Immune activation in patients with admission blood pressure above 185/110 mm Hg in acute ischemic stroke

by

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Abstract

Background: An admission blood pressure over 185/110 mm Hg is associated with increased risk of recombinant tissue plasminogen activator (r-tPA)-related hemorrhagic transformation (HT). Stroke guidelines recommend blood pressure (BP) above 185/110 mm Hg be lowered before r-tPA treatment. How high blood pressure increases blood brain barrier disruption and risk of HT remains poorly understood. We evaluated peripheral leukocyte activation in stroke patients in relation to elevated admission blood pressure and potential contribution to blood brain barrier disruption. To study whether differences in immune response between patients in both groups existed past admission, we also analyzed differential gene expression for these groups at 5 hours and 24 hours after stroke onset.

Methods: Blood samples from acute ischemic stroke patients were collected within 3 hours (prior to treatment with thrombolytic), 5 hours and 24 hours of stroke onset. Patients were grouped by admission BP above 185/110 mm Hg (n=19) and BP below 185/110 mm Hg (n=47). Total blood RNA was assessed by whole genome microarray and differential gene expression for admission, 5 hour and 24-hour time points was analyzed by ANCOVA. Functional analysis of identified genes was performed. Correlation analysis was conducted to identify genes associated with systolic blood pressure (SBP).

Results: Strokes with admission BP above 185/110 mm Hg had 226 genes differentially expressed at admission (within 3 hours of stroke onset) as compared to strokes with BP below 185/110 mm Hg ($p < 0.05$, fold change $\geq |1.2|$). In the higher BP group, SBP remained significantly elevated at 5-hours ($p < 0.05$) and non-significantly elevated at 24 hours, whereas in

the lower BP group, SBP stabilized at 5 hours. Therefore, we also evaluated differential gene expression between the higher and lower BP group at 5 hours and 24 hours post-stroke. At 5 hours, 923 genes were differentially expressed between the higher and lower BP groups and at 24 hours, 422 genes were differentially expressed by admission blood pressure ($p < 0.05$, fold change $\geq |1.2|$). Key genes associated with BP above 185/110 mm Hg included *EDN3* (Endothelin-3), *MMP21* (Matrix metallopeptidase 21), *MMP*-25 (matrix metallopeptidase 25), *MMP*-28 (matrix metallopeptidase 28), *TLR4* (toll-like receptor 4), *AREG (*amphiregulin), CAV-*1* (caveolin 1) and *CCR2* (Chemokine receptor 2). Key pathways were associated with adaptive immunity, IL-17 and T_H17 signalling, TLR signalling and nitric oxide signalling. 99 genes linearly correlated with systolic blood pressure including *CCR2* ($r = -0.32$, $P = 0.0009$), and *AREG* ($r = 0.286$, $P = 0.024$,) ($r > |0.2|$, $p < 0.05$).

Conclusions: A blood pressure greater than 185/110 mm Hg is associated with differential immune activation in patients with acute ischemic stroke which persists for at least the first 24 hours after stroke. These differences may contribute to blood brain barrier disruption and risk of HT in acute stroke patients with very high admission blood pressure. Whether modulating immune activation could reduce blood brain barrier disruption and risk of HT requires further study.

Preface

This research was conducted at the University of Alberta under the supervision and guidance of Dr. Glen Jickling, Dr. Brad Kerr and Dr. Ian Winship. Ethics approval for this study was received by the University of Alberta Research Ethics Board (Pro00066577). The enrollment of study participants and gathering of blood samples were done as part of the CLEAR Stroke Trial by the CLEAR Trial Investigators. The designing and running of microarray experiments were conducted at the Department of Neurology, University of California Davis, Sacramento, USA by members of the Frank Sharp lab including, Dr. Bradley P Ander, Dr. Boryana Stamova, Dr. Glen Jickling and Dr. Frank R Sharp. I contributed to this project by conducting the literature review, analysing gene expression data, conceptualizing, and investigating how gene expression changes at later time points, preparing figures and tables, and writing the manuscript for chapter 2. In all steps of the process, I received support from my supervisor, Dr. Glen Jickling and committee members Dr Brad Kerr and Ian Winship. I also received support in conducting statistical analysis from Dr. Karen Buro of the Department of Mathematics and Statistics of MacEwan University. This work received funding support from CIHR.

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Chapter 1: Literature Review

General Introduction

Stroke is one of the main causes of disability and mortality globally, with rates expected to increase with an aging global population [1]. Around 71% of strokes are ischemic strokes of the brain, spinal cord or retina [2]. One of the main treatments for acute ischemic stroke is thrombolysis using recombinant tissue plasminogen activator (r-tPA) [3]. However, considerable risk is involved in administering r-tPA due to a severe bleeding complication called hemorrhagic transformation (HT) [4]. Thrombolytic-related hemorrhagic transformation is bleeding into the brain and is associated with outcomes such as death and major disability [4]. While major trials of r-tPA treatment and current treatment guidelines for acute ischemic stroke have been designed to carefully select patients to reduce risk of HT, around 6.1% of patients still hemorrhaged during the NINDs r-tPA trial [5, 6]. Better understanding of what causes bleeding in these patients may ultimately reduce risks of stroke treatment and make more patients eligible for treatment who are otherwise left untreated during acute stroke due to high risk of HT.

Hemorrhagic transformation (HT) is related to breakdown of the blood brain barrier (BBB) [7]. Immune response to stroke can worsen BBB breakdown, thereby increasing risk of HT [4]. One of the main modifiable risk factors for HT is high blood pressure during the acute phase of ischemic stroke [4]. High blood pressure and a history of hypertension (HTN) are also associated with activation of the immune system [8]. It is likely that patients with very high BP at the onset of acute stroke may also have an immune profile that may be linked to greater damage to the BBB and therefore, increased risk of bleeding.

The aim of this chapter is to review the literature on blood pressure in acute ischemic stroke and its link to immune activation and hemorrhagic transformation. In chapter 2, I answer the following question: How is high blood pressure during the acute stage of ischemic stroke related to immune response to stroke, thereby increasing risk of BBB disruption? Here, I begin by providing a brief introduction to ischemic stroke including pathophysiology and immune response. I then discuss the link between hypertension and the immune system. Finally, I discuss

how blood pressure is increased during acute stroke, its treatment and link to hemorrhagic transformation.

For this thesis, the most relevant threshold of blood-pressure cut-off is BP above 185/110 mm Hg before treatment as that is the blood pressure mentioned in the guidelines for r-tPA treatment of stroke [6]. However, much of the literature on hypertension has traditionally defined hypertension as blood-pressure above 140/90 mm Hg [9]. Furthermore, the threshold for separating normotension from hypertension has changed over the decades, with Pickering mentioning 8 different cut-offs for defining hypertension in 1986 and AHA recently lowering the threshold for stage 1 hypertension to BP above 130/80 mm Hg [10, 11]. I have included a brief section on definition of hypertension, further discussing this.

Acute Ischemic Stroke

Pathophysiology of ischemic stroke

The main causes of ischemic strokes are thrombosis of cerebral blood vessels, embolism from the heart (cardioembolism) or from a different artery, and cerebral small vessel disease [12]. Thrombosis of cerebral blood vessels occurs because of atherosclerosis [2, 3]. Cardio embolism occur because of atrial fibrillation, valve disease or thrombi from the left ventricle [3]. Artery-to-artery embolism arise from atherosclerotic plaques or the carotid, vertebral or intracranial vessels [3]. Stenosis of extracranial and intracranial vessels may also result in reduced blood flow to the brain, causing watershed ischemia [3]. Cerebral small vessel disease affects the small penetrating arteries of the brain and is responsible for lacunar strokes, leukoaraiosis (white matter hyperintensities), cerebral microbleeds and intracerebral hemorrhage [2]. Accordingly, ischemic stroke is classified into subtypes based on etiology, namely, large artery atherosclerosis (occlusion or stenosis of a major artery supplying blood to brain), cardioembolic (occlusion due to embolism from the heart), small-vessel occlusion (also called lacunar), stroke of known etiology (due to rare causes of stroke) and cryptogenic stroke (where the cause is unknown) [13]. The main risk factors for stroke include hypertension, atrial fibrillation, diabetes, smoking, hyperlipidemia and carotid stenosis [3].

Ischemic strokes involve a reduction in cerebral blood flow and blood pressure in an area of the brain [14]. Loss or reduction of cerebral perfusion compromises the brain's metabolism, leading to loss of electrical activity and resulting in neurological deficits [14]. This process is time dependent and within a few hours of ischemia the tissue dies if not reperfused [14].The tissue with at this marginal perfusion is termed the ischemic penumbra [14, 15]. Damage to brain tissue depends on the magnitude of reduction in blood flow as well as the time for which flow is impaired [14, 15]. With time, the size of the penumbra decreases as cells begin to die [14]. The cellular plasma membrane fails leading to cytotoxic edema and protein and DNA degradation [14, 16]. Neurons depolarize and release glutamate [14, 16]. Glutamate binds to receptors on post-synaptic cells leading to phospholipase activation, arachidonic acid production, nitric oxide (NO) production, protein misfolding, activation of proteases, lipases and endonucleases, and membrane damage [14, 16]. Astrocytes become activated and produce trophic factors which increases their glucose uptake, further exacerbating ischemia [2]. In oligodendrocytes, excitotoxicity leads to demyelination, Wallerian degeneration and white matter loss [2]. Free radicals are produced, causing mitochondrial injury, DNA damage and fragmentation, activation of pro-apoptotic proteins and further production of reactive oxygen species (ROS) [14]. DNA fragmentation and damage result in cell death through apoptosis and necrosis [14].

Immune response to stroke

Cell damage during ischemia and production of reactive oxygen species activate the immune system [16]. There is a localized immune response within the brain wherein microglia, mast cells, perivascular macrophages, astrocytes, and endothelial cells are activated [16, 17]. This immune activation results in the production of proinflammatory cytokines, chemokines and reactive oxygen species which activate immune cells in the periphery leading to infiltration of peripheral immune cells into the brain [16, 17]. Inflammatory genes are upregulated in peripheral leukocytes (mostly likely neutrophils and monocytes) of patients with acute ischemic stroke as early as 3 hours after the onset of stroke [18]. Brain lesions from ischemic stroke patients show accumulation of granulocytes, T cells, peripheral monocyte-derived macrophages, and proliferation of microglia [19]. Within the brain, peripheral immune cells contribute to post-stroke inflammation and repair and both innate and adaptive immunity is involved in this response [16, 17]. In mice, monocytes contribute to the dominant immune response in acute

stroke [20, 21]. Whereas in humans, polymorphonuclear leukocytes (PMNLs) and mononuclear cells seem to be the most dominant cell types to respond [18]. Post-stroke inflammation may be involved in further damage to the brain and breakdown of the BBB. CCR2 -/- mice show reduced monocyte infiltration into the brain after ischemic stroke which is associated with smaller infarct sizes, reduced leakiness of the BBB, and reduced edema formation [22]. At the same time, the immune system also plays a protective role in post-stroke repair [23]. In fact, depletion of inflammatory $CCR2^{hi}$ $CX3CR1^{lo}$ monocytes too early after ischemic stroke may disrupt post-stroke repair because these cells adopt an anti-inflammatory macrophage phenotype later on [23]. The immune system has been explored as a potential target for post-stroke therapies to limit damage to the brain and to promote repair [24]. Using mass cytometry of peripheral blood leukocytes, a technique which combines flow cytometry with mass spectrometry, and elastic net regularized regression modelling, Tsai et. al, showed that the peripheral immune response to stroke can be divided into three main phases [25]. These stages peak at 2 days, 5 days, and 90 days after stroke [25]. They also compared features of immune cells including frequencies and activity of cellular proteins and transcription factors involved in cell signalling between these peak timepoints, and at 365 days after stroke [25]. The main feature of the acute phase which peaks at 2 days is response by innate immune cells [25]. There is increased signalling in transcription factors related to sterile inflammation including STAT3 in monocytes, myeloid-derived suppressor cells (MDSCs) and dendritic cells, and STAT1 in neutrophils [25]. This regulation is in comparison to the immune response at 1 year rather than to pre-stroke immune response in the periphery [25]. The main feature of the intermediate phase which peaks at 5 days is increased CREB signalling in adaptive immune cells including T_{regs} and TH1 cells [25]. The late phase, between 90 days – 1 year, involves a combination of innate and adaptive immune responses [25].

Blood brain barrier disruption

Immune activation and subsequent production of matrix metalloproteinases (MMPs) and ROS result in disruption of the blood-brain-barrier (BBB) [16, 26]. BBB disruption allows infiltration of peripheral cells into brain parenchyma [26]. The blood brain barrier is a barrier that separates the CNS from peripheral blood [27]. It is formed by a tight layer of endothelial cells embedded in basal lamina [27]. These endothelial cells are surrounded by astrocytic end-feet, pericytes,

vascular smooth muscle cells, neurons, and microglia, which is altogether referred to as the neurovascular unit (NVU) [28, 29]. The BBB strictly controls transport of substances and cells from the blood to the brain and vice-versa [30]. This has a protective function, guarding the brain against pathogens and other harmful materials [28]. Breakdown of the blood-brain barrier is associated with cerebral edema, which is linked to worse outcomes after stroke [28].

Hemorrhagic Transformation of acute ischemic stroke

Hemorrhagic transformation (HT) is bleeding into the brain after ischemic stroke because of BBB breakdown [4, 7]. Disruption of the BBB after ischemia allows blood to enter into brain [7]. As previously discussed, production of ROS, MMPs and inflammatory response to brain can disrupt the BBB by breaking down basal lamina and decreasing expression of tight junctions (TJ) [7]. The role of immune response to stroke in disruption of the BBB and increased risk of HT has been previously reviewed [4, 31]. According to ECASS criteria, HT can be classified into two main types based on computed tomography (CT) imaging: Hemorrhagic infraction (HI) (petechial infraction without space occupying effect) and parenchymal hematoma (PH) hemorrhage with mass effect [32]. These two types are further divided into HI1 (small petechial HI) and HI2 (confluent petechial HI) and PH1 (less than or equal to 30% of infarct, mild mass effect) and PH2 (more than 30% of infract, marked mass effect or clot remote from infarcted area) [32]. HT can also be classified as symptomatic or asymptomatic HT [4]. Symptomatic HT can be defined as bleeding accompanied by NIHSS increase of ≥ 4 points within 36 hrs of stroke onset or death [4]. There are also other definitions that have been used in studies for defining HT [33]. The main definitions include ECASS-II, SITS-SICH, and NINDS trial and differ slightly [5, 33]. Hemorrhagic transformation is related to adverse outcomes after stroke [32]. PH2 is associated with clinical deterioration (increase of at least 4 points on NIHSS at 24 hrs after baseline) and death at 3 months, after adjusting for age and baseline NIHSS [32]. However, HI within the first 36 hours of stroke has also been associated with improvement [32]. This is likely because some bleeding can be a sign of early recanalization and restoration of blood flow to the brain [32]. The main risk-factors for HT include use of aspirin or aspirin and clopidogrel; severity of stroke; elevated blood glucose; age; weight; time to treatment; elevated blood pressure and history of hypertension [34]. The greater the number of risk factors in a patient, the

greater the overall risk of HT [34]. Out of all these factors, elevated blood pressure can be managed with the use of anti-hypertensive medications.

Treatment with tissue plasminogen activator and risk of HT

While some hemorrhage after stroke may be a normal consequence of reperfusion, r-tPA treatment greatly increases the risk of bleeding [7, 33]. Recombinant tissue plasminogen activator (r-tPA) is the main thrombolytic used to treat acute ischemic strokes [33]. tPA works by cleaving plasminogen into plasmin, which then breaks down fibrin in blood clots [33]. HT is one of the main complications of treatment with r-tPA, and the "most feared" [33]. Stroke guidelines include several factors that need to be considered when selecting patients who are eligible for r-tPA treatment, the most important of which is time to treatment [6]. According to current guidelines, patients need to be within 4.5 hours of symptom onset to be treated with r-tPA [6]. In some cases, patients can be selected to receive r-tPA beyond 4.5 hours after onset based on brain imaging, NIHSS and size of infarct lesion [6]. Other factors that are related to bleeding risk and need to be considered include platelet count, INR ratio, numbers and presence of cerebral microbleeds and use of the anticoagulant within the last 24-48 hours [6].

There are several mechanisms through which treatment with r-tPA increases risk of HT after stroke. The main mechanisms are thought to be disruption of the blood coagulation cascade and reduced fibrinogen levels which impacts blood clotting [33]. However, r-tPA may also lead to HT by increasing disruption of the blood brain barrier through possible effects on peripheral neutrophils and T cells [35].

Hypertension and the immune system

The immune system is involved in the pathogenesis of hypertension [8, 36, 37]. I begin this section by providing a brief introduction to hypertension as a disease, including the definition and pathogenesis of hypertension. I then describe the link between hypertension and immune system activation. I also discuss how the blood brain barrier is damaged in hypertension and the role of inflammation in BBB damage. Lastly, I discuss how pre-existing inflammation due to hypertension might contribute to the immune response in ischemic stroke.

Hypertension Background

Defining hypertension

Defining hypertension is complicated. This is mainly because blood pressure is a continuous, quantitative variable and no biological threshold is apparent in frequency distributions of blood pressure where a dividing line between hypertension and normotension can be drawn [10]. Any attempts to create a cut-off are subjective [10, 38]. Furthermore, the relationship between high blood pressure and its adverse effects is also linear and quantitative, with risks of cardiovascular events increasing after BP > 115 mm Hg systolic [10, 38, 39]. The main reason for defining hypertension is to establish a target blood pressure at which treatment should start because the risks of having untreated hypertension at that BP exceed the costs of its treatment[10, 40-42]. Pickering further proposed the idea that the treatment threshold of BP may be different for everyone, based on that person's individual risks of having elevated blood pressure [41].

This complexity in defining hypertension is evident in the differing criteria for levels of hypertension in the American, European, and Canadian guidelines. In 2017, American Heart Association (AHA) changed their guidelines to define **normal** clinic BP as ≤ 120/80 mm Hg; **Elevated** BP as SBP between 120-129 mm Hg and diastolic BP ≤ 80 mm Hg; **Stage 1 hypertension** as SBP between 130-139 mm Hg and DBP between 80-89 mm Hg; **Stage 2 hypertension** as SBP ≥ 140/90 mm Hg; and **hypertensive crisis** as SBP ≥ 180 and/or DBP ≥ 120 mm Hg [11]. These guidelines were based on evidence linking increasing blood-pressure to risk of cardiovascular disease including stroke and are meant to guide decisions about the prevention and treatment of hypertension in untreated patients [11]. The guidelines for defining hypertension when ambulatory and home BP monitoring is used are different. This may be because in most patients, ambulatory and home BP readings are lower than clinic BP readings [11, 41]. The AHA guidelines also present a guide for BP conversion from office readings to self-monitored readings [11]. For home BP monitoring, normal BP is below 120/80 mm Hg; Elevated BP is SBP between 120-129 mm Hg and diastolic BP ≤ 80 mm Hg; Stage 1 hypertension is 130/80 mm Hg; Stage 2 hypertension is 135/85 mm Hg [11]. For ambulatory BP monitoring, a 24-hr BP below 115/75 mm Hg is considered normal; SBP between 115-124 mm Hg and DBP under 75 mm Hg is considered elevated; Stage 1 hypertension is BP ≥ 125/75 mm Hg; and stage 2 hypertension is BP ≥ 130/80 mm Hg [11]. The 2018 European guidelines have a

different classification for defining blood pressure thresholds. **Optimal** blood pressure is defined as BP ≤ 120/80 mm Hg; **Normal** BP is defined as SBP between 120-129 mm Hg and/or DBP between 80-84 mm Hg; **High normal** BP is defined as SBP between 130-139 mm Hg and/or DBP between 85-89 mm Hg; **Grade I hypertension** is defined as SBP between 140-159 mm Hg and/or DBP between 90-99 mm Hg; **Grade 2 hypertension** is defined as SBP between 160-179 mm Hg and/or DBP between 100-109 mm Hg; **Grade 3 hypertension** is defined as SBP ≥ 180 mm Hg and/or DBP ≥ 110 mm Hg; **Isolated systolic hypertension** is defined as SBP ≥ 140 mm Hg and DBP ≤ 90 mm Hg [43]. Hypertension Canada's most recent 2020 guidelines classify office BP readings of SBP between 130-139 mm Hg and DBP between 85-89 mm Hg as high-normal; BP ≥ 140/90 mm Hg is considered high [42]. Where ambulatory BP monitoring is used, an awake BP ≥ 135/85 mm Hg, and a 24-hr BP ≥ 130/80 mm Hg is considered high [42]. For home BP monitoring, BP ≥ 135/85 mm Hg is considered high [42]. In patients with diabetes, the cut off is lower, with an office BP ≥ 130/80 mm Hg being classified as high [42]. The Canadian hypertension guidelines classify severe BP increase with acute ischemic stroke as a hypertensive emergency and recommend immediate treatment [42]. For treatment of blood pressure in acute ischemic stroke beyond the first 72 hours, HC guidelines recommend BP be lowered to below 140/90 mm Hg [42].

This issue of producing cut off points for blood pressure is also echoed in the debate around which thresholds blood pressure should be lowered to. Further details of these discussions are provided in the section on treatment of blood pressure in stroke.

Regulation of blood pressure and the pathogenesis of hypertension

Regulation of blood pressure

Systolic blood pressure (SBP) is the blood pressure applied to the walls of the arteries during systole, whereas diastolic blood pressure (DBP) is the pressure of blood on the walls of the arteries during diastole [44]. Blood flow refers to how much blood is moving past a given point in a unit period of time [45]. Since both blood pressure and blood flow change during the cardiac cycle as the heart pumps blood, other helpful ways of referring to blood pressure and blood flow are mean arterial pressure (MAP) and cardiac output (CO) [45]. Mean arterial pressure (MAP) is "the pressure in a single cardiac cycle divided by the duration of the cycle", which in humans is

around 95 mm Hg [45]. The “mean total blood flow in the circulation” is the cardiac output (CO) of the heart, expressed as litres/min, and is a function of heart rate and stroke volume [45]. Stroke volume is the amount of blood pumped in a single heartbeat [46]. Thereby, blood pressure is the product of total cardiac output and peripheral vascular resistance [9, 46].

Since blood pressure is the product of cardiac output and vascular resistance, and cardiac output is the product of heart rate and stroke volume, any factor that affects heart rate, stroke volume, or peripheral vascular resistance affects blood pressure [36, 37, 47]. Thereby, the main organs involved in regulation of blood pressure include the heart, blood-vessels, kidneys, and brain [36, 44, 47]. In the short term, blood pressure is regulated by neuro-hormonal reflex arcs involving the sympathetic and parasympathetic nervous systems [47]. Within the brain, the major blood pressure control centres involve the medulla and hypothalamus, however the cerebral cortex can also be involved in regulating BP in response to stress [47]. Activation of the sympathetic nervous system results in release of epinephrine and norepinephrine which act on the heart and blood vessels to regulate BP [47]. Over the long term, from hours to days, blood pressure is regulated by vasoactive substances that affect blood vessels and non-vasoactive substances that control extracellular fluid volume by controlling salt-water balance in the kidneys [47]. The main systems that control salt-water balance include the renin-angiotensin-aldosterone system (RAAS), the autonomic nervous system, anti-diuretic hormone arginine vasopressin (AVP) secreted by the pituitary gland and production of atrial natriuretic peptide (ANP) by cardiomyocytes [47]. In hypertension, the immune system is also involved in the regulation of blood pressure by impacting the organs involved in blood pressure control [36, 48]. However, in the absence of hypertension, it is unclear whether or how immune cells might be involved in the normal regulation of blood pressure.

Pathogenesis of hypertension

Hypertension is classified into two main types: essential hypertension with no known cause and secondary hypertension when the cause of high BP is known [10, 46]. Approximately 90% of patients with hypertension have essential hypertension [46]. The Page Mosaic model has pointed out that hypertension is likely a result of imbalance of complex interactions between multiple pathways and organ systems involved in the regulation of blood pressure including the nervous,

cardiovascular, endocrine, and renal systems [49, 50]. These systems are impacted by lifestyle, genetic, environmental, humoral, anatomical etc. factors which are involved in hypertension [51]. Within patients with essential hypertension, there is likely variability in causes of elevated blood pressure, so high blood pressure is a result of "discrete hypertensive syndromes" rather than one specific condition [52]. There is also variability within patients in the trajectory of BP rise over their lifetimes, which might represent differences in underlying pathology and presence of risk factors [10]. Similarly, there are differences in pathology between essential hypertension and malignant hypertension [10, 52]. SBP is also known to increase with age, whereas DBP rises till 50-60 and there is a sex interaction with BP in males being higher – however, male sex and age while associated with higher BP are not believed to be causal factors for hypertension [9, 52]. Some of the major pathological processes that result in hypertension include increased activation of the sympathetic nervous system and RAAS, endothelial dysfunction, salt-sensitivity, oxidative stress, genetic susceptibility, and involvement of the immune system [44, 46].

Using the Page Mosaic model, DG Harrison pointed out the roles of oxidative stress and inflammation in the pathogenesis of hypertension [51]. Inflammation and oxidative stress are often linked, with oxidative stress leading to an inflammatory response in organs [51]. Inflammation is related to each of the eight facets of the Page Mosaic model [51]. These include: Polymorphisms of genes like IL-23, TNFα and IL-6; hemodynamics affecting immune cell adhesion and chemotaxis; endothelial damage and neoantigen production; humoral and endocrine signals activating immune cells; neuroinflammation affecting CNS control of sympathetic outflow; activation of T cells and macrophages due to diet and stress; inflammation of organs involved in BP regulation; and involvement of inflammation in vascular hypertrophy [51]. To study the effects of thymus-dependent cells on early hypertension and chronic hypertension, Svendsen looked at blood pressure elevations in DOCA-salt-treated animals with and without a thymus in both the early and late stages of hypertension (21, 57 and 78 days after DOCA-salt treatment) [53]. They compared blood pressure elevations between athymic (nude mice lacking a thymus), thymus grafted mice (nude mice which received a thymus transplant from NMRI mice) and thymic mice [53]. The study showed that in the early stages after salt challenge, blood pressure increased in all mice strains [53]. However, in the later stages, blood

pressure elevation was not maintained in athymic mice as compared to thymus grafted and thymic mice [53]. Transplantation of the thymus in nude mice returned their ability to maintain a high blood pressure in the chronic stage [53]. Taken together, these results showed a causal relationship between thymus-dependent immune cells and maintenance of high blood pressure in chronic hypertension [53].The blood vessels in kidneys of most hypertensive mice at this stage also showed infiltration of "round" cells, most likely monocytes, lymphocytes, granulocytes and plasma cells [53]. This was absent in the kidneys of most nude mice [53].

Hypertension and immune system

Immune system activation in hypertension

The main cell types involved in an inflammatory response to hypertension include cytotoxic T cells, T helper cells, γδT cells, B cells, dendritic cells, monocytes and macrophages [36]. These cells are thought to promote inflammation and target organ damage in hypertension [36]. However, immune cells like Treg cells, iNKT cells, Choline acetyltransferase- expressing CD4+ T cells and myeloid deprived suppressor cells are thought to have a protective role in suppressing hypertension [36]. Angiotensin-II induces production of ROS in dendric cells (DCs) [54]. Oxidative stress due to increased ROS produces isoketals (also called isolevuglandins) which react with proteins and modify them [54]. Modified proteins activate DCs which secrete IL-1ß, IL-6, and IL-23 and activate $CD8^+$ T cells [54]. These T cells then secrete IL-17, TNFα, and IFN-γ, and damage kidneys and blood vessels [54]. Isolevuglandins also affect monocytes in a similar fashion [54]. DCs and monocytes with isolevuglandins have also been found in humans with hypertension [54]. Monocytes also accumulate in blood vessel walls of animals with hypertension and the CCR2 receptor may be involved in monocyte trafficking [55]. Using a CCR2 antagonist decreases monocyte infiltration and reduces blood pressure [55]. T cells are also involved in the production of IL-17 because of Ang-II infusion in animal models [56]. IL-17 KO mice show elevation in blood pressure initially, but hypertension is not sustained [56]. This study also found increase in IL-17 levels in patients with diabetes and hypertension, regardless of anti-hypertensive medication use [56]. Overall, it is possible that different aspects of the inflammatory response are involved in different effects of hypertension on target organ damage [36]. It is also likely that as hypertension progresses, damage caused by inflammation may further impact blood pressure regulation and exacerbate hypertension [36, 37]. What remains to

be seen is the timeframe of how and when this immune response starts in hypertension and whether different immune mediators might be involved causing or maintaining hypertension over time [36]. In humans, levels of inflammatory cytokines TNFα, IL-1β and IL-10 have been found to be elevated in resistant hypertension, relating hypertension to increased immune activation [57].

Target Organ Damage in hypertension

In animal models, hypertension-associated immune activation plays a role in endothelial dysfunction; compromised vasodilation; vascular hypertrophy and remodelling; vascular fibrosis and collagen deposition; oxidative injury; arterial rarefaction; and matrix metalloproteinase (MMP) production [37, 58, 59]. In blood vessels, hypertension is known to cause rarefaction (loss of vessels) and remodeling (narrowing of vessel lumen) – which causes an increase in peripheral vascular resistance and possibly reduced blood flow [29]. In the brain, hypertension-associated vessel remodeling and endothelial dysfunction cause shifting of the autoregulatory curve to higher blood pressures [58]. This makes the brain more susceptible to the effects of ischemia as autoregulation is more likely to fail at lower blood pressures leaving cerebral blood flow dependent on blood pressure [58]. Hypertension also impacts the blood-brain barrier and the neurovascular unit by affecting endothelial cells, pericytes, astrocytes and microglia [60-62]. It is also likely that many hypertensive-related changes to cerebral circulation go unnoticed till significant damage to blood vessels results in more severe pathology and symptoms [63]. Hypertension is also a risk factor for dementia, along with diseases of cerebral blood vessels like cerebral small vessel disease [59].

Blood brain barrier damage in hypertension

In hypertension, inflammation, endothelial dysfunction, vascular remodelling, reactive oxygen species and production of MMPs increase disruption of the blood brain barrier (BBB) [58, 64, 65]. Below, I summarize some of the mechanisms by which hypertension increases blood-brain-barrier disruption. In the next section, I focus on the role of inflammation in hypertension in damaging the blood brain barrier. Of importance is that much of the literature summarized is from animal studies and our knowledge of mechanisms of how hypertension and resulting inflammation impact the BBB in humans is less clear [64].

Studies in animal models have shown that the BBB permeability is increased in spontaneously hypertensive rats and stroke prone spontaneously hypertensive rats, particularly around the hypothalamus [66]. There may be two mechanisms for this increased permeability: Increased transcellular transport through endothelial cells and paracellular transport between subsequent endothelial cells [66]. Whereas Ueno et al. only found evidence of increased vascular permeability through increased trans-endothelial transport, Lippoldt et al. found no differences in vascular permeability in young rats [66, 67]. Lippoldt also did not observe differences in vessel wall morphology in young WKY, SHR or SHRSP [67]. However, they did observe differences in distribution of TJs in brain endothelial cells as well as differences in endothelial cell polarity in SHRSP, which might lead to increased barrier permeability as the animals aged [67]. Even an acute hypertensive response and elevation in BP increases BBB permeability and downregulation of claudins mRNA in endothelial cells [68]. In this study, the acute hypertensive response referred to elevations of blood pressure of about 35% for at least 8 days [68]. The same study also found decreased activity of superoxide dismutase (SOD), pointing towards high oxidative stress in brains of hypertensive rats [68]. Similarly, another mouse model of transverse aortic coarctation in which blood pressure is acutely increased in one brain hemisphere, leading to hyperperfusion of brain tissue, showed a breakdown of the blood-brain-barrier, oxidative stress and inflammation [69]. Specifically, they found increase in mRNA levels of IL-1ß and TNFα in brain tissue [69]. ROS can react with NO reducing NO bioavailability and producing peroxynitrite [70]. *In vitro* BBB models show that peroxynitire accumulation can further damage the blood brain barrier increasing permeability across the barrier, whereas peroxynitrite catalysts which remove peroxynitrite can reduce this damage [70]. There are also direct effects of Angiotensin-II on blood brain barrier permeability [71]. Angiotensin binds to Angiotensin-II Type I (AT_1) receptor on endothelial cells to increase BBB permeability as determined by *in vitro* BBB models [71]. Cerebral microvascular endothelial cells of rats with Ang-II associated hypertension also show decreases in mRNA levels of tight junction proteins like Claudin-5 and Zona-Occludens 1 [72]. When AT_1 receptor blocker losartan is administered, these TJ mRNA levels increase to normal [72].

Role of inflammation in blood brain barrier damage in hypertension

An undamaged BBB is thought to be important for blocking the entry of peripheral Ang-II and inflammatory immune cells into brain [64]. In hypertension, Ang-II binds to endothelial cells to disrupt the BBB [71]. A study with fluorescently labelled Ang-II showed that Ang-II from the circulation co-localised with neurons and microglia in the brains of hypertensive animals with disrupted blood brain barriers [61]. Indeed, microglial activation has been found in the brains of hypertensive animals whereby treatment with minocycline reduced blood pressure and mRNA levels of IL-1ß, IL-6 and TNFα in these animals [73]. Furthermore, minocycline treatment increased levels of IL-10 which has found been to be helpful in reducing blood pressure [73]. Ablation of activated microglia using diphtheria toxin in hypertensive animals also reduced blood pressure [74]. Furthermore, adoptive transfer of activated microglia to the brains of normotensive mice resulted in elevated blood pressure [74]. These studies suggest that inflammation in the brain may not only be a result of hypertension but may also be involved in maintaining or exacerbating high blood pressure. In addition to microglia, perivascular macrophages (PVM) are also involved in BBB disruption in hypertensive animals through production of free radicals [72]. Depletion of these macrophages using chlodronate reduces BBB permeability in hypertensive animals [72]. While PVMs also express AT_1 receptor, this increase in BBB permeability is likely the result of an interaction between the effects of Ang-II on the endothelium and on PVMs [72].

Of note is that production of cytokines and oxidative stress by activated microglia and PVMs may contribute to further damage of the BBB [27]. Inflammatory cytokines like IL-1ß and TNFα increase expression of adhesion protein ICAM-1 in human brain microvascular endothelial cells [75]. IL-1ß also acts on endothelial cells to increase mRNA levels of proinflammatory cytokines like IL-1ß, IL-6, IL-8 and TNFα [75]. Finally, IL-1ß and TNFα also induce secretion of MMP-2 from endothelial cells [75]. In *in vitro* BBB models, IL-1ß also increased BBB permeability and increased migration of monocytes and T cells across the BBB [75]. Therefore, these cytokines may be involved in signalling and entry of peripheral immune cells into the brain through a disrupted BBB.

Peripheral leukocytes are also involved in BBB damage in hypertension. Peripheral leukocytes in hypertensive animals have increased expression of Mac-1 which is important in cell adhesion and infiltration into the vessel wall [76]. This expression is reduced by treatment of these animals with AT_1 receptor antagonist [76]. A study of chimeric SHR with bone marrow from non-hypertensive WKY animals showed decrease in blood pressure in SHR with BM transplant [77]. On the other hand, chimeric WKY rats with BM from SHR showed an increase in activated microglia and elevation of blood pressure, suggesting that peripheral immune cells are involved in neuroinflammation in hypertensive animals [77]. Bone marrow mononucleolar cells from hypertensive animals also showed increased mRNA production of proinflammatory markers like CCL2, INF∂, IL-1ß, TLR4 and TNFα [77]. T_H17 cells and IL-17 have also been found in brains of hypertensive rats [78].

Role of hypertension in immune response to stroke

Given the destructive effects of hypertension on cerebral vasculature, it is possible that patients with pre-existing vascular damage due to hypertension "get a double hit when they experience a stroke" [63]. Similarly, given that hypertension is linked to immune activation and neuroinflammation, it is possible that the immune system is "doubly activated" or responds more strongly after stroke in hypertensive patients. In patients with acute ischemic stroke, high SBP has been associated with increased levels of serum C-reactive protein [79].Considering that most patients with acute ischemic strokes are hypertensive, studies of inflammatory response to stroke likely do capture aspects of immune response to a hypertensive brain [63]. However, very little is known about the specific contribution of hypertension-related-inflammation to immunity after stroke, particularly in humans.

One factor that complicates studies of immune response to hypertension in stroke is the presence of an acute hypertensive response in patients. Most patients with acute ischemic strokes are admitted with high blood pressure which spontaneously declines over the next few days[80-83]. A rise in blood pressure within 24 hrs of stroke onset that is above the patient's normal blood pressure levels has been termed an acute hypertensive response (AHR) and may be different from previous hypertension [84]. Acute hypertensive responses are not specific to stroke but are found in other diseases like traumatic brain injury as well [85]. Presence of chronic hypertension

is a risk factor for the acute hypertensive response, however up to 20% of stroke patients with AHR may have no history of HTN [84-86] .

While most studies of inflammation in hypertension are focused on chronic hypertension, the acute hypertensive response may have a different immune profile than that of chronic hypertension. Poulet et al., found that an acute hypertensive response also leads to generation of superoxide, production of pro-inflammatory cytokines and increased permeability of the blood brain barrier [69]. However, this response was not studied in animals with stroke. By inducing an acute hypertensive response in mice with chronic hypertension, Wakisaka et. al, showed that acute rise in BP could induce intracerebral hemorrhage (ICH) [87]. Occurrence of ICH was related to increase in oxidative stress and MMP activity [87]. While this study did not look at ischemic strokes, it suggests that an acute BP rise in an animal with chronic hypertension can damage the BBB and inflammation might be involved [87]. Rodriguez-Yanez et al., studied immune response as determined by blood levels of IL-6, TNFα, ICAM-1, VCAM-1 and MMP-9 in acute ischemic stroke patients with new onset or chronic hypertension [86]. Patients with new-onset hypertension (no prior recorded history of hypertension before ischemic stroke) showed increased levels of all inflammatory mediators as compared to chronically hypertensive patients [86]. This study was done within 24 hours of stroke onset. They also found that increased numbers of genes correlated with SBP in new-onset hypertensives as compared to patients with chronic hypertension [86]. However, determining an accurate history of hypertension is complicated because not all hypertensive patients are diagnosed.

Blood Pressure and the treatment of Acute Ischemic Stroke

Hypertension is a main risk factor for stroke whereby a decrease in diastolic blood pressure by 10 mm Hg reduces the risk of stroke by 56% [88]. There is also a continuous positive association between increased SBP and risk of stroke [88]. The prevalence of hypertension in modern societies is also high and so is the lifetime risk of developing hypertension - 90% of people who are normotensive at 55 will be hypertensive after this age [88]. There is interest in researching and treating hypertension in stroke because hypertension is the main modifiable risk factor for stroke [88]. In the acute stage of stroke however, there are still controversies in whether and how hypertension should be treated [89]. High blood pressure during stroke is thought to be

protective by helping to perfuse an ischemic brain [90]. Therefore, there is fear of worsening ischemia by lowering blood pressure [90]. However, high pressure during acute stroke is also associated with worse outcomes [89]. Most importantly, high blood pressure in acute stroke is associated with increased risk of bleeding after r-tPA therapy [91]. Blood pressure lowering is recommended when there is malignant hypertension (BP above 220/120 mm Hg) or when the patient is eligible for r-tPA therapy [3, 6].

In this section, I first discuss the natural history of BP during the acute phase of stroke and mechanisms for why BP rises. I then discuss the treatment of blood pressure in stroke including current guidelines for treatment, justification for guidelines and studies linking high blood pressure during acute stroke to risk of hemorrhagic transformation.

Blood Pressure in acute ischemic stroke

Natural history of blood pressure in acute ischemic stroke

Most patients with stroke present to the hospital with very high blood pressure and this blood pressure declines spontaneously over the first few minutes, hours, and days [80-83]. Approximately 84% of stroke patients have BP over 150/90 mm Hg over the first 24 hours of stroke admission [83]. Approximately 69% of patients with acute stroke have very high admission blood pressure (SBP>170 mm Hg or DBP > 100 mm Hg) as compared to age and sex matched patients admitted to the emergency department for various conditions [81]. Prevalence of severely elevated blood pressure with SBP > 185 mm Hg has also been reported [92]. A study of acute blood pressure after stroke in 563,704 US adults, found that 13% of patients (N=74,586) came in with "severely elevated SBP" between 185-219 mm Hg, whereas 0.1% of patients (N=791) presented with SBP > 220 mm Hg [92]. Though some of these values could be attributable to higher levels of hypertension in stroke patients vs. controls, a 2016 study of pre-hospital blood pressures between strokes and stroke-mimics reported similar findings that pre-hospital mean SBP is higher in stroke patients than in stroke mimics [80, 81]. All studies have reported similar findings for diastolic BPs [80-83].

This transient rise in BP after stroke is different from hypertension and has been termed an **acute hypertensive response (AHR)** to stroke [81, 84]. An acute hypertensive response is defined as

"BP above 140/90 mm Hg on two readings taken at least 5 minutes apart, within 24 hours of stroke symptom onset" [84]. The definition of AHR is a practical one useful for understanding the prevalence of the response, but may not be helpful when understanding underlying mechanisms [84]. There is variability between patients in blood pressure decline after stroke which is used to distinguish types of AHR [82, 84]. There is a positive correlation between admission blood pressures and extent of blood pressure decline, with patients with the highest admission BPs showing the most decline over the first four days, likely due to regression towards the mean [81, 82]. Based on patterns of blood pressure decline, Qureshi categorized the acute hypertensive response into four types: "blood pressure declines spontaneously; no decline or increase in BP, regardless of medication; modest decline with medication (between 10-15%); intense decline with medication (greater than 20%)" [84].

There are a few aspects to consider in these studies of natural history of blood pressure in stroke: timing of blood pressure measurement; effect of masked hypertension or white coat effect; and effect of hypertension and anti-hypertensive medications. If BP declines spontaneously, then the timing since stroke onset at which patients are admitted to hospital and when their BP is taken is thereby important [93]. The closest time to onset of stroke for which blood pressure data has been reported has been 19 ± 13 min [82]. So far, there is lack of human data about how blood pressure changes at the very onset of stroke. However, a study of normotensive rats showed that blood pressure increases within minutes of middle cerebral artery occlusion [94]. A similar acute hypertensive response is seen in dogs and rabbits, though it doesn't occur in each animal and the degree of blood pressure rise seems to vary [49, 95]. In all the above human studies, blood pressure was also measured either in the hospital, or by ambulance personnel. As such, it is difficult to estimate any effects of masked hypertension or the white coat effect on these measurements. History of HTN and use of anti-hypertensive medications is discussed in the section below.

Factors associated with the acute hypertensive response

Patients with previous hypertension have higher admission blood pressures than patients with no previous diagnosis of hypertension [96, 97]. This association holds for all subtypes of ischemic strokes and when 24-hr BP monitoring is used in hospital [81, 83, 96, 97]. However, accurately

determining a previous history of hypertension can be complicated [98]. In some studies, a history of hypertension is determined using previous diagnosis of HTN; by talking to the patient's doctor, family members or the patients and use of anti-hypertensive medications [82]. Vemmos et al., used blood pressure values up to a month after stroke to estimate possible history of hypertension at stroke onset [97]. Many people with hypertension are not aware that they have hypertension [99]. The numbers of patients who are unaware of their hypertension range from approximately 35% within the United States and approximately 45% globally [99]. Furthermore, even if they are diagnosed and treated, compliance with medication may be poor [99-101]. Since hypertension is a risk factor for stroke, the proportion of patients who do not adhere to medication may be higher in patients with AIS [99]. Third, even after taking medication their BP may be uncontrolled [97, 100, 101].

Previous use of anti-hypertensive medication may also be related to BP in acute stroke [83]. Wallace and Levy studied the natural history of BP decline in patients with diagnosed HTN with and without previous anti-hypertensive medications, and patients with no previous diagnosis of hypertension [83]. In patients with a previous history of hypertension, who were not taking anti-hypertensive medication prior to stroke, blood pressure declined even without medications during the first week. [83]. Surprisingly, patients with a previous history of HTN, who were using anti-hypertensive medications had higher admission BPs (mean 214/118 mm Hg) than people with prior history and without anti-hypertensive therapy (mean 181/95 mm Hg) [83]. The decline in blood pressure was sharper in hypertensive patients on medications and at day 10, their average SBP was still higher (mean 162/97 mm Hg) than SBP in patients with a history of HTN plus no prior anti-hypertensive medication use (mean 181/95 mm Hg) [83]. It is important to note that is study was published in 1981 so patients were not treated with reperfusion therapy for ischemic strokes [83]. It is possible that patients with higher blood pressures may have been more likely to be prescribed anti-hypertensive medications, explaining the results of this study.

Other important factors are sex, age, type of stroke and comorbid conditions. When distinguishing by sex, women were more likely to have had a previous diagnosis of hypertension (as determined by treatment for hypertension) (58.2% vs. 43.0%, $p<0.001$, N=843) [96]. These results are not surprising because even outside an acute stroke setting, women in general have

higher awareness, treatment, and control of hypertension [99]. The SBP on admission was significantly higher in women than in men [96]. Age is also correlated with higher admission blood pressure [96]. However, when considering subgroup analysis by type of stroke, age was negatively associated with 24-hr DBP after stroke in lacunar stroke and strokes of undetermined cause [97]. SBP rise is positively associated with age [9]. However, DBP increases with age up to 60 years after which DBP declines with increasing age [9]. The factors associated with 24 hr blood pressure after stroke also differ by type of stroke. In general, patients with ICH and lacunar strokes have the highest BPs during acute stroke [80, 82, 96]. No significant difference in mean blood pressures were found in patients with reference to cardiac failure and diabetes, though patients with diabetes were more likely to have a previous history of hypertension treatment [96]. Vemmos et al., however found that histories of coronary artery disease and heart failure were negatively associated with SBP in patients with cardioembolic stroke [97]. The explanation that they presented was that these patients may have lower functioning of the left ventricle and lowered cardiac output [97].

Reasons for blood pressure rise during acute stroke

There may be several reasons why patients may have an acute BP rise after stroke, and most of them are still not well understood [84, 98, 102]. It is likely that there are several factors at play at the same time, and it may be difficult to distinguish individual effects due to any one cause. Some factors that might contribute include stress from being hospitalized, pain, vomiting [98]. Additional factors that have been discussed in relation to this response include the effect of plasma catecholamines that are released after stroke; having a full bladder; the brain's response to hypoxia; uncontrolled blood pressure from pre-existing hypertension; Cushing's reflex; size of infarct; location of the infarct being in a part of brain that regulates BP or the autonomic nervous system; some other effect of stroke because BP drops after recanalization; NO release after stroke; and post-stroke infections resulting in release of catecholamines and pro-inflammatory cytokines [84, 96, 102].

Treatment of blood pressure in stroke

Guidelines for treatment of hypertension in acute stroke

Lowering admission blood pressure below 185/110 mm Hg

Guidelines for the treatment of ischemic stroke recommend blood pressure be lowered below 185/110 mm Hg before treatment with r-tPA [6]. The blood pressure threshold of 185/110 mm Hg is based on pilot studies and the NINDS 1995 trial of r-tPA for thrombolysis in acute ischemic stroke [5, 103, 104]. The NINDS trial in 1995 tested the effectiveness of r-tPA vs. placebo in acute stroke [5]. While the NINDS trial showed success, 6.4% of patients treated with r-tPA had symptomatic intracerebral hemorrhage (sICH) while 0.6 % of patients given placebo showed sICH [5].

Maintenance of blood pressure after r-tPA treatment

The guidelines also recommend that blood pressure be maintained below 180/105 mm Hg for the first 24 hours after r-tPA treatment [6]. In the NINDS r-tPA trial, one of the rationales given for a higher incidence of bleeding in patients treated with r-tPA was that high blood pressure after treatment is also associated with risks of bleeding [5] . Therefore, BP was lowered below 180/105 within the first 24 hours after r-tPA treatment [6]. A post-hoc analysis of blood pressure treatment in the NINDS r-tPA trial showed that there was an association between needing BP to be lowered below 180/105 mm Hg post-r-tPA with worse outcomes at 3 months[6]. However, a causative relationship between high BP after r-tPA treatment and worse outcomes cannot be drawn from this analysis and the exact reasons for this association were unclear [6]. A further study showed that blood pressure variability within the first 24 hours, and particularly within the first 6 hours after r-tPA treatment is also associated with risk of HT [105]. These studies show that while high admission blood pressure is an important risk factor for HT, the profile of blood pressure over the first 24 hours after r-tPA treatment must also be considered. While not specific to HT, other studies have shown that the trajectory of BP in the first 24 hours of admission may be associated with outcomes after stroke [106-108]. It remains to be seen whether blood pressure trajectories are associated with HT after treatment with r-tPA. In any case, the research on BP trajectories shows that there is variability between patients in BP trajectories, which might require different management after stroke [107]. Whether these trajectories are associated with different immune profiles after stroke may also be an area of further interest [107].

Relationship of blood pressure to risk of hemorrhagic transformation

Justification for guidelines and association of blood pressure to risk of HT

Prior to being used as a thrombolytic in acute stroke, r-tPA had been used as treatment for heart attack and there was a warning that treatment with r-tPA may be linked to cerebral hemorrhage in patients with blood pressures above 180/110 mm Hg [109]. In the initial NIH pilot study for the NINDS trial, patients were treated with r-tPA (alteplase) within 90 minutes of stroke onset and blood pressures above systolic 200 mm Hg and diastolic 120 mm Hg were lowered before treatment [103]. However, after systemic hemorrhaging in two patients, those with MAP above 133 mm Hg were excluded from the study [103]. The same blood pressure threshold (MAP of 133-135 mm Hg) was used in the second NIH pilot study of r-tPA, in which treatment time was extended from 90 to 180 mins and in further r-tPA trials (BP>185/110 mm Hg) [5, 104, 110, 111]. In the pilot studies, diastolic BP > 100 mm Hg was associated with risk of HT [112]. There were also pilot studies of r-tPA (duteplase) conducted by the TPA Acute Stroke Study Group (ASSG) in which time to treatment was up to 8 hrs after symptom onset; patients with pre-treatment BP > 200/120 mm Hg, or those with a history of malignant hypertension were excluded [112, 113]. This study found that 30.8% of patients had HT (HI and PH) and 9.6% of these patients had clinical deterioration (N=104) [113]. The only factor that was significantly different between patients who suffered HT and those who didn't was time to treatment with patients with HT having received later treatment on average [113]. This study did not find any relationship between admission BP and rates of HT [113]. However, other studies have found an association between admission (or pre-tPA) blood pressures and risks of HT and are described below.

In an analysis of 31 627 patients from the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register (SIRS-ISTR), systolic blood pressure and history of hypertension were found to be risk factors for symptomatic intracerebral hemorrhage (sICH) [34]. The register contained information on patients with AIS who were treated with IV-tPA in 699 centres and 34 countries, majority of them in Europe [34]. They defined sICH as PH2 plus an increase of at least 4 NIHSS points or death, seen between 22-36 hrs post r-tPA [34]. They also compared results using their definition to results using the ECASS-II and NINDS definitions of sICH [34]. They found that 1.8% of patients had sICH using the SITS-MOST definition,

whereas 5.1% and 7.4% of patients had sICH according to the ECASS-II and NINDS criteria [34]. Using the risk factors associated with sICH, they presented a scoring scale to predict the risk of sICH in individual patients [34]. In their final scoring scale, SBP over 146 mm Hg (OR 1.6, 95% CI (1.3-2.0) and history of hypertension were included as independent risk factors for sICH [34]. While this analysis found that odds of sICH increased about a SBP of 146 mm Hg, the exact blood pressure at which risk of HT increases is still unknown [6]. Similarly, another pos-hoc analysis of the SITS-ISTR showed that in adult patients below 50, baseline SBP on admission was associated with sICH [114].

Evidence for lowering blood pressure below 185/110 mm Hg before r-tPA treatment also comes from analysis of protocol violations [91]. An analysis of 534 patients with BP over 185/110 mm Hg who were treated with r-tPA showed that hypertension and protocol violations were associated with risk of sICH [91]. The pre-treatment BP was also significantly higher in patients with sICH as compared to patients without sICH [91]. Pre-treatment with SBP was also associated with risk of sICH [91].

There are a few factors that need to be considered when studying rates of HT in different studies. Firstly, there are differences in definitions of HT in different studies, leading to differences in rates of hemorrhages reported and making direct comparisons between studies difficult [33]. The main definitions used have been ECASS-II, SITS-SICH, and NINDS trial [5, 33]. There are also problems in defining HT based on symptomatic vs. asymptomatic bleeding [32]. In some cases, there may be clinical deterioration and HI, but clinical deterioration may not be related specifically to petechial hemorrhage and may be due to other effects of stroke [32]. It also possible that symptoms of HT may be missed within the early stages after thrombolysis (24-36 hrs) if HT occurs in an area of brain that is already infracted [33]. Another inconsistency among various definitions and studies of HT is that of timing after r-TPA treatment or symptom onset at which a CT scan is completed to determine the presence of bleeding [33]. Studies that do not assess for HT beyond 24 hours might underreport rates of HT. In the ECASS-II definition, a timeline of 36 hours is provided to assess for bleeding [32].

Mechanisms for why high BP is related to risk of HT post-tPA

Several mechanisms may be used to explain the link between high blood pressure and r-tPA related HT. Generally, patients with high post-stroke blood pressures have histories of hypertension, which is associated with target organ damage to the brain and to the blood brain barrier [66, 96, 97]. It is also possible that BBB damage due to loss of cerebral autoregulation during stroke and resulting cerebral hyper perfusion may be involved [115].

Within patients with high blood pressure, there may also be variability in the underlying reason for BBB related damage and therefore HT, based on the duration of hypertension and the type of hypertension (for example, malignant vs. benign hypertension). In malignant hypertension, a sharper rise in blood pressure is seen over time, there is target organ damage to brain, blood vessels and kidneys, and blood pressures are extremely high (Above 179/109 mm Hg) [10, 116, 117]. Hypertensive crises, though not completely understood, even without the context of acute stroke are associated with BBB damage and possible upregulation of proinflammatory immune responses [117]. In contrast, in patients with benign hypertension, the increase in blood pressure with age is much less severe and there is less underlying target organ damage [10]. There may also be variability in the acute hypertensive response itself. Interestingly, in rabbits, three main types of blood pressure responses are seen after MCAo: a sharp rise in BP that lasts a few seconds followed by a sharp decline and hypotension; a rise in blood pressure that lasts for minutes; and finally, no change in blood pressure [95]. The third group had less incidence of HT, which is not surprising given that this study found an association between AHR and HT [95]. To date, there are no studies associating types of hypertensions with BP rise in acute stroke, mostly because of the complexity involved in understanding the mechanism of essential hypertension in each patient and in understanding the mechanisms of the acute hypertensive response.

Furthermore, given that gene expression in peripheral leukocytes can be used to predict risk of HT in acute ischemic stroke, it is likely that hypertension-related activation of peripheral leukocytes also plays a part in HT risk [31, 118]. Inflammatory mediators secreted in hypertension including IL-6, TNF, MCP-1, ROS, MMP-2 and MMP-9 are also associated with greater disruption of the blood brain barrier and risk of HT [31]. However, the exact link

between immune response to stroke and very high blood pressure above 185/110 mm Hg in the setting of acute stroke is still unknown.

Thesis objectives

The purpose of this thesis was to study immune activation in acute ischemic stroke patients with admission BP > 185/110 mm Hg. Specifically, we wanted to understand whether very high blood pressure in acute ischemic stroke is related to increased activation of the immune system. We also wanted to identify genes and pathways that may be related to increased BBB damage in patients with hypertension and stroke. To do this, we examined microarray gene expression in patients with acute ischemic stroke with admission BP above and below 185/110 mm Hg. We separated patients into two groups: higher BP group (admission BP > 185/110 mm Hg) and lower BP group (admission BP < 185/110 mm Hg) and analyzed differential gene expression between both groups using ANCOVA. We also noticed that at 5 hours, SBP remained significantly elevated in patients in the higher admission BP group whereas blood pressure stabilized in the lower admission BP group. Therefore, we also analyzed differential gene expression for these groups at 5 hours and 24 hours after stroke onset. The study is presented in chapter 2.

Chapter 2: Immune Activation in Patients with Acute Ischemic Stroke and Admission Blood Pressure Greater Than 185/110 mm Hg

Introduction

Approximately 84% of patients who present to hospital after ischemic stroke have elevated blood pressure which declines spontaneously [80-83]. A high blood pressure after stroke is both protective and associated with worse outcomes [89]. High blood pressure is thought to be helpful in perfusing the ischemic brain and thereby reducing damage [90]. Alternatively, high blood pressures in acute stroke can increase risk of recombinant tissue plasminogen activator (rtPA)-related hemorrhagic transformation (HT) [34, 91, 112, 114]. HT is an unfavourable consequence of treatment with r-tPA and is associated with death and poor stroke outcomes [119]. While management of blood pressure in acute stroke is an area of ongoing research and debate, guidelines recommend that BP be lowered below 185/110 mm Hg before treatment with r-tPA [6]. This is mainly to reduce risk of r-tPA related hemorrhagic transformation [120]. Exactly how acute hypertension during stroke onset increases risk of r-tPA-related HT is not well understood. Improved understanding of how high blood pressure increases the risk of hemorrhagic transformation could improve the safety profile of r-tPA and provide information to guide personalized treatment decisions for hypertension in acute ischemic stroke [107].

Disruption of the blood brain barrier (BBB) is thought to be one of the main mechanisms involved in HT [4]. Loss of cerebral autoregulation and resulting hyper-perfusion which damages the BBB have been suggested as a mechanism of BP-related HT [115]. High blood pressure is also associated with immune activation which contributes to endothelial dysfunction, compromised vasodilation, vascular remodelling, vascular fibrosis and collagen deposition, oxidative injury, arterial rarefaction, and matrix metalloproteinase (MMP) production [37, 58]. All these inflammatory processes can promote disruption of the blood brain barrier in HT [31, 58]. In patients with strokes however, the relationship of high admission-BP to immune activation and subsequent BBB damage is not clear. In patients with resistant hypertension, inflammatory cytokines TNF-α, IL-1β and IL-10 are elevated [57]. In patients with acute ischemic stroke, high systolic blood pressure is associated with an increase in serum C-reactive

protein [79]. Such immune activation could contribute to the increased risk of r-tPA-related hemorrhagic transformation associated with a BP above 185/110 mm Hg.

In this study we sought to evaluate whether acute ischemic stroke patients with an admission BP above 185/110 mm Hg have differences in their peripheral immune system that could contribute to blood brain barrier disruption and risk of r-tPA-related hemorrhagic transformation. We analyzed gene expression in peripheral blood leukocytes of patients presenting to hospital with acute ischemic stroke within 3 hours of stroke onset. Gene expression in peripheral blood of stroke patients has previously been shown to differentiate strokes with and without HT [118]. We divided patients into two groups: those with admission blood pressures above 185/110 mm Hg and those with admission blood pressures below 185/110 mm Hg. We then analyzed differential gene expression in both groups and performed pathway analysis to identify pathways related to BBB disruption. We hypothesized that in patients with admission BP >185/110 mm Hg, there would be greater overall activation of the immune system, specifically in pathways involved in BBB disruption.

Acute stroke guidelines present a blood pressure threshold of 185/110 mm Hg in relation to management of blood pressure before r-tPA treatment [6]. After r-tPA treatment, guidelines recommend maintaining BP below 180/105 mm Hg for the first 24 hours after stroke [6]. However, we also analyzed differences in gene expression between the higher and lower BP groups using a cut-off of 185/110 mm Hg at 5 hours and 24 hours after stroke. The rationale for looking at differences in gene expression for the higher and lower group past rt-PA treatment were two-fold. In a previous study, Tang et al., showed that gene expression in peripheral leukocytes of patients with stroke vs. healthy controls changes over time [18]. By analyzing gene expression at admission, 5 hours, and 24 hours after stroke onset, they found that genes related to immune response begin to be regulated at admission [18]. However, most genes were not significantly differentially regulated till at least the 5 hour and 24-hour periods post-stroke [18]. We also noticed that at 5 hrs, SBP remained significantly increased in strokes in the higher BP group, regardless of BP medication use to comply with guidelines. Whereas, in the lower group BP stabilised from 5 hours onwards. At 24 hrs, there was no significant difference in BP between groups (though BP was elevated by 10 mm Hg in the higher group).

Methods

Study participants

Blood samples were collected from patients enrolled in the CLEAR trial of acute ischemic stroke (NCT00250991 at Clinical-Trials.gov). Detailed methods of the trial were previously reported [121]. The CLEAR trial was a multicentre randomized trial which assessed the safety of eptifibatide in combination with recombinant tissue-plasminogen activator (rt-PA) for thrombolysis within 3 hours of ischemic stroke onset. Eptifibatide is an antagonist of the glycoprotein IIb/IIIa receptor on platelets and prevents platelet aggregation [122]. It is used along with thrombolytics in the treatment of acute coronary syndrome to increase thrombolysis [121]. Eptifibatide in combination with low-dose r-tPA vs. standard dose r-tPA was used in the CLEAR trial to assess whether a combination of Eptifibatide and r-tPA could increase recanalization [121]. Ethics permission for the trial was obtained from institutional review boards at each study site and written informed consent was obtained from study participants. Patients were included if they had a diagnosis of acute ischemic stroke; National Institutes of Health Stroke Scale (NIHSS) >5; age between 18-80 years; time from symptom onset to treatment less than 3 hours; Glucose > 50 and < 400 mg/dL; INR <1.4; and platelet count > 100,000/mm^3 [121]. In addition to other factors, patients were excluded if they had a history of intracerebral hemorrhage; evidence of hemorrhage on imaging; and blood pressure at the time of treatment above 185/110 mm Hg,or requiring aggressive treatment to lower blood pressure below this cut-off [121].

For genomic analyses, blood was collected from patients at admission, 5-hour and 24-hour time points after symptom onset. For the admission analysis, 67 CLEAR trial participants for whom admission blood samples prior to treatment with thrombolytic were available were selected. These patients were further divided into two groups based on admission blood pressure taken before treatment with r-tPA. There were 48 patients in the group with admission BP below 185/110 mm Hg (termed lower BP group) and 19 patients in the group with admission BP above 185/110 mm Hg (termed higher BP group). During microarray analysis, significant variation due to possible technical artifacts was found in 3 samples, which were excluded from further analysis. Therefore, the final number of patients analyzed in the lower BP group was 45. As not

all patients had genomic data available for all three time points, the number of patients whose genomic data were available for the 5-hour time points and 24-hour time points were 66 each. Of the 66 patients for whom 5-hour genomic data were available, two were excluded due to possible technical artifacts, bringing the total number of patients whose data was analyzed to 64. Patients in the 5-hours sample and the 24-hour sample were similarly divided into two groups by admission BP below 185/110 mm Hg (termed lower BP group) and admission BP above 185/110 mm Hg (termed higher BP group).

Patients with leukemia or lymphoma, blood dyscrasia, HIV, Hep C, active infection or on immunosuppressive therapy were excluded because of impact on leukocyte RNA. Hemorrhagic transformation was classified using the ECASS criteria as HI1, HI2, PH-1 and PH-2 [32]. In this study we reported on rates of HI-2, PH-1 and PH-2 because they are associated with worse outcomes [4]. Symptomatic HT was classified as an increase in NIHSS of ≥ 4 points within 36 hours of stroke onset.

Blood pressure measurements

In the CLEAR trial, blood pressures were measured at admission, 3 hours (pre-treatment), 5 hours (post-treatment), and 24 hours post-stroke. Most important for genomic analysis is that blood was drawn at admission (between 2-3 hrs of stroke onset) and before treatment with thrombolytic to account for effects of medication [18]. In this study we analyzed admission, 5-hour and 24-hour blood pressures to correspond with the timing of blood draw. The 3-hour blood pressure was lower in the higher BP group to comply with guidelines before r-tPA treatment (data not shown).

Sample processing and microarray

Methods for processing of whole blood, RNA isolation and microarray for these samples have been described previously [18, 118, 123]. Briefly, blood samples were collected into PAXgene tubes (PreAnalytiX, Hilden, Germany) and stored at -80°C. PAXgene tubes protect RNA from degradation and reduce post-collection gene induction. The majority of RNA in a PAXgene tube is from circulating leukocytes including neutrophils, monocytes, B-cells, T-cells and immature platelets. Technical variation was controlled for in the experiment by processing all samples in

the same laboratory by one individual. Total RNA was isolated according to manufacturer's protocols (PAXgene blood RNA kit; PreAnalytiX, Hilden, Germany). RNA concentration was measured using Nano-Drop (Thermo Fisher Scientific, Waltham, MA) and quality analyzed by Agilent 2100 Bioanalyzer (Agilent, Santa Clara, CA). All samples had an A_{260}/A_{280} ratio ≥ 2.0 and 28S/18S RNA ratio ≥ 1.8. cDNA transcription, amplification and labelling were done using NuGEN's Ovation Whole Blood Solution (NuGEN Technologies, San Carlos, CA). Labelled cDNA from each sample was hybridized to the Affymetrix Human U133 Plus 2.0 GeneChips (Affymetrix, Santa Clara, CA). A Fluidics Station 450 was used to wash and process arrays, which were then scanned on a GeneChip Scanner 3000.

Analysis of microarray data

Microarray probe intensity values (CEL files) were preprocessed using Robust Multi-Chip Average (RMA) and $\log_2$ transformation [124]. Quality assessment of microarray data included: assessment of poly-A controls to monitor target labelling; assessment of hybridization controls to monitor sample hybridization efficiency; assessment of 3'/5' ratios of internal control genes (β-actin and GAPDH) to check for RNA quality and double stranded cDNA synthesis; and visualization of normalized probe intensities using histograms and box and whiskers plots. Principal component analysis (PCA) was performed to visualize the data and assess for presence of batch effects. Analysis of microarray data was done using Partek Genomics Suite 6.4 (Partek Inc., St. Louis, MO).

Statistical Analysis

Differences in patient characteristics between the high and low BP groups were assessed by t-test, Chi-square, Wilcoxon's rank-sum or Fisher's exact tests as appropriate (R version 3.2.4, Vienna, Austria). A P value < 0.05 was considered statistically significant. Univariate analysis and a review of previous literature were used to identify possible confounding variables and factors that were different between strokes with an admission BP >185/110 mm Hg and strokes with an admission BP <185/110 mm Hg. Differential gene expression between the lower and higher blood pressure groups was assessed using Analysis of Covariance (ANCOVA). Blood pressure groups, age, sex and batch were included in the ANCOVA model. Benjamini-Hochberg false discovery rate (FDR) correction for multiple comparisons was performed to identify genes

that were significantly differentially expressed. However, the statistical criteria may have been too stringent for our dataset when comparing patients with high blood pressure and strokes to patients with higher blood pressure and strokes. Therefore, to capture biologically relevant information, probe-sets with a P value <0.05 and fold-change ≥ |1.2| were considered significantly differentially expressed. Three separate ANCOVAs were done for the admission, 5-hours and 24-hours samples to compare changes at each stage between the higher and lower BP groups. This does not provide information on genes that are significantly regulated between higher and lower BP groups over time but allows for a preliminary comparison between higher and lower BP groups at different time points.

PCA was performed using the probe sets that were found to be differentially expressed between the two groups to summarize and visualize expression patterns. Pathway analysis was performed using Ingenuity Pathway Analysis software with over-representation assessed by Fisher's exact test (IPA, Ingenuity Systems®, www.ingenuity.com). Pearson's correlation was performed to identify probe sets that correlated with systolic blood pressure (SBP). A P value < 0.05 and r > |0.2| were considered statistically significant after FDR correction did not show significantly correlated genes. Continuous variables are presented as mean ± standard deviation (SD) and ordinal variables as median ± interquartile range (IQR).

Results

Patient characteristics

A total of 66 r-tPA eligible patients with acute ischemic stroke were studied. The mean age was 67 ± 13 years and 29 (44%) were female. The mean admission SBP was 158.42 ± 29.7 mm Hg. The mean DBP on admission was 84 ± 13 mm Hg. 45 (68%) of patients had a history of hypertension. All samples were collected within 3 hours of stroke onset. Blood pressure and genomic data was analyzed for patients at admission, 5-hours and 24-hours post stroke. Data was analyzed for 64 patients at admission and 5-hours, and for 66 patients at 24-hours. The same 19 patients were included in the higher SBP group at all time points.

At the admission timepoint, genomic analysis was performed for 64 patients. There were 19 patients with admission BP above 185/110 mm Hg (higher BP group) and 45 with BP below

185/110 mm Hg (lower BP group) (Table 1). The mean SBP in the higher group was 192.3 ± 27.7 mm Hg. The mean DBP was 96.1 ± 15.4 mm Hg. In the lower group, mean SBP was 143.4 ± 17.9 mm Hg and mean DBP was 80.5 ± 14.8 mm Hg. History of hypertension in the higher SBP group was higher (78.9%) as compared to the lower SBP group (62.2%), but this trend was not statistically significant ($p > 0.05$). No significant differences were present between groups for age, sex, NIHSS, etiology of stroke, randomization to r-tPA or tPA plus eptifibatide, baseline white blood cell and red blood cell count, or in history of hypertension, diabetes, and hyperlipidemia.

At the 5-hours timepoint, analysis was performed for 64 patients with 19 patients in the higher BP group and 45 patients in the lower BP group (table 2). The 5-hour SBP for patients in the higher group dropped to 161 ± 37.4 mm Hg but was still significantly higher than SBP for patients in the lower group (139.7 ± 23.5 mm Hg) ($p < 0.05$). The DBP for patients in the higher group also dropped to 76 ± 17.1 mm Hg but was not significantly different from DBP in the lower BP group (74.3 ± 16.6 mm Hg) ($p > 0.05$). No other significant differences were present between the higher and lower BP group.

At the 24-hour timepoint, genomic data was analyzed for 47 patients with 19 patients in the higher SBP group (table 3). At this time point, the mean SBP in the higher group dropped further to 150.93 ± 20.2 mm Hg. While still elevated, this was not significantly different from the SBP in the lower BP group (138.43 ± 23.9 mm Hg). The DBP for the higher group at this time point was 70.7 ± 18.5 mm Hg and was also not significantly different from the DBP in the lower BP group (71.87 ± 15.3 mm Hg) ($p > 0.05$).

Out of the 47 patients studied, 11 developed HT. Using the ECASS-II definition, 3 patients had PH-1, 3 patients had PH-2 and 5 patients had HI-2. Of these patients, 3 developed sICH. 9 out of the 11 patients had a history of HTN. The mean age was 78.7 ± 10.7 years. 4 were female (36%). The median NIHSS score at baseline was 13 (8.5, 15). 4 patients with HT were in the higher BP group (Mean SBP: 184 ± 5.6, Mean DBP 103.3 ± 13.5), whereas 7 were in the lower BP group (Mean SBP: 146.5 ± 24.2, Mean DBP: 73 ± 15.5). All patients who developed sICH were in the higher admission BP group and had histories of HTN.

Differential gene expression at admission

There were 226 differentially expressed genes between the higher and lower blood pressure groups ($p < 0.05$, fold change $\geq |1.2|$) (Gene list shown in supplementary table 1). A principal components analysis plot displaying the separation of the 226 genes between strokes with higher and lower BP is shown in figure 1. Of the 226 genes, 116 genes (51.3%) were increased in the higher blood pressure group including *EDN3* (Endothelin-3), *CYTL1* (Cytokine-like 1) and *MMP21* (Matrix metallopeptidase 21). 110 genes were decreased in the higher blood pressure group including *CAV-1* (caveolin 1) and *CCR2* (Chemokine receptor 2).

Pathway analysis of the 226 genes revealed over-representation of canonical pathways associated with adaptive immunity (B cell development, T helper cell differentiation, T_H1 pathways, T_H1 and T_H2 activation pathways, T_H2 pathway, CD28 signalling in T helper cells), dendritic cell maturation, neuroinflammation signalling pathway, caveolar mediated endocytosis signalling, IL-17 signalling, IL-22 signalling, NO signalling, sirtuin signalling and leukocyte extravasation signalling (pathway list shown in supplementary table 2).

To evaluate the relationship between lower systolic blood pressure and the 226 genes that were found to be different between higher and lower groups, a correlation analysis was performed (Supplementary Table 3). A significant relationship between SBP and 75 genes was found including *CCR2*, *CYTL1*, *HRH1* (Histamine Receptor H1), *KLKB1* (kallikrein B1) and *CLDN10 (*claudin 10) ($r>|0.2|$, $p<0.05$). *CCR2* was negatively correlated with SBP whereas *CYTL1*, *HRH1*, *KLKB1* and *CLDN10* were positively associated with SBP.

Differential gene expression at 5 hours

At 5 hours, 923 genes were differentially expressed between the higher and lower blood pressure groups ($p < 0.05$, fold change $\geq |1.2|$) (Gene list shown in supplementary table 4). The PCA plot of these 923 genes is shown in figure 2. As compared to the PCA plot of differential expression at admission (figure 1), this plot showed greater overlap between gene expression in the higher and lower BP groups. Based on expression of these 923 genes, patients in the higher group were clustered together while patients in the lower BP group showed greater spread.

635 (68.8%) genes were increased in strokes with higher blood pressure including: *IL1A* (interleukin 1 alpha), *MMP25* (matrix metallopeptidase 25), *MMP28* (matrix metallopeptidase 28), *TLR4* (toll-like receptor 4), *TLR8* (toll-like receptor 8), *CYTL1* (cytokine like 1), *CLDN10* (claudin 10) and *CD46* (CD46 molecule, complement regulatory protein). 288 genes were decreased including: *IL27RA* (interleukin 27 receptor, alpha), *TLR7* (toll-like receptor 7), and *CCR3* chemokine (C-C motif) receptor 3.

Pathway analysis of these differentially expressed genes showed the following canonical pathways were over-represented: iNOS signalling, leucocyte extravasation, IL-1 signalling, IL-22 signalling, NFkB, TLR signalling, B cell receptor signalling, HMGB1 signalling, IL-6 signalling, TGF-B signalling, T_H17 activation and dendritic cell maturation. Pathway list is shown in supplementary table S5.

Out of the 923 genes that were differentially expressed, 20 were correlated with SBP ($r > |0.2|$, $p < 0.05$) (supplementary table S6). *CCR3* (Chemokine C-C motif receptor 3) ($P = 0.0024$, r -0.438) and *P2RY2* (purinergic receptor P2Y, G-protein coupled, 2) ($p = 0.011$, r – 0.32) were negatively associated with increasing SBP. *AREG* (amphiregulin) was positively associated with increasing SBP ($p = 0.024$, r 0.286). ($r > |0.2|$, $p<0.05$).

Differential gene expression at 24 hours

422 genes were differentially expressed between the higher and lower blood pressure groups at 24 hours ($p < 0.05$, fold change $\geq |1.2|$) (Gene list shown in supplementary table 7). A PCA plot of these differentially expressed genes showed no apparent difference between strokes with higher admission BP as compared to strokes with lower admission BP (figure 3). Of the 422 genes, 175 genes (41.5%) were increased in the higher blood pressure group including *TLR5* (toll-like receptor 5) and *IL1R1* (interleukin 1 receptor, type I). 247 genes were decreased in the higher blood pressure group including: *ANGPT1* (angiopoietin 1), *TNFSF11* (tumor necrosis factor (ligand) superfamily, member 11) and *CXCL6* (chemokine (C-X-C motif) ligand 6). Pathway analysis of the 422 genes revealed over-representation of the following canonical pathways: T_H1 Pathway, IL-23 Signaling Pathway, HMGB1 Signaling, Dendritic Cell

Maturation, Neuroinflammation Signaling Pathway, TLR signalling, T_H17 signalling and angiopoietin signalling (selected pathway list shown in supplementary table 8). At the 24-hour time point, correlation of differentially expressed genes with SBP showed only 4 genes associated with SBP ($r > |0.2|$, $p < 0.05$). 2 genes were uncharacterized. The other two were *ANGPT1* (angiopoietin 1) ($p = 0.013$, r 0.33) and *GP5* (glycoprotein V (platelet)) ($p = 0.0079$, r -0.35).

Discussion

General discussion of findings

Ischemic stroke remains a leading cause of adult disability and mortality. Increasing access to reperfusion therapy by reducing the risk of r-tPA related HT could improve stroke outcomes. An admission blood pressure >185/110 mm Hg is associated with increased risk of HT. In the present study we found acute stroke patients with a BP >185/110 mm Hg at admission have 226 genes expressed differentially in circulating blood cells compared to patients with BP <185/110 mm Hg. These genes are differentially expressed very early on in stroke as blood was drawn at admission, within 3 hours of stroke onset. We also found that at 5 hours, 932 genes were differentially expressed and at 24 hours, 422 genes were differentially expressed when comparing groups by admission BP. Our statistical methods do not allow us to identify differentially expressed genes and pathways that change over time. However, they do suggest changes in immune response by admission blood pressure at 5 hour and 24 hours respectively.

At 5 and 24 hours, differences in gene expression were found between the higher and lower BP groups despite blood pressure control to comply with guidelines. The exact mechanisms for why genes are differentially expressed by admission BP at 5 hours and 24 hours and their contribution to BBB disruption are unclear and need further study. Some possible reasons are discussed below.

First, we found that in the higher admission BP group, SBP remained significantly elevated at 5-hours so some of this increase in differentially expressed genes may be explained by elevated blood pressure in the higher SBP group at 5 hours. However, only 20 differentially expressed genes at this time point significantly correlated with SBP so it is possible that there may be other

underlying factors impacting differential immune response by admission BP. It is also possible that less differentially expressed genes correlated with BP at this time because BP had been lowered.

Secondly, we did not specifically study the influence of blood pressure variability or elevations above 180/105 mm Hg after treatment with r-tPA on immune response. BP variability, especially within the first 6 hours of ischemia is also linked to increased rates of HT [105]. We did notice that at 5-hours, BP increased above 180/105 mm Hg in 2 patients, and both had sICH. However, in our study, it was not possible to study immune activation between patients with BP > 180/105 mm Hg and under 180/105 mm Hg after r-tPA treatment because we only had two patients in that group at 5-hours. Blood pressure elevations above 185/105 mm Hg within the first 24 hours after r-tPA treatment have not been found to be significantly related to risk of sICH [125]. When blood pressure elevations do occur, they are more likely to be in patients with higher mean admission blood pressures (Mean admission SBP = 160 mm Hg) [125]. It is possible that after treatment with r-tPA, these factors might influence immune response by blood pressure in addition to the effects of raised SBP.

It also takes time for genes to be regulated in acute stroke and for changes to become apparent [18]. It is possible that the higher numbers of differentially expressed genes at 5-hours present some aspect of the earlier immune response to BP at admission. By studying gene expression at this later time point, we may be able to get more information about immune response at admission that may be pre-disposing to HT. On the PCA plot of differentially expressed genes at 5-hours, we did see clustering together of patients in the higher admission BP group, even though there was no apparent separation of these patients from the lower BP group. These data seem to suggest that differences in the immune systems of patients with admission BP >185/110 mm Hg and BP < 185/110 mm Hg may become apparent in the later stages even after blood pressure has been lowered. Indeed, Angiotensin-II induced damage to the BBB and activation of microglia in hypertension is not always coupled with elevated blood pressure [61, 126]. An animal study using hydralazine (vasodilator) vs. losartan (AT_1 receptor antagonist) to lower blood pressure showed that hydralazine, while lowering blood pressure did not result in less damage to the BBB, whereas losartan did [61]. Angiotensin-II also has direct proinflammatory

effects on leukocytes including monocytes, dendritic cells and T-cells by binding to the AT_1 receptor [127]. Ang-II is involved in TLR4 signalling and the secretion of IL-17 by T cells [127]. Interestingly, IL-17 and T_H17 pathways were found in our gene lists at each of the three time points studied and *TLR4* expression was increased in the higher BP group at 5-hours. It is also possible that inflammation can occur before a rise in blood pressure is seen, so an inflammatory response might precede an acute hypertensive response to stroke [86]. The relationship between Ang-II induced inflammation in acute stroke regardless of blood pressure needs further study.

Genes and pathways identified

Some selected genes identified in our study included *EDN3* (Endothelin-3), *MMP21* (Matrix metallopeptidase 21), *MMP*-25 (matrix metallopeptidase 25), *MMP*-28 (matrix metallopeptidase 28), *TLR4* (toll-like receptor 4), *AREG (*amphiregulin), CAV-*1* (caveolin 1) and *CCR2* (Chemokine receptor 2). *EDN3, MMP21, MMP-25, MMP-28, TLR4,* and *AREG* were increased in the very high blood pressure group. *CCR2* and *CAV-1* were decreased in the higher BP group. We also found regulation of pathways associated with adaptive immunity, IL-17, T_H17, dendritic cells, TLR signalling and NO oxide signalling. These genes and their associated pathways provide preliminary insight into potential immune mechanisms that may contribute to increased risk of blood brain barrier disruption and HT in patients with very high admission blood pressure. The biological roles of selected genes and possible relationship to BBB disruption is discussed below.

Endothelin-3 (ET-3) was increased in the higher BP group. Endothelins are vasoconstrictors produced by endothelial cells and can also act on vascular endothelin receptors to increase cyclo-oxygenase, cytochrome p-450 and nitric oxide synthase [128]. Most of the research on endothelins has been conducted on endothelin-1 (ET-1) and little is known about the role of endothelin-3 in stroke or hemorrhagic transformation. However, endothelin-3 binds to one of the receptors for endothelin-1, the ET_B receptor [128]. Endothelin-1 binding to ET_B receptor has vasodilatory effects. Endothelin-1 secreted by endothelial cells is thought to induce autocrine signalling in endothelial cells, resulting in production of vasoactive substances like NO [128]. During inflammation, immune cells can also secrete vasoactive substances like histamine and bradykinin that increase blood flow to the site of damage [129]. It is possible that endothelin-3

upregulation by immune cells may be involved in a similar response and may modulate endothelial dependent vasoconstriction and relaxation. T cells, B cells, monocytes and neutrophils also express both ET_A and ET_B receptors and treatment with ET-1 results in production of inflammatory cytokines by CD+ T cells- an effect that is blocked by ET receptor antagonists of for both ET_A and ET_B receptors [130]. After ischemia, the endothelin system (involving ET-1, ET-2, ET-3 and receptors ET_A and ET_B) is involved in proinflammatory signalling and increased BBB permeability [131]. While details on the role of ET-3 in acute ischemic stroke remain unclear, an increase may contribute to cerebral endothelial dysfunction and permeability in the higher blood pressure group.

Matrix metallopeptidase 21 (*MMP-21)* is a member of the MMP family that is expressed in human leukocytes including monocytes, B cells and T cells [132, 133]. MMPs have catalytic function such as gelatinase (MMP-2, MMP-9), collagenase, matrilysin, or stromelysin activity [132, 134]. For MMP-21 the catalytic activity appears to be novel, with yet to be identified substrate [132, 134]. *MMP-25* mRNA is increased in monocytes treated with IFNγ, IL-1 and TNFα and MMP-25 may be involved in the innate immune response [135, 136] Little is known about the exact roles of MMP-21, MMP-25 and MMP-28 in stroke; however, they could be markers of increased immune activation and could play a role in leukocyte extravasation into brain parenchyma.

Toll-like receptor 4 (*TLR4)* was increased in patients with high blood pressure. TLR4 signalling is involved in chronic inflammation in hypertension [137]. TLR4 can be activated in hypertension by DAMPs like angiotensin, CRP, uric acid and heat shock proteins and results in activation of the inflammasome, IL-1β and IL-18 signalling [8]. In our study, IL-1 signalling pathways were also over-represented at 5-hours when *TLR4* was upregulated. Blockage or knock out of TLR4 in some animal models results in lowered blood pressure and resistance to developing Ang-II infused hypertension [48]. The role of TLR4 has also been well characterized in stroke and HT. After stroke, mice lacking functional TLR4 signalling have smaller infarct sizes, better outcomes, and lower production of proinflammatory INFβ and MMP-9 [138]. *In vitro* cell cultures have shown that DAMP (HMGB1) binding to TLR4 on astrocytes and neurons is involved in production of MMP-9 by these cells [139]. It is possible that DAMPs have a

similar effect on peripheral leukocytes after stroke. Interestingly, we also observed pathways associated with HMGB1 signalling in our study. When considering HT, mice with functional TLR4 showed an increase in HT rates and severity after later reperfusion as compared to mice without TLR4 [140]. This showed that TLR4 is involved in injury to brain that results in HT [140].

We also found increased expression of *amphiregulin (AREG)* in our gene list. Amphiregulin belongs to the family of epidermal growth factor (EGF)-like molecules and is produced by a variety of innate and adaptive immune cells in humans including basophils, eosinophils, mast cells, neutrophils, group 2 innate lymphoid cells (ILC2s), dendritic cells and CD4 + T cells [141]. Amphiregulin interacts with the epidermal growth factor receptor (EFGR) and is involved in several immune functions including type 2 inflammation, tissue repair, fibrosis, and suppression of inflammation by T_{regs} [141]. In animal models, amphiregulin is also produced by classically activated M1 macrophages after challenge with LPS and TLR4 blockage prevents production of amphiregulin, IL-1ß, TNFα and IL-6 [142]. In a previous study of genes associated with HT in acute stroke, *AREG* was differentially expressed between patients with HT and without HT with expression of amphiregulin being higher in strokes with HT [118]. *AREG* was also one of the genes that could predict patients at increased risk of HT [118]. In cancer cells, amphiregulin increases MMP-9 expression and a similar mechanism may be involved in increased risk of HT [118, 143]. Amphiregulin is also shown to increase production of VEGF which is involved in increased angiogenesis [144]. While angiogenesis is thought to be an important part of tissue repair after injury, angiogenesis and vessel remodelling very early after stroke may increase risk of HT by increasing BBB permeability [4]. Increased production of VEGF early after stroke is involved in increasing risk of HT and inhibition of VEGF-signalling using anti-VEGF antibodies reduced MMP-9 activity and HT in animal models [145]. Amphiregulin is also produced by T_{reg} cells after tissue injury where it activates local TGF-ß, suppresses inflammation and increases differentiation of pericytes into myofibroblasts resulting in secretion of extra cellular matrix proteins to restore barrier function [146]. In hypertension, binding of IgG antibodies to Fcγ receptors on macrophages in blood vessel walls results in production of TGF-ß which increases vascular remodelling and fibrosis [36]. TGF-ß secretion by monocyte derived macrophages in animal models after stroke is thought to helpful in post-stroke

repair and decreases risk of HT after stroke related injury to the brain [23, 147]. T_{regs} have also been shown to accumulate in brains of mice after ischemic stroke where they produce amphiregulin [148]. Amphiregulin production by T_{regs} downregulates the IL-6-STAT3 signalling pathway in astrocytes which suppresses neuroinflammation [148]. These changes are mainly seen in the chronic stage of inflammation after stroke, however considering hypertension results in chronic neuroinflammation and disruption of the BBB in stroke, it may be possible that immune response to stroke in a hypertensive brain may involve an early upregulation of T_{reg} cells and amphiregulin production [64]. T_{reg} cells are also important in hypertension where T_{reg} cell numbers are decreased in the spontaneously hypertensive rat and modulation of T_{reg} numbers by IL-10 lowers blood pressure [36]. T_{reg} cells are thought to modulate blood pressure through anti-inflammatory effects, but whether production of amphiregulin is also involved in T_{reg} modulation of blood pressure would be an interesting area of further research [36]. These studies point towards harmful as well as protective roles of amphiregulin secretion. Therefore, the secretion of amphiregulin by different immune cell subtypes, timing of secretion, and the exact mechanisms of how increased amphiregulin is related to increased risk of HT and hypertension need to be elucidated.

We found that *CCR2* expression as decreased in the higher BP group. In monocytes, *CCR2* mRNA expression can decrease because of activation by LPS, IL1 and TNFα which might explain the possible decrease in the higher BP group [149]. A study of monocytes and T cells in MS showed that cells uptake CCL2 (possibly via receptor mediated endocytosis) and decrease expression of CCR2 as they migrate across the BBB [150]. It is possible that a similar response was seen in our study. However further comparison with controls and validation is needed to understand how levels of CCR2 may be changing.

Cav-1 was decreased in the higher blood pressure group. Caveolin-1 (Cav-1) is a component of caveolae, which are invaginations in the plasma membrane of cells and organelles [151]. Caveolae have functions involved in endocytosis, transcytosis, calcium and eNOS signalling, mechanosensation and invasion of pathogens into cells [152, 153].Most studies of caveolin-1 have focussed on its role in endothelial cells because mice lacking Cav-1 show endothelial defects [154]. In endothelial cells, a decrease in Cav-1 results in impaired nitric oxide production

through its direct effects on endothelial nitric oxide synthase (eNOS) [155]. Mice with disrupted caveolin-1 show increased MMP activity and blood brain barrier permeability after ischemia-reperfusion [156]. A study of serum caveolin-1 levels in acute ischemic stroke patients showed that Cav-1 levels were significantly decreased in patients with HI-2 and sHT as compared to other acute stroke patients [157]. However, there was no significant difference in serum Cav-1 levels between HI-2 and sHT levels when compared with non-stroke controls [157]. In immune cells, the exact functions of caveolin-1 may depend on the type of immune cell, activation state of the cell and possibly the species being studied [158].The role of caveolin-1 in peripheral leukocytes in stroke is not known and because caveolin-1 is involved in many signalling pathways, the exact role is difficult to predict. A decrease of Cav-1 in acute ischemic stroke may influence several of these functions and requires further study in specific immune cell subtypes.

Significance and Limitations

Guidelines recommend that blood pressure be maintained below 180/105 mm Hg during the first 24 hours after stroke to reduce risk of HT [6]. However, the target blood pressure threshold to reduce risk of HT is unknown [6]. The ENCHANTED trial evaluated blood pressure lowering after thrombolysis to either SBP < 180 mm Hg over 72 hours (guideline recommended) or intensive BP lowering of SBP <130-140 mm Hg over 1 hour [159]. The results indicated that intensive blood pressure lowering decreases risk of HT, but there was no difference in outcomes between both groups to change guidelines [159]. The investigators suggested that underlying mechanisms related to blood pressure reduction and outcomes in ischemic stroke be investigated [159]. In our study several genes correlated with systolic pressure. These genes may identify potential targets that BP reduction benefits. Furthermore, we found that there were still differences in immune system activation between patients with admission BP > 185/110 mm Hg and below when guideline recommended BP management was used after thrombolysis. It is possible that that this difference in immune response that persisted between patients with guideline recommended BP lowering is reduced when BP is lowered to 130-140 mm Hg. As such, some of the differentially expressed genes and pathways identified in our study may help to explain the immune mechanisms behind why blood pressure lowering to 130-140 mm Hg reduces risk of HT. With further analysis, differences in genetics and immune response by BP in these genes and pathways may be used to select patients who may benefit most from BP

lowering. This would help move the modulation of BP in acute stroke towards a personalized medicine approach in patients whereby BP is only reduced in patients who benefit most from BP reduction as shown by their individualized risk of HT. In any case, our study provides preliminary evidence that differences in blood pressure response to acute stroke are linked to underlying biology which can be further studied to increase understanding of the acute hypertensive response to stroke. Greater knowledge of the acute hypertensive response to stroke may help in achieving better understanding of how blood pressure should be managed. Further studies are needed to assess the relationship of blood pressure reduction to immune activation in acute ischemic stroke.

Recently, Kim et al., also reported that patients can be divided into 5 BP groups based on the trajectory of SBP within the first 24 hours of stroke [108]. Patients in the persistently high SBP trajectory had the highest blood pressures on admission (mean SBP 192.4±1.9 mm Hg) which remained elevated during the first 24-hours after stroke (mean SBP 177.7±1.1 at 6 hrs, 173±1.4 at 24 hrs) [108]. Patients in the "rapidly stabilized" BP trajectory had lower mean admission blood pressures (mean SBP 182.1±1.9) which settled at 140 mm Hg at 24 hours [108].While they did not look at HT as an outcome specifically, the highest BP trajectory was associated with the worst outcomes [108]. In our study, we found that blood pressure was still significantly elevated at 5 hours in the higher BP group and at 24 hours the blood pressure was elevated but not significantly. In this study, we did not evaluate whether differences in gene expression are significant over time so we cannot draw conclusions about how expression of particular genes is changing over time. Plus, we did not have measurements of blood pressure in patients in the higher and lower group beyond admission, 3 hour, 5 hours, and 24 hours so it is difficult to determine trajectory over time. We also had very small sample sizes to be able to evaluate trajectory differences. However, there may be a possibility that many patients with admission BP > 185/110 mm Hg fall within the BP trajectory of patients whose blood pressure remains elevated. It may be possible that these patients may have higher immune activation within the first 24 hours of acute ischemic stroke, predisposing to HT. Further studies of differences in immune response between patients with distinct BP trajectories after stroke may help to understand the underlying mechanisms behind why some patients fall into distinct trajectory groups. Whether genomics at admission can be used to predict which patients fall in the higher

blood pressure trajectories and how that is related to risk of HT is another interesting area for further study.

Patients with acute ischemic stroke with admission BP>185/110 mm Hg were found to have an activation of the immune system that may predispose to r-tPA related HT. In addition, we showed that differences in immune response by admission BP > 185/110 mm Hg may be seen for hours afterwards, even when admission blood pressure has been lowered, though the underlying mechanisms need further study. Strengths are early acquisition of blood sample (mean 1.5 hours of stroke onset) prior to r-tPA administration and whole genome evaluation of immune system. However, this is a preliminary study providing initial insight to peripheral immune activation in patients with very high blood pressure in stroke. When adjusting for multiple corrections using the Benjamini-Hochberg false discovery rate (FDR), we did not find any genes significantly differentially expressed between the higher BP group and the lower BP group. Similarly, we did not find any genes significantly correlated with SBP after FDR correction. Therefore, there is high chance of type I error in our results. A reason for these findings may be that our study is comparing gene expression between patients with stroke and prior histories of hypertension in both groups. Genetically, these groups are very similar. While many of the genes identified are biologically plausible, further study in larger cohorts is required.

A blood pressure cut-off of 185/110 mm Hg was used because of its importance in clinical practice and stroke guidelines. There were patients in both groups that had admission SBPs very close to the cut-off threshold of 185/110 mm Hg. While clinically important, the underlying biology may not be precisely related to this pressure threshold, thus further study in a range of blood pressures ranges in acute stroke are needed. We also had high numbers of patients with hypertension in both groups, so as compared to controls, it is hard to draw conclusions about regulation of pathways. It is possible that our data might show a gene downregulated between our BP groups, but as compared to a stroke patient without hypertension, or a patient with hypertension but without acute stroke, that gene might be highly upregulated. The patients in our study were also candidates for r-tPA and patients whose blood pressure could not be lowered below 185/110 mm Hg were not included. We therefore might miss meaningful information

about the complete picture of immune system activation in relation to very high post-stroke blood pressures.

Gene expression data for patients at 5-hours and 24-hours likely reflects the impact of anti-hypertensive medications, thrombolytic, and eptifibatide. Some commonly used anti-hypertensive medications in the management of blood pressure in acute stroke are labetalol and propranolol, both of which are ß-receptor antagonists [89]. Mononuclear leukocytes have receptors for catecholamines which are blocked by propranolol, so beta blockers affect immune response [160, 161]. How beta blocker use affects immune response in acute stroke in humans needs further study. Use of anti-hypertensive and r-tPA is nonetheless representative of treatment in the clinical setting. Patients were also treated with eptifibatide, which is not routinely used in practice. Two main ways in which treatment with eptifibatide might impact our results is by anti-platelet effects on the immune system and by increasing risk of bleeding. Platelets secrete cytokines and growth factors that can activate other cells in the immune system and so there is a possibility that using an anti-platelet drug might have anti-inflammatory effects by inhibiting interactions between platelets and leukocytes [162]. In patients with unstable angina undergoing treatment with coronary angioplasty, treatment with eptifibatide did not significantly decrease the numbers of CD45+/HLA-DR+ cells as compared to controls without eptifibatide treatment [162]. CD4/CD8 ratios were also not different between these groups (changes in CD4/CD8 ratios are markers of immune function and immune senescence) [162, 163]. Finally, levels of CRP were also similar between the two groups [162]. This study did not assess for differences in other immune cells so an interaction between eptifibatide use and effects on other immune cells may still be possible. A common side-effect of treatment with eptifibatide is immune thrombocytopenia (reduced numbers of platelets) and hypotension is one of the symptoms of thrombocytopenia [164]. The incidence of thrombocytopenia in patients treated with eptifibatide may be lower than 0.6% [164]. One of the mechanisms suggested for thrombocytopenia is immune-related damage to platelets as the immune system recognizes eptifibatide bound to the GP IIb/IIIa receptor as an antigen and mounts an immune response [164]. Healthy subjects may have such antibodies to eptifibatide but there are also conflicting reports that suggest patients do not show an immune response to eptifibatide as a drug, as shown by a lack of anti-eptifibatide antibodies in sera of treated patients [164, 165]. The low percentage of people who show this

response may be the reason for discrepancy between studies. In our cohort, there was no significant difference in the numbers of patients treated with r-tPA or combination therapy between the higher and lower BP groups. More importantly, subjects in our study showed differences in immune response between the three timepoints despite any immune-suppressive effects of eptifibatide. Eptifibatide use may also increase rates of ICH [121]. However, in the CLEAR trial the dose of eptifibatide used was less than half that used in standard practice and patients with combination treatment had one sICH whereas those treated with r-tPA alone had two sICH (P = 0.17) [121]. Asymptomatic HT showed similarly lower rates in the combination group as compared to treatment group. Regardless, further study in only r-tPA-treated cohorts is needed.

In conclusion, a high admission BP above 185/110 mm Hg is associated with differential immune activation which persists for at least the first 24 hours after stroke. These differences may contribute to blood brain barrier disruption and risk of HT in acute stroke patients with very high admission BP. Whether immune-related genes could be used to select patients at greater risk of HT for BP lowering and whether modulating immune activation could reduce blood brain barrier disruption and risk of HT requires further study.

Figures and tables

Table 1. Characteristics of acute ischemic stroke patients with admission blood pressure below 185/110 mm Hg and above 185/110 mm Hg

Variables	**Admission BP < 185/110 mm Hg**	**Admission BP > 185/110 mm Hg**	**P value**
Number of patients, n	45	19	N/A
Age, years (SD)	65.2 (13.8)	70.2 (10.2)	0.11
Male, n (%)	26 (57.7%)	14 (73.6%)	0.27
History of hypertension, n (%)	28 (62.2%)	15 (78.9%)	0.25
Systolic BP on admission, mm Hg (SD)	143.4 (17.9)	192.3 (27.7)	3.8×10^{-13}
Diastolic BP on admission, mm Hg (SD)	80.5 (14.8)	96.1 (15.4)	0.00033
Hemorrhagic transformation, n (%)	7 (15%)	4 (21%)	0.72
Diabetes history, n (%)	8 (17.7%)	4 (21%)	0.73
Admission glucose, mg/dL (SD)	123.5 (31.2)	122.8 (37.7)	0.94
Hyperlipidemia, n (%)	12 (26.7%)	2 (10.5%)	0.20
Atrial Fibrillation, n (%)	10 (22.3%)	2 (10.5%)	0.48
NIHSS Baseline (IQR)	13 (9, 17)	12 (6, 16.5)	0.79
Cause Large Vessel, n (%)	7 (15.6%)	3 (15.8%)	0.99
Cause Cardioembolic, n (%)	18 (40%)	8 (42%)	0.99
Cause Cryptogenic, n (%)	17 (37.8%)	7 (36.8%)	0.99
Cause Other, n (%)	3 (6.7%)	1 (5.3%)	0.99
Treatment with r-tPA only, n (%)	10 (22.2%)	6 (31.6%)	0.49
Treatment with r-tPA + eptifibatide, n (%)	33 (73.3%)	13 (68.4%)	0.49
Platelet baseline, 10^3/mcL (SD)	254.6 (79.0)	242.7 (72.7)	0.57
WBC baseline, 10^3/mcL (SD)	8.2 (2.3)	8.7 (2.7)	0.45
RBC baseline, 10^3/mcL (SD)	4.5 (0.59)	4.7 (0.62)	0.44

BP: Blood pressure; SD: Standard Deviation; IQR: Interquartile Range; NIHSS: National Institutes of Health Stroke Scale; WBC: White Blood Cell; RBC: Red Blood Cell

Table 2. Characteristics of patients included in the 5-hour genomic analysis

Variables	Admission BP < 185/110 mm Hg	Admission BP > 185/110 mm Hg	P value
Number of patients, n	45	19	N/A
Age, years (SD)	65.8 (13.4)	70.2 (10.2)	0.16
Male, n (%)	22 (48%)	14 (73%)	0.07
History of hypertension, n (%)	28 (62.2%)	15 (78.9%)	0.31
Systolic BP on admission, mm Hg (SD)	143.9 (17.4)	192.3 (27.7)	$2.60x10^{-7}$
Diastolic BP on admission, mm Hg (SD)	79 (14.6)	96.1 (15.4)	$8.5x10^{-5}$
Systolic BP at 5-hours, mm Hg (SD)	139.7 (23.5)	161 (37.4)	0.03
Diastolic BP at 5-hours, mm Hg (SD)	74.3 (16.6)	76 (17.1)	0.7
Hemorrhagic transformation, n (%)	5 (11.1%)	4 (21%)	0.30
Diabetes history, n (%)	9 (20%)	4 (21%)	0.92
Admission glucose, mg/dL (SD)	123.8 (29.9)	122.8 (37.7)	0.91
Hyperlipidemia, n (%)	11 (24.4%)	2 (10.5%)	0.21
Atrial Fibrillation, n (%)	9 (20%)	2 (10.5%)	0.36
NIHSS Baseline (IQR)	13 (10, 17)	12 (6, 16.5)	0.62
Cause Large Vessel, n (%)	7 (15.5%)	3 (15.8%)	0.99
Cause Cardioembolic, n (%)	18 (40%)	8 (42%)	0.99
Cause Cryptogenic, n (%)	18 (40%)	7 (36.8%)	0.99
Cause Other, n (%)	2 (4%)	1 (5.3%)	0.99
Treatment with r-tPA only, n (%)	10 (22.2%)	6 (31.6%)	0.43
Treatment with r-tPA + eptifibatide, n (%)	35 (77.7%)	13 (68.4%)	0.43
Platelet baseline, 10^3/mcL (SD)	262.4 (80)	242.7 (72.7)	0.36
WBC baseline, 10^3/mcL (SD)	8.2 (2.3)	8.7 (2.7)	0.46
RBC baseline, 10^3/mcL (SD)	4.6 (0.6)	4.7 (0.62)	0.38

BP: Blood pressure; SD: Standard Deviation; IQR: Interquartile Range; NIHSS: National Institutes of Health Stroke Scale; WBC: White Blood Cell; RBC: Red Blood Cell

Table 3. Characteristics of patients included in the 24-hour genomic analysis

Variables	Admission BP < 185/110 mm Hg	Admission BP > 185/110 mm Hg	P value
Number of patients, n	47	19	N/A
Age, years (SD)	65.5 (13.7)	70.2 (10.2)	0.18
Male, n (%)	23 (49%)	14 (73%)	0.07
History of hypertension, n (%)	29 (61.7%)	15 (78.9%)	0.25
Systolic BP on admission, mm Hg (SD)	144.7 (16.8)	192.3 (27.7)	$3.62x10^{-7}$
Diastolic BP on admission, mm Hg (SD)	79 (15.1)	96.1 (15.4)	0.00013
Systolic BP at 24 hours, mm Hg (SD)	138.43 (23.9)	150.93 (20.2)	0.07
Diastolic BP at 24 hours, mm Hg (SD)	71.87 (15.3)	70.7 (18.5)	0.80
Hemorrhagic transformation, n (%)	6 (12.8%)	4 (21%)	0.40
Diabetes history, n (%)	10 (21.3%)	4 (21%)	0.98
Admission glucose, mg/dL (SD)	125.5 (30.0)	122.8 (37.7)	0.76
Hyperlipidemia, n (%)	11 (23.4%)	2 (10.5%)	0.23
Atrial Fibrillation, n (%)	9 (19.1%)	2 (10.5%)	0.86
NIHSS Baseline (IQR)	7.5 (9.5, 17)	12 (6, 16.5)	0.67
Cause Large Vessel, n (%)	7 (14.8%)	3 (15.8%)	0.97
Cause Cardioembolic, n (%)	18 (38%)	8 (42%)	0.97
Cause Cryptogenic, n (%)	18 (38%)	7 (36.8%)	0.97
Cause Other, n (%)	4 (8.5%)	1 (5.3%)	0.97
Treatment with r-tPA only, n (%)	9 (19.1%)	6 (31.6%)	0.28
Treatment with r-tPA + eptifibatide, n (%)	38 (80.9%)	13 (68.4%)	0.28
Platelet baseline, 10^3/mcL (SD)	260.4 (79.6)	242.7 (72.7)	0.40
WBC baseline, 10^3/mcL (SD)	8.4 (2.8)	8.7 (2.7)	0.61
RBC baseline, 10^3/mcL (SD)	4.5 (0.6)	4.7 (0.62)	0.29

BP: Blood pressure; SD: Standard Deviation; IQR: Interquartile Range; NIHSS: National Institutes of Health Stroke Scale; WBC: White Blood Cell; RBC: Red Blood Cell

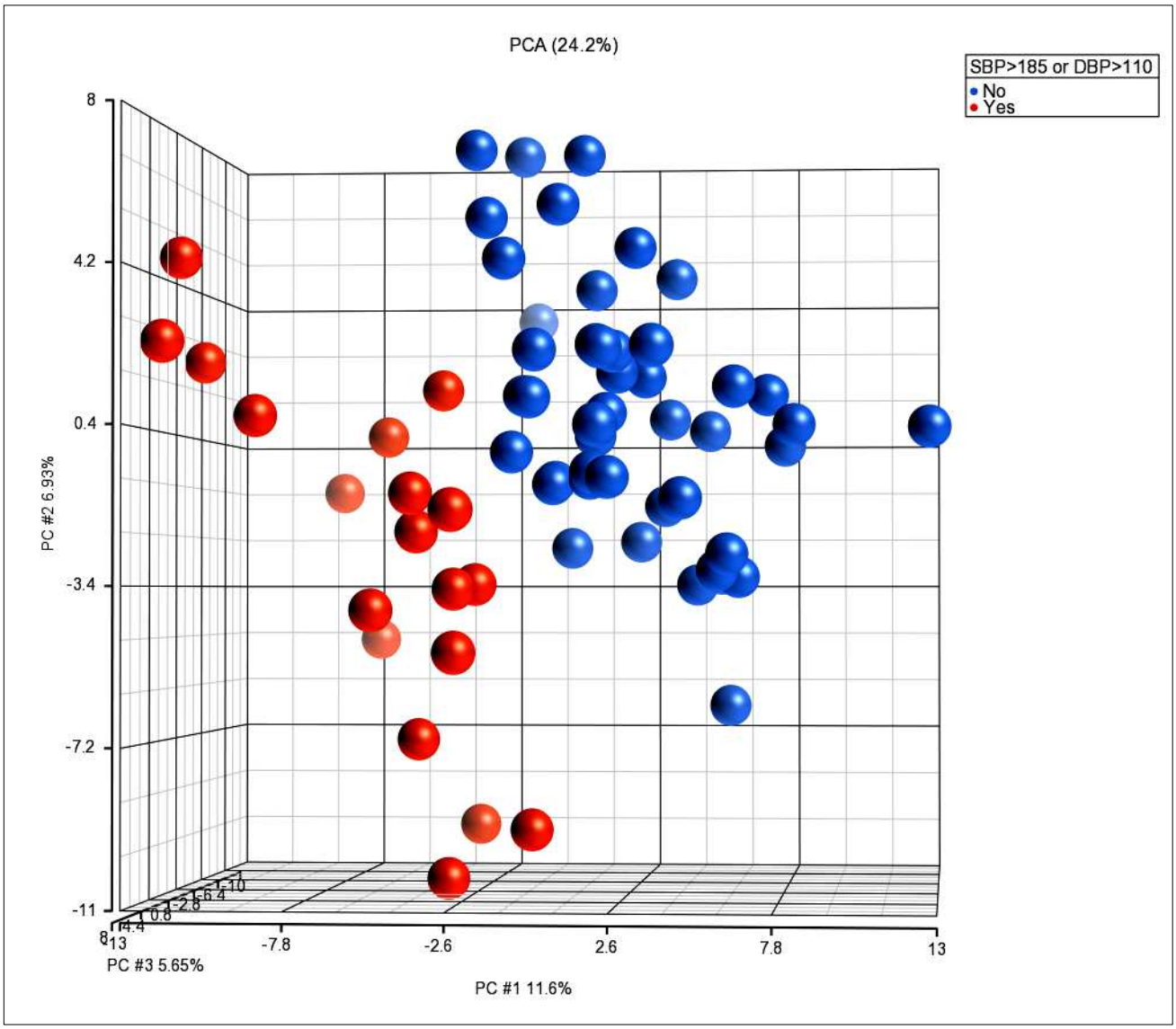

Figure 1. Pattern of differential gene expression by admission blood pressures within 3 hours after stroke onset. Principal component analysis plot showing the separation of acute ischemic stroke patients by admission blood pressure >185/110 mm Hg (n=19; red spheres) from patients with blood pressure <185/110 mm Hg (n= 45; blue spheres) based on the 226 differentially expressed genes within 3 hours after stroke onset. Differential gene expression was analyzed by ANCOVA. Genes with a P value < 0.05 and fold-change ≥ |1.2| were considered differentially expressed. Differentially expressed genes included *EDN3* (Endothelin-3), *MMP21* (Matrix metallopeptidase 21), *CAV-1* (caveolin 1) and *CCR2* (Chemokine receptor 2).

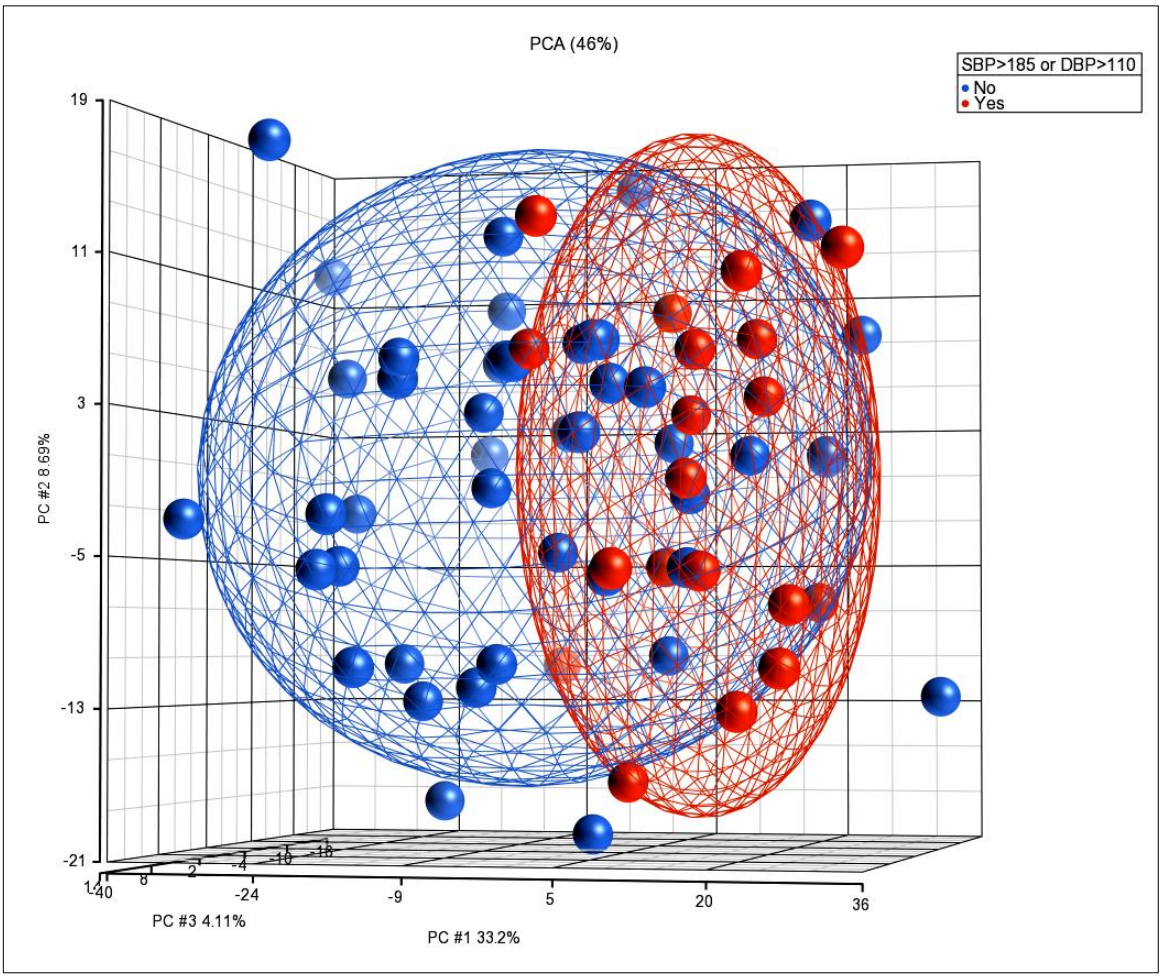

Figure 2. Pattern of differential gene expression by admission blood pressures at 5 hours after stroke onset. Principal component analysis plot showing the separation of acute ischemic stroke patients by admission blood pressure >185/110 mm Hg (n=19; red spheres and ellipsoid) from patients with blood pressure <185/110 mm Hg (n= 45; blue spheres and ellipsoid). This PCA plot is based on the expression of 923 genes that were differentially expressed between both groups at 5 hours after stroke onset. Differential gene expression was analyzed by ANCOVA. Genes with a P value < 0.05 and fold-change ≥ |1.2| were considered differentially expressed. Differentially expressed genes included *MMP25* (matrix metallopeptidase 25), *MMP28* (matrix metallopeptidase 28), *TLR4* (toll-like receptor 4), *TLR8* (toll-like receptor 8), *CYTL1* (cytokine like 1), *TLR7* (toll-like receptor 7) and *CCR3* chemokine (C-C motif) receptor 3. Ellipsoids are drawn with a SD of 2.

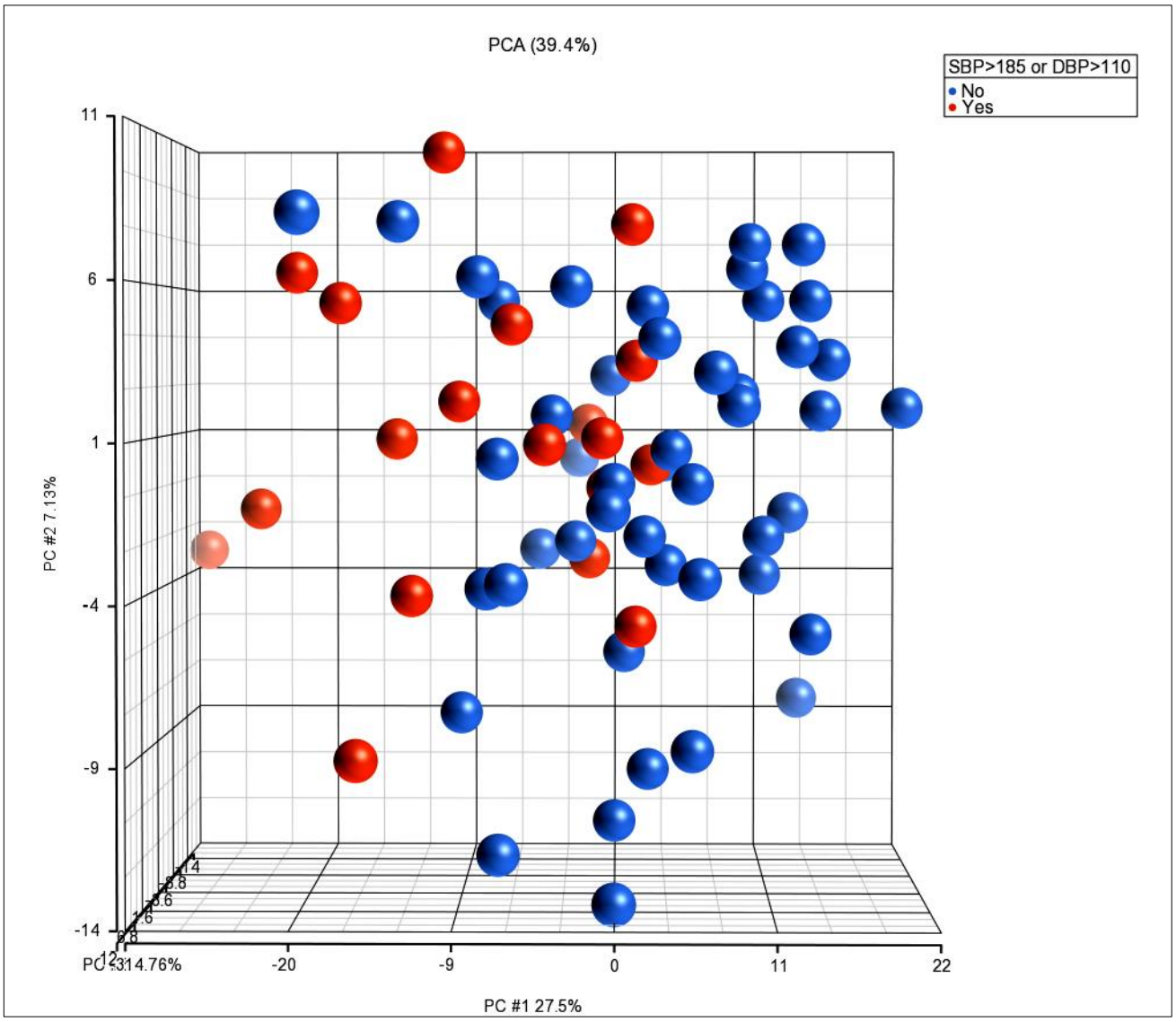

Figure 3. Pattern of differential gene expression by admission blood pressures at 24 hours after stroke onset. Principal component analysis plot showing the separation of acute ischemic stroke patients by admission blood pressure >185/110 mm Hg (n=19; red spheres) from patients with blood pressure <185/110 mm Hg (n= 47; blue spheres). This PCA plot is based on the expression of 422 genes that were differentially expressed between both groups at 24 hours after stroke onset. Differential gene expression was analyzed by ANCOVA. Genes with a P value < 0.05 and fold-change ≥ |1.2| were considered differentially expressed. Differentially expressed genes included *TLR5* (toll-like receptor 5) and *ANGPT1* (angiopoietin 1).

Conclusions

Using gene expression in peripheral leukocytes, we showed that there are differences in immune response by admission blood pressure in patients with BP > 185/110 mm Hg and BP < 185/110 mm Hg. By analyzing differential gene expression by admission blood pressure at several time points, we were able to show that there are differences in gene expression in patients who come in with admission BP > 185/110 mm Hg and under that are seen even after blood pressure has been lowered. The exact reasons and mechanisms for why these differences persist need further study of blood pressure course in patients with admission BP > 185/110 mm Hg and a greater understanding of immune activation related to the acute hypertensive response after stroke. While this is a preliminary study and findings need to be validated, the pathways and genes identified could be studied further to identify mechanisms of BBB injury related to hypertension in acute stroke.

Hemorrhagic transformation is a major complication of stroke treatment with r-tPA and a key reason that blood pressure needs to be lowered in acute stroke despite risks of hypoperfusing the brain [6]. Blood pressure is an easily modifiable factor which can ameliorate some of the risks associated with HT. However, there are many issues that remain in the treatment of blood pressure in acute ischemic stroke. Firstly, blood pressure is a quantitative variable making it difficult to mark an arbitrary cut-off point at which risks of hypoperfusing the brain are greater than the risks of bleeding after treatment. Secondly, the response of blood pressure to stroke is complicated and poorly understood. While efforts have been made to characterize the acute hypertensive response to stroke, there are still many points that are unclear. The mechanisms of acute hypertensive response seem to be many [84], and thus far, it has been impossible to characterize the underlying mechanisms in each patient. Furthermore, the presence of an acute hypertensive response to stroke at the moment of stroke and outside of a white-coat-hypertension or stress-inducing-hospital-setting have not been studied. As with animal studies [49, 95], it is possible that not all patients show this response so acute BP elevations that are seen are due to pre-existing hypertension. Attempts have been made to delineate an acute hypertensive response to stroke from pre-existing hypertension [86], but there are issues with that as well. In many patients, especially younger patients, hypertension may not have been diagnosed before their first

stroke. There may be differential effects of anti-hypertensive medications and some patients may have controlled vs. uncontrolled hypertension, despite taking medications.

Trajectory studies [108], while not perfect, have been a way to move forward in identifying sub-groups of patients that show differential blood pressure responses after stroke. By studying differential responses in patients by blood pressure after r-tPA treatment, it may be possible to begin to understand aspects of the acute hypertensive response in further detail. An intriguing possibility is that by analyzing differences in patient characteristics between different trajectories, we may be able to identify underlying mechanisms that separate patients with an acute hypertensive response from those who do not show this response. Genetic studies can aid in this as well. Using immune profiles, genetic studies may be able to delineate between patients with an acute hypertensive response vs. those with BP elevation due to chronic hypertension as well as their association with BBB disruption. By doing this, we may be able to further refine patients who are at most risk of bleeding post-r-tPA and would benefit from blood pressure reduction vs. patients who can tolerate elevated blood pressure.

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Appendix

Table S1. Differentially expressed genes in strokes with admission BP > 185/110 mm Hg and BP < 185/110 mm Hg at admission

Affymetrix Probeset ID	Entrez Gene	Gene Symbol	Gene Title	P value	Fold-Change (Higher BP vs. Lower BP)
213831_at	3117	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	0.0242622	-5.80195
209480_at	3119	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	0.0221983	-4.22447
236203_at	3117	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	0.00901389	-3.64622
221491_x_at	3119 /// 3123 /// 3124 /// 3125 /// 3126 /// 3127 /// 3128 /// 3129 ///	HLA-DQB1 /// HLA-DRB1 /// HLA-DRB2 /// HLA-DRB3 /// HLA-DRB4 ///	major histocompatibility complex, class II, DQ beta 1 /// major histocompatibility comp	0.0230613	-3.06758

	3130 /// 105369	HLA-DRB5 /// HLA-DRB6 /// HLA-DRB7 /// HLA-DRB8 /// LOC105369230			
212999_x_at	3119 /// 3120	HLA-DQB1 /// HLA-DQB2	major histocompatibility complex, class II, DQ beta 1 /// major histocompatibility comp	0.0147624	-2.02447
1552908_at	148823	GCSAML	germinal center-associated, signaling and motility-like	0.0126084	-1.53146
1558603_at	5342	PLGLB2	plasminogen-like B2	0.0105498	-1.50286
232530_at	5337	PLD1	phospholipase D1, phosphatidylcholine-specific	0.0179069	-1.4993
1568781_at	7390	UROS	uroporphyrinogen III synthase	0.0004165 2	-1.47914
226646_at	10365	KLF2	Kruppel-like factor 2	0.0284546	-1.43061
211654_x_at	3119	HLA-DQB1	major histocompatibility	0.012564	-1.42928

			complex, class II, DQ beta 1		
1561504_s_at	340156	MYLK4	myosin light chain kinase family member 4	0.0169564	-1.41756
215891_s_at	2760	GM2A	GM2 ganglioside activator	0.0128093	-1.41271
226736_at	91612	CHURC1	churchill domain containing 1	0.0287476	-1.37309
205871_at	5342 /// 5343	PLGLB1 /// PLGLB2	plasminogen-like B1 /// plasminogen-like B2	0.0331092	-1.36263
229943_at	10206	TRIM13	tripartite motif containing 13	0.0423397	-1.36193
1558785_a_at	8490	RGS5	regulator of G-protein signaling 5	0.00836585	-1.33774
230780_at	730091	LINC00886	long intergenic non-protein coding RNA 886	0.0265027	-1.33203
1555786_s_at	645687	LINC00520	long intergenic non-protein coding RNA 520	0.0264493	-1.32896
208076_at	8360	HIST1H4D	histone cluster 1, H4d	0.0247521	-1.3173
1561699_a_at	100874205	ATP11A-AS1	ATP11A antisense RNA 1	0.0322317	-1.31362
1562028_at	896	CCND3	cyclin D3	0.0447533	-1.30772

237210_at	4798	NFRKB	nuclear factor related to kappaB binding protein	0.000582323	-1.30643
226065_at	144165	PRICKLE1	prickle homolog 1	0.00679331	-1.30591
228362_s_at	441168	FAM26F	family with sequence similarity 26, member F	0.0446018	-1.30083
238164_at	9712	USP6NL	USP6 N-terminal like	0.0492845	-1.29652
1553214_a_at	79741	CCDC7	coiled-coil domain containing 7	0.0393423	-1.28794
226947_at	375513 /// 728411 /// 101929200 /// 106660612	GUSBP1 /// GUSBP4 /// LINC00680 /// LOC101929200	glucuronidase, beta pseudogene 1 /// glucuronidase, beta pseudogene 4 /// long intergen	0.00241483	-1.28513
207794_at	729230	CCR2	chemokine (C-C motif) receptor 2	0.0290454	-1.28494
237032_x_at	26037	SIPA1L1	signal-induced proliferation-associated 1 like 1	0.0249773	-1.2838
229391_s_at	441168	FAM26F	family with sequence similarity 26, member F	0.0464503	-1.28233

202269_x_at	2633	GBP1	guanylate binding protein 1, interferon-inducible	0.0282607	-1.28194
231577_s_at	2633	GBP1	guanylate binding protein 1, interferon-inducible	0.0414821	-1.27564
229390_at	441168	FAM26F	family with sequence similarity 26, member F	0.0436003	-1.27458
203065_s_at	857	CAV1	caveolin 1	0.0354637	-1.27301
232303_at	57507	ZNF608	zinc finger protein 608	0.00784775	-1.26365
215495_s_at	23034	SAMD4A	sterile alpha motif domain containing 4A	0.00707513	-1.26261
232196_at	150082	LCA5L	Leber congenital amaurosis 5-like	0.00350764	-1.2604
1555448_at	55745	AP5M1	adaptor-related protein complex 5, mu 1 subunit	0.0450965	-1.25036
219865_at	29092	LINC00339	long intergenic non-protein coding RNA 339	0.00661253	-1.24964
220328_at	80012	PHC3	polyhomeotic homolog 3 (Drosophila)	0.0158744	-1.24852

214077_x_at	4213	MEIS3P1	Meis homeobox 3 pseudogene 1	0.0264829	-1.24698
235678_at	2760	GM2A	GM2 ganglioside activator	0.0439176	-1.24656
216213_at	4750	NEK1	NIMA-related kinase 1	0.0258762	-1.24597
204324_s_at	27333	GOLIM4	golgi integral membrane protein 4	0.00541617	-1.24557
239966_at	4208	MEF2C	myocyte enhancer factor 2C	0.020741	-1.24403
219984_s_at	57110	HRASLS	HRAS-like suppressor	0.029301	-1.2425
1554460_at	7903	ST8SIA4	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4	0.0287266	-1.2425
220119_at	64097	EPB41L4A	erythrocyte membrane protein band 4.1 like 4A	0.013256	-1.23765
227556_at	29922	NME7	NME/NM23 family member 7	0.0327061	-1.23744
AFFX-HUMISGF3A/M97935_MA_at	6772	STAT1	signal transducer and activator of transcription 1	0.0350127	-1.23716
216717_at	55578	SUPT20H	SPT20 homolog, SAGA complex component	0.036482	-1.23696
1554894_a_at	84105	PCBD2	pterin-4 alpha-carbinolamine	0.0185223	-1.2269

			dehydratase/dimerization cofactor of hepatocyte nuclear fa		
1553244_at	2187	FANCB	Fanconi anemia complementation group B	0.0348384	-1.22523
215116_s_at	1759	DNM1	dynamin 1	0.0344837	-1.22433
1561132_at	60625	DHX35	DEAH (Asp-Glu-Ala-His) box polypeptide 35	0.0224952	-1.2237
210800_at	1678	TIMM8A	translocase of inner mitochondrial membrane 8 homolog A (yeast)	0.0356901	-1.22234
228855_at	283927	NUDT7	nudix hydrolase 7	0.0430564	-1.22231
201243_s_at	481	ATP1B1	ATPase, Na+/K+ transporting, beta 1 polypeptide	0.0492172	-1.22127
225655_at	29128	UHRF1	ubiquitin-like with PHD and ring finger domains 1	0.0276316	-1.21995
226878_at	3111	HLA-DOA	major histocompatibility complex, class II, DO alpha	0.0401344	-1.21959
1555227_a_at	79694	MANEA	mannosidase, endo-alpha	0.029695	-1.21797

206757_at	8654	PDE5A	phosphodiesterase 5A, cGMP-specific	0.0189721	-1.21713
241755_at	7385	UQCRC2	ubiquinol-cytochrome c reductase core protein II	0.02756	-1.21609
231833_at	155435	RBM33	RNA binding motif protein 33	0.0304763	-1.21577
1557236_at	80830	APOL6	apolipoprotein L, 6	0.0106193	-1.21189
1559078_at	53335	BCL11A	B-cell CLL/lymphoma 11A (zinc finger protein)	0.015991	-1.20975
1563839_at	51256	TBC1D7	TBC1 domain family, member 7	0.0244065	-1.20865
AFFX-HUMISGF3A/M97935_5_at	6772	STAT1	signal transducer and activator of transcription 1	0.018417	-1.2075
1568840_at	25879	DCAF13	DDB1 and CUL4 associated factor 13	0.0025502 4	-1.20692
242507_at	100874034	UBXN7-AS1	UBXN7 antisense RNA 1	0.0295568	-1.20555
213624_at	10924	SMPDL3A	sphingomyelin phosphodiesterase, acid-like 3A	0.0415948	-1.20525
1569142_at	10206	TRIM13	tripartite motif containing 13	0.0208689	-1.20491

1558557_at	57020	C16orf62	chromosome 16 open reading frame 62	0.0457712	-1.20401
1568126_at	302	ANXA2	annexin A2	0.0499793	-1.2022
1555396_s_at	340602	CXorf67	chromosome X open reading frame 67	0.0129998	1.20382
213272_s_at	57146	TMEM159	transmembrane protein 159	0.00599965	1.20526
243686_at	158038	LINGO2	leucine rich repeat and Ig domain containing 2	0.0141714	1.20565
213035_at	23243	ANKRD28	ankyrin repeat domain 28	0.0336611	1.20658
203069_at	9900	SV2A	synaptic vesicle glycoprotein 2A	0.0170378	1.20697
239517_at	3694 /// 100505984	ITGB6 /// LOC100505984	integrin beta 6 /// uncharacterized LOC100505984	0.00356336	1.20753
243476_at	4763	NF1	neurofibromin 1	0.026768	1.20839
1560830_a_at	147646	C19orf84	chromosome 19 open reading frame 84	0.0475822	1.21061
220003_at	55282	LRRC36	leucine rich repeat containing 36	0.0446686	1.21122
230954_at	140688	NOL4L	nucleolar protein 4-like	0.0199672	1.21221

219693_at	56895	AGPAT4	1-acylglycerol-3-phosphate O-acyltransferase 4	0.0456494	1.21234
209695_at	11156	PTP4A3	protein tyrosine phosphatase type IVA, member 3	0.044017	1.21241
205330_at	4330	MN1	meningioma (disrupted in balanced translocation) 1	0.0374579	1.21283
1552835_at	163486	DENND1B	DENN/MADD domain containing 1B	0.033338	1.21438
1552373_s_at	132321	C4orf33	chromosome 4 open reading frame 33	0.0339564	1.21538
214099_s_at	9659 /// 100996724	LOC100996724 /// PDE4DIP	phosphodiesterase 4D interacting protein-like /// phosphodiesterase 4D interacting prot	0.00812496	1.21557
1569519_at	25832 /// 55672 /// 149013 /// 200030 /// 400818 ///	LOC100996763 /// LOC102724250 /// NBPF1 /// NBPF10 /// NBPF11 /// NBPF12 /// NBPF14 /// NBPF19 ///	notch homolog 2 N-terminal-like protein /// neuroblastoma breakpoint family member 1 //	0.0279341	1.2168

	728841 /// 100132406 /// 100996763	NBPF26 /// NBPF8 /// NBPF9			
214763_at	26027	ACOT11	acyl-CoA thioesterase 11	0.00652945	1.21795
64900_at	79583	TMEM231	transmembrane protein 231	0.0379497	1.21797
237281_at	158798	AKAP14	A kinase (PRKA) anchor protein 14	0.0294309	1.22012
230725_at	84250	SLF1	SMC5-SMC6 complex localization factor 1	0.0164952	1.22018
1568706_s_at	10677	AVIL	advillin	0.0263929	1.22062
210069_at	1375 /// 386593	CHKB-CPT1B /// CPT1B	CHKB-CPT1B readthrough (NMD candidate) /// carnitine palmitoyltransferase 1B (muscle)	0.0336505	1.22107
232662_x_at	84293	FAM213A	family with sequence similarity 213, member A	0.020598	1.22138
223652_at	57412	AS3MT	arsenite methyltransferase	0.0119376	1.2216

1561890_at	170371	C10orf128	chromosome 10 open reading frame 128	0.00582559	1.22169
221887_s_at	25861	DFNB31	deafness, autosomal recessive 31	0.0322392	1.2227
208190_s_at	51599	LSR	lipolysis stimulated lipoprotein receptor	0.0266035	1.22354
242060_x_at	51131	PHF11	PHD finger protein 11	0.0220214	1.22412
205579_at	3269	HRH1	histamine receptor H1	0.0448982	1.22497
239417_x_at	347744	C6orf52	chromosome 6 open reading frame 52	0.0311785	1.22539
1552592_at	118856	MMP21	matrix metallopeptidase 21	0.00672924	1.22741
1558688_at	441461	STX17-AS1	STX17 antisense RNA 1	0.00636388	1.22901
229080_at	136227	COL26A1	collagen, type XXVI, alpha 1	0.0063458	1.22994
228101_at	320 /// 101929802	APBA1 /// LOC101929802	amyloid beta (A4) precursor protein-binding, family A, member 1 /// uncharacterized LOC	0.0149945	1.23067

215039_at	339524	LINC01140	long intergenic non-protein coding RNA 1140	0.0432843	1.23102
211673_s_at	4337	MOCS1	molybdenum cofactor synthesis 1	0.000572564	1.23255
236534_at	149428	BNIPL	BCL2/adenovirus E1B 19kD interacting protein like	0.0199574	1.23336
229921_at	3798	KIF5A	kinesin family member 5A	0.0117516	1.23579
1556019_at	160897	GPR180	G protein-coupled receptor 180	0.00716539	1.23925
223791_at	100132948 /// 100133121 /// 102725186 /// 105379444	FAM27B /// FAM27C /// LOC102725186 /// LOC105379444	family with sequence similarity 27, member B /// family with sequence similarity 27, me	0.020497	1.24518
206541_at	3818	KLKB1	kallikrein B1	0.0335473	1.24661
235498_at	127255	LRRIQ3	leucine-rich repeats and IQ motif containing 3	0.0391902	1.24762
206766_at	8515	ITGA10	integrin alpha 10	0.0236887	1.24872
223740_at	79992	AGPAT4-IT1	AGPAT4 intronic transcript 1	0.0213488	1.24913

203894_at	27175	TUBG2	tubulin, gamma 2	0.00139132	1.24959
209502_s_at	10458	BAIAP2	BAI1-associated protein 2	0.0202004	1.25
206753_at	8608	RDH16	retinol dehydrogenase 16 (all-trans)	0.00181192	1.25063
228450_at	144100	PLEKHA7	pleckstrin homology domain containing, family A member 7	0.0344013	1.25229
220410_s_at	157922	CAMSAP1	calmodulin regulated spectrin-associated protein 1	0.00594456	1.25518
238254_at	342926	ZNF677	zinc finger protein 677	0.0316632	1.25538
243324_x_at	3842	TNPO1	transportin 1	0.0211103	1.25675
219199_at	27125	AFF4	AF4/FMR2 family, member 4	0.0146045	1.25732
205088_at	10046	MAMLD1	mastermind-like domain containing 1	0.0361252	1.26206
214704_at	22980	TCF25	transcription factor 25 (basic helix-loop-helix)	0.00986725	1.2652
230250_at	5787	PTPRB	protein tyrosine phosphatase, receptor type, B	0.030742	1.26978

232111_at	100507043	TUNAR	TCL1 upstream neural differentiation-associated RNA	0.0200165	1.27179
209693_at	23245	ASTN2	astrotactin 2	0.00855785	1.27224
225450_at	154810	AMOTL1	angiomotin like 1	0.00310264	1.27417
217104_at	400410	ST20	suppressor of tumorigenicity 20	0.0193278	1.27572
227099_s_at	387763	C11orf96	chromosome 11 open reading frame 96	0.0180355	1.27607
230636_s_at	687	KLF9	Kruppel-like factor 9	0.0170403	1.27935
224904_at	55066	PDPR	pyruvate dehydrogenase phosphatase regulatory subunit	0.00246044	1.27936
219821_s_at	54438	GFOD1	glucose-fructose oxidoreductase domain containing 1	0.00108966	1.27958
220591_s_at	80258	EFHC2	EF-hand domain (C-terminal) containing 2	0.0432084	1.2819
227893_at	100128782	LINC00476	long intergenic non-protein coding RNA 476	0.0232463	1.28257

1561146_at	55737	VPS35	VPS35 retromer complex component	0.0118838	1.28377
1557465_at	283521	LINC00282	long intergenic non-protein coding RNA 282	0.0312424	1.28723
219182_at	79583	TMEM231	transmembrane protein 231	0.000544301	1.28967
237241_at	1894	ECT2	epithelial cell transforming 2	0.0104644	1.29357
209691_s_at	55715	DOK4	docking protein 4	0.033102	1.313
213060_s_at	1117	CHI3L2	chitinase 3-like 2	0.0364944	1.32125
208399_s_at	1908	EDN3	endothelin 3	0.0224305	1.32228
47553_at	25861	DFNB31	deafness, autosomal recessive 31	0.0146561	1.32452
205328_at	9071	CLDN10	claudin 10	0.0188252	1.33332
235467_s_at	3749	KCNC4	potassium channel, voltage gated Shaw related subfamily C, member 4	0.0118086	1.34508
213174_at	23508	TTC9	tetratricopeptide repeat domain 9	0.00167947	1.34601
219837_s_at	54360	CYTL1	cytokine like 1	0.0111558	1.35678

224049_at	89822	KCNK17	potassium channel, two pore domain subfamily K, member 17	0.0312347	1.35824
204755_x_at	3131	HLF	hepatic leukemia factor	0.03442	1.36377
235099_at	152189	CMTM8	CKLF-like MARVEL transmembrane domain containing 8	0.00232714	1.37176
206171_at	140	ADORA3	adenosine A3 receptor	0.00741749	1.38728
214978_s_at	8497	PPFIA4	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein	0.0211151	1.40963
223349_s_at	666	BOK	BCL2-related ovarian killer	0.0246488	1.41999
219758_at	79989	TTC26	tetratricopeptide repeat domain 26	0.0447492	1.42684
231223_at	64478	CSMD1	CUB and Sushi multiple domains 1	0.00524883	1.51375
232825_s_at	92126	DSEL	dermatan sulfate epimerase-like	0.00226581	1.58876
231455_at	400941	LINC00487	long intergenic non-protein coding RNA 487	0.0379851	1.61432

238488_at	51194 /// 100130733	IPO11 /// LRRC70	importin 11 /// leucine rich repeat containing 70	0.00683713	1.63303
212805_at	158471	PRUNE2	prune homolog 2 (Drosophila)	0.0353266	1.74856

Table S2. Pathways associated with differentially expressed genes at admission

Ingenuity Canonical Pathways	**Molecules**
B Cell Development	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
Antigen Presentation Pathway	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
T Helper Cell Differentiation	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1,STAT1
Autoimmune Thyroid Disease Signaling	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
Allograft Rejection Signaling	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
Graft-versus-Host Disease Signaling	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
OX40 Signaling Pathway	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
Nur77 Signaling in T Lymphocytes	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
Calcium-induced T Lymphocyte Apoptosis	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
Type I Diabetes Mellitus Signaling	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1,STAT1
Cdc42 Signaling	HLA-DOA,HLA-DRB1,BAIAP2,HLA-DQA1,HLA-DQB1
Th1 Pathway	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1,STAT1
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
IL-4 Signaling	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1

Th1 and Th2 Activation Pathway	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1,STAT1
iCOS-iCOSL Signaling in T Helper Cells	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
T Cell Exhaustion Signaling Pathway	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1,STAT1
Dendritic Cell Maturation	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1,STAT1
Role of NFAT in Regulation of the Immune Response	HLA-DOA,HLA-DRB1,HLA-DQA1,MEF2C,HLA-DQB1
CD28 Signaling in T Helper Cells	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
Caveolar-mediated Endocytosis Signaling	CAV1,ITGA10,ITGB6
Tyrosine Biosynthesis IV	PCBD2
Th2 Pathway	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
Arsenate Detoxification I (Glutaredoxin)	AS3MT
Phenylalanine Degradation I (Aerobic)	PCBD2
Tetrapyrrole Biosynthesis II	UROS
PKCθ Signaling in T Lymphocytes	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1
tRNA Splicing	SMPDL3A,PDE5A
Heme Biosynthesis II	UROS
Virus Entry via Endocytic Pathways	DNM1,CAV1,ITGB6
Phospholipases	PLD1,HRASLS

Neuroinflammation Signaling Pathway	HLA-DOA,HLA-DRB1,HLA-DQA1,HLA-DQB1,STAT1
Cardiac β-adrenergic Signaling	SMPDL3A,AKAP14,PDE5A
Chondroitin Sulfate Degradation (Metazoa)	GM2A
Choline Biosynthesis III	PLD1
cAMP-mediated signaling	SMPDL3A,AKAP14,ADORA3,PDE5A
Dermatan Sulfate Degradation (Metazoa)	GM2A
RAN Signaling	TNPO1
MSP-RON Signaling Pathway	KLKB1,CCR2
Mitochondrial L-carnitine Shuttle Pathway	CPT1B
Role of BRCA1 in DNA Damage Response	FANCB,STAT1
Cardiomyocyte Differentiation via BMP Receptors	MEF2C
GADD45 Signaling	CCND3
Granulocyte Adhesion and Diapedesis	CLDN10,MMP21,HRH1
IL-7 Signaling Pathway	CCND3,STAT1
Agranulocyte Adhesion and Diapedesis	CLDN10,MMP21,HRH1
Pyrimidine Deoxyribonucleotides De Novo Biosynthesis I	NME7
Macropinocytosis Signaling	USP6NL,ITGB6
IL-22 Signaling	STAT1
Role of JAK1, JAK2 and TYK2 in Interferon Signaling	STAT1

Role of JAK family kinases in IL-6-type Cytokine Signaling	STAT1
CDP-diacylglycerol Biosynthesis I	AGPAT4
Apelin Liver Signaling Pathway	EDN3
Phosphatidylglycerol Biosynthesis II (Non-plastidic)	AGPAT4
PDGF Signaling	CAV1,STAT1
G-Protein Coupled Receptor Signaling	SMPDL3A,HRH1,ADORA3,PDE5A
Antioxidant Action of Vitamin C	PLD1,HRASLS
Protein Kinase A Signaling	SMPDL3A,AKAP14,PTPRB,PDE5A,PTP4A1
DNA Methylation and Transcriptional Repression Signaling	HIST1H4D
Retinoate Biosynthesis I	RDH16
Nitric Oxide Signaling in the Cardiovascular System	CAV1,PDE5A
Role of JAK2 in Hormone-like Cytokine Signaling	STAT1
p38 MAPK Signaling	MEF2C,STAT1
Coagulation System	KLKB1
RhoA Signaling	BAIAP2,PLD1
Interferon Signaling	STAT1
Paxillin Signaling	ITGA10,ITGB6
Gαi Signaling	CAV1,ADORA3
Atherosclerosis Signaling	CCR2,HRASLS
Pancreatic Adenocarcinoma Signaling	STAT1,PLD1
Inhibition of Matrix Metalloproteases	MMP21

Integrin Signaling	CAV1,ITGA10,ITGB6
Rac Signaling	BAIAP2,PLD1
Apelin Endothelial Signaling Pathway	MEF2C,KLF2
BAG2 Signaling Pathway	ANXA2
Role of PKR in Interferon Induction and Antiviral Response	STAT1
Intrinsic Prothrombin Activation Pathway	KLKB1
Dermatan Sulfate Biosynthesis (Late Stages)	DSEL
Pyrimidine Ribonucleotides Interconversion	NME7
Oncostatin M Signaling	STAT1
Pyrimidine Ribonucleotides De Novo Biosynthesis	NME7
Triacylglycerol Biosynthesis	AGPAT4
Phagosome Maturation	HLA-DRB1,TUBG2
iNOS Signaling	STAT1
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	PHC3
IL-9 Signaling	STAT1
Gustation Pathway	SMPDL3A,PDE5A
Transcriptional Regulatory Network in Embryonic Stem Cells	HIST1H4D
Dermatan Sulfate Biosynthesis	DSEL
SPINK1 Pancreatic Cancer Pathway	KLKB1
Mitochondrial Dysfunction	CPT1B,UQCRC2
PCP pathway	PRICKLE1

Relaxin Signaling	SMPDL3A,PDE5A
Sirtuin Signaling Pathway	TIMM8A,CPT1B,UQCRC2
Activation of IRF by Cytosolic Pattern Recognition Receptors	STAT1
Gαq Signaling	HRH1,PLD1
Eicosanoid Signaling	HRASLS
Remodeling of Epithelial Adherens Junctions	DNM1
Cell Cycle: G1/S Checkpoint Regulation	CCND3
PPARα/RXRα Activation	CPT1B,MEF2C
CNTF Signaling	STAT1
ERK5 Signaling	MEF2C
Actin Nucleation by ARP-WASP Complex	BAIAP2
EGF Signaling	STAT1
Hepatic Fibrosis / Hepatic Stellate Cell Activation	STAT1,COL26A1
Thrombopoietin Signaling	STAT1
Role of MAPK Signaling in the Pathogenesis of Influenza	HRASLS
Communication between Innate and Adaptive Immune Cells	HLA-DRB1
Role of JAK1 and JAK3 in γc Cytokine Signaling	STAT1
Endothelin-1 Signaling	PLD1,HRASLS
Cyclins and Cell Cycle Regulation	CCND3
GM-CSF Signaling	STAT1
Osteoarthritis Pathway	ANXA2,MEF2C

Crosstalk between Dendritic Cells and Natural Killer Cells	HLA-DRB1
Leukocyte Extravasation Signaling	CLDN10,MMP21
Clathrin-mediated Endocytosis Signaling	DNM1,ITGB6
Growth Hormone Signaling	STAT1
GDNF Family Ligand-Receptor Interactions	DOK4
Regulation of Actin-based Motility by Rho	BAIAP2
IL-8 Signaling	CCND3,PLD1
Factors Promoting Cardiogenesis in Vertebrates	MEF2C
FLT3 Signaling in Hematopoietic Progenitor Cells	STAT1
IL-3 Signaling	STAT1
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	PLD1
Prolactin Signaling	STAT1
JAK/Stat Signaling	STAT1
GABA Receptor Signaling	DNM1
Salvage Pathways of Pyrimidine Ribonucleotides	NME7
Bladder Cancer Signaling	MMP21
HER-2 Signaling in Breast Cancer	ITGB6
Oxidative Phosphorylation	UQCRC2
NER Pathway	HIST1H4D
TR/RXR Activation	KLF9
Phospholipase C Signaling	MEF2C,PLD1

UVA-Induced MAPK Signaling	STAT1
Cholecystokinin/Gastrin-mediated Signaling	MEF2C
IL-15 Production	STAT1

Table S3. Differentially expressed genes that correlated with SBP at admission

Probeset ID	Entrez Gene	Gene Symbol	Gene Title	r	P value(correlation)
237210_at	4798	NFRKB	nuclear factor related to kappaB binding protein	-0.42424	0.00047656
226947_at	375513 /// 728411 /// 101929200 /// 106660612	GUSBP1 /// GUSBP4 /// LINC00680 /// LOC101929200	glucuronidase, beta pseudogene 1 /// glucuronidase, beta pseudogene 4 /// long intergen	-0.348198	0.00480989
213624_at	10924	SMPDL3A	sphingomyelin phosphodiesterase, acid-like 3A	-0.335178	0.00678175
216213_at	4750	NEK1	NIMA-related kinase 1	-0.325521	0.00867131
207794_at	729230	CCR2	chemokine (C-C motif) receptor 2	-0.323788	0.00905507
226878_at	3111	HLA-DOA	major histocompatibility complex, class II, DO alpha	-0.316307	0.0108864

211654_x_at	3119	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	-0.316073	0.0109484
212999_x_at	3119 /// 3120	HLA-DQB1 /// HLA-DQB2	major histocompatibility complex, class II, DQ beta 1 /// major histocompatibility comp	-0.312024	0.0120731
1559078_at	53335	BCL11A	B-cell CLL/lymphoma 11A (zinc finger protein)	-0.306145	0.0138831
1568126_at	302	ANXA2	annexin A2	-0.302598	0.0150842
232530_at	5337	PLD1	phospholipase D1, phosphatidylcholine-specific	-0.302345	0.0151735
236203_at	3117	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	-0.302173	0.0152343
232303_at	57507	ZNF608	zinc finger protein 608	-0.302058	0.0152748
226065_at	144165	PRICKLE1	prickle homolog 1	-0.294869	0.0180148

1561132_at	60625	DHX35	DEAH (Asp-Glu-Ala-His) box polypeptide 35	-0.290742	0.01977
215891_s_at	2760	GM2A	GM2 ganglioside activator	-0.284966	0.0224689
213831_at	3117	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	-0.276387	0.0270513
204324_s_at	27333	GOLIM4	golgi integral membrane protein 4	-0.275292	0.0276892
1554894_a_at	84105	PCBD2	pterin-4 alpha-carbinolamine dehydratase/dimerization cofactor of hepatocyte nuclear fa	-0.271764	0.029831
209480_at	3119	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	-0.271763	0.0298319
1555227_a_at	79694	MANEA	mannosidase, endo-alpha	-0.270085	0.0308983
229943_at	10206	TRIM13	tripartite motif containing 13	-0.264934	0.0343732
228362_s_at	441168	FAM26F	family with sequence similarity 26, member F	-0.256128	0.0410668

242507_at	101000000	UBXN7-AS1	UBXN7 antisense RNA 1	-0.254473	0.0424385
201243_s_at	481	ATP1B1	ATPase, Na+/K+ transporting, beta 1 polypeptide	-0.249091	0.0471602
219837_s_at	54360	CYTL1	cytokine like 1	0.246635	0.0494542
231223_at	64478	CSMD1	CUB and Sushi multiple domains 1	0.248797	0.0474301
206753_at	8608	RDH16	retinol dehydrogenase 16 (all-trans)	0.253672	0.0431151
217104_at	400410	ST20	suppressor of tumorigenicity 20	0.254534	0.0423868
210069_at	1375 /// 386593	CHKB-CPT1B /// CPT1B	CHKB-CPT1B readthrough (NMD candidate) /// carnitine palmitoyltransferase 1B (muscle)	0.258414	0.0392334
1555396_s_at	340602	CXorf67	chromosome X open reading frame 67	0.261377	0.0369584
232825_s_at	92126	DSEL	dermatan sulfate epimerase-like	0.262299	0.0362732
223740_at	79992	AGPAT4-IT1	AGPAT4 intronic transcript 1	0.263618	0.0353114
223349_s_at	666	BOK	BCL2-related ovarian killer	0.269687	0.0311556

243686_at	158038	LINGO2	leucine rich repeat and Ig domain containing 2	0.27365	0.0286694
238254_at	342926	ZNF677	zinc finger protein 677	0.280982	0.024508
203894_at	27175	TUBG2	tubulin, gamma 2	0.281117	0.0244362
213035_at	23243	ANKRD28	ankyrin repeat domain 28	0.284162	0.0228685
1561890_at	170371	C10orf128	chromosome 10 open reading frame 128	0.286775	0.0215921
205579_at	3269	HRH1	histamine receptor H1	0.293275	0.0186762
236534_at	149428	BNIPL	BCL2/adenovirus E1B 19kD interacting protein like	0.296062	0.017533
1560830_a_at	147646	C19orf84	chromosome 19 open reading frame 84	0.298054	0.0167531
220591_s_at	80258	EFHC2	EF-hand domain (C-terminal) containing 2	0.299137	0.0163417
1568706_s_at	10677	AVIL	advillin	0.307776	0.0133588
1557465_at	283521	LINC00282	long intergenic non-protein coding RNA 282	0.313881	0.0115455
206541_at	3818	KLKB1	kallikrein B1	0.337926	0.00631494
242060_x_at	51131	PHF11	PHD finger protein 11	0.347014	0.00496545

223652_at	57412	AS3MT	arsenite methyltransferase	0.349474	0.00464713
211673_s_at	4337	MOCS1	molybdenum cofactor synthesis 1	0.370658	0.0025697
205328_at	9071	CLDN10	claudin 10	0.405736	0.00088031
1558688_at	441461	STX17-AS1	STX17 antisense RNA 1	0.443496	0.00024218

Table S4. Differentially expressed genes in strokes with admission BP > 185/110 mm Hg and BP < 185/110 mm Hg at 5 hours

Probeset ID	Entrez Gene	Gene Symbol	Gene Title	P value	Fold-Change (Higher vs. Lower BP)
221491_x_at	3119 /// 3123 /// 3124 /// 3125 /// 3126 /// 3127 /// 3128 /// 3129 /// 3130 /// 105369	HLA-DQB1 /// HLA-DRB1 /// HLA-DRB2 /// HLA-DRB3 /// HLA-DRB4 /// HLA-DRB5 /// HLA-DRB6 /// HLA-DRB7 /// HLA-DRB8 /// LOC105369230	major histocompatibility complex, class II, DQ beta 1 /// major histocompatibility comp	0.024203	-3.06695
236203_at	3117	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	0.030767	-2.93776
204141_at	7280	TUBB2A	tubulin, beta 2A class IIa	0.027441	-2.12958
231982_at	284422	SMIM24	small integral membrane protein 24	0.022834	-1.76856

1552410_at	165530	CLEC4F	C-type lectin domain family 4, member F	0.020064	-1.707
210395_x_at	4635	MYL4	myosin light chain 4	0.009495	-1.68071
210088_x_at	4635	MYL4	myosin light chain 4	0.012639	-1.65946
216054_x_at	4635	MYL4	myosin light chain 4	0.012581	-1.6575
239853_at	147700	KLC3	kinesin light chain 3	0.032369	-1.60127
217274_x_at	4635	MYL4	myosin light chain 4	0.013514	-1.58696
202007_at	4811	NID1	nidogen 1	0.011823	-1.57445
235428_at	100507316	MINCR	MYC-induced long noncoding RNA	0.00064	-1.56844
214273_x_at	8131	NPRL3	NPR3-like, GATOR1 complex subunit	0.037795	-1.55543
203289_s_at	8131	NPRL3	NPR3-like, GATOR1 complex subunit	0.048795	-1.53957
216549_s_at	55633	TBC1D22B	TBC1 domain family, member 22B	0.029064	-1.50241
209807_s_at	4784	NFIX	nuclear factor I/X (CCAAT-binding transcription factor)	0.049551	-1.48372
224822_at	10395	DLC1	DLC1 Rho GTPase activating protein	0.031768	-1.4689
223062_s_at	29968	PSAT1	phosphoserine aminotransferase 1	0.020417	-1.46298
223963_s_at	10644	IGF2BP2	insulin-like growth factor 2 mRNA binding protein 2	0.047881	-1.44664

201250_s_at	6513	SLC2A1	solute carrier family 2 (facilitated glucose transporter), member 1	0.041135	-1.44398
206710_s_at	23136	EPB41L3	erythrocyte membrane protein band 4.1-like 3	0.003858	-1.43585
215621_s_at	3495	IGHD	immunoglobulin heavy constant delta	0.033573	-1.435
240744_at	93979	CPA5	carboxypeptidase A5	0.032894	-1.43212
234440_at	28516	TRDV3	T cell receptor delta variable 3	0.048641	-1.42908
1568781_at	7390	UROS	uroporphyrinogen III synthase	0.002228	-1.42805
213674_x_at	3495	IGHD	immunoglobulin heavy constant delta	0.018715	-1.42627
1552582_at	150000	ABCC13	ATP binding cassette subfamily C member 13, pseudogene	0.042585	-1.41645
222830_at	29841	GRHL1	grainyhead-like transcription factor 1	0.045642	-1.41563
231798_at	9241	NOG	noggin	0.028166	-1.40765
235276_at	94240	EPSTI1	epithelial stromal interaction 1 (breast)	0.023897	-1.40014
229552_at	8739 /// 283454	HRK /// LOC283454	harakiri, BCL2 interacting protein /// uncharacterized LOC283454	0.011995	-1.39558
1558719_s_at	84268	RPAIN	RPA interacting protein	0.002529	-1.3894

220146_at	51284	TLR7	toll-like receptor 7	0.009417	-1.38904
226122_at	57480	PLEKHG1	pleckstrin homology domain containing, family G (with RhoGef domain) member 1	0.026231	-1.38658
211654_x_at	3119	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	0.025651	-1.38481
243928_s_at	10257	ABCC4	ATP binding cassette subfamily C member 4	0.043433	-1.3798
231157_at	158135	TTLL11	tubulin tyrosine ligase-like family member 11	0.001525	-1.3694
234973_at	92745	SLC38A5	solute carrier family 38, member 5	0.025546	-1.36677
235175_at	115361	GBP4	guanylate binding protein 4	0.026227	-1.36032
208304_at	1232	CCR3	chemokine (C-C motif) receptor 3	0.045811	-1.35966
225942_at	57486	NLN	neurolysin (metallopeptidase M3 family)	0.006781	-1.35902
201123_s_at	1984	EIF5A	eukaryotic translation initiation factor 5A	0.024931	-1.35874
201929_s_at	8502	PKP4	plakophilin 4	0.011039	-1.35792
235678_at	2760	GM2A	GM2 ganglioside activator	0.01089	-1.35227
218967_s_at	9317	PTER	phosphotriesterase related	0.029392	-1.3519
220484_at	55283	MCOLN3	mucolipin 3	0.048418	-1.34979

216510_x_at	3493 /// 3500 /// 3507 /// 28396 /// 28442 /// 50802 /// 152098	IGHA1 /// IGHG1 /// IGHM /// IGHV3-23 /// IGHV4-31 /// IGK /// ZCWPW2	immunoglobulin heavy constant alpha 1 /// immunoglobulin heavy constant gamma 1 (G1m ma	0.037183	-1.34969
1557910_at	3326	HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	0.00043	-1.34318
228855_at	283927	NUDT7	nudix hydrolase 7	0.004324	-1.34208
230877_at	3495	IGHD	immunoglobulin heavy constant delta	0.0414	-1.33922
227084_at	1837	DTNA	dystrobrevin, alpha	0.004965	-1.33675
226069_at	144165	PRICKLE1	prickle homolog 1	0.037156	-1.32562
201015_s_at	3728	JUP	junction plakoglobin	0.024167	-1.3206
226065_at	144165	PRICKLE1	prickle homolog 1	0.007764	-1.32
229994_at	4774	NFIA	nuclear factor I/A	0.016221	-1.31566
235122_at	59269	HIVEP3	human immunodeficiency virus type I enhancer binding protein 3	0.027234	-1.31381
221590_s_at	4329	ALDH6A1	aldehyde dehydrogenase 6 family, member A1	0.021195	-1.31237

202947_s_at	2995	GYPC	glycophorin C (Gerbich blood group)	0.034381	-1.31235
243_g_at	4134	MAP4	microtubule associated protein 4	0.003955	-1.31153
209374_s_at	3507	IGHM	immunoglobulin heavy constant mu	0.015884	-1.3097
207090_x_at	22835	ZFP30	ZFP30 zinc finger protein	0.039659	-1.30683
216213_at	4750	NEK1	NIMA-related kinase 1	0.005953	-1.30614
212290_at	6541	SLC7A1	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1	0.021708	-1.30478
217963_s_at	27018	NGFRAP1	nerve growth factor receptor (TNFRSF16) associated protein 1	0.025246	-1.30256
202068_s_at	3949	LDLR	low density lipoprotein receptor	0.017616	-1.3
227898_s_at	286128	ZFP41	ZFP41 zinc finger protein	0.005387	-1.29819
200672_x_at	6711	SPTBN1	spectrin, beta, non-erythrocytic 1	0.001176	-1.29538
204038_s_at	1902	LPAR1	lysophosphatidic acid receptor 1	0.030502	-1.29527
226767_s_at	81889	FAHD1	fumarylacetoacetate hydrolase domain containing 1	0.03553	-1.29463
222451_s_at	51114	ZDHHC9	zinc finger, DHHC-type containing 9	0.000231	-1.29302

209218_at	6713	SQLE	squalene epoxidase	0.015062	-1.29266
1553508_at	259283	MDS2	myelodysplastic syndrome 2 translocation associated	0.025704	-1.29186
227173_s_at	60468	BACH2	BTB and CNC homology 1, basic leucine zipper transcription factor 2	0.003167	-1.28991
228121_at	7042 /// 103611157	TGFB2 /// TGFB2-OT1	transforming growth factor beta 2 /// TGFB2 overlapping transcript 1	0.024348	-1.28921
200671_s_at	6711	SPTBN1	spectrin, beta, non-erythrocytic 1	0.004929	-1.28618
209349_at	10111	RAD50	RAD50 homolog, double strand break repair protein	0.009512	-1.28475
1562681_at	338651	KRTAP5-AS1	KRTAP5-1/KRTAP5-2 antisense RNA 1	0.010316	-1.2847
38521_at	933	CD22	CD22 molecule	0.026956	-1.28313
206873_at	765	CA6	carbonic anhydrase VI	0.040209	-1.28311
204918_s_at	4300	MLLT3	myeloid/lymphoid or mixed-lineage leukemia; translocated to, 3	0.026528	-1.28268
1554930_a_at	2530	FUT8	fucosyltransferase 8 (alpha (1,6) fucosyltransferase)	0.014334	-1.28265
220022_at	55713	ZNF334	zinc finger protein 334	0.009217	-1.28243
230489_at	921	CD5	CD5 molecule	0.016931	-1.28129

221802_s_at	57698	SHTN1	shootin 1	0.047625	-1.28028
203852_s_at	6606 /// 6607	SMN1 /// SMN2	survival of motor neuron 1, telomeric /// survival of motor neuron 2, centromeric	0.024482	-1.27846
229558_at	400506	KNOP1	lysine-rich nucleolar protein 1	0.006371	-1.2779
214359_s_at	3326	HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	0.001642	-1.27759
1561367_a_at	100506622	LINC00540	long intergenic non-protein coding RNA 540	0.02034	-1.2764
213914_s_at	6711	SPTBN1	spectrin, beta, non-erythrocytic 1	0.002366	-1.2761
204581_at	933	CD22	CD22 molecule	0.030877	-1.27373
227853_at	196463	PLBD2	phospholipase B domain containing 2	0.030938	-1.27045
205249_at	1959	EGR2	early growth response 2	0.024954	-1.26922
219205_at	63826	SRR	serine racemase	0.033354	-1.2691
200688_at	23450	SF3B3	splicing factor 3b subunit 3	0.001003	-1.2673
205895_s_at	9221	NOLC1	nucleolar and coiled-body phosphoprotein 1	0.000665	-1.26725
229000_at	58492	ZNF77	zinc finger protein 77	0.023174	-1.26671
226947_at	375513 ///	GUSBP1 /// GUSBP4 ///	glucuronidase, beta pseudogene 1 ///	0.023973	-1.26562

	728411 /// 101929200 /// 106660612	LINC00680 /// LOC101929200	glucuronidase, beta pseudogene 4 /// long intergen		
233436_at	27085	MTBP	MDM2 binding protein	0.019201	-1.26553
1568801_at	81556	VWA9	von Willebrand factor A domain containing 9	0.011271	-1.26508
206206_at	4064	CD180	CD180 molecule	0.026621	-1.26493
206150_at	939	CD27	CD27 molecule	0.021652	-1.26485
204407_at	8458	TTF2	transcription termination factor, RNA polymerase II	0.048833	-1.26367
227744_s_at	3184	HNRNPD	heterogeneous nuclear ribonucleoprotein D	0.0139	-1.26311
211501_s_at	8662	EIF3B	eukaryotic translation initiation factor 3, subunit B	0.021379	-1.26305
208624_s_at	1981	EIF4G1	eukaryotic translation initiation factor 4 gamma, 1	0.009528	-1.26233
216607_s_at	1595 /// 401387	CYP51A1 /// LRRD1	cytochrome P450, family 51, subfamily A, polypeptide 1 /// leucine-rich repeats and dea	0.025631	-1.26101
218430_s_at	64864	RFX7	regulatory factor X, 7	0.022807	-1.26079
1566472_s_at	54884	RETSAT	retinol saturase (all-trans-retinol 13,14-reductase)	0.004197	-1.25948

227935_s_at	84333	PCGF5	polycomb group ring finger 5	0.037963	-1.25902
228298_at	91523	PCED1B	PC-esterase domain containing 1B	0.011263	-1.25892
211776_s_at	23136	EPB41L3	erythrocyte membrane protein band 4.1-like 3	0.031874	-1.25824
203147_s_at	9830	TRIM14	tripartite motif containing 14	0.009095	-1.25824
242702_at	166785	MMAA	methylmalonic aciduria (cobalamin deficiency) cblA type	0.040908	-1.25808
213428_s_at	1291	COL6A1	collagen, type VI, alpha 1	0.046472	-1.25725
213324_at	6714	SRC	SRC proto-oncogene, non-receptor tyrosine kinase	0.048477	-1.25598
202759_s_at	11217 /// 445815	AKAP2 /// PALM2-AKAP2	A kinase (PRKA) anchor protein 2 /// PALM2-AKAP2 readthrough	0.03647	-1.25585
216542_x_at	3493 /// 3500 /// 3507 /// 28445	IGHA1 /// IGHG1 /// IGHM /// IGHV3-20	immunoglobulin heavy constant alpha 1 /// immunoglobulin heavy constant gamma 1 (G1m ma	0.035222	-1.25499
212992_at	113146	AHNAK2	AHNAK nucleoprotein 2	0.012912	-1.25496
219592_at	79648	MCPH1	microcephalin 1	0.004325	-1.25256
203684_s_at	596	BCL2	B-cell CLL/lymphoma 2	0.033042	-1.25236
201561_s_at	22883	CLSTN1	calsyntenin 1	0.003058	-1.25204

229757_at	92345	NAF1	nuclear assembly factor 1 ribonucleoprotein	0.010271	-1.25179
225802_at	116447	TOP1MT	topoisomerase (DNA) I, mitochondrial	0.028143	-1.25114
213746_s_at	2316	FLNA	filamin A, alpha	0.019653	-1.24992
222134_at	8528	DDO	D-aspartate oxidase	0.047165	-1.24985
203099_s_at	9425	CDYL	chromodomain protein, Y-like	0.023433	-1.24972
226694_at	11217 /// 445815	AKAP2 /// PALM2-AKAP2	A kinase (PRKA) anchor protein 2 /// PALM2-AKAP2 readthrough	0.023727	-1.24826
217230_at	7430	EZR	ezrin	0.022169	-1.24759
223961_s_at	1154	CISH	cytokine inducible SH2-containing protein	0.00731	-1.2471
202470_s_at	11052	CPSF6	cleavage and polyadenylation specific factor 6	0.04915	-1.24701
213237_at	400506	KNOP1	lysine-rich nucleolar protein 1	0.00302	-1.24648
208625_s_at	1981	EIF4G1	eukaryotic translation initiation factor 4 gamma, 1	0.00672	-1.24635
209723_at	5272	SERPINB9	serpin peptidase inhibitor, clade B (ovalbumin), member 9	0.001771	-1.24627
200835_s_at	4134	MAP4	microtubule associated protein 4	0.01958	-1.24441
201000_at	16	AARS	alanyl-tRNA synthetase	0.004646	-1.244

225715_at	57521	RPTOR	regulatory associated protein of MTOR, complex 1	0.002742	-1.24385
232753_at	23567	ZNF346	zinc finger protein 346	0.019557	-1.24309
227808_at	29103	DNAJC15	DnaJ (Hsp40) homolog, subfamily C, member 15	0.024767	-1.24291
202915_s_at	9917	FAM20B	family with sequence similarity 20, member B	0.034742	-1.2427
217610_at	441273	SPDYE2	speedy/RINGO cell cycle regulator family member E2	0.014699	-1.24166
228065_at	283149	BCL9L	B-cell CLL/lymphoma 9-like	0.00749	-1.24071
212504_at	22982	DIP2C	disco-interacting protein 2 homolog C	0.031745	-1.24003
226000_at	55917	CTTNBP2NL	CTTNBP2 N-terminal like	0.029116	-1.23961
234902_s_at	55659	ZNF416	zinc finger protein 416	0.010559	-1.23944
210510_s_at	8829	NRP1	neuropilin 1	0.022039	-1.23934
221648_s_at	79814	AGMAT	agmatinase	0.037989	-1.23888
223377_x_at	1154	CISH	cytokine inducible SH2-containing protein	0.014736	-1.23789
217902_s_at	8924	HERC2	HECT and RLD domain containing E3 ubiquitin protein ligase 2	0.016204	-1.23786
201927_s_at	8502	PKP4	plakophilin 4	0.014057	-1.2375

216961_s_at	84268	RPAIN	RPA interacting protein	0.005721	-1.23725
209501_at	1039 /// 101060399	CDR2 /// LOC101060399	cerebellar degeneration related protein 2 /// cerebellar degeneration-related protein 2	0.014188	-1.23579
229252_at	285973	ATG9B	autophagy related 9B	0.049638	-1.23569
200064_at	3326	HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	0.001649	-1.23538
221588_x_at	4329	ALDH6A1	aldehyde dehydrogenase 6 family, member A1	0.037191	-1.2352
230566_at	150291	MORC2-AS1	MORC2 antisense RNA 1	0.018364	-1.23464
206980_s_at	2323	FLT3LG	fms-related tyrosine kinase 3 ligand	0.03375	-1.23456
217234_s_at	7430	EZR	ezrin	0.025091	-1.23452
221223_x_at	1154	CISH	cytokine inducible SH2-containing protein	0.012035	-1.23438
217933_s_at	51056	LAP3	leucine aminopeptidase 3	0.020944	-1.23421
219865_at	29092	LINC00339	long intergenic non-protein coding RNA 339	0.009061	-1.23278
222276_at	55798	METTL2B	methyltransferase like 2B	0.037804	-1.23257
203119_at	79080	CCDC86	coiled-coil domain containing 86	0.005886	-1.23248
208621_s_at	7430	EZR	ezrin	0.026835	-1.23243

224632_at	54865	GPATCH4	G-patch domain containing 4	0.035726	-1.2322
201027_s_at	9669	EIF5B	eukaryotic translation initiation factor 5B	0.001396	-1.23218
222482_at	23648	SSBP3	single stranded DNA binding protein 3	0.036898	-1.23125
211358_s_at	25792	CIZ1	CDKN1A interacting zinc finger protein 1	0.039417	-1.22999
201326_at	908	CCT6A	chaperonin containing TCP1, subunit 6A (zeta 1)	0.00158	-1.22935
212996_s_at	9875	URB1	URB1 ribosome biogenesis 1 homolog (S. cerevisiae)	0.02281	-1.22925
201797_s_at	7407	VARS	valyl-tRNA synthetase	0.009078	-1.22917
35626_at	6448	SGSH	N-sulfoglucosamine sulfohydrolase	0.010202	-1.22859
202188_at	9688	NUP93	nucleoporin 93kDa	0.002566	-1.22834
223384_s_at	89122	TRIM4	tripartite motif containing 4	0.004965	-1.22816
205264_at	10849	CD3EAP	CD3e molecule, epsilon associated protein	0.001714	-1.22772
202474_s_at	3054	HCFC1	host cell factor C1	0.006544	-1.22761
226938_at	26094	DCAF4	DDB1 and CUL4 associated factor 4	0.004333	-1.22736
57715_at	51063	CALHM2	calcium homeostasis modulator 2	0.023981	-1.22735
219528_s_at	64919	BCL11B	B-cell CLL/lymphoma 11B (zinc finger protein)	0.041356	-1.22669

1555741_at	56246	MRAP	melanocortin 2 receptor accessory protein	0.010333	-1.22655
230546_at	22846	VASH1	vasohibin 1	0.028736	-1.22557
204977_at	1662	DDX10	DEAD (Asp-Glu-Ala-Asp) box polypeptide 10	0.041819	-1.22505
1563245_at	100874063	CLYBL-AS2	CLYBL antisense RNA 2	0.002578	-1.22459
208627_s_at	4904	YBX1	Y box binding protein 1	0.011361	-1.22421
205120_s_at	6443	SGCB	sarcoglycan beta	0.020202	-1.22409
215811_at	6622	SNCA	synuclein alpha	0.025588	-1.22331
233341_s_at	84172	POLR1B	polymerase (RNA) I polypeptide B	0.027706	-1.2232
205926_at	9466	IL27RA	interleukin 27 receptor, alpha	0.005606	-1.22303
208897_s_at	8886	DDX18	DEAD (Asp-Glu-Ala-Asp) box polypeptide 18	0.004417	-1.223
208744_x_at	10808	HSPH1	heat shock 105kDa/110kDa protein 1	0.037098	-1.22295
212520_s_at	6597	SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a	0.02204	-1.22274
227153_at	83943	IMMP2L	inner mitochondrial membrane peptidase subunit 2	0.015217	-1.2217
231892_at	84904	ARHGEF39	Rho guanine nucleotide exchange factor 39	0.019178	-1.22111

1567628_at	972	CD74	CD74 molecule, major histocompatibility complex, class II invariant chain	0.020128	-1.22051
200702_s_at	57062	DDX24	DEAD (Asp-Glu-Ala-Asp) box helicase 24	0.007402	-1.22044
221744_at	10238	DCAF7	DDB1 and CUL4 associated factor 7	0.011801	-1.22013
1567627_at	972	CD74	CD74 molecule, major histocompatibility complex, class II invariant chain	0.018287	-1.22006
218897_at	80775	TMEM177	transmembrane protein 177	0.048682	-1.21993
208079_s_at	6790	AURKA	aurora kinase A	0.010526	-1.21932
1555347_at	23042	PDXDC1	pyridoxal-dependent decarboxylase domain containing 1	0.03815	-1.21893
218949_s_at	55278	QRSL1	glutaminyl-tRNA synthase (glutamine-hydrolyzing)-like 1	0.008672	-1.2187
205718_at	3695	ITGB7	integrin beta 7	0.049676	-1.21759
212295_s_at	6541	SLC7A1	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1	0.018847	-1.21734
219204_s_at	63826	SRR	serine racemase	0.008736	-1.21718
211300_s_at	7157	TP53	tumor protein p53	0.017734	-1.21681

215093_at	50814	NSDHL	NAD(P) dependent steroid dehydrogenase-like	0.011881	-1.21678
1554415_at	27097	TAF5L	TAF5-like RNA polymerase II, p300/CBP-associated factor (PCAF)-associated factor, 65kDa	0.002987	-1.216
213750_at	26156	RSL1D1	ribosomal L1 domain containing 1	0.007175	-1.21502
212815_at	10973	ASCC3	activating signal cointegrator 1 complex subunit 3	0.048661	-1.21477
206277_at	5029	P2RY2	purinergic receptor P2Y, G-protein coupled, 2	0.048894	-1.21477
237215_s_at	7037	TFRC	transferrin receptor	0.04635	-1.21393
208758_at	471	ATIC	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase	0.008432	-1.21388
222416_at	5832	ALDH18A1	aldehyde dehydrogenase 18 family, member A1	0.029069	-1.21367
234987_at	25939	SAMHD1	SAM domain and HD domain 1	0.002893	-1.21337
210657_s_at	5414	SEPTIN4	septin 4	0.033864	-1.2133
204917_s_at	4300	MLLT3	myeloid/lymphoid or mixed-lineage leukemia; translocated to, 3	0.046147	-1.21289
223950_s_at	84256	FLYWCH1	FLYWCH-type zinc finger 1	0.030119	-1.2125

209153_s_at	6929	TCF3	transcription factor 3	0.022309	-1.2115
222670_s_at	9935	MAFB	v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog B	0.047919	-1.21133
224634_at	54865	GPATCH4	G-patch domain containing 4	0.017963	-1.21117
225865_x_at	51497	NELFCD	negative elongation factor complex member C/D	0.001311	-1.21103
207255_at	3953	LEPR	leptin receptor	0.022616	-1.211
1559856_s_at	4297	KMT2A	lysine (K)-specific methyltransferase 2A	0.035094	-1.21068
202472_at	4351	MPI	mannose phosphate isomerase	0.010397	-1.21053
207740_s_at	23636	NUP62	nucleoporin 62kDa	0.013797	-1.21026
221733_s_at	54865	GPATCH4	G-patch domain containing 4	0.04544	-1.20996
218590_at	56652	C10orf2	chromosome 10 open reading frame 2	0.002593	-1.20967
212811_x_at	6509	SLC1A4	solute carrier family 1 (glutamate/neutral amino acid transporter), member 4	0.022613	-1.20955
31637_s_at	7067 /// 9572	NR1D1 /// THRA	nuclear receptor subfamily 1, group D, member 1 /// thyroid hormone receptor, alpha	0.045804	-1.20942
221730_at	1290	COL5A2	collagen, type V, alpha 2	0.033371	-1.20894

222666_s_at	10171	RCL1	RNA terminal phosphate cyclase-like 1	0.014512	-1.20885
200708_at	2806	GOT2	glutamic-oxaloacetic transaminase 2, mitochondrial	0.007258	-1.20867
222613_at	57102	C12orf4	chromosome 12 open reading frame 4	0.026724	-1.20804
223403_s_at	84172	POLR1B	polymerase (RNA) I polypeptide B	0.013718	-1.20726
240379_at	8502	PKP4	plakophilin 4	0.027173	-1.20722
225689_at	84892	POMGNT2	protein O-linked mannose N-acetylglucosaminyltransferase 2 (beta 1,4-)	0.033339	-1.2071
225261_x_at	51497	NELFCD	negative elongation factor complex member C/D	0.002001	-1.20618
216863_s_at	22880	MORC2	MORC family CW-type zinc finger 2	0.009617	-1.20507
211953_s_at	3843	IPO5	importin 5	0.030464	-1.20501
242049_s_at	51594	NBAS	neuroblastoma amplified sequence	0.013346	-1.20475
200782_at	308	ANXA5	annexin A5	0.000936	-1.20379
223533_at	84230	LRRC8C	leucine rich repeat containing 8 family, member C	0.018384	-1.2035
221571_at	7187	TRAF3	TNF receptor-associated factor 3	0.005278	-1.20346
214095_at	6472	SHMT2	serine hydroxymethyltransferase 2 (mitochondrial)	0.012386	-1.20313

223323_x_at	54822	TRPM7	transient receptor potential cation channel, subfamily M, member 7	0.029273	-1.20262
242422_at	10146	G3BP1	GTPase activating protein (SH3 domain) binding protein 1	0.038192	-1.20258
224878_at	56061	UBFD1	ubiquitin family domain containing 1	0.006162	-1.20242
204293_at	6448	SGSH	N-sulfoglucosamine sulfohydrolase	0.010918	-1.20241
223743_s_at	51073	MRPL4	mitochondrial ribosomal protein L4	0.020406	-1.2014
221652_s_at	55726	ASUN	asunder spermatogenesis regulator	0.019072	-1.20138
235779_at	284408	ZNF790-AS1	ZNF790 antisense RNA 1	0.039398	-1.20138
228449_at	22880	MORC2	MORC family CW-type zinc finger 2	0.025298	-1.20104
210039_s_at	5588	PRKCQ	protein kinase C, theta	0.029745	-1.20099
200598_s_at	7184	HSP90B1	heat shock protein 90kDa beta (Grp94), member 1	0.019079	-1.20043
200697_at	3098	HK1	hexokinase 1	0.049115	-1.20011
217649_at	7763	ZFAND5	zinc finger, AN1-type domain 5	0.022549	1.20077
1558747_at	23347	SMCHD1	structural maintenance of chromosomes flexible hinge domain containing 1	0.028481	1.20094

207492_at	55768	NGLY1	N-glycanase 1	0.011334	1.20127
215082_at	60481	ELOVL5	ELOVL fatty acid elongase 5	0.027563	1.20128
215044_s_at	10254	STAM2	signal transducing adaptor molecule (SH3 domain and ITAM motif) 2	0.009701	1.20132
214544_s_at	8773	SNAP23	synaptosome associated protein 23kDa	0.012336	1.20171
211574_s_at	4179	CD46	CD46 molecule, complement regulatory protein	0.014263	1.20175
243173_at	164633	CABP7	calcium binding protein 7	0.016761	1.20203
213349_at	23023	TMCC1	transmembrane and coiled-coil domain family 1	0.043437	1.20223
231280_at	23593	HEBP2	heme binding protein 2	0.011654	1.20226
1558965_at	51317	PHF21A	PHD finger protein 21A	0.024412	1.20233
227939_s_at	29896	TRA2A	transformer 2 alpha homolog (Drosophila)	0.025649	1.20244
241627_x_at	55701	ARHGEF40	Rho guanine nucleotide exchange factor (GEF) 40	0.008311	1.20262
205698_s_at	5608	MAP2K6	mitogen-activated protein kinase kinase 6	0.038562	1.20283
214270_s_at	22924	MAPRE3	microtubule-associated protein, RP/EB family, member 3	0.01287	1.20295

241809_at	55924 /// 101928718	FAM212B /// LOC101928718	family with sequence similarity 212, member B /// uncharacterized LOC101928718	0.047367	1.2031
218521_s_at	55284	UBE2W	ubiquitin-conjugating enzyme E2W (putative)	0.014011	1.20313
220404_at	222487	ADGRG3	adhesion G protein-coupled receptor G3	0.041482	1.20335
236951_at	55968	NSFL1C	NSFL1 (p97) cofactor (p47)	0.041411	1.20359
1569709_at	23334	SZT2	seizure threshold 2 homolog (mouse)	0.025694	1.20418
1553157_at	89884	LHX4	LIM homeobox 4	0.016612	1.20423
222619_at	23528	ZNF281	zinc finger protein 281	0.027357	1.20427
222692_s_at	64778	FNDC3B	fibronectin type III domain containing 3B	0.011129	1.20476
207286_at	9662	CEP135	centrosomal protein 135kDa	0.036752	1.20545
1555086_at	6777	STAT5B	signal transducer and activator of transcription 5B	0.024347	1.20547
204195_s_at	5316	PKNOX1	PBX/knotted 1 homeobox 1	0.025719	1.20581
232320_at	10228 /// 103344928	KIAA1614-AS1 /// STX6	KIAA1614 antisense RNA 1 /// syntaxin 6	0.038562	1.20584
207890_s_at	64386	MMP25	matrix metallopeptidase 25	0.013431	1.20597

1560910_at	285755	PPIL6	peptidylprolyl isomerase (cyclophilin)-like 6	0.027384	1.20631
240197_at	6854	SYN2	synapsin II	0.041241	1.20689
209526_s_at	50810	HDGFRP3	hepatoma-derived growth factor, related protein 3	0.01042	1.20773
232135_at	79685	SAP30L	SAP30-like	0.001187	1.20774
232513_x_at	388799	FAM209B	family with sequence similarity 209, member B	0.012805	1.2082
209403_at	84218 /// 390788 /// 414059 /// 414060 /// 729873 /// 729877 /// 101060321 /// 1010603 5	CCL3P1 /// LOC101060389 /// TBC1D3 /// TBC1D3B /// TBC1D3C /// TBC1D3E /// TBC1D3F /// TBC1D3G /// TBC1D3H /// TBC1D3I /// TBC1D3K /// TBC1D3L	chemokine (C-C motif) ligand 3 pseudogene 1 /// TBC1 domain family member-like /// TBC1	0.002089	1.2088
232126_at	27235	COQ2	coenzyme Q2 4-hydroxybenzoate polyprenyltransferase	0.030633	1.2088
242155_x_at	117584	RFFL	ring finger and FYVE-like domain containing E3 ubiquitin protein ligase	0.019623	1.20896

220615_s_at	55711	FAR2	fatty acyl-CoA reductase 2	0.027131	1.20902
1555904_at	10129	FRY	FRY microtubule binding protein	0.026742	1.20912
223460_at	84254	CAMKK1	calcium/calmodulin-dependent protein kinase kinase 1, alpha	0.036393	1.2092
216316_x_at	2710 /// 2713	GK /// GK3P	glycerol kinase /// glycerol kinase 3 pseudogene	0.041839	1.2093
211561_x_at	1432	MAPK14	mitogen-activated protein kinase 14	0.039871	1.20932
211612_s_at	3597	IL13RA1	interleukin 13 receptor, alpha 1	0.045909	1.2095
220832_at	51311	TLR8	toll-like receptor 8	0.036673	1.20964
1555105_a_at	57708	MIER1	mesoderm induction early response 1, transcriptional regulator	0.018672	1.20965
223930_at	26092	TOR1AIP1	torsin A interacting protein 1	0.045872	1.20989
235540_at	2796	GNRH1	gonadotropin releasing hormone 1	0.047055	1.21061
243222_at	80216	ALPK1	alpha kinase 1	0.030152	1.21066
232535_at	222194	RSBN1L	round spermatid basic protein 1-like	0.01259	1.21074
237943_at	23023	TMCC1	transmembrane and coiled-coil domain family 1	0.048826	1.21101
227832_at	114785	MBD6	methyl-CpG binding domain protein 6	0.009133	1.21102

209383_at	1649	DDIT3	DNA-damage-inducible transcript 3	0.016634	1.2116
1568666_at	440503	PLIN5	perilipin 5	0.005002	1.21162
235000_at	4026	LPP	LIM domain containing preferred translocation partner in lipoma	0.012855	1.21186
230000_at	57674	RNF213	ring finger protein 213	0.008842	1.21253
1562511_at	1130	LYST	lysosomal trafficking regulator	0.015479	1.2126
237495_at	143098	MPP7	membrane protein, palmitoylated 7	0.037151	1.21264
1565546_at	50862	RNF141	ring finger protein 141	0.041396	1.21341
1558688_at	441461	STX17-AS1	STX17 antisense RNA 1	0.007087	1.21382
207549_x_at	4179	CD46	CD46 molecule, complement regulatory protein	0.007251	1.21409
235181_at	129450	TYW5	tRNA-yW synthesizing protein 5	0.047081	1.21414
1555167_s_at	10135	NAMPT	nicotinamide phosphoribosyltransferase	0.02199	1.21429
210449_x_at	1432	MAPK14	mitogen-activated protein kinase 14	0.026731	1.2144
1561652_at	8678	BECN1	beclin 1, autophagy related	0.009849	1.21456
204714_s_at	2153	F5	coagulation factor V (proaccelerin, labile factor)	0.024251	1.2146

219577_s_at	10347	ABCA7	ATP binding cassette subfamily A member 7	0.038488	1.21589
1564063_a_at	23200	ATP11B	ATPase, class VI, type 11B	0.006861	1.21601
215310_at	324	APC	adenomatous polyposis coli	0.010646	1.21671
1559413_at	255394	TCP11L2	t-complex 11, testis-specific-like 2	0.03952	1.21685
242707_at	9439	MED23	mediator complex subunit 23	0.038611	1.21697
240233_at	100506714	NUP50-AS1	NUP50 antisense RNA 1 (head to head)	0.022806	1.21709
215185_at	100506190	LINC00963	long intergenic non-protein coding RNA 963	0.019332	1.21727
34408_at	6253	RTN2	reticulon 2	0.039392	1.21731
230250_at	5787	PTPRB	protein tyrosine phosphatase, receptor type, B	0.007662	1.21749
210059_s_at	5603	MAPK13	mitogen-activated protein kinase 13	0.002785	1.21762
212862_at	8760	CDS2	CDP-diacylglycerol synthase 2	0.017467	1.21763
236292_at	55819	RNF130	ring finger protein 130	0.032916	1.2177
1555088_x_at	6777	STAT5B	signal transducer and activator of transcription 5B	0.01511	1.21776
220239_at	55975	KLHL7	kelch-like family member 7	0.029488	1.21777
223674_s_at	56882	CDC42SE1	CDC42 small effector 1	0.030245	1.21843

1559060_a_at	96459	FNIP1	folliculin interacting protein 1	0.029906	1.21876
214846_s_at	57538	ALPK3	alpha kinase 3	0.010565	1.21881
227893_at	100128782	LINC00476	long intergenic non-protein coding RNA 476	0.028514	1.21925
242622_x_at	5728	PTEN	phosphatase and tensin homolog	0.020792	1.21955
230800_at	196883	ADCY4	adenylate cyclase 4	0.028229	1.21968
216129_at	10079	ATP9A	ATPase, class II, type 9A	0.033048	1.21977
224483_s_at	84804	MFSD9	major facilitator superfamily domain containing 9	0.01815	1.21992
233575_s_at	7091	TLE4	transducin-like enhancer of split 4	0.003126	1.22
235816_s_at	266747	RGL4	ral guanine nucleotide dissociation stimulator-like 4	0.034347	1.22056
228335_at	5010	CLDN11	claudin 11	0.047986	1.22065
229214_at	8417	STX7	syntaxin 7	0.024939	1.22075
222745_s_at	79768	KATNBL1	katanin p80 subunit B-like 1	0.006167	1.22092
237338_at	374907	B3GNT8	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 8	0.044677	1.22101

229382_at	55924 /// 101928718	FAM212B /// LOC101928718	family with sequence similarity 212, member B /// uncharacterized LOC101928718	0.01616	1.22105
235156_at	254065	BRWD3	bromodomain and WD repeat domain containing 3	0.030738	1.22108
229312_s_at	80318	GKAP1	G kinase anchoring protein 1	0.016308	1.22115
208499_s_at	5611	DNAJC3	DnaJ (Hsp40) homolog, subfamily C, member 3	0.028639	1.22116
1554556_a_at	23200	ATP11B	ATPase, class VI, type 11B	0.005439	1.22125
231345_s_at	79758	DHRS12	dehydrogenase/reductase (SDR family) member 12	0.017566	1.22151
231099_at	23307	FKBP15	FK506 binding protein 15	0.026999	1.2219
243904_at	134957	STXBP5	syntaxin binding protein 5 (tomosyn)	0.016716	1.22271
243719_at	8859	STK19	serine/threonine kinase 19	0.006259	1.22289
213173_at	22990	PCNX	pecanex homolog (Drosophila)	0.037365	1.22299
236534_at	149428	BNIPL	BCL2/adenovirus E1B 19kD interacting protein like	0.021122	1.22312
229952_at	26030	PLEKHG3	pleckstrin homology domain containing, family G (with RhoGef domain) member 3	0.035568	1.22327
235723_at	54796	BNC2	basonuclin 2	0.023152	1.22328

234787_at	80179	MYO19	myosin XIX	0.029914	1.22359
209502_s_at	10458	BAIAP2	BAI1-associated protein 2	0.049968	1.22394
237439_at	124739	USP43	ubiquitin specific peptidase 43	0.040776	1.22403
1558573_at	28985	MCTS1	malignant T-cell amplified sequence 1	0.007707	1.22423
213844_at	3202	HOXA5	homeobox A5	0.034574	1.22434
210666_at	3423	IDS	iduronate 2-sulfatase	0.005688	1.2248
233305_at	64168	NECAB1	N-terminal EF-hand calcium binding protein 1	0.000964	1.22537
212492_s_at	23030	KDM4B	lysine (K)-specific demethylase 4B	0.046631	1.22606
1554501_at	81628	TSC22D4	TSC22 domain family, member 4	0.023151	1.22628
203389_at	3797	KIF3C	kinesin family member 3C	0.041431	1.22646
229362_at	150962	PUS10	pseudouridylate synthase 10	0.023425	1.22657
228407_at	222663	SCUBE3	signal peptide, CUB domain, EGF-like 3	0.024253	1.22692
229398_at	22931	RAB18	RAB18, member RAS oncogene family	0.00596	1.22724
203525_s_at	324	APC	adenomatous polyposis coli	0.032263	1.22726
233072_at	84628	NTNG2	netrin G2	0.013373	1.22739

202147_s_at	3475	IFRD1	interferon-related developmental regulator 1	0.02393	1.22749
37028_at	23645	PPP1R15A	protein phosphatase 1, regulatory subunit 15A	0.040395	1.2281
243934_at	440836	ODF3B	outer dense fiber of sperm tails 3B	0.00316	1.22811
237591_at	100287569	LINC00173	long intergenic non-protein coding RNA 173	0.041844	1.22844
1555177_at	5562	PRKAA1	protein kinase, AMP-activated, alpha 1 catalytic subunit	0.014661	1.22871
1558711_at	285512	FAM13A-AS1	FAM13A antisense RNA 1	0.003031	1.22929
213559_s_at	168544	ZNF467	zinc finger protein 467	0.025489	1.22937
215321_at	154661	RUNDC3B	RUN domain containing 3B	0.015034	1.22978
204095_s_at	8178	ELL	elongation factor RNA polymerase II	0.020421	1.23026
207764_s_at	10114	HIPK3	homeodomain interacting protein kinase 3	0.039739	1.23095
1559754_at	4050	LTB	lymphotoxin beta (TNF superfamily, member 3)	0.024486	1.23103
228585_at	953	ENTPD1	ectonucleoside triphosphate diphosphohydrolase 1	0.03613	1.23117
230562_at	100507530	MCPH1-AS1	MCPH1 antisense RNA 1	0.012649	1.23118
1552691_at	115761	ARL11	ADP-ribosylation factor like GTPase 11	0.018101	1.23131

1554178_a_at	285172	FAM126B	family with sequence similarity 126, member B	0.012837	1.2315
242280_x_at	80315	CPEB4	cytoplasmic polyadenylation element binding protein 4	0.033623	1.23184
203651_at	9765	ZFYVE16	zinc finger, FYVE domain containing 16	0.023918	1.23196
206155_at	1244	ABCC2	ATP binding cassette subfamily C member 2	0.007714	1.232
239273_s_at	79148	MMP28	matrix metallopeptidase 28	0.028559	1.23273
234006_s_at	56063	TMEM234	transmembrane protein 234	0.008611	1.2328
218739_at	51099	ABHD5	abhydrolase domain containing 5	0.047918	1.23292
235829_at	100526820	CAHM	colon adenocarcinoma hypermethylated (non-protein coding)	0.003726	1.23373
223652_at	57412	AS3MT	arsenite methyltransferase	0.01261	1.23391
221149_at	27202	C5AR2	complement component 5a receptor 2	0.029951	1.23401
230587_at	474171	STGC3	uncharacterized STGC3	0.022612	1.23452
205857_at	6571	SLC18A2	solute carrier family 18 (vesicular monoamine transporter), member 2	0.029357	1.23465
243547_at	283876	LINC00921	long intergenic non-protein coding RNA 921	0.006516	1.23488
1560175_at	55370	PPP4R1L	protein phosphatase 4, regulatory subunit 1-like (pseudogene)	0.024974	1.23506

229311_at	80318	GKAP1	G kinase anchoring protein 1	0.003202	1.23523
217268_at	7879	RAB7A	RAB7A, member RAS oncogene family	0.00542	1.23566
229623_at	441027	TMEM150C	transmembrane protein 150C	0.000541	1.23566
226794_at	134957	STXBP5	syntaxin binding protein 5 (tomosyn)	0.041303	1.23674
205921_s_at	6533	SLC6A6	solute carrier family 6 (neurotransmitter transporter), member 6	0.035984	1.23684
228064_at	388886	LRRC75B	leucine rich repeat containing 75B	0.038556	1.23693
214987_at	2549	GAB1	GRB2-associated binding protein 1	0.009934	1.23758
238986_at	378805	LINC-PINT	long intergenic non-protein coding RNA, p53 induced transcript	0.015152	1.23768
1556588_at	283687	ST20-AS1	ST20 antisense RNA 1	0.047933	1.23818
227004_at	6792	CDKL5	cyclin-dependent kinase-like 5	0.0364	1.23829
232322_x_at	10809	STARD10	StAR-related lipid transfer domain containing 10	0.043525	1.23842
215977_x_at	2710	GK	glycerol kinase	0.043555	1.23878
204800_s_at	79758	DHRS12	dehydrogenase/reductase (SDR family) member 12	0.035899	1.23897
221638_s_at	8675	STX16	syntaxin 16	0.003493	1.23936

240088_at	8654	PDE5A	phosphodiesterase 5A, cGMP-specific	0.010176	1.24062
223863_at	80232	WDR26	WD repeat domain 26	0.049006	1.24064
1553405_a_at	64478	CSMD1	CUB and Sushi multiple domains 1	0.007623	1.24097
213292_s_at	23161	SNX13	sorting nexin 13	0.023339	1.24101
242210_at	7572	ZNF24	zinc finger protein 24	0.018515	1.24108
204531_s_at	672	BRCA1	breast cancer 1, early onset	0.007234	1.24154
1560486_at	6814	STXBP3	syntaxin binding protein 3	0.016395	1.24202
241425_at	9818	NUP58	nucleoporin 58kDa	0.00262	1.24209
232873_at	7581	ZNF33A	zinc finger protein 33A	0.025316	1.24214
221979_at	100129250	TOPORS-AS1	TOPORS antisense RNA 1	0.00238	1.24258
208868_s_at	23710	GABARAPL1	GABA(A) receptor-associated protein like 1	0.020221	1.24266
214746_s_at	168544	ZNF467	zinc finger protein 467	0.018435	1.24369
202014_at	23645	PPP1R15A	protein phosphatase 1, regulatory subunit 15A	0.043212	1.24446
241908_at	148362	BROX	BRO1 domain and CAAX motif containing	0.035565	1.24449
203434_s_at	4311	MME	membrane metallo-endopeptidase	0.024579	1.2453

240845_at	7813	EVI5	ecotropic viral integration site 5	0.02845	1.24635
229608_at	55924 /// 101928718	FAM212B /// LOC101928718	family with sequence similarity 212, member B /// uncharacterized LOC101928718	0.020935	1.24694
230506_at	57150 /// 63914	LINC01590 /// SMIM8	long intergenic non-protein coding RNA 1590 /// small integral membrane protein 8	0.033463	1.24767
243201_at	6173	RPL36A	ribosomal protein L36a	0.00654	1.24795
228894_at	2649	NR6A1	nuclear receptor subfamily 6, group A, member 1	0.023736	1.24848
1563369_at	100287569	LINC00173	long intergenic non-protein coding RNA 173	0.043264	1.24868
1555217_at	55284	UBE2W	ubiquitin-conjugating enzyme E2W (putative)	0.044523	1.24899
226026_at	84925	DIRC2	disrupted in renal carcinoma 2	0.018432	1.2492
217189_s_at	9887	SMG7	SMG7 nonsense mediated mRNA decay factor	0.006584	1.25031
233924_s_at	54536	EXOC6	exocyst complex component 6	0.041189	1.2511
229888_at	144608	C12orf60	chromosome 12 open reading frame 60	0.034802	1.25111
239903_at	7162	TPBG	trophoblast glycoprotein	0.02549	1.25114
228037_at	101929693	RARA-AS1	RARA antisense RNA 1	0.028035	1.25164
1552798_a_at	7099	TLR4	toll-like receptor 4	0.04937	1.25227

229440_at	54502	RBM47	RNA binding motif protein 47	0.006851	1.25267
1555842_at	9266	CYTH2	cytohesin 2	0.010307	1.25293
226490_at	57224	NHSL1	NHS-like 1	0.004444	1.25311
208003_s_at	10725	NFAT5	nuclear factor of activated T-cells 5, tonicity-responsive	0.010235	1.25329
1552480_s_at	5788	PTPRC	protein tyrosine phosphatase, receptor type, C	0.008202	1.25346
242360_at	9079	LDB2	LIM domain binding 2	0.014416	1.25356
243824_at	103352539 /// 105379818	LINC01410 /// LOC105379818	long intergenic non-protein coding RNA 1410 /// uncharacterized LOC105379818	0.045464	1.25425
241817_at	375341	C3orf62	chromosome 3 open reading frame 62	0.010449	1.25497
231133_at	92749	DRC1	dynein regulatory complex subunit 1	0.045856	1.25522
227236_at	10100	TSPAN2	tetraspanin 2	0.007307	1.25524
209082_s_at	80781	COL18A1	collagen, type XVIII, alpha 1	0.026131	1.25591
218924_s_at	1486	CTBS	chitobiase, di-N-acetyl-	0.00204	1.25594
1554291_at	23074	UHRF1BP1L	UHRF1 binding protein 1-like	0.044208	1.25597
231595_at	100129827	MRVI1-AS1	MRVI1 antisense RNA 1	0.021814	1.25606

202695_s_at	9263	STK17A	serine/threonine kinase 17a	0.027731	1.25632
209072_at	4155	MBP	myelin basic protein	0.029106	1.25654
205920_at	6533	SLC6A6	solute carrier family 6 (neurotransmitter transporter), member 6	0.033985	1.25692
223733_s_at	55370	PPP4R1L	protein phosphatase 4, regulatory subunit 1-like (pseudogene)	0.014974	1.25696
219403_s_at	10855	HPSE	heparanase	0.022082	1.25731
1567443_x_at	5663	PSEN1	presenilin 1	0.001597	1.25789
216115_at	4763	NF1	neurofibromin 1	0.022377	1.25816
1564443_at	8847	DLEU2	deleted in lymphocytic leukemia 2 (non-protein coding)	0.008831	1.25863
232639_at	90288	EFCAB12	EF-hand calcium binding domain 12	0.029488	1.25899
1554414_a_at	734	OSGIN2	oxidative stress induced growth inhibitor family member 2	0.04374	1.25913
236808_at	26127	FGFR1OP2	FGFR1 oncogene partner 2	0.007325	1.25922
238903_at	137886	UBXN2B	UBX domain protein 2B	0.018056	1.25952
231385_at	359787	DPPA3	developmental pluripotency associated 3	0.010048	1.25953

238810_at	5991	RFX3	regulatory factor X, 3 (influences HLA class II expression)	0.009129	1.26005
217521_at	3034	HAL	histidine ammonia-lyase	0.002363	1.26024
223995_at	56996	SLC12A9	solute carrier family 12, member 9	0.00783	1.26041
219748_at	79865	TREML2	triggering receptor expressed on myeloid cells-like 2	0.03974	1.26047
214319_at	10129	FRY	FRY microtubule binding protein	0.047016	1.26059
219786_at	9633	MTL5	metallothionein-like 5, testis-specific (tesmin)	0.004029	1.26082
208181_at	8365 /// 105374985	HIST1H4H /// LOC105374985	histone cluster 1, H4h /// uncharacterized LOC105374985	0.016108	1.26175
238019_at	440503	PLIN5	perilipin 5	0.001151	1.26196
78383_at	100129250	TOPORS-AS1	TOPORS antisense RNA 1	0.001672	1.26217
1563229_at	8847	DLEU2	deleted in lymphocytic leukemia 2 (non-protein coding)	0.022636	1.26282
208054_at	26091	HERC4	HECT and RLD domain containing E3 ubiquitin protein ligase 4	0.042283	1.26296
231826_at	57186	RALGAPA2	Ral GTPase activating protein, alpha subunit 2 (catalytic)	0.048112	1.26303

232213_at	57162	PELI1	pellino E3 ubiquitin protein ligase 1	0.023144	1.26305
220777_at	63971	KIF13A	kinesin family member 13A	0.002383	1.26347
232111_at	100507043	TUNAR	TCL1 upstream neural differentiation-associated RNA	0.011887	1.26451
212598_at	23001	WDFY3	WD repeat and FYVE domain containing 3	0.019956	1.2654
239100_x_at	22990	PCNX	pecanex homolog (Drosophila)	0.013508	1.26546
58780_s_at	55701	ARHGEF40	Rho guanine nucleotide exchange factor (GEF) 40	0.024208	1.26732
235699_at	161253	REM2	RAS (RAD and GEM)-like GTP binding 2	0.003942	1.26735
204801_s_at	79758	DHRS12	dehydrogenase/reductase (SDR family) member 12	0.017857	1.26741
230932_at	55819	RNF130	ring finger protein 130	0.02856	1.26746
226363_at	10057	ABCC5	ATP binding cassette subfamily C member 5	0.001867	1.26786
205403_at	7850	IL1R2	interleukin 1 receptor, type II	0.035842	1.26849
212947_at	23315	SLC9A8	solute carrier family 9, subfamily A (NHE8, cation proton antiporter 8), member 8	0.002816	1.2685
1558560_s_at	8548	BLZF1	basic leucine zipper nuclear factor 1	0.01136	1.26959
233123_at	30061	SLC40A1	solute carrier family 40 (iron-regulated transporter), member 1	0.013624	1.27011

213120_at	23074	UHRF1BP1L	UHRF1 binding protein 1-like	0.023407	1.27052
220168_at	55259	CASC1	cancer susceptibility candidate 1	0.009921	1.27056
223103_at	10809	STARD10	StAR-related lipid transfer domain containing 10	0.03425	1.27104
215559_at	368 /// 105369239	ABCC6 /// LOC105369239	ATP binding cassette subfamily C member 6 /// multidrug resistance-associated protein 6	0.021461	1.27202
213288_at	129642	MBOAT2	membrane bound O-acyltransferase domain containing 2	0.010023	1.27343
203223_at	9135	RABEP1	rabaptin, RAB GTPase binding effector protein 1	0.002972	1.27384
232953_at	55251 /// 140849 /// 728323 /// 731275 /// 101927097 /// 102723917 /// 102723928 /// 10	LINC00266-1 /// LINC01347 /// LOC101927097 /// LOC102723917 /// LOC102723928 /// LOC105371423 /// LOC105376332 /// LOC105378582 ///	long intergenic non-protein coding RNA 266-1 /// long intergenic non-protein coding RNA	0.016874	1.27396

		LOC105379690 /// LOC728323 /// PCMTD2			
214161_at	734	OSGIN2	oxidative stress induced growth inhibitor family member 2	0.042432	1.27415
209474_s_at	953	ENTPD1	ectonucleoside triphosphate diphosphohydrolase 1	0.007947	1.27468
219892_at	53346	TM6SF1	transmembrane 6 superfamily member 1	0.00467	1.27497
236154_at	9444	QKI	QKI, KH domain containing, RNA binding	0.025942	1.27567
235745_at	2081	ERN1	endoplasmic reticulum to nucleus signaling 1	0.011249	1.27766
1554127_s_at	253827	MSRB3	methionine sulfoxide reductase B3	0.036406	1.27788
222354_at	50848	F11R	F11 receptor	0.049272	1.27903
1565544_at	50862	RNF141	ring finger protein 141	0.019883	1.27976
232107_at	6391	SDHC	succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa	0.022611	1.28047
213805_at	51099	ABHD5	abhydrolase domain containing 5	0.024934	1.28121
224952_at	26115	TANC2	tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 2	0.007289	1.28123

1568706_s_at	10677	AVIL	advillin	0.026932	1.28204
1555993_at	776	CACNA1D	calcium channel, voltage-dependent, L type, alpha 1D subunit	0.018048	1.2824
214541_s_at	9444	QKI	QKI, KH domain containing, RNA binding	0.035362	1.28292
207691_x_at	953	ENTPD1	ectonucleoside triphosphate diphosphohydrolase 1	0.004626	1.28303
209380_s_at	10057	ABCC5	ATP binding cassette subfamily C member 5	0.006498	1.28315
1569374_at	375341	C3orf62	chromosome 3 open reading frame 62	0.017992	1.28391
233063_s_at	100508120	GMDS-AS1	GMDS antisense RNA 1 (head to head)	0.013448	1.28494
238126_at	100505854	APTR	Alu-mediated CDKN1A/p21 transcriptional regulator (non-protein coding)	0.00856	1.28534
223699_at	84735	CNDP1	carnosine dipeptidase 1 (metallopeptidase M20 family)	0.001781	1.28562
235011_at	10746	MAP3K2	mitogen-activated protein kinase kinase kinase 2	0.038212	1.28593
205118_at	2357	FPR1	formyl peptide receptor 1	0.024591	1.28597
243033_at	5756	TWF1	twinfilin actin binding protein 1	0.001577	1.28625
1557285_at	374	AREG	amphiregulin	0.006043	1.28655

236320_at	149483	CCDC17	coiled-coil domain containing 17	0.012909	1.28655
207366_at	3787	KCNS1	potassium voltage-gated channel, modifier subfamily S, member 1	0.013789	1.28677
232087_at	256643	CXorf23	chromosome X open reading frame 23	0.047487	1.28723
229899_s_at	441951	ZFAS1	ZNFX1 antisense RNA 1	0.003946	1.28818
1565358_at	5914	RARA	retinoic acid receptor, alpha	0.045801	1.2882
206696_at	4935	GPR143	G protein-coupled receptor 143	0.008976	1.28858
207671_s_at	7439	BEST1	bestrophin 1	0.015837	1.28892
211087_x_at	1432	MAPK14	mitogen-activated protein kinase 14	0.000898	1.28911
219334_s_at	64859	NABP1	nucleic acid binding protein 1	0.016281	1.28917
238999_at	10677	AVIL	advillin	0.010248	1.2903
227494_at	2649	NR6A1	nuclear receptor subfamily 6, group A, member 1	0.008179	1.29076
229520_s_at	55668	GPATCH2L	G-patch domain containing 2 like	0.013391	1.29103
206877_at	4084	MXD1	MAX dimerization protein 1	0.029241	1.29129
1567440_at	5663	PSEN1	presenilin 1	0.00041	1.29132
237954_x_at	55701	ARHGEF40	Rho guanine nucleotide exchange factor (GEF) 40	0.008454	1.29138

228409_at	729359	PLIN4	perilipin 4	0.007019	1.29276
1554786_at	57091	CASS4	Cas scaffolding protein family member 4	0.002128	1.29442
238733_at	4193	MDM2	MDM2 proto-oncogene, E3 ubiquitin protein ligase	0.014387	1.2948
240964_at	5728	PTEN	phosphatase and tensin homolog	0.039368	1.29599
207291_at	79056	PRRG4	proline rich Gla (G-carboxyglutamic acid) 4 (transmembrane)	0.038403	1.297
228250_at	96459	FNIP1	folliculin interacting protein 1	0.012531	1.29965
243066_at	80896	NPL	N-acetylneuraminate pyruvate lyase (dihydrodipicolinate synthase)	0.003059	1.29997
230913_at	9619	ABCG1	ATP binding cassette subfamily G member 1	0.028067	1.29998
235095_at	146439	CCDC64B	coiled-coil domain containing 64B	0.04558	1.30025
227992_s_at	147650	SPACA6	sperm acrosome associated 6	0.008033	1.30025
1561615_s_at	6546	SLC8A1	solute carrier family 8 (sodium/calcium exchanger), member 1	0.048078	1.30031
1559739_at	56994	CHPT1	choline phosphotransferase 1	0.025562	1.30085
1554638_at	9765	ZFYVE16	zinc finger, FYVE domain containing 16	0.011114	1.30201

1554442_at	7439	BEST1	bestrophin 1	0.007589	1.30218
209633_at	5523	PPP2R3A	protein phosphatase 2, regulatory subunit B", alpha	0.011528	1.30285
226418_at	51290	ERGIC2	ERGIC and golgi 2	0.005882	1.30343
220034_at	11213	IRAK3	interleukin 1 receptor associated kinase 3	0.030838	1.30373
227855_at	55701	ARHGEF40	Rho guanine nucleotide exchange factor (GEF) 40	0.031504	1.30395
241368_at	440503	PLIN5	perilipin 5	0.002761	1.30572
214606_at	10100	TSPAN2	tetraspanin 2	0.00721	1.30593
206721_at	57821	CCDC181	coiled-coil domain containing 181	0.004353	1.30702
238660_at	23001	WDFY3	WD repeat and FYVE domain containing 3	0.006638	1.30707
1560219_at	51130	ASB3	ankyrin repeat and SOCS box containing 3	0.012124	1.30756
220302_at	4117	MAK	male germ cell-associated kinase	0.019456	1.30759
236241_at	51003	MED31	mediator complex subunit 31	0.010661	1.30794
213174_at	23508	TTC9	tetratricopeptide repeat domain 9	0.008515	1.30875
1554714_at	768211	RELL1	RELT-like 1	0.046971	1.30975
220012_at	56605	ERO1B	endoplasmic reticulum oxidoreductase beta	0.008162	1.31056

1569428_at	1606	DGKA	diacylglycerol kinase alpha	0.006351	1.31089
224836_at	58476	TP53INP2	tumor protein p53 inducible nuclear protein 2	0.034221	1.31126
219434_at	54210	TREM1	triggering receptor expressed on myeloid cells 1	0.001508	1.3122
1557218_s_at	2187	FANCB	Fanconi anemia complementation group B	0.01631	1.31267
238811_at	23200	ATP11B	ATPase, class VI, type 11B	0.001601	1.31457
205328_at	9071	CLDN10	claudin 10	0.028176	1.31492
232081_at	9619	ABCG1	ATP binding cassette subfamily G member 1	0.026514	1.31502
219427_at	79633	FAT4	FAT atypical cadherin 4	0.004371	1.31568
1553736_at	196441	ZFC3H1	zinc finger, C3H1-type containing	0.043544	1.31636
211412_at	23569	PADI4	peptidyl arginine deiminase, type IV	0.035556	1.31734
209160_at	8644	AKR1C3	aldo-keto reductase family 1, member C3	0.040204	1.3179
220326_s_at	55701	ARHGEF40	Rho guanine nucleotide exchange factor (GEF) 40	0.030227	1.318
239119_at	100289274	DNAJC3-AS1	DNAJC3 antisense RNA 1 (head to head)	0.028267	1.31823
226002_at	2549	GAB1	GRB2-associated binding protein 1	0.00611	1.31931

235050_at	154091	SLC2A12	solute carrier family 2 (facilitated glucose transporter), member 12	0.028349	1.31945
207601_at	27284	SULT1B1	sulfotransferase family 1B member 1	0.020958	1.32203
232027_at	23345	SYNE1	spectrin repeat containing, nuclear envelope 1	0.0479	1.32217
214529_at	7252	TSHB	thyroid stimulating hormone, beta	0.026201	1.32542
205513_at	6947	TCN1	transcobalamin I (vitamin B12 binding protein, R binder family)	0.021049	1.32596
214618_at	8837	CFLAR	CASP8 and FADD like apoptosis regulator	0.010403	1.32682
227429_at	283229	CRACR2B	calcium release activated channel regulator 2B	0.002196	1.32771
209135_at	444	ASPH	aspartate beta-hydroxylase	0.048536	1.32772
1553176_at	117157	SH2D1B	SH2 domain containing 1B	0.029375	1.328
224828_at	80315	CPEB4	cytoplasmic polyadenylation element binding protein 4	0.021729	1.32944
214985_at	2131	EXT1	exostosin glycosyltransferase 1	0.003312	1.33035
202543_s_at	2764	GMFB	glia maturation factor, beta	0.035464	1.33093
230585_at	3772	KCNJ15	potassium channel, inwardly rectifying subfamily J, member 15	0.008444	1.33205

1560625_s_at	101928513	CATIP-AS1	CATIP antisense RNA 1	0.013023	1.33235
223349_s_at	666	BOK	BCL2-related ovarian killer	0.042277	1.33254
216789_at	103752589	TMEM92-AS1	TMEM92 antisense RNA 1	0.026803	1.33308
1555049_at	54084	TSPEAR	thrombospondin-type laminin G domain and EAR repeats	0.013591	1.33508
223791_at	100132948 /// 100133121 /// 102725186 /// 105379444	FAM27B /// FAM27C /// LOC102725186 /// LOC105379444	family with sequence similarity 27, member B /// family with sequence similarity 27, me	0.021737	1.33524
223845_at	54621	VSIG10	V-set and immunoglobulin domain containing 10	0.029401	1.33616
1555315_a_at	4117	MAK	male germ cell-associated kinase	0.024265	1.33654
233134_at	9501	RPH3AL	rabphilin 3A-like (without C2 domains)	0.01259	1.33907
235641_at	10221	TRIB1	tribbles pseudokinase 1	0.012237	1.33994
227233_at	10100	TSPAN2	tetraspanin 2	0.015985	1.34057
225503_at	207063	DHRSX	dehydrogenase/reductase (SDR family) X-linked	0.000563	1.34194
228758_at	604	BCL6	B-cell CLL/lymphoma 6	0.008858	1.34255

1558080_s_at	5611	DNAJC3	DnaJ (Hsp40) homolog, subfamily C, member 3	0.001804	1.34347
220010_at	23630	KCNE5	potassium channel, voltage gated subfamily E regulatory beta subunit 5	0.006237	1.34381
238067_at	54885	TBC1D8B	TBC1 domain family, member 8B (with GRAM domain)	0.040265	1.34589
1555953_at	6573	SLC19A1	solute carrier family 19 (folate transporter), member 1	0.001124	1.3469
213812_s_at	10645	CAMKK2	calcium/calmodulin-dependent protein kinase kinase 2, beta	0.006928	1.34788
219837_s_at	54360	CYTL1	cytokine like 1	0.014043	1.34935
1554385_a_at	11240	PADI2	peptidyl arginine deiminase, type II	0.035142	1.3535
1563975_at	55819	RNF130	ring finger protein 130	0.03404	1.35358
1564403_at	101362076	GVQW1	GVQW motif containing 1	0.00235	1.35374
205539_at	10677	AVIL	advillin	0.007984	1.35395
206004_at	7053	TGM3	transglutaminase 3	0.04975	1.35401
240017_at	400960	PCBP1-AS1	PCBP1 antisense RNA 1	0.030087	1.35517
228209_at	84320 /// 100527964	ACBD6 /// LHX4-AS1	acyl-CoA binding domain containing 6 /// LHX4 antisense RNA 1	0.001107	1.35535
1552773_at	338339	CLEC4D	C-type lectin domain family 4, member D	0.045442	1.35604
241360_at	80071	CCDC15	coiled-coil domain containing 15	0.025273	1.35651

205016_at	7039	TGFA	transforming growth factor alpha	0.005391	1.35978
1559777_at	731424	MIR3945HG	MIR3945 host gene	0.048283	1.35986
206269_at	8521	GCM1	glial cells missing homolog 1 (Drosophila)	0.025744	1.36222
236332_at	51635	DHRS7	dehydrogenase/reductase (SDR family) member 7	0.008461	1.3641
212169_at	11328	FKBP9	FK506 binding protein 9	0.035959	1.36566
226207_at	353116	RILPL1	Rab interacting lysosomal protein-like 1	0.002348	1.36611
243476_at	4763	NF1	neurofibromin 1	0.000864	1.36793
1553177_at	117157	SH2D1B	SH2 domain containing 1B	0.042515	1.36922
202199_s_at	6732	SRPK1	SRSF protein kinase 1	0.005369	1.36946
202948_at	3554	IL1R1	interleukin 1 receptor, type I	0.009025	1.37104
240036_at	6397	SEC14L1	SEC14-like lipid binding 1	0.021853	1.37126
1554717_a_at	5144	PDE4D	phosphodiesterase 4D, cAMP-specific	0.023734	1.37237
229213_at	84925	DIRC2	disrupted in renal carcinoma 2	0.022549	1.37273
208200_at	3552	IL1A	interleukin 1 alpha	0.019276	1.37495
235521_at	3200	HOXA3	homeobox A3	0.028971	1.37512

230102_at	2119	ETV5	ets variant 5	0.032165	1.37638
206546_at	10388	SYCP2	synaptonemal complex protein 2	0.020742	1.38047
1555938_x_at	7431	VIM	vimentin	0.00207	1.38331
241703_at	154661	RUNDC3B	RUN domain containing 3B	0.045773	1.38466
223304_at	84255	SLC37A3	solute carrier family 37, member 3	0.010066	1.38576
217104_at	400410	ST20	suppressor of tumorigenicity 20	0.001659	1.39023
209369_at	306	ANXA3	annexin A3	0.010485	1.39028
230722_at	54796	BNC2	basonuclin 2	0.023872	1.39153
224024_at	57222	ERGIC1	endoplasmic reticulum-golgi intermediate compartment 1	0.033683	1.39198
209691_s_at	55715	DOK4	docking protein 4	0.015145	1.39454
205699_at	5608	MAP2K6	mitogen-activated protein kinase kinase 6	0.002657	1.39533
242037_at	444	ASPH	aspartate beta-hydroxylase	0.038735	1.40035
232980_at	55788	LMBRD1	LMBR1 domain containing 1	0.027394	1.40291
1557796_at	55711	FAR2	fatty acyl-CoA reductase 2	0.014484	1.40349
224620_at	5594	MAPK1	mitogen-activated protein kinase 1	0.005058	1.40435

1559469_s_at	57568	SIPA1L2	signal-induced proliferation-associated 1 like 2	0.029236	1.40684
1553991_s_at	54621	VSIG10	V-set and immunoglobulin domain containing 10	0.006777	1.41104
237340_at	116369	SLC26A8	solute carrier family 26 (anion exchanger), member 8	0.005284	1.4142
211389_x_at	3813	KIR3DS1	killer cell immunoglobulin-like receptor, three domains, short cytoplasmic tail, 1	0.03977	1.41727
230846_at	9495	AKAP5	A kinase (PRKA) anchor protein 5	0.020642	1.42005
1569095_at	731424	MIR3945HG	MIR3945 host gene	0.020965	1.42126
217484_at	1378	CR1	complement component (3b/4b) receptor 1 (Knops blood group)	0.005101	1.42481
207289_at	64386	MMP25	matrix metallopeptidase 25	0.030449	1.42489
226578_s_at	1843	DUSP1	dual specificity phosphatase 1	0.026669	1.42572
1554384_at	11240	PADI2	peptidyl arginine deiminase, type II	0.00991	1.42896
228461_at	344558	SH3RF3	SH3 domain containing ring finger 3	0.049577	1.43719
1552772_at	338339	CLEC4D	C-type lectin domain family 4, member D	0.025889	1.4379
232514_at	55582	KIF27	kinesin family member 27	0.012393	1.44013
238478_at	54796	BNC2	basonuclin 2	0.046365	1.44088

207093_s_at	4974	OMG	oligodendrocyte myelin glycoprotein	0.037455	1.44367
217507_at	6556	SLC11A1	solute carrier family 11 (proton-coupled divalent metal ion transporter), member 1	0.018863	1.44505
231874_at	285172	FAM126B	family with sequence similarity 126, member B	0.02851	1.45009
237891_at	4193	MDM2	MDM2 proto-oncogene, E3 ubiquitin protein ligase	0.005478	1.45114
215561_s_at	3554	IL1R1	interleukin 1 receptor, type I	0.011707	1.46329
234709_at	92291	CAPN13	calpain 13	0.009575	1.46378
207443_at	7101	NR2E1	nuclear receptor subfamily 2, group E, member 1	0.040923	1.46571
215175_at	22990	PCNX	pecanex homolog (Drosophila)	0.012911	1.46791
203260_at	51020	HDDC2	HD domain containing 2	0.010711	1.47229
232862_at	51099	ABHD5	abhydrolase domain containing 5	0.009393	1.48916
238983_at	79730	NSUN7	NOP2/Sun domain family, member 7	0.006087	1.50533
231223_at	64478	CSMD1	CUB and Sushi multiple domains 1	0.005506	1.51337
1553972_a_at	875 /// 102724560	CBS /// CBSL	cystathionine-beta-synthase /// cystathionine-beta-synthase like	0.017969	1.5195

223796_at	79937 /// 643827 /// 728577 /// 100289279 /// 105369234	CNTNAP3 /// CNTNAP3B /// CNTNAP3P2 /// LOC100289279 /// LOC105369234	contactin associated protein-like 3 /// contactin associated protein-like 3B /// contac	0.018465	1.53296
226485_at	54621	VSIG10	V-set and immunoglobulin domain containing 10	0.001128	1.53546
238997_at	100130889	PSORS1C3	psoriasis susceptibility 1 candidate 3 (non-protein coding)	0.033224	1.55088
236587_at	23639	LRRC6	leucine rich repeat containing 6	0.013568	1.59536
244065_at	79937 /// 728577 /// 100289279	CNTNAP3 /// CNTNAP3B /// LOC100289279	contactin associated protein-like 3 /// contactin associated protein-like 3B /// contac	0.027178	1.61719
220436_at	643827	CNTNAP3P2	contactin associated protein-like 3 pseudogene 2	0.030719	1.62035
206483_at	23639	LRRC6	leucine rich repeat containing 6	0.01341	1.64998
206177_s_at	383	ARG1	arginase 1	0.036427	1.65901
205239_at	374	AREG	amphiregulin	0.034009	1.75939
233126_s_at	55301	OLAH	oleoyl-ACP hydrolase	0.047245	1.76893

212816_s_at	875 /// 102724560	CBS /// CBSL	cystathionine-beta-synthase /// cystathionine-beta-synthase like	0.022454	1.78166
222945_x_at	55301	OLAH	oleoyl-ACP hydrolase	0.048354	1.79836
231470_at	400680	LINC00664	long intergenic non-protein coding RNA 664	0.017209	1.90573
231581_at	400680	LINC00664	long intergenic non-protein coding RNA 664	0.00796	1.9457
212806_at	158471	PRUNE2	prune homolog 2 (Drosophila)	0.007233	2.02119
212805_at	158471	PRUNE2	prune homolog 2 (Drosophila)	0.019011	2.04177

Table S5.Selected Pathways associated with differentially expressed genes at 5 hours

Ingenuity Canonical Pathways	***Molecules***
Aryl Hydrocarbon Receptor Signaling	*TP53,SRC,IL1A,NFIX,MAPK1,MDM2,SMARCA4,HSP90B1,HSP90AB1,RARA,NFIA,TGFB2,ALDH18A1,ALDH6A1*
B Cell Development	*PTPRC,HLA-DRB1,HLA-DQA1,IGHM,HLA-DQB1,IGHD*
STAT3 Pathway	*SRC,IL1A,IL13RA1,MAPK1,IL1R1,MAPK13,BCL2,IL1R2,MAPK14,CISH,TGFA,TGFB2,IL27RA*
Cdc42 Signaling	*SRC,MAPK14,HLA-DRB1,MAPK1,BAIAP2,HLA-DQA1,MYL4,CDC42SE1,HLA-DQB1,MAPK13,EXOC6,APC*
Toll-like Receptor Signaling	*MAP2K6,TLR4,IL1A,MAPK14,MAPK1,TLR8,TLR7,MAPK13,IRAK3*
p38 MAPK Signaling	*IL1R2,MAP2K6,TP53,IL1A,MAPK14,DDIT3,DUSP1,TGFB2,IL1R1,MAPK13,IRAK3*
B Cell Receptor Signaling	*MAP2K6,PRKCQ,MAPK1,MAPK13,TCF3,BCL6,PTEN,PTPRC,NFAT5,MAPK14,GAB1,CD22,IGHM,MAP3K2,IGHD*
Parkinson's Signaling	*MAPK14,MAPK1,MAPK13,SNCA*

Neuroinflammation Signaling Pathway	*NAIP,TRAF3,MAPK1,TLR8,HLA-DQA1,MAPK13,IL1R1,IRAK3,HLA-DQB1,BCL2,TLR4,MAPK14,HLA-DRB1,NFAT5,GAB1,TLR7,TGFB2,CFLAR,SNCA,PSEN1*
PPARα/RXRα Activation	*MAP2K6,MED23,MAPK1,ADCY4,IL1R1,IL1R2,HSP90B1,MAPK14,HSP90AB1,GK,PRKAA1,TGFB2,STAT5B,GOT2*
IL-7 Signaling Pathway	*MAPK14,MAPK1,GAB1,SLC2A1,IGHM,MAPK13,BCL6,STAT5B,BCL2*
Nitric Oxide Signaling in the Cardiovascular System	*HSP90B1,PRKCQ,CACNA1D,MAPK1,GAB1,HSP90AB1,PRKAA1,SLC7A1,PDE5A,NOS3*
Inhibition of Angiogenesis by TSP1	*TP53,MAPK14,MAPK1,MAPK13,NOS3*
Endoplasmic Reticulum Stress Pathway	*HSP90B1,DDIT3,ERN1,DNAJC3*
UVC-Induced MAPK Signaling	*TP53,SRC,MAPK14,PRKCQ,MAPK1,MAPK13*

Type I Diabetes Mellitus Signaling	*MAP2K6,MAPK14,HLA-DRB1,MAPK1,HLA-DQA1,IL1R1,HLA-DQB1,MAPK13,BCL2*
NF-κB Signaling	*MAP2K6,TRAF3,IL1A,PRKCQ,TLR8,IRAK3,IL1R1,IL1R2,TLR4,GAB1,PELI1,TLR7,TGFA*
IL-10 Signaling	*IL1R2,MAP2K6,IL1A,MAPK14,MAPK1,MAPK13,IL1R1*
Protein Citrullination	*PADI4,PADI2*
RAR Activation	*SRC,MAPK14,PRKCQ,AKR1C3,MAPK1,DUSP1,ADCY4,RARA,TGFB2,MAPK13,STAT5B,SMARCA4,PTEN*
IL-22 Signaling	*MAPK14,MAPK1,MAPK13,STAT5B*
HIF1α Signaling	*TP53,MAPK14,MAPK1,GAB1,SLC2A1,MMP28,MDM2,MAPK13,MMP25,NOS3*
Hypoxia Signaling in the Cardiovascular System	*TP53,HSP90B1,HSP90AB1,UBE2W,MDM2,NOS3,PTEN*
Role of JAK family kinases in IL-6-type Cytokine Signaling	*MAPK14,MAPK1,MAPK13,STAT5B*

PI3K/AKT Signaling	*TP53,HSP90B1,MAPK1,GAB1,HSP90AB1,PPP2R3A,MDM2,NOS3,PTEN,BCL2*
IL-1 Signaling	*MAP2K6,IL1A,MAPK14,MAPK1,ADCY4,MAPK13,IL1R1,IRAK3*
B Cell Activating Factor Signaling	*TRAF3,MAPK14,NFAT5,MAPK1,MAPK13*
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	*MAP2K6,SRC,IL1A,TRAF3,PRKCQ,MAPK1,TLR8,LTB,IL1R1,IRAK3,TCF3,APC,IL1R2,TLR4,MAPK14,NFAT5,GAB1,TLR7*
Dendritic Cell Maturation	*TLR4,IL1A,MAPK14,HLA-DRB1,MAPK1,GAB1,LEPR,HLA-DQA1,LTB,HLA-DQB1,MAPK13,COL18A1*
Superpathway of Citrulline Metabolism	*ALDH18A1,NOS3,ARG1*
Communication between Innate and Adaptive	*TLR4,IL1A,HLA-DRB1,TLR8,TLR7,IGHM,IGHD*

Immune Cells	
AMPK Signaling	*SRC,RAB1A,SLC2A1,MAPK1,RAB7A,MAPK13,NOS3,SMARCA4,MAPK14,GAB1,PPP2R3A,RPTOR,PRKAA1,CAMKK2*
iNOS Signaling	*TLR4,MAPK14,MAPK1,IRAK3,MAPK13*
Leukocyte Extravasation Signaling	*F11R,SRC,CLDN10,CLDN11,MAPK14,PRKCQ,GAB1,MAPK1,MMP28,EZR,MAPK13,MMP25,DLC1*
Acute Myeloid Leukemia Signaling	*MAP2K6,GAB1,MAPK1,FLT3LG,RARA,JUP,TCF3,STAT5B*
PFKFB4 Signaling Pathway	*MAP2K6,TP53,HK1,MAPK1,TGFB2*
OX40 Signaling Pathway	*TRAF3,HLA-DRB1,HLA-DQA1,HLA-DQB1,BCL2*
Nur77 Signaling in T Lymphocytes	*HLA-DRB1,HLA-DQA1,HLA-DQB1,MAP3K2,BCL2*
ErbB Signaling	*MAP2K6,PRKCQ,MAPK14,MAPK1,GAB1,TGFA,MAPK13,AREG*
Antigen Presentation Pathway	*HLA-DRB1,HLA-DQA1,CD74,HLA-DQB1*

TREM1 Signaling	*TLR4,TREM1,MAPK1,TLR8,TLR7,STAT5B*
Hepatic Cholestasis	*IL1R2,TLR4,IL1A,PRKCQ,ADCY4,ABCC2,RARA,TGFB2,LTB,IL1R1,IRAK3*
Xenobiotic Metabolism Signaling	*MAP2K6,IL1A,PRKCQ,MAPK1,ABCC2,MAPK13,HSP90B1,MAPK14,HSP90AB1,GAB1,PPP2R3A,ALDH18A1,SULT1B1,ALDH6A1,MAP3K2*
iCOS-iCOSL Signaling in T Helper Cells	*PTPRC,NFAT5,PRKCQ,HLA-DRB1,GAB1,HLA-DQA1,HLA-DQB1,PTEN*
Apelin Cardiac Fibroblast Signaling Pathway	*TGFB2,PRKAA1,NOS3*
Citrulline Biosynthesis	*ALDH18A1,ARG1*
Role of CHK Proteins in Cell Cycle Checkpoint Control	*TP53,PPP2R3A,SLC19A1,BRCA1,RAD50*
PEDF Signaling	*TP53,MAPK14,MAPK1,GAB1,CFLAR,MAPK13,BCL2*

LPS-stimulated MAPK Signaling	*MAP2K6,TLR4,MAPK14,PRKCQ,MAPK1,GAB1,MAPK13*
Graft-versus-Host Disease Signaling	*IL1A,HLA-DRB1,HLA-DQA1,HLA-DQB1*
BAG2 Signaling Pathway	*TP53,MAPK14,MAPK1,MDM2*
MIF Regulation of Innate Immunity	*TP53,TLR4,MAPK1,CD74*
PPAR Signaling	*IL1R2,IL1A,HSP90B1,MAPK1,HSP90AB1,IL1R1,STAT5B*
Th1 Pathway	*MAP2K6,PRKCQ,HLA-DRB1,GAB1,HLA-DQA1,HLA-DQB1,IL27RA,PSEN1*
Glycine Betaine Degradation	*SRR,SHMT2*
CD40 Signaling	*MAP2K6,TRAF3,MAPK14,MAPK1,GAB1,MAPK13*
RANK Signaling in Osteoclasts	*MAP2K6,SRC,MAPK14,MAPK1,GAB1,MAPK13,MAP3K2*

Epithelial Adherens Junction Signaling	*SRC,BAIAP2,TUBB2A,TGFB2,MYL4,JUP,TCF3,APC,PTEN*
HMGB1 Signaling	*MAP2K6,TLR4,IL1A,MAPK14,MAPK1,GAB1,TGFB2,LTB,IL1R1,MAPK13*
Th1 and Th2 Activation Pathway	*MAP2K6,CCR3,HLA-DRB1,PRKCQ,GAB1,HLA-DQA1,HLA-DQB1,IL27RA,STAT5B,PSEN1*
Role of NFAT in Cardiac Hypertrophy	*MAP2K6,SRC,AKAP5,MAPK14,PRKCQ,CACNA1D,MAPK1,GAB1,ADCY4,TGFB2,MAPK13,SLC8A1*
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	*TLR4,IL1A,PRKCQ,MAPK1,GAB1,TLR8,TLR7,TGFB2,LTB*
LPS/IL-1 Mediated Inhibition of RXR Function	*IL1R2,TLR4,IL1A,ABCC2,RARA,ABCG1,ALDH18A1,IL1R1,ABCC4,ALDH6A1,SULT1B1*

PKCθ Signaling in T Lymphocytes	*HLA-DRB1,PRKCQ,NFAT5,CACNA1D,MAPK1,GAB1,HLA-DQA1,HLA-DQB1,MAP3K2*
Granulocyte Adhesion and Diapedesis	*IL1R2,CLDN10,CLDN11,IL1A,MMP28,EZR,IL1R1,MMP25,FPR1*
IL-6 Signaling	*IL1R2,MAP2K6,IL1A,MAPK14,MAPK1,GAB1,MAPK13,IL1R1*
IL-4 Signaling	*NFAT5,HLA-DRB1,GAB1,IL13RA1,HLA-DQA1,HLA-DQB1*
Tight Junction Signaling	*CLDN10,F11R,CPSF6,CLDN11,PPP2R3A,TGFB2,MYL4,STX16,PTEN*
eNOS Signaling	*HSP90B1,PRKCQ,LPAR1,GAB1,HSP90AB1,ADCY4,PRKAA1,SLC7A1,NOS3*
TGF-β Signaling	*MAP2K6,MAPK14,MAPK1,TGFB2,MAPK13,BCL2*
Wnt/β-catenin Signaling	*TP53,SRC,PPP2R3A,RARA,TGFB2,TLE4,MDM2,TCF3,APC*
Th17 Activation Pathway	*HSP90B1,NFAT5,HSP90AB1,IL1R1,IRAK3*
Autophagy	*WDFY3,BECN1,BCL2,ATG9B*

Sirtuin Signaling Pathway	*TP53,POLR1B,SLC2A1,MAPK1,SDHC,BECN1,NOS3,ATG9B,GABARAPL1,PRKAA1,RPTOR,NAMPT,GOT2*
IL-12 Signaling and Production in Macrophages	*TLR4,PRKCQ,MAPK14,MAPK1,GAB1,RAB7A,TGFB2,MAPK13*
Chemokine Signaling	*SRC,CCR3,MAPK14,MAPK1,MAPK13*
Agranulocyte Adhesion and Diapedesis	*CLDN10,CLDN11,IL1A,MMP28,EZR,MYL4,IL1R1,MMP25,ITGB7*
Calcium-induced T Lymphocyte Apoptosis	*HLA-DRB1,PRKCQ,HLA-DQA1,HLA-DQB1*
TR/RXR Activation	*LDLR,TSHB,AKR1C3,GAB1,SLC2A1,MDM2*
CD28 Signaling in T Helper Cells	*PTPRC,HLA-DRB1,PRKCQ,NFAT5,GAB1,HLA-DQA1,HLA-DQB1*

IL-17A Signaling in Fibroblasts	*MAPK14,MAPK1,MAPK13*
Hematopoiesis from Pluripotent Stem Cells	*IL1A,IGHM,IGHD*
Glucocorticoid Receptor Signaling	*MAPK1,TAF5L,MAPK13,SMARCA4,BCL2,IL1R2,HSP90B1,MAPK14,NFAT5,HSP90AB1,GAB1,DUSP1,TGFB2,PRKAA1,STAT5B*
IL-15 Signaling	*MAPK14,MAPK1,GAB1,MAPK13,STAT5B*
Corticotropin Releasing Hormone Signaling	*PRKCQ,MAPK14,CACNA1D,MAPK1,ADCY4,MAPK13,NOS3*
T Helper Cell Differentiation	*HLA-DRB1,HLA-DQA1,HLA-DQB1,BCL6*
CCR5 Signaling in Macrophages	*MAPK14,PRKCQ,CACNA1D,MAPK1,MAPK13*

Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	*SRC,PRKCQ,MAPK1,EZR,PTEN*
Lymphotoxin β Receptor Signaling	*TRAF3,MAPK1,GAB1,LTB*
NRF2-mediated Oxidative Stress Response	*MAP2K6,MAPK14,PRKCQ,MAPK1,GAB1,ABCC2,DNAJC3,DNAJC15,ABCC4*
IL-17 Signaling	*MAP2K6,MAPK14,MAPK1,GAB1,MAPK13*
VEGF Family Ligand-Receptor Interactions	*PRKCQ,MAPK1,GAB1,NOS3,NRP1*
IL-9 Signaling	*GAB1,CISH,STAT5B*
Acute Phase Response Signaling	*MAP2K6,IL1A,MAPK14,MAPK1,MAPK13,IL1R1,TCF3,NOLC1*

Caveolar-mediated Endocytosis Signaling	*SRC,FLNA,ITGB7,MAP3K2*
Antiproliferative Role of TOB in T Cell Signaling	*MAPK1,TGFB2*
Fc Epsilon RI Signaling	*MAP2K6,MAPK14,PRKCQ,MAPK1,GAB1,MAPK13*
Phagosome Formation	*TLR4,CR1,PRKCQ,GAB1,TLR8,TLR7*
Role of NFAT in Regulation of the Immune Response	*AKAP5,NFAT5,PRKCQ,HLA-DRB1,MAPK1,GAB1,HLA-DQA1,HLA-DQB1*
Antioxidant Action of Vitamin C	*MAPK14,MAPK1,SLC2A1,MAPK13,STAT5B*
CD27 Signaling in Lymphocytes	*MAP2K6,CD27,MAP3K2*

Renin-Angiotensin Signaling	*MAPK14,PRKCQ,MAPK1,GAB1,ADCY4,MAPK13*
VEGF Signaling	*SRC,MAPK1,GAB1,NOS3,BCL2*
Endothelin-1 Signaling	*SRC,PRKCQ,MAPK14,MAPK1,GAB1,ADCY4,MAPK13,NOS3*
Crosstalk between Dendritic Cells and Natural Killer Cells	*TLR4,HLA-DRB1,TLR7,LTB*
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	*TLR4,PRKCQ,MAPK14,MAPK1,GAB1,PPP2R3A,MAPK13,MAP3K2*
Gap Junction Signaling	*SRC,PRKCQ,LPAR1,MAPK1,GAB1,ADCY4,TUBB2A,MAP3K2*
T Cell Receptor Signaling	*PTPRC,NFAT5,PRKCQ,MAPK1,GAB1*

Complement System	*CR1,CD46*
IL-3 Signaling	*PRKCQ,MAPK1,GAB1,STAT5B*
Inhibition of Matrix Metalloproteases	*MMP28,MMP25*
Regulation of the Epithelial-Mesenchymal Transition Pathway	*MAP2K6,MAPK1,GAB1,TGFB2,TCF3,APC,PSEN1*
IL-2 Signaling	*MAPK1,GAB1,STAT5B*
P2Y Purigenic Receptor Signaling Pathway	*P2RY2,PRKCQ,MAPK1,GAB1,ADCY4*
CXCR4 Signaling	*SRC,PRKCQ,MAPK1,GAB1,ADCY4,MYL4*
Regulation of IL-2 Expression in Activated and Anergic T	*NFAT5,MAPK1,TGFB2*

Lymphocytes	
IL-15 Production	*MAP2K6,SRC,TWF1,FLT3LG*
Angiopoietin Signaling	*GAB1,NOS3,STAT5B*
Death Receptor Signaling	*NAIP,CFLAR,BCL2*
Natural Killer Cell Signaling	*PRKCQ,GAB1,MAPK1,SH2D1B*

Table S6. Differentially expressed genes that correlated with SBP at 5 hours

Probeset ID	Entrez Gene	Gene Symbol	Gene Title	r	P value(correlation)
1553157_at	89884	LHX4	LIM homeobox 4	0.250441	0.0496167
1557285_at	374	AREG	amphiregulin	0.286048	0.0242072
206277_at	5029	P2RY2	purinergic receptor P2Y, G-protein coupled, 2	-0.320263	0.0111597
206873_at	765	CA6	carbonic anhydrase VI	-0.337239	0.00735361
208304_at	1232	CCR3	chemokine (C-C motif) receptor 3	-0.378765	0.00239995
211776_s_at	23136	EPB41L3	erythrocyte membrane protein band 4.1-like 3	-0.261429	0.0401261
217189_s_at	9887	SMG7	SMG7 nonsense mediated mRNA decay factor	0.279426	0.0278465
219577_s_at	10347	ABCA7	ATP binding cassette subfamily A member 7	-0.272845	0.031909
220436_at	643827	CNTNAP3P2	contactin associated protein-like 3 pseudogene 2	0.290106	0.022182
222451_s_at	51114	ZDHHC9	zinc finger, DHHC-type containing 9	-0.332684	0.0082427
227992_s_at	147650	SPACA6	sperm acrosome associated 6	-0.277267	0.0291287
229558_at	400506	KNOP1	lysine-rich nucleolar protein 1	-0.260635	0.0407574
230722_at	54796	BNC2	basonuclin 2	0.255278	0.0452344
231223_at	64478	CSMD1	CUB and Sushi multiple domains 1	0.266967	0.0359445
234709_at	92291	CAPN13	calpain 13	0.301376	0.017295

235428_at	100507316	MINCR	MYC-induced long noncoding RNA	-0.38101	0.00224943
238478_at	54796	BNC2	basonuclin 2	0.256921	0.0438206

Table S7. Differentially expressed genes 24 hours.

Probeset ID	Entrez Gene	Gene Symbol	Gene Title	P value	Fold-Change (Higher BP vs. Lower BP)
221491_x_at	3119 /// 3123 /// 3124 /// 3125 /// 3126 /// 3127 /// 3128 /// 3129 /// 3130 /// 105369	HLA-DQB1 /// HLA-DRB1 /// HLA-DRB2 /// HLA-DRB3 /// HLA-DRB4 /// HLA-DRB5 /// HLA-DRB6 /// HLA-DRB7 /// HLA-DRB8 /// LOC105369230	major histocompatibility complex, class II, DQ beta 1 /// major histocompatibility comp	0.022965	-3.04551
236203_at	3117	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	0.035952	-2.79545
227474_at	654433	PAX8-AS1	PAX8 antisense RNA 1	0.048255	-2.03675
204141_at	7280	TUBB2A	tubulin, beta 2A class IIa	0.022622	-1.96978

1553214_a_at	79741	CCDC7	coiled-coil domain containing 7	0.002676	-1.68281
224150_s_at	80321	CEP70	centrosomal protein 70kDa	0.002097	-1.61809
1569136_at	11320	MGAT4A	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme A	0.003764	-1.55619
1560762_at	285972	LINC00996	long intergenic non-protein coding RNA 996	0.029342	-1.49569
230756_at	257101	ZNF683	zinc finger protein 683	0.032445	-1.4693
1555241_at	401466	C8orf59	chromosome 8 open reading frame 59	0.008672	-1.46867
234865_at	28562	TRBV25-1	T cell receptor beta variable 25-1	0.020735	-1.46015
204404_at	6558	SLC12A2	solute carrier family 12 (sodium/potassium/chloride transporter), member 2	0.001522	-1.45429
226646_at	10365	KLF2	Kruppel-like factor 2	0.031387	-1.44197
210517_s_at	9590	AKAP12	A kinase (PRKA) anchor protein 12	0.040449	-1.43266
201291_s_at	7153	TOP2A	topoisomerase (DNA) II alpha	0.033431	-1.40824
210868_s_at	79071	ELOVL6	ELOVL fatty acid elongase 6	0.020765	-1.40612
203632_s_at	51704	GPRC5B	G protein-coupled receptor, class C, group 5, member B	0.029701	-1.40307

234440_at	28516	TRDV3	T cell receptor delta variable 3	0.045715	-1.40269
1568781_at	7390	UROS	uroporphyrinogen III synthase	0.006472	-1.40224
206336_at	6372	CXCL6	chemokine (C-X-C motif) ligand 6	0.044298	-1.38541
227910_at	63929	XPNPEP3	X-prolyl aminopeptidase 3, mitochondrial	0.010594	-1.37807
202988_s_at	5996	RGS1	regulator of G-protein signaling 1	0.038388	-1.37795
231341_at	340146	SLC35D3	solute carrier family 35, member D3	0.037241	-1.37538
204603_at	9156	EXO1	exonuclease 1	0.005137	-1.371
204256_at	79071	ELOVL6	ELOVL fatty acid elongase 6	0.03002	-1.3621
1553215_s_at	79741	CCDC7	coiled-coil domain containing 7	0.008172	-1.36126
223918_at	728637	MEIKIN	meiotic kinetochore factor	0.002285	-1.35435
210643_at	8600	TNFSF11	tumor necrosis factor (ligand) superfamily, member 11	0.018291	-1.35156
1570571_at	55297	CCDC91	coiled-coil domain containing 91	0.003433	-1.35102
235609_at	83990	BRIP1	BRCA1 interacting protein C-terminal helicase 1	0.029879	-1.348
231050_at	117245	HRASLS5	HRAS-like suppressor family, member 5	0.018646	-1.33449

1558719_s_at	84268	RPAIN	RPA interacting protein	0.007813	-1.33446
240063_at	441046	GUSBP5	glucuronidase, beta pseudogene 5	0.044674	-1.33418
1553810_a_at	57650	KIAA1524	KIAA1524	0.004454	-1.33122
239989_at	54875	CNTLN	centlein, centrosomal protein	0.002466	-1.32984
207705_s_at	22981	NINL	ninein-like	0.012766	-1.3271
1555243_x_at	401466	C8orf59	chromosome 8 open reading frame 59	0.03574	-1.3258
226736_at	91612	CHURC1	churchill domain containing 1	0.042437	-1.32476
229390_at	441168	FAM26F	family with sequence similarity 26, member F	0.026082	-1.3234
203553_s_at	11183	MAP4K5	mitogen-activated protein kinase kinase kinase kinase 5	0.017743	-1.32101
205871_at	5342 /// 5343	PLGLB1 /// PLGLB2	plasminogen-like B1 /// plasminogen-like B2	0.039292	-1.31431
1568627_at	57223	PPP4R3B	protein phosphatase 4, regulatory subunit 3B	0.008615	-1.31286
238017_at	195814	SDR16C5	short chain dehydrogenase/reductase family 16C, member 5	0.047778	-1.31188
1565898_at	196074	METTL15	methyltransferase like 15	0.013724	-1.3117
222016_s_at	64288	ZSCAN31	zinc finger and SCAN domain containing 31	0.012734	-1.31011

236471_at	9603	NFE2L3	nuclear factor, erythroid 2-like 3	0.049036	-1.30823
235836_at	439921	MXRA7	matrix-remodelling associated 7	0.025053	-1.30821
242003_at	157697	ERICH1	glutamate rich 1	0.048726	-1.30347
226947_at	375513 /// 728411 /// 101929200 /// 106660612	GUSBP1 /// GUSBP4 /// LINC00680 /// LOC101929200	glucuronidase, beta pseudogene 1 /// glucuronidase, beta pseudogene 4 /// long intergen	0.00561	-1.30032
227491_at	79071	ELOVL6	ELOVL fatty acid elongase 6	0.029652	-1.29788
1568658_at	339804	C2orf74	chromosome 2 open reading frame 74	0.045634	-1.29617
211525_s_at	2814	GP5	glycoprotein V (platelet)	0.026069	-1.29198
1569289_at	54841	BIVM	basic, immunoglobulin-like variable motif containing	0.022715	-1.28966
240890_at	643733	LOC643733	caspase 4, apoptosis-related cysteine peptidase pseudogene	0.025279	-1.28907
1560654_at	283011	FLJ37201	tigger transposable element derived 2 pseudogene	0.017471	-1.28854
206589_at	2672	GFI1	growth factor independent 1 transcription repressor	0.042773	-1.28791

228121_at	7042 /// 103611157	TGFB2 /// TGFB2-OT1	transforming growth factor beta 2 /// TGFB2 overlapping transcript 1	0.048316	-1.28514
236665_at	343099	CCDC18	coiled-coil domain containing 18	0.014206	-1.28464
220459_at	114044	MCM3AP-AS1	MCM3AP antisense RNA 1	0.04031	-1.2842
236150_at	123688	HYKK	hydroxylysine kinase	0.022667	-1.28247
237745_at	641467	TSC22D1-AS1	TSC22D1 antisense RNA 1	0.044102	-1.28234
227711_at	121355	GTSF1	gametocyte specific factor 1	0.044974	-1.2818
236290_at	220164	DOK6	docking protein 6	0.003086	-1.27766
204135_at	11259	FILIP1L	filamin A interacting protein 1-like	0.035603	-1.27669
238844_s_at	4867	NPHP1	nephronophthisis 1 (juvenile)	0.003433	-1.27648
228719_at	125150	ZSWIM7	zinc finger, SWIM-type containing 7	0.037282	-1.27564
230521_at	84904	ARHGEF39	Rho guanine nucleotide exchange factor 39	0.04853	-1.27303
226278_at	258010	SVIP	small VCP/p97-interacting protein	0.035726	-1.26996
1557166_at	27250	PDCD4	programmed cell death 4 (neoplastic transformation inhibitor)	0.048958	-1.26903
1566514_at	143884	CWF19L2	CWF19-like 2, cell cycle control (S. pombe)	0.009448	-1.2672

235516_at	51091	SEPSECS	Sep (O-phosphoserine) tRNA:Sec (selenocysteine) tRNA synthase	0.031299	-1.26605
221683_s_at	80184	CEP290	centrosomal protein 290kDa	0.040355	-1.26548
1559477_s_at	4211	MEIS1	Meis homeobox 1	0.018895	-1.26019
211211_x_at	4068	SH2D1A	SH2 domain containing 1A	0.046704	-1.25917
235561_at	9352	TXNL1	thioredoxin-like 1	0.043652	-1.25915
201929_s_at	8502	PKP4	plakophilin 4	0.038223	-1.2573
1552660_a_at	55322	C5orf22	chromosome 5 open reading frame 22	0.024031	-1.25729
224444_s_at	84791	LINC00467	long intergenic non-protein coding RNA 467	0.044456	-1.25617
230351_at	283481	FGF14-AS2	FGF14 antisense RNA 2	0.030127	-1.2499
241034_at	2744	GLS	glutaminase	0.035532	-1.24956
1556493_a_at	23081	KDM4C	lysine (K)-specific demethylase 4C	0.025936	-1.24634
213983_s_at	23244	PDS5A	PDS5 cohesin associated factor A	0.044747	-1.24547
229822_at	29780 /// 64098	PARVB /// PARVG	parvin, beta /// parvin, gamma	0.014312	-1.24083
1555142_at	150159	SLC9B1	solute carrier family 9, subfamily B (NHA1,	0.006596	-1.24062

			cation proton antiporter 1), member 1		
1556361_s_at	81573	ANKRD13C	ankyrin repeat domain 13C	0.023356	-1.23936
235490_at	84314	TMEM107	transmembrane protein 107	0.049594	-1.23882
205355_at	36	ACADSB	acyl-CoA dehydrogenase, short/branched chain	0.046146	-1.23679
235760_at	64324	NSD1	nuclear receptor binding SET domain protein 1	0.028544	-1.23505
236208_at	4338	MOCS2	molybdenum cofactor synthesis 2	0.039967	-1.23165
1552490_at	246269	LACE1	lactation elevated 1	0.016228	-1.23094
230847_at	56897	WRNIP1	Werner helicase interacting protein 1	0.044785	-1.23066
207471_at	57038	RARS2	arginyl-tRNA synthetase 2, mitochondrial	0.017483	-1.23038
229676_at	55149	MTPAP	mitochondrial poly(A) polymerase	0.013576	-1.22981
1554703_at	9639	ARHGEF10	Rho guanine nucleotide exchange factor 10	0.044591	-1.22887
215890_at	2760	GM2A	GM2 ganglioside activator	0.014669	-1.22845
1553391_at	254158	CXorf58	chromosome X open reading frame 58	0.014372	-1.2278
205608_s_at	284	ANGPT1	angiopoietin 1	0.014514	-1.22755

1555202_a_at	55197	RPRD1A	regulation of nuclear pre-mRNA domain containing 1A	0.012419	-1.22576
1553423_a_at	146857	SLFN13	schlafen family member 13	0.031705	-1.22573
226901_at	284018	C17orf58	chromosome 17 open reading frame 58	0.02532	-1.22539
205835_s_at	64848	YTHDC2	YTH domain containing 2	0.040564	-1.22488
227493_s_at	57456	KIAA1143	KIAA1143	0.039544	-1.2248
228820_at	63929	XPNPEP3	X-prolyl aminopeptidase 3, mitochondrial	0.00634	-1.2245
1555284_at	57679	ALS2	ALS2, alsin Rho guanine nucleotide exchange factor	0.000927	-1.22416
223513_at	55835	CENPJ	centromere protein J	0.018711	-1.22414
228084_at	839 /// 81579	CASP6 /// PLA2G12A	caspase 6 /// phospholipase A2, group XIIA	0.043046	-1.22342
228863_at	27253	PCDH17	protocadherin 17	0.030201	-1.22287
211727_s_at	1353	COX11	COX11 cytochrome c oxidase copper chaperone	0.035009	-1.22256
213392_at	124152	IQCK	IQ motif containing K	0.032399	-1.2225
203145_at	10615	SPAG5	sperm associated antigen 5	0.006093	-1.22224

203989_x_at	2149	F2R	coagulation factor II (thrombin) receptor	0.036258	-1.22203
232444_at	387119	CEP85L	centrosomal protein 85kDa-like	0.049251	-1.2219
244546_at	54205	CYCS	cytochrome c, somatic	0.008645	-1.22156
215064_at	6309	SC5D	sterol-C5-desaturase	0.008939	-1.22128
1556616_a_at	54758	KLHDC4	kelch domain containing 4	0.030741	-1.22083
227967_at	114791	TUBGCP5	tubulin, gamma complex associated protein 5	0.025574	-1.22052
1569021_at	5286	PIK3C2A	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 alpha	0.033069	-1.22025
225686_at	348235	SKA2	spindle and kinetochore associated complex subunit 2	0.046018	-1.21887
223539_s_at	8293 /// 728492	SERF1A /// SERF1B	small EDRK-rich factor 1A (telomeric) /// small EDRK-rich factor 1B (centromeric)	0.017368	-1.218
227481_at	154043	CNKSR3	CNKSR family member 3	0.028518	-1.21769
244662_at	55777	MBD5	methyl-CpG binding domain protein 5	0.022524	-1.2172
1556613_s_at	286148	DPY19L4	dpy-19-like 4 (C. elegans)	0.017201	-1.21632

217373_x_at	4193	MDM2	MDM2 proto-oncogene, E3 ubiquitin protein ligase	0.023134	-1.21476
1554068_s_at	144577	C12orf66	chromosome 12 open reading frame 66	0.04695	-1.21427
1554470_s_at	29068	ZBTB44	zinc finger and BTB domain containing 44	0.041668	-1.21347
203856_at	7443	VRK1	vaccinia related kinase 1	0.021693	-1.21256
242623_x_at	389362	PSMG4	proteasome (prosome, macropain) assembly chaperone 4	0.03655	-1.21155
210671_x_at	5599	MAPK8	mitogen-activated protein kinase 8	0.004569	-1.21025
234405_s_at	51808	PHAX	phosphorylated adaptor for RNA export	0.033583	-1.21013
210837_s_at	5144	PDE4D	phosphodiesterase 4D, cAMP-specific	0.032478	-1.20618
212241_at	81488 /// 145781	GCOM1 /// POLR2M	GRINL1A complex locus 1 /// polymerase (RNA) II (DNA directed) polypeptide M	0.039489	-1.20483
228997_at	54952	TRNAU1AP	tRNA selenocysteine 1 associated protein 1	0.046948	-1.2027
209349_at	10111	RAD50	RAD50 homolog, double strand break repair protein	0.044239	-1.20257
225511_at	51704	GPRC5B	G protein-coupled receptor, class C, group 5, member B	0.007004	-1.2025

244767_at	118924	FRA10AC1	fragile site, folic acid type, rare, fra(10)(q23.3) or fra(10)(q24.2) candidate 1	0.044824	-1.20215
1553114_a_at	5753	PTK6	protein tyrosine kinase 6	0.032705	1.20056
1557729_at	2869	GRK5	G protein-coupled receptor kinase 5	0.044776	1.20111
207085_x_at	1438	CSF2RA	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)	0.03985	1.20188
236207_at	6744	SSFA2	sperm specific antigen 2	0.02029	1.2022
215754_at	950	SCARB2	scavenger receptor class B, member 2	0.011553	1.20232
202806_at	1627	DBN1	drebrin 1	0.011314	1.20233
215883_at	1495	CTNNA1	catenin (cadherin-associated protein), alpha 1	0.021336	1.2024
225557_at	64651	CSRNP1	cysteine-serine-rich nuclear protein 1	0.02489	1.20293
1554283_at	25819	NOCT	nocturnin	0.024241	1.20394
209071_s_at	8490	RGS5	regulator of G-protein signaling 5	0.017565	1.20413
227438_at	80216	ALPK1	alpha kinase 1	0.006541	1.20437

219577_s_at	10347	ABCA7	ATP binding cassette subfamily A member 7	0.0304	1.20494
217904_s_at	23621	BACE1	beta-site APP-cleaving enzyme 1	0.020127	1.20513
1556608_a_at	30844	EHD4	EH domain containing 4	0.035118	1.20517
243727_at	144402	CPNE8	copine VIII	0.047056	1.20587
210069_at	1375 /// 386593	CHKB-CPT1B /// CPT1B	CHKB-CPT1B readthrough (NMD candidate) /// carnitine palmitoyltransferase 1B (muscle)	0.042621	1.20614
215185_at	101000000	LINC00963	long intergenic non-protein coding RNA 963	0.025448	1.20657
230361_at	727957	MROH1	maestro heat-like repeat family member 1	0.039437	1.20663
243323_s_at	463	ZFHX3	zinc finger homeobox 3	0.036889	1.20728
213922_at	146057	TTBK2	tau tubulin kinase 2	0.00137	1.20747
217189_s_at	9887	SMG7	SMG7 nonsense mediated mRNA decay factor	0.01942	1.2075
210070_s_at	1375 /// 386593	CHKB-CPT1B /// CPT1B	CHKB-CPT1B readthrough (NMD candidate) /// carnitine palmitoyltransferase 1B (muscle)	0.037179	1.20757
1570328_s_at	140834	LINC01620	long intergenic non-protein coding RNA 1620	0.043483	1.20773

216503_s_at	8028	MLLT10	myeloid/lymphoid or mixed-lineage leukemia; translocated to, 10	0.017366	1.2079
204914_s_at	6664	SOX11	SRY box 11	0.002356	1.20811
222462_s_at	23621	BACE1	beta-site APP-cleaving enzyme 1	0.030295	1.20848
206682_at	10462	CLEC10A	C-type lectin domain family 10, member A	0.049341	1.20869
230369_at	23432	GPR161	G protein-coupled receptor 161	0.011479	1.20919
223103_at	10809	STARD10	StAR-related lipid transfer domain containing 10	0.036889	1.2092
223846_at	64343	AZI2	5-azacytidine induced 2	0.008835	1.20943
205026_at	6777	STAT5B	signal transducer and activator of transcription 5B	0.044039	1.2097
214936_at	23143	LRCH1	leucine-rich repeats and calponin homology (CH) domain containing 1	0.005395	1.21003
222988_s_at	252839	TMEM9	transmembrane protein 9	0.001822	1.21054
239764_at	101000000	ITPR1-AS1	ITPR1 antisense RNA 1 (head to head)	0.021195	1.21096
215867_x_at	771	CA12	carbonic anhydrase XII	0.018043	1.21152

236492_at	5520	PPP2R2A	protein phosphatase 2, regulatory subunit B, alpha	0.02429	1.21153
232111_at	101000000	TUNAR	TCL1 upstream neural differentiation-associated RNA	0.02341	1.21401
235928_at	100000000	ZNF503-AS2	ZNF503 antisense RNA 2	0.034229	1.21405
221232_s_at	26287	ANKRD2	ankyrin repeat domain 2 (stretch responsive muscle)	0.018598	1.21406
230725_at	84250	SLF1	SMC5-SMC6 complex localization factor 1	0.032167	1.21545
1569792_a_at	254013	METTL20	methyltransferase like 20	0.023136	1.21896
203645_s_at	9332	CD163	CD163 molecule	0.044905	1.21923
219757_s_at	54916	TMEM260	transmembrane protein 260	0.036051	1.21937
232148_at	8439	NSMAF	neutral sphingomyelinase activation associated factor	0.047269	1.2195
243475_at	867	CBL	Cbl proto-oncogene, E3 ubiquitin protein ligase	0.041751	1.21967
214357_at	92346	C1orf105	chromosome 1 open reading frame 105	0.030102	1.21967
216973_s_at	3217	HOXB7	homeobox B7	0.033913	1.22133
205424_at	9755	TBKBP1	TBK1 binding protein 1	0.026627	1.22376

207982_at	3010	HIST1H1T	histone cluster 1, H1t	0.037498	1.22755
225759_x_at	79789	CLMN	calmin (calponin-like, transmembrane)	0.029594	1.22869
1568717_a_at	23307	FKBP15	FK506 binding protein 15	0.023351	1.22877
210757_x_at	1601	DAB2	Dab, mitogen-responsive phosphoprotein, homolog 2 (Drosophila)	0.037524	1.22894
222692_s_at	64778	FNDC3B	fibronectin type III domain containing 3B	0.030198	1.23064
206155_at	1244	ABCC2	ATP binding cassette subfamily C member 2	0.009731	1.23216
233490_at	51164	DCTN4	dynactin 4 (p62)	0.00928	1.23235
1570511_at	55160	ARHGEF10L	Rho guanine nucleotide exchange factor 10 like	0.008775	1.23311
207759_s_at	27185 /// 100303453	DISC1 /// TSNAX-DISC1	disrupted in schizophrenia 1 /// TSNAX-DISC1 readthrough (NMD candidate)	0.020489	1.2345
202821_s_at	4026	LPP	LIM domain containing preferred translocation partner in lipoma	0.020908	1.23611
241817_at	375341	C3orf62	chromosome 3 open reading frame 62	0.01052	1.23654
240313_at	63948	DMRTB1	DMRT-like family B with proline-rich C-terminal, 1	0.025798	1.23706
208536_s_at	10018	BCL2L11	BCL2-like 11 (apoptosis facilitator)	0.012821	1.23726

222453_at	79901	CYBRD1	cytochrome b reductase 1	0.033464	1.23823
205308_at	51101	ZC2HC1A	zinc finger, C2HC-type containing 1A	0.025232	1.23833
220371_s_at	56996	SLC12A9	solute carrier family 12, member 9	0.00798	1.23836
219806_s_at	56935	SMCO4	single-pass membrane protein with coiled-coil domains 4	0.023815	1.24167
223095_at	83742	MARVELD1	MARVEL domain containing 1	0.005808	1.24287
210787_s_at	10645	CAMKK2	calcium/calmodulin-dependent protein kinase kinase 2, beta	0.036543	1.2434
1553729_s_at	254050	LRRC43	leucine rich repeat containing 43	0.039796	1.24357
213120_at	23074	UHRF1BP1L	UHRF1 binding protein 1-like	0.036207	1.24563
226490_at	57224	NHSL1	NHS-like 1	0.002791	1.24665
214400_at	3640	INSL3	insulin-like 3 (Leydig cell)	0.024725	1.2491
1555842_at	9266	CYTH2	cytohesin 2	0.013737	1.24921
231345_s_at	79758	DHRS12	dehydrogenase/reductase (SDR family) member 12	0.013773	1.24951
235112_at	158405	KIAA1958	KIAA1958	0.020672	1.24964
204800_s_at	79758	DHRS12	dehydrogenase/reductase (SDR family) member 12	0.034489	1.25183

212448_at	23327	NEDD4L	neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin pr	0.024934	1.25211
220535_at	55138	FAM90A1	family with sequence similarity 90, member A1	0.005861	1.25346
1558365_at	5230	PGK1	phosphoglycerate kinase 1	0.021203	1.25453
225189_s_at	65059	RAPH1	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	0.003492	1.25506
220168_at	55259	CASC1	cancer susceptibility candidate 1	0.037291	1.25841
1555396_s_at	340602	CXorf67	chromosome X open reading frame 67	0.004691	1.26002
1554730_at	79772	MCTP1	multiple C2 domains, transmembrane 1	0.018893	1.26135
1570119_at	23047	PDS5B	PDS5 cohesin associated factor B	0.040364	1.26377
210711_at	84719	LINC00260	long intergenic non-protein coding RNA 260	0.014778	1.2651
216243_s_at	3557	IL1RN	interleukin 1 receptor antagonist	0.039173	1.26599
227697_at	9021	SOCS3	suppressor of cytokine signaling 3	0.037602	1.26617
1556770_a_at	222235	FBXL13	F-box and leucine-rich repeat protein 13	0.009936	1.26848

235019_at	1368	CPM	carboxypeptidase M	0.027256	1.27036
202948_at	3554	IL1R1	interleukin 1 receptor, type I	0.046675	1.27069
238834_at	91807	MYLK3	myosin light chain kinase 3	0.018483	1.27073
204437_s_at	2348	FOLR1	folate receptor 1 (adult)	0.03059	1.27115
207823_s_at	199	AIF1	allograft inflammatory factor 1	0.013437	1.27248
228056_s_at	256236	NAPSB	napsin B aspartic peptidase, pseudogene	0.020744	1.27459
228176_at	1903	S1PR3	sphingosine-1-phosphate receptor 3	0.018447	1.27563
221887_s_at	25861	DFNB31	deafness, autosomal recessive 31	0.022321	1.27804
1553991_s_at	54621	VSIG10	V-set and immunoglobulin domain containing 10	0.047669	1.27855
205141_at	283	ANG	angiogenin, ribonuclease, RNase A family, 5	0.041084	1.27885
205539_at	10677	AVIL	advillin	0.021779	1.27963
1562648_at	55704	CCDC88A	coiled-coil domain containing 88A	0.044006	1.27986
207323_s_at	4155	MBP	myelin basic protein	0.015165	1.28114
228055_at	256236	NAPSB	napsin B aspartic peptidase, pseudogene	0.0255	1.28118

1560625_s_at	102000000	CATIP-AS1	CATIP antisense RNA 1	0.046283	1.28141
202581_at	3303 /// 3304	HSPA1A /// HSPA1B	heat shock 70kDa protein 1A /// heat shock 70kDa protein 1B	0.033046	1.28822
229213_at	84925	DIRC2	disrupted in renal carcinoma 2	0.020611	1.29056
239001_at	4257	MGST1	microsomal glutathione S-transferase 1	0.013567	1.29181
224904_at	55066	PDPR	pyruvate dehydrogenase phosphatase regulatory subunit	0.001142	1.29258
228342_s_at	57538	ALPK3	alpha kinase 3	0.007951	1.29356
220302_at	4117	MAK	male germ cell-associated kinase	0.022331	1.29653
235699_at	161253	REM2	RAS (RAD and GEM)-like GTP binding 2	0.003037	1.29691
232639_at	90288	EFCAB12	EF-hand calcium binding domain 12	0.020361	1.29817
243934_at	440836	ODF3B	outer dense fiber of sperm tails 3B	0.004193	1.29888
226485_at	54621	VSIG10	V-set and immunoglobulin domain containing 10	0.046358	1.30043
220037_s_at	10894	LYVE1	lymphatic vessel endothelial hyaluronan receptor 1	0.037865	1.30167
229499_at	92291	CAPN13	calpain 13	0.012845	1.30368

1557432_at	9462	RASAL2	RAS protein activator like 2	0.042042	1.30644
209072_at	4155	MBP	myelin basic protein	0.009436	1.30767
1557465_at	283521	LINC00282	long intergenic non-protein coding RNA 282	0.041941	1.30971
216264_s_at	3913	LAMB2	laminin, beta 2 (laminin S)	0.004592	1.31098
219236_at	79957	PAQR6	progestin and adipoQ receptor family member VI	0.036219	1.31198
214846_s_at	57538	ALPK3	alpha kinase 3	0.004213	1.31311
1554833_at	55784	MCTP2	multiple C2 domains, transmembrane 2	0.032806	1.31359
205158_at	6038	RNASE4	ribonuclease, RNase A family, 4	0.035284	1.31364
224534_at	83999	KREMEN1	kringle containing transmembrane protein 1	0.044848	1.31604
220137_at	54621	VSIG10	V-set and immunoglobulin domain containing 10	0.031274	1.31664
1557727_at	400960	PCBP1-AS1	PCBP1 antisense RNA 1	0.026974	1.31775
1564274_at	286223	C9orf47	chromosome 9 open reading frame 47	0.026638	1.31892
238983_at	79730	NSUN7	NOP2/Sun domain family, member 7	0.046379	1.32127
243476_at	4763	NF1	neurofibromin 1	0.007567	1.32138

234321_x_at	57224	NHSL1	NHS-like 1	0.000823	1.3226
229638_at	79191	IRX3	iroquois homeobox 3	0.024891	1.32642
226974_at	23327	NEDD4L	neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin pr	0.005474	1.32871
241418_at	344887	LOC344887	NmrA-like family domain containing 1 pseudogene	0.017674	1.33048
226355_at	25886	POC1A	POC1 centriolar protein A	0.000903	1.3319
236287_at	83937	RASSF4	Ras association (RalGDS/AF-6) domain family member 4	0.003916	1.33591
238999_at	10677	AVIL	advillin	0.005656	1.3368
214618_at	8837	CFLAR	CASP8 and FADD like apoptosis regulator	0.01734	1.33938
1554717_a_at	5144	PDE4D	phosphodiesterase 4D, cAMP-specific	0.031072	1.33946
232898_at	1601	DAB2	Dab, mitogen-responsive phosphoprotein, homolog 2 (Drosophila)	0.007436	1.3482
1568706_s_at	10677	AVIL	advillin	0.004397	1.34926
1554384_at	11240	PADI2	peptidyl arginine deiminase, type II	0.039964	1.35297

214572_s_at	3640	INSL3	insulin-like 3 (Leydig cell)	0.008146	1.35303
230585_at	3772	KCNJ15	potassium channel, inwardly rectifying subfamily J, member 15	0.006153	1.35648
213812_s_at	10645	CAMKK2	calcium/calmodulin-dependent protein kinase kinase 2, beta	0.010507	1.35766
1555315_a_at	4117	MAK	male germ cell-associated kinase	0.008532	1.35798
233999_s_at	79989	TTC26	tetratricopeptide repeat domain 26	0.010838	1.35977
232953_at	55251 /// 140849 /// 728323 /// 731275 /// 101927097 /// 102723917 /// 102723928 /// 10	LINC00266-1 /// LINC01347 /// LOC101927097 /// LOC102723917 /// LOC102723928 /// LOC105371423 /// LOC105376332 /// LOC105378582 /// LOC105379690 ///	long intergenic non-protein coding RNA 266-1 /// long intergenic non-protein coding RNA	0.013055	1.35982

		LOC728323 /// PCMTD2			
202023_at	1942	EFNA1	ephrin-A1	0.009447	1.36382
209502_s_at	10458	BAIAP2	BAI1-associated protein 2	0.006644	1.36455
244734_at	64779	MTHFSD	methenyltetrahydrofolate synthetase domain containing	0.042225	1.37422
236013_at	777	CACNA1E	calcium channel, voltage-dependent, R type, alpha 1E subunit	0.040567	1.38121
226266_at	9489	PGS1	phosphatidylglycerophosphate synthase 1	0.013934	1.38268
217104_at	400410	ST20	suppressor of tumorigenicity 20	0.004782	1.38799
214535_s_at	9509	ADAMTS2	ADAM metallopeptidase with thrombospondin type 1 motif 2	0.017058	1.39202
216233_at	9332	CD163	CD163 molecule	0.032794	1.39612
232980_at	55788	LMBRD1	LMBR1 domain containing 1	0.025542	1.39623
227475_at	94234	FOXQ1	forkhead box Q1	0.047304	1.39773
203476_at	7162	TPBG	trophoblast glycoprotein	0.040088	1.40137
1553405_a_at	64478	CSMD1	CUB and Sushi multiple domains 1	0.000282	1.40375

210166_at	7100	TLR5	toll-like receptor 5	0.009591	1.40395
219059_s_at	10894	LYVE1	lymphatic vessel endothelial hyaluronan receptor 1	0.024152	1.40962
233305_at	64168	NECAB1	N-terminal EF-hand calcium binding protein 1	0.022739	1.41657
1559777_at	731424	MIR3945HG	MIR3945 host gene	0.041509	1.42052
227733_at	57156	TMEM63C	transmembrane protein 63C	0.026766	1.42422
206483_at	23639	LRRC6	leucine rich repeat containing 6	0.031383	1.45579
1559650_at	100000000	JAZF1-AS1	JAZF1 antisense RNA 1	0.031066	1.46824
1557961_s_at	100000000	C8orf88	chromosome 8 open reading frame 88	0.016558	1.4829
207010_at	2560	GABRB1	gamma-aminobutyric acid (GABA) A receptor, beta 1	0.006456	1.5046
236587_at	23639	LRRC6	leucine rich repeat containing 6	0.020534	1.51206
204787_at	11326	VSIG4	V-set and immunoglobulin domain containing 4	0.033304	1.53459
1553920_at	158401	C9orf84	chromosome 9 open reading frame 84	0.032416	1.55755
231223_at	64478	CSMD1	CUB and Sushi multiple domains 1	0.003529	1.5845

233504_at	158401	C9orf84	chromosome 9 open reading frame 84	0.006445	1.7357

Table S8. Table S8. Selected Pathways associated with differentially expressed genes at 24 hours

Ingenuity Canonical Pathways	**Molecules**
Th1 Pathway	SOCS3,TNFSF11,HLA-DRB1,PIK3C2A,HLA-DQA1
IL-23 Signaling Pathway	SOCS3,TNFSF11,PIK3C2A,IL23A
PKCθ Signaling in T Lymphocytes	CACNA1E,HLA-DRB1,PIK3C2A,MAPK8,HLA-DQA1
HMGB1 Signaling	TNFSF11,PIK3C2A,TGFB2,MAPK8,IL1R1
Dendritic Cell Maturation	HLA-DRB1,PIK3C2A,IL1RN,MAPK8,HLA-DQA1,IL23A
Aryl Hydrocarbon Receptor Signaling	TRIP11,MGST1,TGFB2,MAPK8,MDM2,NFIB
Neuroinflammation Signaling Pathway	HLA-DRB1,TLR5,PIK3C2A,GLS,HLA-DQA1,TGFB2,MAPK8,GABRB1,BACE1,CFLAR,IL1R1,PLA2G12A
IL-6 Signaling	SOCS3,PIK3C2A,IL1RN,MAPK8,IL1R1
Th2 Pathway	SOCS3,HLA-DRB1,PIK3C2A,GFI1,HLA-DQA1,STAT5B
NF-κB Signaling	AZI2,TNFSF11,TLR5,PIK3C2A,IL1RN,MAPK8,IL1R1
PPARα/RXRα Activation	CPT1B,TGFB2,MAPK8,IL1R1,STAT5B
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	TNFSF11,HLA-DRB1,TLR5,IL1RN,HLA-DQA1,IL23A
IL-22 Signaling	SOCS3,MAPK8,STAT5B

Role of JAK family kinases in IL-6-type Cytokine Signaling	SOCS3,MAPK8,STAT5B
Th1 and Th2 Activation Pathway	SOCS3,TNFSF11,HLA-DRB1,PIK3C2A,GFI1,HLA-DQA1,STAT5B
IL-10 Signaling	SOCS3,IL1RN,MAPK8,IL1R1
Parkinson's Signaling	MAPK8,CYCS
IL-9 Signaling	SOCS3,PIK3C2A,STAT5B
OX40 Signaling Pathway	HLA-DRB1,HLA-DQA1,MAPK8
Nur77 Signaling in T Lymphocytes	HLA-DRB1,HLA-DQA1,CYCS
Chronic Myeloid Leukemia Signaling	PIK3C2A,TGFB2,MDM2,STAT5B
Antigen Presentation Pathway	HLA-DRB1,HLA-DQA1
Autoimmune Thyroid Disease Signaling	HLA-DRB1,HLA-DQA1
Toll-like Receptor Signaling	TLR5,IL1RN,MAPK8
IL-2 Signaling	PIK3C2A,MAPK8,STAT5B
Th17 Activation Pathway	SOCS3,IL1R1,IL23A

Wnt/β-catenin Signaling	PPP2R2A,TGFB2,MDM2,KREMEN1,SOX11
Cdc42 Signaling	HLA-DRB1,BAIAP2,MAPK8,HLA-DQA1
Communication between Innate and Adaptive Immune Cells	HLA-DRB1,TLR5,IL1RN
Role of JAK1 and JAK3 in γc Cytokine Signaling	SOCS3,PIK3C2A,STAT5B
CD28 Signaling in T Helper Cells	HLA-DRB1,PIK3C2A,MAPK8,HLA-DQA1
IL-17A Signaling in Airway Cells	PIK3C2A,MAPK8,CXCL6
MIF Regulation of Innate Immunity	MAPK8,PLA2G12A
T Cell Exhaustion Signaling Pathway	HLA-DRB1,PIK3C2A,PPP2R2A,MAPK8,HLA-DQA1
GM-CSF Signaling	PIK3C2A,CSF2RA,STAT5B
Citrulline Biosynthesis	GLS
Growth Hormone Signaling	SOCS3,PIK3C2A,STAT5B
GDNF Family Ligand-Receptor Interactions	PIK3C2A,DOK6,MAPK8
Angiopoietin Signaling	PIK3C2A,ANGPT1,STAT5B
TNFR1 Signaling	MAPK8,CYCS

IL-12 Signaling and Production in Macrophages	PIK3C2A,MAPK8,TGFB2,IL23A
Epithelial Adherens Junction Signaling	TUBB2A,BAIAP2,CTNNA1,TGFB2
Apoptosis Signaling	MAPK8,CYCS,BCL2L11
CD27 Signaling in Lymphocytes	MAPK8,CYCS
Role of Cytokines in Mediating Communication between Immune Cells	IL1RN,IL23A
PPAR Signaling	IL1RN,IL1R1,STAT5B
Tight Junction Signaling	PPP2R2A,CTNNA1,TGFB2,CNKSR3
Glucocorticoid Receptor Signaling	PIK3C2A,IL1RN,HSPA1A/HSPA1B,MAPK8,TGFB2,CD163,STAT5B
iCOS-iCOSL Signaling in T Helper Cells	HLA-DRB1,PIK3C2A,HLA-DQA1
T Helper Cell Differentiation	HLA-DRB1,HLA-DQA1
Remodeling of Epithelial Adherens Junctions	TUBB2A,CTNNA1
T Cell Receptor Signaling	CBL,PIK3C2A,MAPK8

Acute Phase Response Signaling	SOCS3,IL1RN,MAPK8,IL1R1
HIF1α Signaling	PIK3C2A,MAPK8,MDM2
Phagosome Maturation	DCTN4,HLA-DRB1,TUBB2A
Antiproliferative Role of TOB in T Cell Signaling	TGFB2
Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	CYCS
NRF2-mediated Oxidative Stress Response	MGST1,PIK3C2A,ABCC2,MAPK8
TNFR2 Signaling	MAPK8
CCR5 Signaling in Macrophages	CACNA1E,MAPK8
IL-7 Signaling Pathway	PIK3C2A,STAT5B
Sirtuin Signaling Pathway	PGK1,CPT1B,GLS,HIST1H1T,BCL2L11
Inhibition of Angiogenesis by TSP1	MAPK8
IL-17 Signaling	PIK3C2A,MAPK8
TGF-β Signaling	TGFB2,MAPK8

Nitric Oxide Signaling in the Cardiovascular System	CACNA1E,PIK3C2A
Endothelin-1 Signaling	PIK3C2A,MAPK8,PLA2G12A
Renin-Angiotensin Signaling	PIK3C2A,MAPK8
CCR3 Signaling in Eosinophils	PIK3C2A,PLA2G12A