	ENST00000347770	AZIN1	1.45	2.49E-03
PSR08019740.hg.1	ENST00000347770	AZIN1	1.42	2.22E-02

PSR08008713.hg.1	ENST00000518738	ATP6V1C1	1.41	1.81E-02
PSR08008727.hg.1	ENST00000518738	ATP6V1C1	2.01	1.65E-03
PSR08008829.hg.1	NM_015420	DCAF13	1.53	4.18E-03
PSR08008901.hg.1	ENST00000507740	RIMS2	-1.42	9.12E-03
PSR08000761.hg.1	ENST00000221086	MTMR9	1.46	1.96E-02
PSR08000774.hg.1	ENST00000221086	MTMR9	1.49	2.92E-02
PSR08000950.hg.1	ENST00000400085	ZNF705D	1.41	4.61E-02
PSR08009380.hg.1	ENST00000522112	MAL2	1.40	2.96E-02
PSR08020513.hg.1	ENST00000259486	ENPP2	1.40	4.05E-02
PSR08009742.hg.1	ENST00000521166	FAM91A1	1.50	1.77E-02
PSR08009744.hg.1	ENST00000521166	FAM91A1	1.58	1.45E-02
PSR08009751.hg.1	ENST00000521166	FAM91A1	1.46	6.54E-03
PSR08009770.hg.1	ENST00000521166	FAM91A1	1.41	2.22E-02
PSR08009776.hg.1	ENST00000334705	FAM91A1	1.56	2.99E-03
PSR08009923.hg.1	ENST00000519140	KIAA0196-AS1	1.42	2.97E-02
PSR08021226.hg.1	ENST00000519540	FAM49B	1.49	2.35E-02
PSR08021232.hg.1	ENST00000519540	FAM49B	1.52	2.13E-02
PSR08021234.hg.1	ENST00000519540	FAM49B	1.49	4.98E-02
PSR08021443.hg.1	ENST00000519445	KCNQ3	-1.44	4.26E-03
PSR08021513.hg.1	ENST00000377901	TMEM71	1.47	4.30E-02
PSR08010212.hg.1	ENST00000395390	PHF20L1	1.44	5.02E-03
PSR08010233.hg.1	NM_198513	PHF20L1	1.44	2.81E-02
PSR08010243.hg.1	ENST00000361997	PHF20L1	1.45	3.79E-02
PSR08010569.hg.1	BC144226	DENND3	-1.42	8.55E-03
PSR08001265.hg.1	ENST00000518936	PCM1	1.40	1.27E-02
PSR08001315.hg.1	ENST00000327578	PCM1	1.89	1.01E-02
PSR08001489.hg.1	ENST00000397977	INTS10	1.68	1.44E-02
PSR08002644.hg.1	ENST00000276440	DOCK5	1.46	2.88E-02
PSR08002658.hg.1	ENST00000276440	DOCK5	1.52	8.66E-03
PSR08002660.hg.1	ENST00000276440	DOCK5	1.61	4.66E-02
PSR08002671.hg.1	ENST00000276440	DOCK5	1.48	2.02E-02
PSR08002682.hg.1	ENST00000276440	DOCK5	1.44	1.24E-02
PSR08002708.hg.1	NM_024940	DOCK5	1.55	4.29E-02
PSR08013599.hg.1	ENST00000221200	KCTD9	1.42	4.38E-02
PSR08002779.hg.1	NM_001177591	PPP2R2A	1.48	1.50E-02
PSR08003188.hg.1	NM_017412	FZD3	1.52	1.17E-02
PSR08014145.hg.1	NM_015254	KIF13B	1.68	4.11E-02
PSR08014268.hg.1	ENST00000256255	TMEM66	-1.49	1.20E-02
PSR08004017.hg.1	NM_001164232	DDHD2	1.45	1.94E-02
PSR08004022.hg.1	NM_001164232	DDHD2	1.46	4.88E-02
PSR08004217.hg.1	BC126406	ADAM9	1.48	1.46E-02
PSR08004219.hg.1	BC126406	ADAM9	1.56	1.06E-02
PSR08004228.hg.1	BC126406	ADAM9	1.41	1.47E-02
PSR08004524.hg.1	ENST00000396987	AGPAT6	1.45	7.12E-03
PSR08015217.hg.1	ENST00000523340	SLC20A2	1.47	4.24E-03
PSR08004826.hg.1	ENST00000531610	CHRNB3	-1.48	1.96E-03
PSR08004838.hg.1	NM_032410	HOOK3	1.73	1.15E-02
PSR08004841.hg.1	NM_032410	HOOK3	1.53	7.64E-03
PSR08004843.hg.1	NM_032410	HOOK3	1.52	3.31E-02

PSR08015762.hg.1	NM_201437	TCEA1	1.43	3.19E-02
PSR08016150.hg.1	BC041124	NSMAF	1.70	4.97E-02
PSR08005746.hg.1	ENST00000525508	CHD7	1.40	4.55E-02
PSR08016422.hg.1	NM_004820	CYP7B1	1.80	1.92E-02
PSR08016423.hg.1	NM_004820	CYP7B1	1.57	4.38E-02
PSR08016427.hg.1	NM_004820	CYP7B1	1.46	4.67E-02
PSR08016428.hg.1	NM_004820	CYP7B1	1.43	4.40E-02
PSR08016485.hg.1	NM_001242318	PDE7A	1.50	4.65E-02
PSR08016486.hg.1	NM_001242318	PDE7A	1.46	1.83E-02
PSR08016490.hg.1	NM_001242318	PDE7A	1.45	4.57E-02
PSR08016492.hg.1	NM_001242318	PDE7A	1.46	3.89E-02
PSR08016493.hg.1	NM_001242318	PDE7A	1.69	1.66E-02
PSR08016500.hg.1	NM_001242318	PDE7A	1.57	3.39E-02
PSR08016568.hg.1	NM_025054	VCPIP1	1.48	2.22E-02
PSR08017258.hg.1	BC140876	JPH1	2.17	1.81E-03
PSR08006871.hg.1	NM_024721	ZFHX4	1.57	4.05E-02
PSR08012128.hg.1	ENST00000276282	MFHAS1	1.48	4.77E-02
PSR08017916.hg.1	NM_172239	REXO1L1	2.14	2.60E-02
PSR08007496.hg.1	ENST00000519007	DECR1	1.43	3.72E-02
PSR08000596.hg.1	ENST00000523246	LOC157273	1.57	1.56E-02
PSR08000605.hg.1	ENST00000518619	LOC157273	1.48	3.90E-02
PSR08018379.hg.1	NM_001198679	RUNX1T1	1.77	4.67E-02
PSR08007780.hg.1	ENST00000425545	TMEM67	1.41	5.38E-03
PSR08018665.hg.1	ENST00000297591	KIAA1429	1.63	2.81E-02
PSR08007930.hg.1	ENST00000414645	DPY19L4	1.52	1.18E-02
PSR08007953.hg.1	ENST00000523731	INTS8	1.62	1.40E-02
PSR08008257.hg.1	ENST00000445593	LAPTM4B	1.60	7.00E-05
PSR08008259.hg.1	ENST00000445593	LAPTM4B	1.48	7.33E-03
PSR08008262.hg.1	ENST00000445593	LAPTM4B	1.58	1.24E-02
PSR08018890.hg.1	ENST00000287038	RPL30	-1.42	2.79E-03
PSR08018887.hg.1	ENST00000287038	RPL30	-1.42	7.17E-03
PSR08018891.hg.1	ENST00000287038	RPL30	-1.50	1.55E-03
PSR08000669.hg.1	ENST00000317173	MSRA	-1.43	1.29E-02
PSR09017416.hg.1	ENST00000325350	C9orf156	2.19	8.12E-04
PSR09005348.hg.1	ENST00000473205	ANP32B	-1.40	2.48E-02
PSR09005479.hg.1	ENST00000374994	TGFBR1	1.49	2.96E-02
PSR09005480.hg.1	ENST00000374994	TGFBR1	1.43	4.17E-02
PSR09017651.hg.1	NM_015051	ERP44	1.43	3.62E-02
PSR09017656.hg.1	NM_015051	ERP44	1.46	8.59E-03
PSR09017660.hg.1	NM_015051	ERP44	1.46	3.75E-02
PSR09005720.hg.1	NM_019592	RNF20	1.44	2.04E-02
PSR09017838.hg.1	NM_005502	ABCA1	1.49	9.65E-03
PSR09017841.hg.1	NM_005502	ABCA1	1.52	1.77E-02
PSR09017842.hg.1	NM_005502	ABCA1	1.43	1.44E-02
PSR09017846.hg.1	NM_005502	ABCA1	1.75	1.63E-03
PSR09017885.hg.1	ENST00000423487	ABCA1	1.57	1.05E-03
PSR09006057.hg.1	NM_001244713	RAD23B	1.45	6.32E-03
PSR09006071.hg.1	NM_002874	RAD23B	1.51	1.56E-02
PSR09018324.hg.1	ENST00000338205	KIAA0368	1.43	7.54E-03

PSR09018340.hg.1	ENST00000374378	KIAA0368	1.40	7.26E-03
PSR09018343.hg.1	ENST00000374378	KIAA0368	1.40	3.42E-02
PSR09018350.hg.1	ENST00000374378	KIAA0368	1.40	4.67E-02
PSR09018484.hg.1	ENST00000374255	PTBP3	1.56	2.06E-02
PSR09006840.hg.1	BC137286	CNTRL	1.73	3.11E-02
PSR09006841.hg.1	BC137286	CNTRL	1.75	3.62E-02
PSR09019604.hg.1	ENST00000498479	RC3H2	1.41	2.09E-02
PSR09019607.hg.1	NM_001100588	RC3H2	1.42	4.33E-03
PSR09019970.hg.1	ENST00000324460	HSPA5	1.51	2.17E-02
PSR09007519.hg.1	ENST00000470056	GAPVD1	1.56	1.75E-02
PSR09007522.hg.1	ENST00000470056	GAPVD1	1.45	4.07E-02
PSR09020015.hg.1	ENST00000373505	MAPKAP1	1.44	3.22E-02
PSR09020019.hg.1	ENST00000373511	MAPKAP1	1.44	3.74E-02
PSR09020021.hg.1	ENST00000373511	MAPKAP1	1.40	2.45E-02
PSR09008121.hg.1	ENST00000373064	SLC25A25	1.59	3.42E-02
PSR09008136.hg.1	ENST00000373064	SLC25A25	1.74	4.77E-03
PSR09012090.hg.1	BC144564	MPDZ	1.41	2.23E-02
PSR09020828.hg.1	BC063644	C9orf114	-1.55	4.16E-02
PSR09021055.hg.1	BC017570	C9orf78	1.42	3.97E-02
PSR09009163.hg.1	ENST00000493417	GPR107	1.59	3.14E-02
PSR09009333.hg.1	ENST00000372376	FUBP3	1.40	3.10E-03
PSR09009359.hg.1	ENST00000372376	FUBP3	1.60	3.37E-03
PSR09021339.hg.1	NM_007344	TTF1	1.66	1.43E-02
PSR09009763.hg.1	BC094774	GTF3C4	1.43	2.94E-02
PSR09010813.hg.1	ENST00000432785	TRAF2	-1.41	2.67E-02
PSR09012316.hg.1	ENST00000380850	TTC39B	1.46	3.47E-02
PSR09000862.hg.1	ENST00000380821	SNAPC3	1.41	4.12E-02
PSR09000863.hg.1	ENST00000380807	SNAPC3	1.54	4.41E-02
PSR09012903.hg.1	ENST00000397292	PLAA	1.62	1.88E-02
PSR09013185.hg.1	BC002876	SMU1	1.79	2.41E-02
PSR09013319.hg.1	NM_004925	AQP3	-1.46	3.33E-02
PSR09013992.hg.1	ENST00000396757	CD72	2.85	2.23E-02
PSR09002301.hg.1	NM_021111	RECK	1.45	2.18E-02
PSR09002307.hg.1	NM_021111	RECK	1.53	5.70E-03
PSR09002431.hg.1	BC036940	ZCCHC7	1.40	2.46E-02
PSR09014451.hg.1	ENST00000490516	EXOSC3	1.41	4.66E-02
PSR09014528.hg.1	NM_147195	ANKRD18A	1.72	3.56E-02
PSR09002700.hg.1	BC171793	ANKRD20A3	1.70	4.60E-02
PSR09002789.hg.1	ENST00000478448	LOC101060578	1.48	3.09E-02
PSR09014778.hg.1	BC140809	ANKRD20A3	1.70	4.60E-02
PSR09014780.hg.1	ENST00000459943	ANKRD20A4	1.56	3.81E-02
PSR09002874.hg.1	ENST00000377564	CNTNAP3B	1.43	3.37E-02
PSR09011751.hg.1	ENST00000381895	SPATA6L	1.48	8.27E-03
PSR09000384.hg.1	ENST00000381858	CDC37L1	1.95	2.00E-02
PSR09000385.hg.1	ENST00000381858	CDC37L1	1.42	9.80E-03
PSR09000387.hg.1	ENST00000381858	CDC37L1	1.63	1.77E-02
PSR09000389.hg.1	NM_017913	CDC37L1	1.41	1.05E-02
PSR09000456.hg.1	ENST00000539801	JAK2	1.47	1.81E-02
PSR09002967.hg.1	ENST00000424345	LOC100996870	2.03	1.55E-02
PSR09003018.hg.1	BC171793	ANKRD20A3	1.46	6.10E-03

PSR09003021.hg.1	BC171793	ANKRD20A3	1.70	4.60E-02
PSR09015023.hg.1	ENST00000377449	CBWD6	1.61	2.31E-02
PSR09015039.hg.1	ENST00000468061	CBWD6	1.47	2.52E-02
PSR09015056.hg.1	ENST00000377445	CBWD6	1.53	2.66E-02
PSR09015066.hg.1	ENST00000536466	CBWD6	1.70	2.24E-02
PSR09015078.hg.1	ENST00000377439	CBWD6	2.15	2.10E-02
PSR09015079.hg.1	ENST00000536466	CBWD6	1.52	1.99E-02
PSR09015150.hg.1	ENST00000461932	LOC101060578	1.77	5.65E-03
PSR09015159.hg.1	ENST00000461932	LOC101060578	1.80	7.81E-03
PSR09015193.hg.1	ENST00000377384	LOC101060578	1.59	4.69E-02
PSR09003162.hg.1	ENST00000377338	LOC101060578	1.59	2.86E-02
PSR09003169.hg.1	ENST00000377339	LOC101060578	1.48	1.14E-02
PSR09003287.hg.1	NM_000144	FXN	1.43	3.08E-02
PSR09000732.hg.1	ENST00000381309	KDM4C	1.52	3.97E-02
PSR09003320.hg.1	NM_004817	TJP2	1.42	2.74E-02
PSR09003329.hg.1	NM_004817	TJP2	1.47	2.87E-02
PSR09015515.hg.1	ENST00000297785	ALDH1A1	1.45	2.92E-02
PSR09015518.hg.1	ENST00000297785	ALDH1A1	1.48	1.65E-02
PSR09015520.hg.1	ENST00000297785	ALDH1A1	1.44	6.73E-03
PSR09015525.hg.1	NM_000689	ALDH1A1	1.46	6.41E-04
PSR09015528.hg.1	NM_000689	ALDH1A1	1.44	3.14E-02
PSR09015530.hg.1	NM_000689	ALDH1A1	1.42	3.69E-02
PSR09015538.hg.1	NM_000689	ALDH1A1	1.81	1.16E-02
PSR09016192.hg.1	NM_177937	GOLM1	-2.07	5.84E-04
PSR09016209.hg.1	ENST00000452279	ISCA1	-1.43	7.77E-03
PSR09016228.hg.1	NM_001185074	ZCCHC6	1.59	1.44E-02
PSR09016234.hg.1	NM_001185074	ZCCHC6	1.40	3.46E-02
PSR09016238.hg.1	ENST00000375963	ZCCHC6	1.60	2.70E-02
PSR09016239.hg.1	ENST00000375961	ZCCHC6	1.80	3.87E-02
PSR09004488.hg.1	BC019325	GADD45G	-1.43	1.37E-02
PSR09004491.hg.1	BC019325	GADD45G	-1.53	1.02E-02
PSR09004494.hg.1	BC019325	GADD45G	-1.43	2.30E-03
PSR09016804.hg.1	BC026154	IPPK	1.49	9.92E-03
PSR09005083.hg.1	ENST00000288985	ERCC6L2	3.09	8.99E-03
PSR09005086.hg.1	ENST00000288985	ERCC6L2	1.55	2.04E-02
PSR0X016369.hg.1	ENST00000372902	TIMM8A	1.55	1.30E-02
PSR0X006457.hg.1	NM_001184875	GPRASP2	-1.41	2.70E-04
PSR0X006811.hg.1	NM_017416	IL1RAPL2	-1.88	2.25E-03
PSR0X017232.hg.1	BC034959	ACSL4	1.44	2.98E-02
PSR0X017247.hg.1	BC034959	ACSL4	1.43	4.28E-02
PSR0X017535.hg.1	NM_001168302	KLHL13	-1.41	6.76E-03
PSR0X017668.hg.1	NM_080632	UPF3B	1.54	2.16E-02
PSR0X017679.hg.1	NM_080632	UPF3B	1.51	3.98E-02
PSR0X017683.hg.1	NM_080632	UPF3B	1.64	2.65E-02
PSR0X017806.hg.1	BC036216	CUL4B	1.43	2.52E-02
PSR0X017837.hg.1	BC011930	C1GALT1C1	1.61	2.31E-02
PSR0X017981.hg.1	NM_001081550	THOC2	1.49	1.54E-02
PSR0X017982.hg.1	NM_001081550	THOC2	1.54	2.26E-02
PSR0X017990.hg.1	NM_001081550	THOC2	2.06	2.73E-02
PSR0X017998.hg.1	NM_001081550	THOC2	1.45	8.90E-03

PSR0X018015.hg.1	NM_001081550	THOC2	1.51	2.71E-02
PSR0X007937.hg.1	NM_001167	XIAP	1.66	1.34E-02
PSR0X008077.hg.1	ENST00000357121	OCRL	1.44	1.63E-02
PSR0X008081.hg.1	ENST00000357121	OCRL	1.40	2.02E-02
PSR0X008095.hg.1	ENST00000357121	OCRL	1.58	3.35E-03
PSR0X008180.hg.1	ENST00000218147	BCORL1	-1.44	4.64E-02
PSR0X018222.hg.1	ENST00000370978	ZNF280C	1.42	5.00E-02
PSR0X018226.hg.1	ENST00000370978	ZNF280C	1.73	2.47E-02
PSR0X018396.hg.1	ENST00000460462	RAP2C	-1.43	1.87E-02
PSR0X018442.hg.1	ENST00000370836	HS6ST2	1.65	3.92E-02
PSR0X018443.hg.1	ENST00000370836	HS6ST2	1.59	4.36E-02
PSR0X008612.hg.1	ENST00000370695	SLC9A6	1.82	2.89E-03
PSR0X008628.hg.1	ENST00000370701	SLC9A6	1.42	3.02E-02
PSR0X008735.hg.1	BC009896	HTATSF1	1.60	3.37E-02
PSR0X008736.hg.1	BC009896	HTATSF1	1.66	1.35E-03
PSR0X008738.hg.1	BC009896	HTATSF1	1.66	9.37E-03
PSR0X008740.hg.1	BC009896	HTATSF1	1.45	6.38E-03
PSR0X011564.hg.1	ENST00000316715	GPM6B	1.65	2.61E-02
PSR0X011570.hg.1	BC047295	GPM6B	1.79	2.09E-02
PSR0X011574.hg.1	ENST00000316715	GPM6B	1.91	3.78E-02
PSR0X019087.hg.1	NM_001184749	SLITRK4	2.19	3.94E-03
PSR0X019089.hg.1	NM_001184749	SLITRK4	1.67	4.70E-02
PSR0X019091.hg.1	NM_001184749	SLITRK4	1.78	1.83E-02
PSR0X019092.hg.1	NM_001184749	SLITRK4	1.75	2.13E-02
PSR0X019093.hg.1	NM_001184749	SLITRK4	2.43	1.69E-03
PSR0X009006.hg.1	NM_001185081	FMR1	1.42	3.20E-03
PSR0X009013.hg.1	NM_001185081	FMR1	1.49	4.96E-02
PSR0X009022.hg.1	NM_001185081	FMR1	1.48	3.75E-02
PSR0X009043.hg.1	NM_001185081	FMR1	1.58	3.12E-02
PSR0X009820.hg.1	ENST00000253122	SLC6A8	-1.40	1.59E-03
PSR0X009823.hg.1	BC081558	SLC6A8	-1.47	4.47E-02
PSR0X010652.hg.1	ENST00000457026	BRCC3	1.66	2.95E-02
PSR0X020842.hg.1	ENST00000334398	TMLHE	1.44	2.25E-02
PSR0X011795.hg.1	ENST00000545766	AP1S2	1.79	4.36E-02
PSR0X001025.hg.1	ENST00000400004	MAGEB17	-1.44	2.48E-02
PSR0X011897.hg.1	ENST00000380084	RBBP7	-1.41	2.59E-02
PSR0X011990.hg.1	ENST00000476595	RS1	-1.41	3.40E-03
PSR0X012117.hg.1	ENST00000518578	MAP3K15	-1.40	6.08E-03
PSR0X012290.hg.1	BC067851	EIF1AX	1.42	4.59E-03
PSR0X012301.hg.1	ENST00000379565	RPS6KA3	1.44	4.73E-02
PSR0X012318.hg.1	ENST00000540702	RPS6KA3	1.95	4.12E-03
PSR0X012332.hg.1	ENST00000379548	RPS6KA3	1.65	1.60E-02
PSR0X012338.hg.1	ENST00000540702	RPS6KA3	1.47	6.81E-03
PSR0X012348.hg.1	NM_153270	KLHL34	1.82	3.73E-02
PSR0X001557.hg.1	ENST00000535562	ZFX	1.44	1.17E-02
PSR0X012578.hg.1	NM_004019	DMD	1.54	1.42E-02
PSR0X012633.hg.1	ENST00000535280	DMD	1.45	1.24E-02
PSR0X012667.hg.1	NM_004007	DMD	1.43	9.47E-03
PSR0X012728.hg.1	ENST00000432389	DYNLT3	1.62	3.56E-02
PSR0X002111.hg.1	ENST00000486558	ATP6AP2	-1.41	2.64E-02

PSR0X003087.hg.1	NM_006743	RBM3	1.53	3.14E-02
PSR0X013458.hg.1	BC002851	PCSK1N	-1.44	2.42E-03
PSR0X003842.hg.1	NM_001127899	CLCN5	1.51	1.36E-02
PSR0X014378.hg.1	BC112127	SMC1A	1.40	4.76E-03
PSR0X014382.hg.1	BC112127	SMC1A	1.43	4.36E-03
PSR0X014512.hg.1	NM_031407	HUWE1	1.43	4.82E-02
PSR0X004417.hg.1	ENST00000262850	RRAGB	1.79	3.99E-03
PSR0X015030.hg.1	NM_001199687	EDA2R	-1.77	3.68E-02
PSR0X004662.hg.1	NM_173834	YIPF6	1.50	2.99E-02
PSR0X015261.hg.1	NM_001025265	CXorf65	-1.61	3.37E-03
PSR0X005225.hg.1	ENST00000395779	TAF1	1.52	4.97E-03
PSR0X005253.hg.1	ENST00000538124	TAF1	1.41	4.38E-03
PSR0X005274.hg.1	ENST00000449580	TAF1	1.53	2.41E-02
PSR0X015479.hg.1	ENST00000373560	HDAC8	-1.47	2.66E-02
PSR0X016096.hg.1	ENST00000537751	CHM	1.57	3.13E-02
PSR0Y000649.hg.1	ENST00000463199	DDX3Y	1.82	6.47E-03
PSR0Y001947.hg.1	ENST00000454978	RBMY1J	2.21	1.80E-02
PSR0Y000920.hg.1	NM_001006117	RBMY1J	2.21	1.80E-02
PSR0Y002016.hg.1	BC047480	DAZ4	1.46	3.85E-02
PSR0Y002020.hg.1	BC047480	DAZ4	1.72	1.47E-02
PSR0Y002025.hg.1	BC047480	DAZ4	1.94	4.71E-02
PSR0Y002030.hg.1	ENST00000382510	DAZ4	1.94	4.71E-02
PSR0Y002035.hg.1	NM_001005375	DAZ4	1.94	4.71E-02
PSR0Y000992.hg.1	NM_020364	DAZ3	1.94	4.71E-02
PSR0Y000997.hg.1	NM_020364	DAZ3	1.72	1.47E-02
PSR0Y002108.hg.1	BC113005	DAZ3	1.72	1.47E-02
PSR0Y002113.hg.1	BC113005	DAZ3	1.94	4.71E-02
PSR0Y001066.hg.1	ENST00000440066	DAZ4	1.94	4.71E-02
PSR0Y001071.hg.1	ENST00000440066	DAZ4	1.94	4.71E-02
PSR0Y001076.hg.1	ENST00000382432	DAZ4	1.72	1.47E-02
PSR0Y001080.hg.1	ENST00000382432	DAZ4	1.46	3.85E-02
PSR0Y000233.hg.1	NM_003411	ZFY	1.44	4.08E-02
PSR0Y000288.hg.1	NM_022573	TSPY2	1.85	3.27E-02
PSR0Y000395.hg.1	ENST00000477879	TSPY8	1.58	4.52E-02
PSR0Y000405.hg.1	ENST00000477879	TSPY8	1.60	4.95E-02
PSR0Y000422.hg.1	BC075016	TSPY3	1.43	2.11E-02
PSR0Y000442.hg.1	BC121114	TSPY3	1.58	4.52E-02
PSR0Y000451.hg.1	BC121114	TSPY3	1.60	4.95E-02
PSR0Y000461.hg.1	NM_003308	TSPY1	1.57	4.78E-03
PSR0Y000465.hg.1	NM_003308	TSPY1	2.40	3.59E-03
PSR0Y001540.hg.1	ENST00000427622	FAM197Y3	1.44	1.61E-02
PSR0Y000493.hg.1	ENST00000444056	TSPY10	1.58	4.52E-02

Table 7.5 List of DEI in females

Probeset ID	RefSeq	Gene Symbol	Fold-Change	p-value
PSR01046007.hg.1	NM_001199773	PSMA5	1.59	4.25E-03
PSR01015069.hg.1	BC108729	GSTM4	1.42	1.63E-02
PSR01015128.hg.1	ENST00000241337	GSTM2	1.63	1.45E-02
PSR01015131.hg.1	NM_001142368	GSTM2	1.56	3.29E-02
PSR01015146.hg.1	ENST00000309851	GSTM1	2.03	2.20E-02
PSR01015153.hg.1	ENST00000309851	GSTM1	1.42	1.63E-02
PSR01015154.hg.1	ENST00000309851	GSTM1	1.54	1.63E-02
PSR01015155.hg.1	BC024005	GSTM1	3.78	4.21E-03
PSR01015157.hg.1	BC024005	GSTM1	2.42	8.30E-03
PSR01015162.hg.1	BC024005	GSTM1	1.50	7.78E-03
PSR01015163.hg.1	BC024005	GSTM1	1.63	1.45E-02
PSR01015178.hg.1	BC058881	GSTM5	1.49	3.92E-03
PSR01015189.hg.1	BC058881	GSTM5	2.20	7.38E-03
PSR01033917.hg.1	NM_004958	MTOR	1.46	4.78E-02
PSR01046756.hg.1	NM_001193431	PTPN22	1.55	1.29E-02
PSR01047474.hg.1	NM_001080470	ZNF697	1.40	2.17E-02
PSR01048845.hg.1	NM_001024599	HIST2H2BF	1.49	9.20E-04
PSR01048847.hg.1	NM_001024599	HIST2H2BF	1.50	2.32E-02
PSR01018003.hg.1	BC060324	HIST2H2AC	1.47	1.64E-02
PSR01018123.hg.1	ENST00000369111	CA14	-1.41	4.51E-04
PSR01018127.hg.1	ENST00000369111	CA14	-1.46	1.68E-02
PSR01018578.hg.1	BC063014	TNFAIP8L2	-1.45	4.80E-02
PSR01049904.hg.1	BC004517	MRPL9	1.54	3.41E-02
PSR01050616.hg.1	ENST00000271854	NUP210L	-1.49	1.82E-02
PSR01050629.hg.1	ENST00000271854	NUP210L	-1.42	4.41E-03
PSR01051372.hg.1	ENST00000497188	CLK2	1.49	2.71E-02
PSR01051718.hg.1	ENST00000368321	KIAA0907	1.47	4.84E-02
PSR01052051.hg.1	ENST00000368256	CCT3	1.41	4.33E-02
PSR01052056.hg.1	ENST00000472765	CCT3	1.56	2.97E-02
PSR01053220.hg.1	BC113893	SLAMF6	1.67	3.12E-03
PSR01024896.hg.1	NM_001127710	PRG4	-1.60	3.32E-02
PSR01035344.hg.1	NM_001161727	PLA2G2A	2.05	3.87E-02
PSR01057546.hg.1	ENST00000235932	RAB7L1	1.46	2.21E-02
PSR01027416.hg.1	ENST00000400959	TRAF3IP3	-1.85	2.13E-02
PSR01027742.hg.1	BC110883	PPP2R5A	1.65	3.76E-02
PSR01058813.hg.1	ENST00000350027	TAF1A	1.40	2.46E-03
PSR01058870.hg.1	ENST00000540964	TLR5	1.54	2.87E-02
PSR01030057.hg.1	ENST00000282841	GGPS1	1.67	4.35E-03
PSR01004594.hg.1	ENST00000495365	LYPLA2	1.40	2.08E-02
PSR01036330.hg.1	BC010074	SRSF10	1.61	9.28E-03
PSR01036501.hg.1	BC063891	STPG1	1.66	1.35E-02
PSR01036704.hg.1	NM_203401	STMN1	1.64	1.87E-03
PSR01037132.hg.1	ENST00000374025	CD164L2	-1.49	9.36E-03
PSR01008140.hg.1	ENST00000506017	KCNQ4	1.66	3.32E-05
PSR01009398.hg.1	ENST00000372222	KIF2C	-1.43	1.07E-03
PSR01009401.hg.1	ENST00000493027	KIF2C	-1.58	2.31E-02

PSR01041903.hg.1	NM_002370	MAGOH	1.49	2.02E-02
PSR01041905.hg.1	ENST00000462941	MAGOH	1.54	2.82E-02
PSR01042886.hg.1	ENST00000271002	ITGB3BP	1.52	2.93E-02
PSR01011445.hg.1	ENST00000371086	DLEU2L	1.83	1.10E-03
PSR01011449.hg.1	ENST00000371086	DLEU2L	1.56	1.58E-02
PSR01011432.hg.1	NM_032437	EFCAB7	1.56	1.74E-02
PSR01011435.hg.1	NM_032437	EFCAB7	1.51	3.64E-03
PSR01011437.hg.1	NM_032437	EFCAB7	1.59	2.05E-02
PSR01011438.hg.1	NM_032437	EFCAB7	1.59	3.11E-02
PSR01011439.hg.1	ENST00000461039	EFCAB7	1.50	8.44E-03
PSR01043217.hg.1	NM_001114120	DEPDC1	1.59	8.51E-03
PSR01043332.hg.1	ENST00000477096	ZRANB2	1.78	4.02E-02
PSR01001564.hg.1	ENST00000476864	CAMTA1	1.47	1.57E-02
PSR01001568.hg.1	ENST00000476864	CAMTA1	1.44	4.00E-02
PSR01012603.hg.1	NM_001172309	NEXN	1.89	3.45E-02
PSR01033394.hg.1	NM_001561	TNFRSF9	-1.82	1.12E-02
PSR01043870.hg.1	NM_014021	SSX2IP	1.44	4.69E-02
PSR01044336.hg.1	NM_018284	GBP3	1.71	4.62E-02
PSR01044795.hg.1	BC038511	TMED5	1.45	2.08E-02
PSR1_gl000191_random000017.hg.1	NM_001191006	SRSF10	1.64	1.08E-02
PSR10020182.hg.1	ENST00000260702	LOXL4	1.58	9.32E-03
PSR10000077.hg.1	NM_012341	GTPBP4	1.48	1.58E-02
PSR10009311.hg.1	ENST00000369727	SFR1	1.52	2.19E-02
PSR10009693.hg.1	NM_001199492	PDCD4	1.57	3.62E-02
PSR10022043.hg.1	ENST00000369263	ABLIM1	-1.48	2.78E-02
PSR10010106.hg.1	ENST00000485065	TRUB1	-1.61	3.62E-03
PSR10010139.hg.1	ENST00000355044	ATRNL1	-1.78	4.89E-02
PSR10010844.hg.1	ENST00000338354	DMBT1	-1.41	2.17E-02
PSR10001472.hg.1	NM_002438	MRC1	1.51	4.79E-02
PSR10001523.hg.1	NM_002438	MRC1	1.51	4.79E-02
PSR10002716.hg.1	ENST00000489388	CREM	1.80	2.56E-02
PSR10002732.hg.1	NM_182721	CREM	1.46	2.11E-02
PSR10006995.hg.1	NM_152872	FAS	1.50	1.78E-03
PSR11027091.hg.1	ENST00000525934	SLN	-1.44	4.96E-02
PSR11012273.hg.1	BC093654	DDX10	1.61	2.24E-02
PSR11027425.hg.1	ENST00000525823	CRYAB	1.67	4.70E-02
PSR11014179.hg.1	BC137171	SORL1	1.48	4.92E-02
PSR11029073.hg.1	ENST00000263577	CDON	1.51	1.14E-02
PSR11029098.hg.1	ENST00000263577	CDON	1.47	3.26E-02
PSR11002764.hg.1	NM_001030273	ARNTL	1.52	6.27E-03
PSR11002768.hg.1	NM_001030273	ARNTL	1.51	2.36E-02
PSR11002779.hg.1	NM_001030273	ARNTL	1.72	1.19E-02
PSR11002780.hg.1	NM_001030273	ARNTL	1.62	6.28E-03
PSR11002782.hg.1	NM_001030273	ARNTL	1.69	8.79E-03
PSR11002783.hg.1	NM_001030273	ARNTL	1.40	4.01E-02
PSR11002791.hg.1	NM_001030273	ARNTL	1.52	1.13E-02
PSR11003422.hg.1	ENST00000541255	PRMT3	1.51	3.62E-02
PSR11003433.hg.1	ENST00000541255	PRMT3	1.49	7.55E-03
PSR11018824.hg.1	ENST00000529533	MUC15	1.56	1.39E-03
PSR11018948.hg.1	NM_001143811	BDNF	1.71	4.04E-02

PSR11019108.hg.1	ENST00000534812	IMMP1L	1.47	4.60E-02
PSR11005340.hg.1	NM_175732	PTPMT1	1.87	7.31E-03
PSR11005486.hg.1	BC140748	OR4A16	1.45	1.32E-02
PSR11005930.hg.1	ENST00000535361	STX3	1.40	3.91E-02
PSR11022211.hg.1	ENST00000394651	SLC22A6	-1.44	1.05E-02
PSR11022213.hg.1	NM_153276	SLC22A6	-1.70	6.01E-03
PSR11022655.hg.1	ENST00000377390	SF1	1.42	2.19E-02
PSR11007864.hg.1	NM_001048218	SCYL1	1.65	4.87E-02
PSR11007995.hg.1	ENST00000394224	SIPA1	-1.67	7.90E-03
PSR11008319.hg.1	ENST00000421552	KLC2	1.51	4.14E-03
PSR11017212.hg.1	BC140729	OR2D2	1.49	1.48E-02
PSR11024581.hg.1	NM_001146209	PDE2A	1.54	5.95E-04
PSR11010883.hg.1	ENST00000526731	ANKRD42	1.46	3.14E-02
PSR11011080.hg.1	NM_007173	PRSS23	-1.70	3.61E-02
PSR11011086.hg.1	ENST00000533902	PRSS23	-1.44	3.65E-03
PSR11011092.hg.1	ENST00000533902	PRSS23	-1.43	4.98E-02
PSR11026082.hg.1	ENST00000528341	NOX4	1.76	5.08E-03
PSR11026090.hg.1	ENST00000413594	NOX4	1.46	1.93E-02
PSR11026171.hg.1	ENST00000320585	CHORDC1	1.77	4.18E-02
PSR11026172.hg.1	ENST00000320585	CHORDC1	1.53	2.28E-02
PSR11026173.hg.1	ENST00000320585	CHORDC1	1.57	3.38E-02
PSR11026174.hg.1	ENST00000320585	CHORDC1	1.68	2.14E-02
PSR11026175.hg.1	ENST00000320585	CHORDC1	1.53	1.85E-02
PSR11026176.hg.1	ENST00000529726	CHORDC1	1.76	1.87E-02
PSR11026177.hg.1	ENST00000320585	CHORDC1	1.55	1.86E-02
PSR11026179.hg.1	ENST00000320585	CHORDC1	1.61	1.80E-02
PSR11026182.hg.1	ENST00000530765	CHORDC1	1.88	8.02E-03
PSR11026183.hg.1	ENST00000320585	CHORDC1	1.48	3.42E-02
PSR11026184.hg.1	BC072461	CHORDC1	1.61	2.15E-02
PSR11002373.hg.1	ENST00000299606	ZNF143	1.54	4.88E-02
PSR11026518.hg.1	ENST00000278520	CCDC82	1.80	8.68E-03
PSR12024672.hg.1	ENST00000337514	IGF1	1.71	2.27E-02
PSR12024673.hg.1	ENST00000337514	IGF1	1.65	3.15E-02
PSR12024678.hg.1	NM_000618	IGF1	1.56	1.30E-02
PSR12024679.hg.1	NM_000618	IGF1	1.77	4.96E-02
PSR12024694.hg.1	ENST00000307046	IGF1	1.83	1.00E-02
PSR12024710.hg.1	ENST00000307000	PAH	-1.45	4.06E-03
PSR12010835.hg.1	ENST00000377854	ACACB	2.69	2.39E-04
PSR12011786.hg.1	BC152423	TPCN1	1.40	4.61E-02
PSR12027404.hg.1	ENST00000540285	ABCB9	1.48	3.85E-02
PSR12016625.hg.1	ENST00000266397	ERP27	1.51	4.43E-03
PSR12016738.hg.1	ENST00000537304	LMO3	1.54	3.71E-02
PSR12016740.hg.1	ENST00000537304	LMO3	1.82	2.45E-02
PSR12016741.hg.1	ENST00000537304	LMO3	1.96	5.16E-03
PSR12016745.hg.1	ENST00000534946	LMO3	1.43	4.30E-02
PSR12016750.hg.1	ENST00000534946	LMO3	1.82	2.33E-02
PSR12016759.hg.1	NM_018640	LMO3	1.84	8.80E-03
PSR12002758.hg.1	NM_001244683	PDE3A	1.47	1.52E-02
PSR12002764.hg.1	NM_001244683	PDE3A	1.53	2.92E-03
PSR12002771.hg.1	NM_001244683	PDE3A	1.58	7.80E-03

PSR12002773.hg.1	ENST00000359062	PDE3A	1.43	2.56E-04
PSR12003257.hg.1	NM_003622	PPFIBP1	1.97	1.86E-02
PSR12003700.hg.1	NM_198578	LRRK2	1.51	4.53E-02
PSR12018482.hg.1	NM_018018	SLC38A4	1.64	2.94E-02
PSR12018486.hg.1	ENST00000266579	SLC38A4	1.97	3.90E-02
PSR12018503.hg.1	ENST00000266579	SLC38A4	1.93	3.57E-02
PSR12005991.hg.1	ENST00000546500	HNRNPA1	1.51	4.77E-03
PSR12021961.hg.1	ENST00000551116	DDIT3	1.44	1.68E-02
PSR12001628.hg.1	BC117439	CLEC4A	1.40	1.37E-02
PSR12008967.hg.1	ENST00000378580	LRRIQ1	1.41	3.35E-02
PSR12023698.hg.1	BC126166	KITLG	1.58	1.26E-02
PSR12009232.hg.1	ENST00000548537	SOCS2	1.56	4.65E-02
PSR13006202.hg.1	ENST00000267068	N4BP2L2	1.40	3.74E-02
PSR13006383.hg.1	NM_001144983	CCDC169	-1.45	2.29E-02
PSR13006405.hg.1	NM_015087	SPG20	1.56	2.34E-02
PSR13008438.hg.1	ENST00000478591	TBC1D4	1.58	1.55E-02
PSR13009333.hg.1	ENST00000340807	GPR18	1.80	5.49E-04
PSR14007879.hg.1	ENST00000341267	DLK1	-1.40	2.86E-02
PSR14000189.hg.1	ENST00000250416	PARP2	-1.67	2.34E-02
PSR14010680.hg.1	NM_000257	MYH7	-1.45	6.26E-03
PSR14003842.hg.1	ENST00000395151	DACT1	1.58	1.48E-02
PSR14003844.hg.1	NM_016651	DACT1	1.46	2.13E-02
PSR14003991.hg.1	ENST00000406854	PCNXL4	1.59	1.15E-02
PSR14004289.hg.1	ENST00000357395	SYNE2	2.05	4.25E-02
PSR14004317.hg.1	ENST00000553455	SYNE2	1.43	2.37E-02
PSR14013886.hg.1	ENST00000342835	SPTB	1.58	2.00E-02
PSR14013890.hg.1	ENST00000389721	SPTB	1.82	1.73E-02
PSR14004541.hg.1	ENST00000359118	CHURC1	1.44	4.83E-02
PSR14004542.hg.1	ENST00000359118	CHURC1	1.40	4.93E-02
PSR14013949.hg.1	ENST00000436278	RAB15	1.43	1.86E-03
PSR14004830.hg.1	ENST00000556491	ARG2	2.12	1.97E-02
PSR14016550.hg.1	ENST00000337425	SERPINA9	-1.42	1.39E-02
PSR15003161.hg.1	ENST00000323030	DUOXA2	-1.71	1.21E-02
PSR15013998.hg.1	NM_001110	ADAM10	1.49	2.82E-02
PSR15005181.hg.1	ENST00000560591	MAP2K5	1.56	2.40E-02
PSR15015668.hg.1	BC000481	PKM	-1.43	1.21E-02
PSR15015671.hg.1	BC000481	PKM	-1.41	1.56E-02
PSR15015675.hg.1	BC000481	PKM	-1.44	2.06E-02
PSR15015689.hg.1	BC000481	PKM	-1.43	3.33E-02
PSR15015749.hg.1	ENST00000395258	CELF6	-1.46	9.63E-03
PSR15006602.hg.1	ENST00000559554	CHRNA5	1.59	3.44E-02
PSR15006605.hg.1	ENST00000559554	CHRNA5	1.47	4.79E-02
PSR15006606.hg.1	NM_000745	CHRNA5	1.52	8.52E-03
PSR15007652.hg.1	ENST00000421325	AGBL1	-1.44	1.61E-02
PSR15007655.hg.1	ENST00000421325	AGBL1	-1.50	1.23E-03
PSR15007656.hg.1	ENST00000421325	AGBL1	-1.46	1.02E-02
PSR15007674.hg.1	ENST00000421325	AGBL1	-1.44	9.58E-03
PSR15007725.hg.1	ENST00000332810	AEN	1.59	9.55E-03
PSR15008711.hg.1	ENST00000556053	LINC00924	1.47	9.45E-03
PSR16011279.hg.1	ENST00000431526	ZNF598	1.54	4.61E-02

PSR16001536.hg.1	BC012103	PDPK1	1.46	1.92E-02
PSR16014118.hg.1	NM_015171	XPO6	1.41	1.90E-02
PSR16011640.hg.1	BC009726	PRSS22	-1.59	3.31E-02
PSR16001811.hg.1	ENST00000549213	IL32	1.63	3.75E-02
PSR16001812.hg.1	ENST00000440815	IL32	1.62	3.59E-02
PSR16001813.hg.1	ENST00000549213	IL32	1.58	2.74E-02
PSR16006569.hg.1	NM_014669	NUP93	1.44	3.52E-02
PSR16016297.hg.1	NM_003905	NAE1	1.42	3.81E-02
PSR16012295.hg.1	BC108283	CARHSP1	-1.53	1.37E-02
PSR17002451.hg.1	NM_004278	PIGL	1.54	3.19E-02
PSR17017805.hg.1	NM_015986	CRLF3	1.47	6.58E-03
PSR17000320.hg.1	NM_001100398	RAP1GAP2	-1.78	2.66E-02
PSR17018022.hg.1	ENST00000268850	RFFL	1.46	3.86E-02
PSR17000357.hg.1	NM_004937	CTNS	1.79	7.21E-03
PSR17000360.hg.1	NM_004937	CTNS	1.64	4.42E-02
PSR17018607.hg.1	NM_198836	ACACA	1.42	3.20E-02
PSR17000362.hg.1	NM_004937	CTNS	1.94	2.26E-02
PSR17000366.hg.1	NM_004937	CTNS	1.44	1.33E-02
PSR17018682.hg.1	NM_198882	SYNRG	1.48	9.61E-03
PSR17019732.hg.1	NM_033188	KRTAP4-5	-1.63	1.98E-02
PSR17008984.hg.1	NM_016001	UTP18	1.45	1.43E-02
PSR17023801.hg.1	BC036710	FTSJ3	1.47	2.02E-02
PSR17000898.hg.1	NM_019013	FAM64A	1.63	1.23E-02
PSR17024465.hg.1	ENST00000340001	ABCA9	1.41	3.02E-02
PSR17024468.hg.1	NM_080283	ABCA9	1.41	2.14E-02
PSR17024476.hg.1	ENST00000482072	ABCA9	1.49	1.66E-02
PSR17024479.hg.1	NM_080283	ABCA9	1.53	4.29E-03
PSR17024484.hg.1	NM_080283	ABCA9	1.73	9.31E-03
PSR17024486.hg.1	NM_080283	ABCA9	1.43	1.50E-02
PSR17024493.hg.1	NM_080283	ABCA9	1.54	3.37E-02
PSR17024501.hg.1	NM_080283	ABCA9	1.40	2.78E-02
PSR17024515.hg.1	NM_080283	ABCA9	1.44	1.50E-02
PSR17024521.hg.1	NM_080283	ABCA9	1.42	3.58E-02
PSR17024522.hg.1	ENST00000453749	ABCA9	1.49	3.09E-02
PSR17010515.hg.1	ENST00000243457	KCNJ2	1.46	1.09E-02
PSR17010518.hg.1	ENST00000243457	KCNJ2	1.51	1.58E-02
PSR17010552.hg.1	ENST00000245479	SOX9	1.43	4.96E-02
PSR17012001.hg.1	ENST00000336301	RNF213	1.49	3.75E-03
PSR18001483.hg.1	ENST00000217740	RNF125	1.53	1.17E-02
PSR18001984.hg.1	ENST00000245121	KATNAL2	-1.43	1.18E-04
PSR18005439.hg.1	ENST00000432185	CCDC68	1.43	3.09E-02
PSR18005443.hg.1	BC029508	CCDC68	1.76	2.17E-02
PSR18002672.hg.1	BC069442	SERPINB7	-1.43	1.34E-03
PSR19004278.hg.1	NM_018467	USE1	1.52	1.10E-02
PSR19019268.hg.1	NM_001166056	PEPD	1.43	2.88E-02
PSR19006977.hg.1	ENST00000410018	CATSPERG	1.43	1.23E-02
PSR19008601.hg.1	NM_182490	ZNF227	1.42	3.88E-03
PSR19009675.hg.1	ENST00000344846	SYNGR4	-2.13	4.40E-02
PSR19009991.hg.1	ENST00000359342	CGB2	-1.58	3.12E-02
PSR19012960.hg.1	NM_001010879	ZIK1	1.40	1.64E-03

PSR19025768.hg.1	BC152426	ZNF154	1.46	8.23E-03
PSR19014980.hg.1	ENST00000394456	GTF2F1	1.44	6.54E-03
PSR19013468.hg.1	BC001442	RNF126	1.43	1.02E-02
PSR02000663.hg.1	ENST00000396242	TAF1B	1.45	1.85E-02
PSR02009828.hg.1	BC067507	IL1R1	1.80	4.49E-02
PSR02010600.hg.1	ENST00000437679	LIMS3L	-1.78	3.42E-02
PSR02010983.hg.1	ENST00000541869	POLR1B	1.44	1.13E-02
PSR02001096.hg.1	NM_145175	FAM84A	1.40	8.34E-03
PSR02038502.hg.1	BC009288	NR4A2	1.91	3.75E-02
PSR02038520.hg.1	BC009288	NR4A2	1.48	4.61E-02
PSR02038525.hg.1	BC009288	NR4A2	1.73	2.54E-02
PSR02025666.hg.1	BC038971	FAM49A	1.72	1.30E-03
PSR02025667.hg.1	ENST00000406434	FAM49A	1.61	1.77E-02
PSR02025674.hg.1	ENST00000406434	FAM49A	1.46	4.45E-02
PSR02039634.hg.1	ENST00000355999	STK39	1.40	6.21E-04
PSR02015434.hg.1	NM_007023	RAPGEF4	1.47	1.78E-03
PSR02015447.hg.1	NM_007023	RAPGEF4	1.41	2.81E-02
PSR02040153.hg.1	ENST00000419609	MLK7-AS1	1.89	4.18E-03
PSR02015522.hg.1	ENST00000306721	CDCA7	1.56	4.37E-02
PSR02017119.hg.1	ENST00000392316	MYO1B	1.42	6.29E-03
PSR02017616.hg.1	ENST00000485106	AOX1	1.54	2.88E-02
PSR02017620.hg.1	ENST00000485106	AOX1	1.45	4.03E-02
PSR02043844.hg.1	NM_001608	ACADL	1.49	3.48E-02
PSR02044454.hg.1	ENST00000295683	CXCR1	1.64	4.16E-02
PSR02044843.hg.1	BC030986	NHEJ1	1.85	1.38E-02
PSR02045090.hg.1	ENST00000498660	TUBA4A	1.41	2.63E-02
PSR02022202.hg.1	BC005874	EIF4E2	1.47	3.36E-02
PSR02046881.hg.1	ENST00000393621	HDAC4	-1.47	5.72E-03
PSR02001638.hg.1	NM_014971	EFR3B	1.43	4.02E-02
PSR02004094.hg.1	NM_001033557	PPM1B	1.84	3.20E-02
PSR02004097.hg.1	ENST00000378551	PPM1B	1.56	3.26E-02
PSR02004099.hg.1	ENST00000378551	PPM1B	1.45	2.72E-02
PSR02004685.hg.1	ENST00000430487	GTF2A1L	1.42	3.66E-02
PSR02004686.hg.1	ENST00000430487	GTF2A1L	1.54	2.01E-02
PSR02029637.hg.1	ENST00000494539	CLHC1	1.53	1.24E-02
PSR02030521.hg.1	NM_001005739	VPS54	1.67	2.11E-03
PSR02030829.hg.1	ENST00000409862	CNRIP1	1.50	8.45E-04
PSR02006515.hg.1	ENST00000462695	ZNF638	1.57	3.87E-02
PSR20009098.hg.1	NM_198391	FLRT3	1.62	4.64E-02
PSR20009099.hg.1	NM_198391	FLRT3	1.94	3.94E-02
PSR20009106.hg.1	NM_198391	FLRT3	1.93	2.82E-02
PSR20009107.hg.1	ENST00000341420	FLRT3	1.66	2.23E-02
PSR20007743.hg.1	BC140936	DEFB128	-1.40	3.48E-02
PSR20001610.hg.1	ENST00000262544	SEC23B	1.53	4.47E-04
PSR20011780.hg.1	ENST00000372970	OSER1	1.83	4.78E-02
PSR20005837.hg.1	ENST00000559286	TSHZ2	2.00	2.51E-02
PSR20005926.hg.1	NM_001324	CSTF1	-1.70	3.31E-02
PSR20008701.hg.1	ENST00000379019	GPCPD1	1.41	4.65E-02
PSR20008702.hg.1	ENST00000379019	GPCPD1	1.66	3.23E-02
PSR20008716.hg.1	ENST00000379019	GPCPD1	1.50	4.00E-02

PSR20008718.hg.1	ENST00000379019	GPCPD1	1.54	2.38E-02
PSR21000533.hg.1	ENST00000535828	USP16	1.55	2.39E-02
PSR21004493.hg.1	NM_001160302	SYNJ1	1.41	4.60E-02
PSR21004512.hg.1	NM_001160302	SYNJ1	1.44	3.15E-02
PSR21004531.hg.1	NM_016631	PAXBP1	1.53	3.99E-02
PSR21004535.hg.1	NM_013329	PAXBP1	1.55	5.94E-03
PSR21004544.hg.1	ENST00000290178	PAXBP1	1.49	2.94E-02
PSR21005172.hg.1	ENST00000309117	DSCR3	1.54	2.27E-02
PSR21005332.hg.1	ENST00000380900	PSMG1	1.72	3.47E-02
PSR21005333.hg.1	ENST00000380900	PSMG1	1.66	4.34E-02
PSR21005335.hg.1	ENST00000380900	PSMG1	1.43	3.87E-02
PSR21005340.hg.1	ENST00000380900	PSMG1	1.74	1.06E-02
PSR21005362.hg.1	ENST00000333229	BRWD1	-3.09	3.08E-04
PSR21005836.hg.1	NM_001098402	ZBTB21	1.48	2.43E-03
PSR22001603.hg.1	ENST00000390298	IGLV7-43	-1.52	2.01E-02
PSR22010061.hg.1	ENST00000406876	RTDR1	-1.51	1.35E-02
PSR22002809.hg.1	ENST00000413389	UPB1	-1.42	2.85E-02
PSR22011615.hg.1	NM_014303	PES1	1.72	5.92E-03
PSR22012017.hg.1	ENST00000461833	RFPL3S	1.45	5.54E-04
PSR22012231.hg.1	ENST00000453997	MB	-1.42	3.67E-02
PSR03001199.hg.1	NM_001018115	FANCD2	1.43	4.83E-02
PSR03029388.hg.1	ENST00000471694	CD47	1.58	3.14E-03
PSR03033605.hg.1	NM_173653	SLC9A9	1.76	3.39E-02
PSR03014325.hg.1	BC068494	AGTR1	1.40	3.82E-02
PSR03015604.hg.1	ENST00000357388	SMC4	1.54	2.79E-02
PSR03002129.hg.1	ENST00000339732	GALNT15	1.44	4.03E-02
PSR03035292.hg.1	ENST00000461846	SERPINI2	1.41	1.41E-02
PSR03016038.hg.1	NM_001185056	CLDN11	1.49	3.39E-03
PSR03016237.hg.1	ENST00000361589	NLGN1	1.60	3.57E-03
PSR03036416.hg.1	ENST00000414362	MCF2L2	1.66	2.96E-02
PSR03036419.hg.1	ENST00000414362	MCF2L2	1.77	3.36E-02
PSR03016926.hg.1	ENST00000461813	KLHL24	1.62	4.63E-02
PSR03017006.hg.1	NM_182537	HTR3D	-1.61	1.64E-02
PSR03036906.hg.1	ENST00000537818	ETV5	1.49	7.05E-03
PSR03036931.hg.1	ENST00000537818	ETV5	1.66	1.14E-02
PSR03036933.hg.1	ENST00000537818	ETV5	1.53	6.69E-03
PSR03036956.hg.1	BC089411	DGKG	1.48	9.46E-03
PSR03036959.hg.1	BC089411	DGKG	1.49	6.76E-03
PSR03036962.hg.1	BC089411	DGKG	1.47	8.77E-03
PSR03036963.hg.1	BC089411	DGKG	1.61	1.10E-02
PSR03037198.hg.1	BC150184	BCL6	1.42	4.26E-02
PSR03037200.hg.1	BC150184	BCL6	1.44	1.29E-03
PSR03037201.hg.1	BC150184	BCL6	1.51	1.21E-02
PSR03037220.hg.1	BC150184	BCL6	1.45	2.15E-03
PSR03037221.hg.1	NM_001130845	BCL6	1.59	1.24E-03
PSR03037222.hg.1	NM_001130845	BCL6	1.63	2.92E-03
PSR03037223.hg.1	ENST00000232014	BCL6	1.44	3.12E-03
PSR03037224.hg.1	ENST00000496823	BCL6	1.43	6.82E-03
PSR03037225.hg.1	ENST00000496823	BCL6	1.41	2.31E-02
PSR03003108.hg.1	ENST00000307296	PDCD6IP	1.43	1.69E-02

PSR03000029.hg.1	NM_001253388	CHL1	1.62	2.18E-02
PSR03023328.hg.1	ENST00000292327	MYL3	-1.50	1.27E-02
PSR03023329.hg.1	ENST00000395869	MYL3	-1.48	1.62E-02
PSR03023332.hg.1	ENST00000292327	MYL3	-1.48	4.43E-03
PSR03023333.hg.1	ENST00000292327	MYL3	-1.52	7.84E-03
PSR03023336.hg.1	ENST00000292327	MYL3	-1.46	3.38E-03
PSR03023337.hg.1	ENST00000292327	MYL3	-1.57	5.09E-03
PSR03023338.hg.1	ENST00000292327	MYL3	-1.52	1.91E-02
PSR03023891.hg.1	ENST00000358459	PLXNB1	-1.44	3.50E-03
PSR03024110.hg.1	ENST00000328333	COL7A1	-1.42	5.13E-03
PSR03005944.hg.1	ENST00000451634	CCDC36	2.14	1.57E-02
PSR03026786.hg.1	ENST00000294241	DCP1A	1.44	1.74E-02
PSR03008047.hg.1	ENST00000383718	SLMAP	1.81	3.53E-03
PSR03008621.hg.1	ENST00000469661	KBTBD8	1.43	4.31E-02
PSR03008622.hg.1	BC117487	KBTBD8	1.66	4.17E-02
PSR03008623.hg.1	BC117487	KBTBD8	1.74	3.73E-02
PSR03008624.hg.1	ENST00000469661	KBTBD8	1.95	8.52E-03
PSR03008626.hg.1	BC117487	KBTBD8	1.74	1.76E-02
PSR03008629.hg.1	NM_032505	KBTBD8	1.76	2.62E-02
PSR03028878.hg.1	BC013610	CLDND1	-1.40	1.49E-03
PSR03028887.hg.1	BC013610	CLDND1	-1.49	1.19E-03
PSR03028886.hg.1	BC013610	CLDND1	-1.46	1.23E-03
PSR03028877.hg.1	BC013610	CLDND1	-1.43	3.26E-04
PSR04019651.hg.1	NM_000667	ADH1A	1.53	3.38E-02
PSR04019654.hg.1	BC074738	ADH1A	1.56	4.49E-02
PSR04019677.hg.1	ENST00000305046	ADH1B	1.66	4.67E-02
PSR04008120.hg.1	NM_001184705	HADH	1.45	2.45E-02
PSR04020847.hg.1	ENST00000394634	CFI	1.60	1.62E-02
PSR04009299.hg.1	ENST00000296464	HSPA4L	1.54	2.35E-02
PSR04021972.hg.1	BC012087	SLC7A11	1.45	1.44E-02
PSR04022340.hg.1	ENST00000508084	INPP4B	1.47	9.72E-03
PSR04010252.hg.1	ENST00000339690	EDNRA	1.61	1.67E-02
PSR04022978.hg.1	ENST00000263981	FBXW7	1.48	1.29E-02
PSR04014493.hg.1	NM_001145852	PROM1	1.46	3.09E-02
PSR04014495.hg.1	NM_001145852	PROM1	1.60	4.60E-02
PSR04011364.hg.1	NM_153027	FAM218A	-1.48	2.41E-02
PSR04023718.hg.1	NM_001012967	DDX60L	1.79	4.49E-02
PSR04023773.hg.1	ENST00000515088	DDX60L	1.47	2.97E-02
PSR04011542.hg.1	ENST00000335742	PALLD	1.59	4.28E-02
PSR04023977.hg.1	ENST00000353187	AADAT	1.59	1.66E-03
PSR04023980.hg.1	ENST00000353187	AADAT	1.49	1.76E-02
PSR04011714.hg.1	BC046129	GALNT7	1.46	4.19E-02
PSR04024234.hg.1	ENST00000280187	GPM6A	1.40	2.28E-02
PSR04012368.hg.1	BC088376	ANKRD37	1.48	1.84E-02
PSR04012371.hg.1	ENST00000335174	ANKRD37	1.69	3.92E-02
PSR04003122.hg.1	NM_001104629	C4orf19	1.50	2.61E-02
PSR04017302.hg.1	NM_001891	CSN2	1.57	5.82E-03
PSR04017310.hg.1	BC038982	IGJ	2.03	3.45E-02
PSR04005913.hg.1	ENST00000355810	ART3	1.46	3.30E-02
PSR04018196.hg.1	NM_001145794	ANTXR2	1.45	3.39E-02

PSR04018266.hg.1	ENST00000335927	RASGEF1B	1.60	3.02E-02
PSR04007043.hg.1	BC140716	HERC5	1.60	1.14E-02
PSR05023340.hg.1	ENST00000553117	ALDH7A1	1.58	2.68E-02
PSR05008999.hg.1	ENST00000304858	HSPA4	1.70	1.91E-02
PSR05024312.hg.1	ENST00000481195	PPP2CA	1.54	3.22E-02
PSR05012130.hg.1	BC136438	SLC36A1	1.40	3.44E-02
PSR05012740.hg.1	BC023521	THG1L	1.50	5.32E-03
PSR05016878.hg.1	NM_019000	FAM134B	1.68	3.87E-02
PSR05014088.hg.1	ENST00000239243	MSX2	-1.44	4.05E-02
PSR05029858.hg.1	BC144275	C5orf60	-1.61	9.97E-03
PSR05001809.hg.1	NM_002185	IL7R	1.62	6.00E-03
PSR05001810.hg.1	NM_002185	IL7R	1.46	5.10E-03
PSR05018149.hg.1	BC143645	FYB	1.97	4.03E-02
PSR05002183.hg.1	BC063851	C7	1.50	3.12E-02
PSR05002729.hg.1	ENST00000256759	FST	1.40	3.13E-02
PSR05002731.hg.1	ENST00000256759	FST	1.47	2.25E-02
PSR05002738.hg.1	ENST00000256759	FST	1.97	2.80E-03
PSR05002742.hg.1	ENST00000256759	FST	1.76	1.01E-02
PSR05002743.hg.1	ENST00000256759	FST	1.43	1.58E-02
PSR05002868.hg.1	ENST00000230640	SKIV2L2	1.71	3.74E-02
PSR05003110.hg.1	ENST00000396776	GAPT	1.57	1.85E-02
PSR05004147.hg.1	BC064557	GTF2H2D	1.53	5.87E-03
PSR05004337.hg.1	BC171919	GTF2H2B	1.40	5.70E-03
PSR05004423.hg.1	BC062723	SMN1	1.58	3.59E-02
PSR05004687.hg.1	ENST00000503084	TNPO1	2.08	4.19E-03
PSR05004838.hg.1	ENST00000296792	UTP15	1.48	1.25E-02
PSR05004840.hg.1	ENST00000296792	UTP15	1.50	3.93E-02
PSR05004848.hg.1	ENST00000296792	UTP15	1.49	1.34E-02
PSR05004945.hg.1	NM_000521	HEXB	1.44	3.08E-02
PSR05004946.hg.1	NM_000521	HEXB	1.50	4.27E-02
PSR05004975.hg.1	NM_014886	NSA2	1.86	1.67E-02
PSR05004980.hg.1	NM_014886	NSA2	1.53	3.37E-02
PSR05005157.hg.1	ENST00000379730	IQGAP2	1.59	2.89E-02
PSR05005199.hg.1	ENST00000379730	IQGAP2	1.62	3.11E-02
PSR05005200.hg.1	ENST00000379730	IQGAP2	1.56	7.90E-03
PSR05016463.hg.1	ENST00000264669	FASTKD3	1.97	1.85E-03
PSR05005582.hg.1	ENST00000350881	THBS4	-2.09	3.98E-02
PSR05005592.hg.1	ENST00000350881	THBS4	-1.91	3.85E-02
PSR05020999.hg.1	ENST00000504396	DHFR	-1.53	4.47E-02
PSR05021004.hg.1	ENST00000504396	DHFR	-1.53	2.18E-02
PSR05021007.hg.1	ENST00000504396	DHFR	-1.41	4.67E-02
PSR05021257.hg.1	BC030828	EDIL3	1.83	3.26E-02
PSR05021266.hg.1	BC030828	EDIL3	1.47	4.81E-02
PSR05006023.hg.1	ENST00000509578	COX7C	1.44	4.95E-02
PSR05021348.hg.1	ENST00000515293	TMEM161B	1.43	1.18E-02
PSR05006269.hg.1	ENST00000296619	GPR98	1.55	2.41E-04
PSR05006456.hg.1	NM_152548	FAM81B	-1.60	5.56E-04
PSR06015248.hg.1	ENST00000379433	NEDD9	1.68	1.96E-02
PSR06010864.hg.1	ENST00000332958	RFX6	-1.44	1.61E-02
PSR06011050.hg.1	NM_001446	FABP7	-1.60	4.19E-02

PSR06011052.hg.1	NM_001446	FABP7	-1.90	2.82E-02
PSR06011056.hg.1	NM_001446	FABP7	-2.08	9.96E-03
PSR06012254.hg.1	ENST00000367609	GPR126	1.88	5.99E-03
PSR06012744.hg.1	NM_005715	UST	1.49	3.30E-03
PSR06028418.hg.1	ENST00000367088	DYNLT1	1.64	5.61E-03
PSR06028877.hg.1	ENST00000361731	SFT2D1	1.46	3.55E-02
PSR06028885.hg.1	ENST00000487841	SFT2D1	1.55	1.76E-02
PSR06002307.hg.1	ENST00000440790	ZNF192P1	-1.41	6.77E-03
PSR06002390.hg.1	ENST00000442674	GPX5	-1.48	2.47E-03
PSR06002555.hg.1	BC062991	HLA-F	1.44	8.28E-03
PSR06002687.hg.1	ENST00000376802	HLA-A	2.25	1.76E-02
PSR06018143.hg.1	NM_005510	DOM3Z	1.68	1.31E-02
PSR06004804.hg.1	ENST00000422592	HLA-DPB1	1.76	3.72E-02
PSR06004806.hg.1	ENST00000422592	HLA-DPB1	1.47	2.70E-02
PSR06005008.hg.1	ENST00000374516	PHF1	-1.44	9.51E-03
PSR06005790.hg.1	ENST00000373715	SRSF3	1.49	1.48E-02
PSR06005791.hg.1	ENST00000373715	SRSF3	1.48	3.49E-02
PSR06005793.hg.1	NM_003017	SRSF3	1.54	3.34E-02
PSR06021265.hg.1	ENST00000486570	CLIC5	1.44	3.57E-02
PSR06021272.hg.1	ENST00000486570	CLIC5	1.88	1.87E-02
PSR06021273.hg.1	ENST00000486570	CLIC5	1.59	1.77E-02
PSR06021344.hg.1	ENST00000274793	PLA2G7	1.61	1.92E-03
PSR06021543.hg.1	NM_001190986	CRISP3	2.03	1.52E-02
PSR06021550.hg.1	BC101539	CRISP3	1.57	7.57E-03
PSR06014819.hg.1	NM_000129	F13A1	1.56	4.05E-02
PSR06008425.hg.1	ENST00000322773	COL19A1	1.62	2.89E-02
PSR06008435.hg.1	ENST00000393344	COL19A1	1.55	2.68E-02
PSR6_apd_hap1000268.hg.1	NM_021253	TRIM39	1.44	9.22E-03
PSR6_cox_hap2000203.hg.1	BC021708	HLA-G	1.42	2.20E-02
PSR6_dbb_hap3000374.hg.1	NM_021253	TRIM39	1.44	9.22E-03
PSR6_dbb_hap3001867.hg.1	BC013184	HLA-DPB1	1.76	3.72E-02
PSR6_dbb_hap3001869.hg.1	BC013184	HLA-DPB1	1.47	2.70E-02
PSR6_qbl_hap6000183.hg.1	NM_002127	HLA-G	1.42	2.20E-02
PSR6_qbl_hap6000232.hg.1	NM_001242758	HLA-A	2.38	1.79E-02
PSR6_qbl_hap6000370.hg.1	NM_172016	TRIM39	1.44	9.22E-03
PSR6_qbl_hap6003530.hg.1	NM_004557	NOTCH4	1.47	3.63E-02
PSR6_ssto_hap7000366.hg.1	NM_172016	TRIM39	1.44	9.22E-03
PSR6_ssto_hap7003261.hg.1	NM_004557	NOTCH4	1.47	3.63E-02
PSR6_ssto_hap7003405.hg.1	BC007920	HLA-DRB1	2.09	2.58E-02
PSR07025791.hg.1	ENST00000442166	PCOLCE-AS1	-1.40	3.66E-03
PSR07011122.hg.1	NM_001197079	IFRD1	1.66	4.54E-02
PSR07011127.hg.1	ENST00000429071	IFRD1	1.69	4.37E-02
PSR07011154.hg.1	NM_001197079	IFRD1	1.42	2.01E-02
PSR07013353.hg.1	ENST00000285968	NUP205	1.47	2.95E-02
PSR07013358.hg.1	ENST00000285968	NUP205	1.48	3.14E-02
PSR07013730.hg.1	ENST00000414508	TBXAS1	-1.42	4.99E-02
PSR07031765.hg.1	BC043404	NCAPG2	1.54	2.27E-03
PSR07001803.hg.1	ENST00000476135	HDAC9	1.67	2.10E-02
PSR07000351.hg.1	NM_198950	NUDT1	1.40	4.82E-02
PSR07002776.hg.1	NM_182898	CREB5	1.99	7.51E-03

PSR07002946.hg.1	ENST00000409123	WIPF3	2.12	7.38E-03
PSR07000946.hg.1	NM_001097622	OCM	-1.42	1.32E-02
PSR07005667.hg.1	ENST00000489774	AUTS2	1.42	2.75E-02
PSR07005668.hg.1	NM_001127231	AUTS2	1.84	3.15E-03
PSR07005680.hg.1	NM_001127231	AUTS2	1.83	3.96E-03
PSR07005699.hg.1	NM_001127231	AUTS2	1.55	1.86E-02
PSR07022585.hg.1	NM_032952	MLXIPL	1.44	4.55E-02
PSR07006616.hg.1	ENST00000006777	RHBDD2	1.41	4.55E-02
PSR07024212.hg.1	NM_194455	KRIT1	-1.55	1.76E-03
PSR07024797.hg.1	ENST00000444334	ASNS	1.65	3.53E-03
PSR07025330.hg.1	ENST00000303915	ZNF3	1.65	3.29E-02
PSR08019264.hg.1	BC023520	PABPC1	2.22	2.17E-02
PSR08019641.hg.1	ENST00000518205	UBR5	1.64	3.70E-02
PSR08019918.hg.1	ENST00000311955	ABRA	2.23	1.61E-02
PSR08009114.hg.1	ENST00000378402	PKHD1L1	1.55	1.41E-02
PSR08009121.hg.1	ENST00000378402	PKHD1L1	1.49	7.76E-03
PSR08009127.hg.1	ENST00000378402	PKHD1L1	1.56	1.28E-02
PSR08009171.hg.1	ENST00000378402	PKHD1L1	1.53	1.03E-02
PSR08009172.hg.1	ENST00000378402	PKHD1L1	1.40	7.44E-04
PSR08001022.hg.1	ENST00000524591	KIAA1456	-1.42	4.23E-03
PSR08001027.hg.1	ENST00000524591	KIAA1456	-1.43	1.51E-02
PSR08001030.hg.1	NM_001099677	KIAA1456	-1.62	1.56E-03
PSR08012552.hg.1	NM_024767	DLC1	-1.75	1.25E-02
PSR08001080.hg.1	NM_006765	TUSC3	1.55	1.75E-02
PSR08002657.hg.1	ENST00000276440	DOCK5	1.60	4.20E-02
PSR08002710.hg.1	ENST00000276440	DOCK5	1.44	1.86E-02
PSR08014281.hg.1	ENST00000523643	RBPMS-AS1	-1.89	1.22E-02
PSR08015020.hg.1	NM_001142446	ANK1	-1.42	1.70E-02
PSR08015028.hg.1	NM_020477	ANK1	-1.44	2.83E-02
PSR08015031.hg.1	ENST00000522231	ANK1	-1.45	2.99E-02
PSR08015216.hg.1	ENST00000523340	SLC20A2	1.58	2.46E-02
PSR08015952.hg.1	ENST00000316981	PLAG1	1.45	3.31E-02
PSR08006985.hg.1	ENST00000455036	ZBTB10	1.52	2.22E-02
PSR08000555.hg.1	NM_153332	ERI1	1.75	3.64E-02
PSR08018385.hg.1	NM_001198679	RUNX1T1	-1.44	3.14E-02
PSR08000614.hg.1	ENST00000522110	TNKS	1.42	1.74E-02
PSR08007953.hg.1	ENST00000523731	INTS8	1.41	2.65E-02
PSR09017544.hg.1	BC035071	GABBR2	-1.51	7.47E-03
PSR09017856.hg.1	NM_005502	ABCA1	1.43	3.28E-02
PSR09017858.hg.1	NM_005502	ABCA1	1.46	1.07E-02
PSR09006043.hg.1	ENST00000457913	ZNF462	1.42	1.74E-02
PSR09017985.hg.1	BC033094	IKBKAP	1.48	3.52E-02
PSR09017986.hg.1	BC033094	IKBKAP	1.56	2.63E-02
PSR09018136.hg.1	NM_002829	PTPN3	1.58	1.53E-02
PSR09018139.hg.1	NM_002829	PTPN3	1.60	6.19E-03
PSR09018140.hg.1	NM_002829	PTPN3	1.61	6.19E-03
PSR09018141.hg.1	NM_002829	PTPN3	1.55	2.94E-02
PSR09018142.hg.1	NM_002829	PTPN3	1.47	4.23E-02
PSR09018143.hg.1	NM_002829	PTPN3	1.48	4.38E-02
PSR09018145.hg.1	NM_002829	PTPN3	1.50	1.28E-02

PSR09018147.hg.1	NM_001145369	PTPN3	1.52	3.24E-02
PSR09018149.hg.1	NM_001145369	PTPN3	1.69	9.37E-03
PSR09018150.hg.1	ENST00000497739	PTPN3	1.69	4.06E-02
PSR09018151.hg.1	ENST00000497739	PTPN3	1.66	2.53E-02
PSR09018154.hg.1	NM_002829	PTPN3	1.65	2.14E-02
PSR09018155.hg.1	NM_002829	PTPN3	1.69	5.82E-03
PSR09018156.hg.1	NM_002829	PTPN3	1.42	3.25E-02
PSR09018158.hg.1	NM_002829	PTPN3	1.67	6.89E-03
PSR09018159.hg.1	NM_002829	PTPN3	1.68	6.90E-03
PSR09018160.hg.1	NM_002829	PTPN3	1.50	1.59E-02
PSR09018161.hg.1	NM_002829	PTPN3	1.89	1.44E-02
PSR09018163.hg.1	NM_002829	PTPN3	1.40	3.91E-02
PSR09018164.hg.1	NM_002829	PTPN3	1.45	2.64E-02
PSR09018489.hg.1	ENST00000374255	PTBP3	1.41	2.73E-02
PSR09019309.hg.1	NM_005047	PSMD5	1.43	4.48E-02
PSR09019314.hg.1	NM_005047	PSMD5	1.48	4.04E-03
PSR09007566.hg.1	NM_001134778	PBX3	1.47	2.56E-02
PSR09021369.hg.1	NM_022779	DDX31	1.46	3.10E-03
PSR09011651.hg.1	NM_002919	RFX3	1.52	2.92E-02
PSR09001587.hg.1	NM_147134	NFX1	1.45	1.22E-02
PSR09001677.hg.1	ENST00000379405	PRSS3	-1.40	1.70E-02
PSR09000051.hg.1	ENST00000453981	DOCK8	1.57	2.77E-04
PSR09000094.hg.1	ENST00000453981	DOCK8	1.48	1.63E-02
PSR09000390.hg.1	ENST00000381854	CDC37L1	1.43	3.92E-02
PSR09000438.hg.1	ENST00000539801	JAK2	1.76	4.02E-02
PSR09000440.hg.1	ENST00000539801	JAK2	1.68	4.40E-02
PSR09000445.hg.1	ENST00000539801	JAK2	1.51	3.32E-02
PSR09000458.hg.1	ENST00000487310	JAK2	1.76	7.90E-04
PSR09003509.hg.1	BC053584	GDA	2.06	3.12E-02
PSR09016491.hg.1	BC008197	NFIL3	1.93	4.28E-02
PSR09017212.hg.1	ENST00000464512	AAED1	-1.44	4.17E-02
PSR0X016813.hg.1	ENST00000451301	MORF4L2	1.57	2.90E-02
PSR0X016814.hg.1	ENST00000372620	MORF4L2	1.75	5.26E-03
PSR0X017356.hg.1	ENST00000496551	DCX	-2.22	1.09E-03
PSR0X017770.hg.1	NM_001122606	LAMP2	1.56	2.37E-02
PSR0X007939.hg.1	NM_001167	XIAP	1.54	3.90E-03
PSR0X000683.hg.1	ENST00000380668	PRPS2	1.46	2.11E-02
PSR0X008644.hg.1	NM_001167819	FHL1	1.40	1.05E-02
PSR0X010720.hg.1	NM_005840	SPRY3	1.63	1.82E-02
PSR0X000160.hg.1	NM_001171038	ASMT	-1.54	1.41E-02
PSR0X012151.hg.1	ENST00000397804	SH3KBP1	-1.52	1.09E-02
PSR0X003389.hg.1	NM_001032384	PQBP1	-1.62	1.88E-02
PSR0Y000123.hg.1	ENST00000381241	ASMT	-1.54	1.41E-02
PSR0Y000243.hg.1	NM_139214	TGIF2LY	1.47	3.65E-02
PSR0Y001153.hg.1	ENST00000369437	SPRY3	1.63	1.82E-02

Table 7.6 List of pathways for DEG identified from males

Ingenuity Canonical Pathways	p-value	Molecules
PPARα/RXRα Activation	1.91E-05	MED23,TGFBR1,IL1RAPL2,PRKAB1,CKAP5,CYP2C18,KRAS,IL1R1,JAK2,NFKB1,ABCA1,CAND1,PLCZ1,ACADL,PLCB4,PRKAR2B,GPD2,FASN,PRKAG2,MAP3K7,PRKAR1B,MEF2C,CHUK,NFKBIB,MAP4K4,PRKAR1A
PI3K/AKT Signaling	2.63E-04	ITGB1,PPP2R2A,YWHAB,GSK3A,KRAS,JAK2,NFKB1,OCRL,PPP2R5A,EIF4E,INPP5F,LIMS1,PPP2R3A,PIK3CG,PPP2R2B,PPP2R5C,CHUK,NFKBIB,THEM4
Protein Ubiquitination Pathway	8.51E-04	HLA-B, DNAJC3, USP54, DNAJC13, HSPA5, PSMC5, USP3, HSPA4, DNAJC5G, UBE2B, USP47, USP16, USP40, DNAJC16, PSMB4, UBE4B, DNAJC2, USP1, DNAJB9, DNAJB14, USP33, XIAP, ANAPC4, PSMC1, PSMA5, PSMA4, PSMD1, USP46, USP34, DNAJC7
AMPK Signaling	9.33E-04	PBRM1,PFKFB3,PRKAB1,PPP2R2A,CHRNB1,ARID2,CHRNA10,PIK3R4,PPP2R5A,SMARCD3,PRKAR2B,PTPN11,PPP2R3A,PIK3CG,FASN,PPP2R2B,SIRT1,PRKAR1B,PRKAG2,MAP3K7,PPP2R5C,ACACA,FRS2,PRKAR1A
CTLA4 Signaling in Cytotoxic T Lymphocytes	1.35E-03	PPP2R2A,AP1S2,HLA-B,CLTC,JAK2,PIK3R4,PPP2R5A,PTPN11,PPP2R3A,PIK3CG,PPP2R2B,CD86,PPP2R5C,FRS2,AP1G1
CDK5 Signaling	1.35E-03	ITGB1,PPP2R2A,PPP1R3C,ITGA6,KRAS,PPP2R5A,PPP1CC,PRKAR2B,PPP2R3A,PPP2R2B,PRKAG2,LAMB1,PRKAR1B,PPP2R5C,PRKAR1A
TNFR2 Signaling	1.55E-03	TRAF2,LTA,TBK1,CHUK,NFKBIB,NFKB1,XIAP
Histamine Degradation	1.86E-03	HNMT,ALDH1A1,ALDH3B1,ALDH9A1,ALDH7A1
ERK/MAPK Signaling	1.91E-03	PPARG,ITGB1,YWHAB,PPP2R2A,VRK2,PPP1R3C,KRAS,PIK3R4,PPP2R5A,EIF4E,PLA2G2A,DOCK1,PPP1CC,TLN2,PRKAR2B,PTPN11,PPP2R3A,PIK3CG,PPP2R2B,PRKAR1B,PRKAG2,PPP2R5C,FRS2,PRKAR1A
Regulation of eIF4 and p70S6K Signaling	1.95E-03	ITGB1,PPP2R2A,EIF4G3,KRAS,PIK3R4,EIF2S1,PPP2R5A,EIF4E,PTPN11,PPP2R3A,PIK3CG,PPP2R2B,AGO3,EIF2B5,EIF3A,PPP2R5C,RPS15A,RPS3,FRS2,EIF1AX
Role of CHK Proteins in Cell Cycle Checkpoint Control	2.29E-03	PPP2R2A,PPP2R3A,PPP2R2B,HUS1,MRE11A,PPP2R5C,TLK1,RFC1,RAD50,PPP2R5A

Glucocorticoid Receptor Signaling	2.51E-03	PBRM1,TGFBR1,PRKAB1,POLR2J,SLPI,KRAS,ARID2,JAK2,CD163,HSPA5,NFKB1,PIK3R4,NR3C1,PTGES3,HMGB1,HSPA4,PIK3CG,MAP3K7,CHUK,NFKBIB,FRS2,CREBZF,POLR2J2/POLR2J3,TAF9,CCNH,SMARCD3,TRAF2,TAF1,PTPN11,PRKAG2,GTF2H1
Hereditary Breast Cancer Signaling	3.31E-03	POLR2J2/POLR2J3,PBRM1,HDAC8,HDAC2,GADD45G,BARD1,POLR2J,RFC1,ARID2,MRE11A,KRAS,PIK3R4,RAD50,SMARCD3,RB1,PTPN11,PIK3CG,FRS2
mTOR Signaling	3.31E-03	MAPKAP1,PRKAB1,PPP2R2A,RPS6KA3,EIF4G3,KRAS,PIK3R4,RICTOR,PDGFC,PPP2R5A,EIF4E,PLD1,ATG13,PTPN11,PPP2R3A,PIK3CG,PPP2R2B,EIF3A,PRKAG2,PPP2R5C,RPS15A,RPS3,FRS2
Neuroprotective Role of THOP1 in Alzheimer's Disease	3.31E-03	MME,PRKAR2B,HLA-B,PRKAR1B,PRKAG2,GNRH2,IDE,PRKAR1A
Fatty Acid α-oxidation	4.47E-03	TMLHE,ALDH1A1,ALDH3B1,ALDH9A1,ALDH7A1
NF-κB Signaling	4.57E-03	TGFBR1,HDAC2,RELB,TBK1,KRAS,IL1R1,PIK3R4,NFKB1,IGF2R,IL18,TRAF2,PTPN11,BMPR1A,PIK3CG,LTA,MAP3K7,TDP2,CHUK,NFKBIB,MAP4K4,FRS2
Mitotic Roles of Polo-Like Kinase	6.31E-03	SLK,SMC3,ANAPC4,PPP2R2A,PPP2R3A,PPP2R2B,PPP2R5C,ANAPC7,PPP2R5A,SMC1A
Insulin Receptor Signaling	6.46E-03	PPP1R3C,GSK3A,KRAS,JAK2,PIK3R4,OCRL,EIF4E,PPP1CC,PRKAR2B,INPP5F,PTPN11,PIK3CG,PRKAR1B,EIF2B5,PRKAG2,FRS2,PRKAR1A
PEDF Signaling	6.92E-03	PPARG,TCF4,PTPN11,PIK3CG,KRAS,DOCK3,CHUK,CFLAR,NFKBIB,NFKB1,PIK3R4,FRS2
IL-6 Signaling	7.08E-03	IL6ST,IL1RAPL2,KRAS,IL1R1,JAK2,PIK3R4,NFKB1,TRAF2,IL18,PTPN11,PIK3CG,MAP3K7,CHUK,NFKBIB,FRS2,MAP4K4
Estrogen Receptor Signaling	7.59E-03	POLR2J2/POLR2J3,TAF9,CCNH,MED23,CCNC,POLR2J,KRAS,NR3C1,TAF1,CTBP2,MED21,SPEN,GTF2H1,G6PC,MED13L,MED4
Dopamine Receptor Signaling	8.71E-03	PPP1CC,PRKAR2B,PPP2R2A,PPP2R3A,PPP1R3C,PPP2R2B,PRKAR1B,PRKAG2,PPP2R5C,PPP2R5A,PRKAR1A
Telomerase Signaling	8.71E-03	HDAC8,HDAC2,PPP2R2A,KRAS,PIK3R4,PPP2R5A,PTGES3,RB1,PTPN11,PPP2R3A,PIK3CG,PPP2R2B,PPP2R5C,FRS2
Sonic Hedgehog Signaling	8.91E-03	PRKAR2B,PRKAR1B,PRKAG2,HHIP,PRKAR1A,DYRK1A
Protein Kinase A Signaling	9.33E-03	TCF4,TGFBR1,PDE7A,PTPN2,PPP1R3C,AKAP9,GSK3A,NFKB1,PTPN12,PPP1CC,DUSP3,CAMK2D,RYR3,PRKAR1B,TDP2,PDE4D,CHUK,NFKBIB,GRK7,PTPRG,PTPRK,ADD2,YWHAB,ITPR2,PDE4B,ANAPC7,PTP4A1,PLCZ1,ANAPC4,PLCB4,PRKAR2B,PTPN11,CREM,PRKAG2,KDELR2,PRKAR1A

Tight Junction Signaling	9.77E-03	TJP2,TGFBR1,PPP2R2A,NAPG,NFKB1,PPP2R5A,MPDZ,PRKAR2B,PPP2R3A,NUDT21,PPP2R2B,PRKAR1B,MYH3,PRKAG2,STX16,PPP2R5C,CSTF3,PRKAR1A,NECTIN2
DNA Double-Strand Break Repair by Non-Homologous End Joining	9.77E-03	LIG4,MRE11A,XRCC4,RAD50
Cardiac β-adrenergic Signaling	1.15E-02	PDE7A,PPP2R2A,PPP1R3C,AKAP9,PDE4B,PPP2R5A,PPP1CC,PRKAR2B,PPP2R3A,PPP2R2B,PRKAR1B,PRKAG2,TDP2,PPP2R5C,PDE4D,PRKAR1A
Germ Cell-Sertoli Cell Junction Signaling	1.17E-02	ITGB1,MAP3K15,TGFBR1,CFL1,WASL,ITGA6,KRAS,PIK3R4,CDH2,CTNNA2,AGGF1,PTPN11,SORBS1,KEAP1,PIK3CG,FER,MAP3K7,FRS2,NECTIN2
L-carnitine Biosynthesis	1.17E-02	TMLHE,ALDH9A1
PPAR Signaling	1.17E-02	PPARG,TRAF2,IL18,IL1RAPL2,MAP3K7,KRAS,IL1R1,CHUK,NFKBIB,NFKB1,MAP4K4,PDGFC
Role of PKR in Interferon Induction and Antiviral Response	1.23E-02	TRAF2,MAP3K7,CHUK,EIF2S1,NFKBIB,NFKB1,RNASEL
Chronic Myeloid Leukemia Signaling	1.41E-02	RB1,TGFBR1,PTPN11,MECOM,HDAC2,HDAC8,PIK3CG,CTBP2,KRAS,CHUK,PIK3R4,NFKB1,FRS2
Ceramide Signaling	1.51E-02	PTPN11,PPP2R2A,PPP2R3A,PIK3CG,PPP2R2B,PPP2R5C,KRAS,NFKB1,PIK3R4,FRS2,NSMAF,PPP2R5A
RAN Signaling	1.62E-02	KPNA5,TNPO1,RAN,KPNA1
Mouse Embryonic Stem Cell Pluripotency	1.62E-02	IL6ST,TCF4,FZD3,KRAS,JAK2,PIK3R4,XIAP,PTPN11,BMPR1A,PIK3CG,MAP3K7,FRS2,ID4
Leptin Signaling in Obesity	1.78E-02	PLCZ1,PLCB4,PRKAR2B,PTPN11,PIK3CG,PRKAR1B,PRKAG2,JAK2,PIK3R4,FRS2,PRKAR1A
Aldosterone Signaling in Epithelial Cells	1.82E-02	ITPR2,DNAJC13,DNAJC3,DNAJC2,KRAS,PIK3R4,HSPA5,DNAJB9,DNAJB14,PLCZ1,DNAJC5G,HSPA4,PLCB4,PTPN11,PIK3CG,DNAJC16,FRS2,DNAJC7
BMP signaling pathway	1.91E-02	PRKAR2B,BMPR1A,BMP3,PRKAR1B,PRKAG2,MAP3K7,KRAS,NFKB1,XIAP,PRKAR1A
Breast Cancer Regulation by Stathmin1	1.91E-02	ITPR2,PPP2R2A,ARHGEF15,ARHGEF7,PPP1R3C,KRAS,PIK3R4,PPP2R5A,PPP1CC,PLCB4,CAMK2D,PRKAR2B,PTPN11,PPP2R3A,PIK3CG,PPP2R2B,PRKAR1B,PRKAG2,PPP2R5C,FRS2,PRKAR1A
HIPPO signaling	1.91E-02	DLG1,PPP1CC,SAV1,TJP2,PPP2R2A,YWHAB,PPP2R3A,PPP1R3C,PPP2R2B,PPP2R5C,PPP2R5A
Oxidative Ethanol Degradation III	2.00E-02	ALDH1A1,ALDH3B1,ALDH9A1,ALDH7A1

NF-κB Activation by Viruses	2.09E-02	ITGB1,TRAF2,PTPN11,PIK3CG,ITGA6,KRAS,CHUK,NFKBIB,NFKB1,PIK3R4,FRS2
Cell Cycle Regulation by BTG Family Proteins	2.19E-02	RB1,PPP2R2A,PPP2R3A,PPP2R2B,PPP2R5C,PPP2R5A
Nucleotide Excision Repair Pathway	2.19E-02	POLR2J2/POLR2J3,CCNH,ERCC6,POLR2J,GTF2H1,RAD23B
CD40 Signaling	2.40E-02	TRAF2,PTPN11,LTA,PIK3CG,MAP3K7,CHUK,NFKBIB,NFKB1,PIK3R4,FRS2
Lymphotoxin β Receptor Signaling	2.63E-02	TRAF2,PTPN11,LTA,PIK3CG,RELB,CHUK,NFKB1,PIK3R4,FRS2
eNOS Signaling	2.69E-02	PRKAB1,ITPR2,CHRNB1,CHRNA10,PIK3R4,HSPA5,PDGFC,HSPA4,AQP3,PRKAR2B,PTPN11,PIK3CG,PRKAR1B,PRKAG2,FRS2,PRKAR1A
EIF2 Signaling	2.75E-02	EIF2AK1,EIF2AK4,RPL30,RPL7L1,EIF4G3,KRAS,PIK3R4,EIF2S1,EIF4E,PPP1CC,PTPN11,PIK3CG,AGO3,EIF3A,EIF2B5,RPS15A,RPS3,FRS2,EIF1AX
Neuropathic Pain Signaling In Dorsal Horn Neurons	2.82E-02	PLCZ1,PLCB4,CAMK2D,PRKAR2B,PTPN11,ITPR2,PIK3CG,PRKAR1B,PRKAG2,KCNQ3,PIK3R4,FRS2,PRKAR1A
IL-10 Signaling	2.82E-02	CCR1,IL18,IL1RAPL2,MAP3K7,IL1R1,CHUK,NFKBIB,NFKB1,MAP4K4
Type II Diabetes Mellitus Signaling	2.88E-02	PPARG,PRKAB1,NFKB1,PIK3R4,TRAF2,PTPN11,PIK3CG,MAP3K7,PRKAG2,ACSL4,CHUK,NFKBIB,NSMAF,FRS2
Virus Entry via Endocytic Pathways	2.95E-02	ITGB1,CD55,PTPN11,ITSN1,PIK3CG,CLTC,HLA-B,ITGA6,KRAS,PIK3R4,CXADR,FRS2
Putrescine Degradation III	2.95E-02	ALDH1A1,ALDH3B1,ALDH9A1,ALDH7A1
GNRH Signaling	3.24E-02	MAP3K15,ITPR2,DNM3,GNRH2,KRAS,NFKB1,PLCB4,PRKAR2B,CAMK2D,MAP3K7,PRKAR1B,PRKAG2,DNM1L,PRKAR1A
ATM Signaling	3.31E-02	SMC3,GADD45G,TP73,MRE11A,TLK1,CBX5,RAD50,SMC1A
Role of NFAT in Cardiac Hypertrophy	3.31E-02	IL6ST,TGFBR1,HDAC8,HDAC2,ITPR2,KRAS,PIK3R4,PLCZ1,PLCB4,CAMK2D,PRKAR2B,PTPN11,PIK3CG,PRKAR1B,PRKAG2,MAP3K7,MEF2C,FRS2,PRKAR1A
DNA Methylation and Transcriptional Repression Signaling	3.55E-02	HDAC2,RBBP7,ARID4B,DNMT1
Tryptophan Degradation X (Mammalian, via Tryptamine)	3.55E-02	ALDH1A1,ALDH3B1,ALDH9A1,ALDH7A1
Netrin Signaling	3.55E-02	PRKAR2B,RYR3,PRKAR1B,PRKAG2,ABLIM1,PRKAR1A

CNTF Signaling	3.63E-02	IL6ST,PTPN11,PIK3CG,RPS6KA3,KRAS,JAK2,PIK3R4,FRS2
Superpathway of Inositol Phosphate Compounds	3.63E-02	PPFIA1,MTMR9,PTPN2,IPPK,PPTC7,PIK3R4,HACD2,PTPN12,OCRL,PPP2R5A,PLCZ1,PLCB4,PPP1CC,PTPN11,INPP5F,PPP2R3A,PIK3CG,CD86,EYA4,RNGTT,FRS2
Cleavage and Polyadenylation of Pre-mRNA	3.72E-02	PAPOLA,NUDT21,CSTF3
IGF-1 Signaling	3.80E-02	PRKAR2B,PTPN11,YWHAB,PIK3CG,PRKAR1B,PRKAG2,KRAS,JAK2,PIK3R4,CYR61,FRS2,PRKAR1A
p70S6K Signaling	3.80E-02	PPP2R2A,YWHAB,KRAS,PIK3R4,PPP2R5A,PLD1,PLCZ1,PLCB4,PTPN11,PPP2R3A,PIK3CG,PPP2R2B,PPP2R5C,FRS2
Melanocyte Development and Pigmentation Signaling	3.98E-02	PRKAR2B,PTPN11,PIK3CG,PAX3,PRKAR1B,RPS6KA3,PRKAG2,KRAS,PIK3R4,FRS2,PRKAR1A
IL-4 Signaling	4.07E-02	PTPN11,INPP5F,PIK3CG,KRAS,HLA-DQB1,JAK2,PIK3R4,OCRL,FRS2,NR3C1
Ethanol Degradation IV	4.17E-02	ALDH1A1,ALDH3B1,ALDH9A1,ALDH7A1
Endoplasmic Reticulum Stress Pathway	4.17E-02	TRAF2,DNAJC3,EIF2S1,HSPA5
Hepatic Cholestasis	4.37E-02	CYP7B1,TJP2,IL1RAPL2,IL1R1,NFKB1,TRAF2,IL18,PRKAR2B,ABCB4,LTA,PRKAR1B,MAP3K7,PRKAG2,CHUK,NFKBIB,PRKAR1A
Polyamine Regulation in Colon Cancer	4.79E-02	PPARG,TCF4,AZIN1,KRAS
Role of p14/p19ARF in Tumor Suppression	4.90E-02	RB1,PTPN11,PIK3CG,TTF1,PIK3R4,FRS2

Table 7.7 List of pathways for DEG identified from females

Ingenuity Canonical Pathways	p-value	Molecules
Allograft Rejection Signaling	2.63E-04	HLA-G,HLA-DRB1,HLA-A,HLA-F,HLA-DPB1,FAS
Assembly of RNA Polymerase I Complex	5.01E-04	TAF1A,POLR1B,TAF1B
Antigen Presentation Pathway	5.89E-04	HLA-G,HLA-DRB1,HLA-A,HLA-F,HLA-DPB1
Type I Diabetes Mellitus Signaling	8.51E-04	HLA-G,HLA-DRB1,HLA-A,SOCS2,IL1R1,JAK2,HLA-F,FAS
Glutathione-mediated Detoxification	9.55E-04	GSTM1,GSTM2,GSTM5,GSTM4
Biotin-carboxyl Carrier Protein Assembly	1.02E-03	ACACB,ACACA
Autoimmune Thyroid Disease Signaling	1.07E-03	HLA-G,HLA-DRB1,HLA-A,HLA-F,FAS
Graft-versus-Host Disease Signaling	1.32E-03	HLA-G,HLA-DRB1,HLA-A,HLA-F,FAS
OX40 Signaling Pathway	3.31E-03	HLA-G,HLA-DRB1,HLA-A,HLA-F,HLA-DPB1
Lysine Degradation II	3.39E-03	AADAT,ALDH7A1
Lysine Degradation V	3.39E-03	AADAT,ALDH7A1
Adipogenesis pathway	3.47E-03	HDAC9,ARNTL,RUNX1T1,HDAC4,DDIT3,DLK1,FBXW7,SOX9
LPS/IL-1 Mediated Inhibition of RXR Function	6.03E-03	GSTM1,GSTM2,UST,GSTM5,GSTM4,FABP7,IL1R1,ABCA1,ALDH7A1,ABCB9
Hepatic Fibrosis / Hepatic Stellate Cell Activation	7.24E-03	COL19A1,IGF1,EDNRA,MYH7,IL1R1,MYL3,AGTR1,FAS,COL7A1
AMPK Signaling	9.12E-03	MTOR,ACACB,PPP2CA,PPM1B,PDPK1,ACACA,CHRNA5,CREB5,PPP2R5A
Cdc42 Signaling	1.10E-02	HLA-G,IQGAP2,HLA-DRB1,HLA-A,HLA-F,HLA-DPB1,MYL3
Aryl Hydrocarbon Receptor Signaling	1.38E-02	GSTM1,GSTM2,GSTM5,GSTM4,DHFR,FAS,ALDH7A1
Asparagine Biosynthesis I	1.86E-02	ASNS
Communication between Innate and Adaptive Immune Cells	1.91E-02	HLA-G,HLA-DRB1,TLR5,HLA-A,HLA-F
Ethanol Degradation II	2.14E-02	ADH1A,ADH1B,ALDH7A1
phagosome maturation	2.34E-02	LAMP2,NOX4,HLA-DRB1,HLA-A,TUBA4A,DYNLT1
Guanosine Nucleotides Degradation III	2.40E-02	GDA,AOX1

Crosstalk between Dendritic Cells and Natural Killer Cells	2.57E-02	HLA-G,HLA-DRB1,HLA-A,HLA-F,FAS
LXR/RXR Activation	2.63E-02	MLXIPL,ACACA,ARG2,IL1R1,HADH,ABCA1
PI3K/AKT Signaling	2.75E-02	MTOR,SYNJ1,PPP2CA,PDPK1,JAK2,PPP2R5A
Noradrenaline and Adrenaline Degradation	2.75E-02	ADH1A,ADH1B,ALDH7A1
Xenobiotic Metabolism Signaling	3.09E-02	GSTM1,GSTM2,HDAC4,UST,GSTM5,PPP2CA,GSTM4,MAP2K5,PPP2R5A,ALDH7A1
Telomere Extension by Telomerase	3.09E-02	TNKS,HNRNPA1
CTLA4 Signaling in Cytotoxic T Lymphocytes	3.72E-02	PPP2CA,HLA-A,JAK2,PTPN22,PPP2R5A
Choline Degradation I	3.72E-02	ALDH7A1
Cardiolipin Biosynthesis II	3.72E-02	PTPMT1
Neuroprotective Role of THOP1 in Alzheimer's Disease	3.89E-02	HLA-G,HLA-A,HLA-F
3-phosphoinositide Degradation	4.68E-02	INPP4B,SYNJ1,PTPMT1,PTPN22,PPP2R5A,NUDT1
Purine Nucleotides Degradation II (Aerobic)	4.90E-02	GDA,AOX1