Autism Spectrum Disorder in Children with Prader-Willi Syndrome

by

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Abstract

Prader-Willi syndrome (PWS) is a genetic disorder caused by the lack of paternal expression from chromosome 15q11-13. The PWS phenotype includes hypotonia and failure to thrive during infancy, followed by hyperphagia, insatiable appetite, cognitive delay, problem behaviors, and social impairments in childhood. Various comparisons have been made between PWS and autism spectrum disorder (ASD), due to the overlap in phenotype of social impairment and problem behaviors, including restricted or repetitive behaviors. The study of ASD symptoms in individuals with PWS has largely been confined to older adolescents and adults, rather than younger children. This thesis contains two studies: first, a systematic review investigating the core ASD symptoms in PWS; and second, a descriptive study investigating ASD-related social communication impairment in younger children with PWS. The systematic review determined that no studies have had a mean age of less than eight years old, although some studies have found fewer ASD symptoms in children with PWS compared to adolescents and adults with PWS. The descriptive study used various assessments in children with PWS to measure ASD-related social communication impairment and general social skills, and to describe the social communication impairment that exists in children with PWS. We found disparity in results between the ASD questionnaires and the gold-standard ASD observational assessment (i.e. Autism Diagnostic Observation Schedule-2). Although our sample size was limited, this study paves the way for future studies to not only identify ASD symptoms in children with PWS, but also to determine the appropriateness of various ASD assessments within the PWS population. Additionally, future studies should determine appropriate early intervention for PWS children, focusing on their unique behavioural needs.

Preface

This thesis is an original work by Jeff Bennett. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Social Communication Development in Children with Prader-Willi syndrome", No. 00051250, January 8, 2015.

Chapter 2 of this thesis has been accepted for publication (with minor revisions) by American Journal of Medical Genetics, Part A, as J.A. Bennett, T. Germani, A.M. Haqq, and L. Zwaigenbaum, "Autism Spectrum Disorder in Prader-Willi Syndrome: A Systematic Review." I was responsible for the concept formation, data collection and analysis, as well as the manuscript composition. T. Germani assisted with the data collection and contributed to manuscript edits. A.M. Haqq and L. Zwaigenbaum were the supervisory authors and were involved with concept formation and manuscript edits.

Chapter 3 of this thesis will be submitted for publication as J.A. Bennett, A.M. Haqq, and L. Zwaigenbaum, "Development of Social Communication in Children with Prader-Willi Syndrome: A Direct Comparison to Autism Spectrum Disorder- Study Protocol." I was responsible for concept formation and manuscript composition. A.M. Haqq and L. Zwaigenbaum were the supervisory authors and were involved with concept formation and manuscript edits.

Chapter 4 of this thesis will be submitted for publication as J.A. Bennett, S. Hodgetts, M.L. Mackenzie, A.M. Haqq, and L. Zwaigenbaum, "Investigating Autism-Related Social Communication Impairment in Children with Prader-Willi syndrome: A Descriptive Study." I was responsible for concept formation, data collection and analysis, as well as the manuscript composition. The remaining authors all assisted with concept formation and manuscript edits, with L. Zwaigenbaum and A.M. Haqq as supervisory authors.

Dedication

To my dear wife, Carli, my son, Austin, and all of his future siblings ☺

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List of Abbreviations

ADI-R	Autism Diagnostic Interview- Revised
ADOS-2	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
CBE	Clinical Best Estimate
DEL	Deletion (genetic subtype)
PWS	Prader-Willi Syndrome
RRB	Restricted or Repetitive Behaviours
SCQ	Social Communication Questionnaire
SRS-2	Social Responsiveness Scale-2
SSIS-RS	Social Skills Improvement System- Rating Scales
UPD	Uniparental Disomy (genetic subtype)

Chapter 1: Introduction

Background

Prader-Willi syndrome (PWS) is a genetic disorder caused by the lack of expression of the paternal contribution of chromosome 15q11-13, either due to deletion (DEL; 60-70%), uniparental disomy (UPD; 20-30%), or a rare imprinting center defect (1-3%) [Cassidy et al. 2012]. PWS is rare (1 in 10 000-30 000), and is usually noticed in the first few months of life because of failure to thrive and low muscle tone present from birth. During early childhood, children with PWS develop an insatiable appetite and hyperphagia, which can lead to morbid obesity and comorbidities such as insulin resistance, Type 2 diabetes and cardiovascular disease.

The majority of research in PWS has tended to focus on management of growth and nutrition issues, such as overcoming hyperphagia and obesity using modified diets [Loehr et al. 2015; Miller et al. 2013] and the use of growth hormone treatment to help normalize height [Haqq et al. 2003; Lindgren and Lindberg 2008] and body composition [Myers et al. 2007]. However, some parents have expressed even greater concerns over problem behaviours and social impairments that commonly affect children with PWS [Dykens et al. 2011]. In fact, research that compared children with PWS to children with Down Syndrome and non-specific mental retardation found significantly higher rates of problem behaviours in children with PWS, such as skin picking, obsessions, arguing, tantrums, and compulsions [Dimitropoulos et al. 2001; Dykens and Kasari 1997]. In addition, various social impairments have been identified in individuals with PWS. Rosner et al. [2004] compared social competence in individuals with PWS, Down syndrome, and William's syndrome, and found that the PWS group was significantly lower in participation in clubs or organizations, as well as interactions with others. In addition, Key et al. [2013] used event-related potentials to determine that PWS children with the UPD genetic subtype may show

atypical face vs. object recognition and that both UPD and DEL subtypes had potentially altered processing, attention to and/or recognition of faces and facial expressions. Finally, Koenig et al. [2004] showed that PWS individuals performed significantly worse than individuals with similar levels of intellectual disability on a social attribution task, which measures one's ability to make appropriate social attributions from an ambiguous visual display.

In an attempt to explain the social impairments and problem behaviours present in people with PWS, some researchers have compared PWS to autism spectrum disorder (ASD). Currently, the prevalence of ASD in PWS is estimated at about 25%, with the prevalence in the UPD subtype (38%) about twice as high as the DEL subtype (19%) [Veltman et al. 2005]. A literature review by Dykens et al. [2011] found similarities between individuals with PWS and ASD in the area of restricted and repetitive behaviours, including insistence on sameness, repetitive questioning, and narrow interests. However, they also found unique attributes in PWS such as skin picking and hoarding; in contrast, stereotypies and more diverse and severe self-injurious behaviours are more common in ASD. More recent studies have compared social responsiveness using the Social Responsiveness Scale (SRS) [Constantino and Gruber 2005] in adolescents with PWS compared to those with ASD [Dimitropoulos et al. 2013]. In this study, Dimitropoulos et al. [2013] found that subjects with the UPD subtype showed a similar profile of impairment to ASD on most of the SRS domains; in contrast, patients with the DEL subtype showed significantly less impairment. Additionally, Zyga et al. [2014] compared individual play in children age 7 to 13 with PWS versus ASD, and found that both groups were similarly affected, with scores significantly below normative data on organization, imagination, and affective expression.

Due to its lack of consistent biomarkers or genetic defects, ASD is characterized by the presence of two core symptoms based on caregiver report and clinical observation: (1) impairment of

social communication; and (2) highly restricted or repetitive behaviours and interests [American Psychiatric Association (APA) 2013]. Although no definitive genetic markers have been found to cause ASD, various genetic defects are associated with higher incidences of ASD, including defects related to chromosome 15q11-13 [Vorstman et al. 2006; Vorstman and Ophoff 2013]. Indeed, Schaaf et al. [2013] found varying core PWS symptoms in four individuals with ASD (e.g. hypotonia [3 of 4], problems feeding at birth [3 of 4], excessive weight gain before age six [3of 4], and hyperphagia [2 of 4]) who had truncating mutations on the *MAGEL2* gene, found in the 15q11-13 region, although none met genetic criteria for PWS.

ASD Assessment

Some of the most common ASD assessments used in the PWS population include the Social Communication Questionnaire (SCQ)[Rutter et al. 2003a], Social Responsiveness Scale (SRS) [Constantino and Gruber 2005], and the Autism Diagnostic Observation Schedule (ADOS)[Lord et al. 2006]. However, none of the measures have been validated for use in a PWS population, and each has potential limitations within the PWS sample due primarily to their cognitive delay. For example, compared with the SCQ validation sample of persons with ASD, people without ASD (but with IQs below 70) scored less than four points from the proposed ASD cut-off of 15 [Rutter et al. 2003a]. Furthermore, individuals without ASD (but IQ less than 50) scored within one point of the ASD cut-off on the SCQ. Given that the average IQ in PWS is 60 to 70 [Cassidy et al. 2012], this means that higher ASD scores on the SCQ may be confounded by intellectual disability. The SRS manual [Constantino and Gruber 2005] gives similar caution that the SRS was validated using individuals with IQ greater than 70, and that use in individuals with IQ less than 70 needs to take into account the social challenges that exist for individuals with intellectual disability. Lastly, the ADOS [Lord et al. 2006] was designed to differentiate ASD from

intellectual disability, but has poorer discriminative quality in children with accompanying complex behavioural issues [Molloy et al. 2011]. Validation of any of these instruments will need to be compared to the current gold standard for ASD diagnosis, which is expert clinical judgement.

With relevant caveats about the validity of assessments currently used to evaluate ASD symptoms in this population, several groups have reported that the UPD genetic subtype generally demonstrates higher ASD symptomatology than the DEL subtype. This could be related to the overexpression of chromosome 15q11-13 in UPD [Vorstman and Ophoff 2013]. Individuals with a duplication of chromosome 15 have higher risk for ASD, and individuals with UPD carry two copies of the maternal chromosome 15q11-13.

Research investigating ASD symptoms in children with PWS is lacking [Dykens et al. 2011]. The youngest mean sample age for any study investigating ASD in PWS is eight years old [Ali et al. 2013]. In contrast, behavioural manifestations of ASD have been reported as early as 12 months of age, and ASD can be diagnosed reliably by 18 to 24 months in a clinical setting [Ozonoff et al. 2010; Zwaigenbaum et al. 2005]. Additionally, there is an extensive literature on behavioural features and developmental trajectories in ASD from two years and on.

ASD in Other Genetic Syndromes (Fragile X and Down syndrome)

Two other genetic syndromes associated with increased rates of ASD have reported reliable early identification of ASD: Fragile X syndrome (FXS) and Down syndrome. For example, Scambler et al. [2007] found high levels of sensitivity (75%) and specificity (92%), relative to expert clinical judgement in identifying co-occurring ASD in children under three years of age with FXS using the Denver Criteria [Baird et al. 2000] for the Checklist for Autism in Toddlers [Baron-Cohen et al. 2000]. Small sample size (n=17; 4 diagnosed with ASD) was a limiting

factor in this study. Hernandez et al. [2009] conducted a three year longitudinal study of boys with FXS (n=56; 30-88 months at baseline) by performing yearly clinical ASD assessments to determine stability of ASD diagnosis in FXS over time. They reported 68% diagnostic agreement over the three years, supporting the findings that diagnosis of ASD in FXS can reliably occur in the preschool years. In addition, more than 1000 parents of children with FXS were asked in a US national parent survey about co-diagnosis of ASD [Bailey et al. 2008]. In total, 40% of parents responded that their child had also received a diagnosis of ASD. Furthermore, the majority of parents who responded that their child had been co-diagnosed with ASD also reported their child has attention problems, anxiety, and/or hyperactivity. Interestingly, when Rogers et al. [2001] compared children with FXS, ASD, and developmental delay using the gold standard ASD assessment tools, the ADOS and Autism Diagnostic Interview-Revised (ADI-R) [Rutter et al. 2003b], they found similar profiles on the ADOS between children with ASD and children with FXS who exceeded cut-off for ASD, and similar profiles between the children with developmental delay and the children with FXS who did not exceed cut-off of ASD.

In children with Down syndrome, DiGuiseppi et al. [2010] found that ASD can also reliably be diagnosed in the preschool years. They found that the combined sensitivity of the Modified Checklist for Autism in Toddlers [Robins et al. 2001] and SCQ was excellent (87.5%), although specificity was not adequate (49.9%). Potential confounders to specificity included intellectual disability and impaired executive function, both of which may appear as social communication impairment. Interestingly, it appears that ASD is most frequently found in children with DS who have co-occurring intellectual disability [Moss and Howlin 2009].

These findings in both FXS and Down syndrome suggest that early identification of ASD in genetic syndromes is possible, although the phenotype of co-occurring ASD within each genetic

syndrome may be distinct. Even though early identification is not the focus of this study, the results from our study could help to identify which ASD-like symptoms are most prevalent in younger children with PWS. The difficulty in identifying ASD symptoms in a genetic syndrome is distinguishing which symptoms are features of the syndrome itself, and which symptoms are specifically associated with ASD. Understanding these nuances could help determine which of the current ASD assessments may be useful for identification of ASD in children with PWS.

Study Justification and Objectives

Although a review of ASD in PWS was published in 2011 [Dykens et al.], a recent surge of research investigating ASD in PWS in the last four years justified an updated literature review. Furthermore, the last formal systematic review that included a prevalence estimate of ASD in PWS was published ten years ago [Veltman et al. 2005], and studies published since then have included larger sample sizes and more diverse samples. Since the review by Veltman et al. [2005] was published, the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist has been released [Moher et al. 2009]. The PRISMA checklist is designed to help authors report all necessary items, including potential risks of bias and inclusion of all papers identified, when writing a systematic review and/or meta-analysis. The majority of scientific journals have adopted PRISMA in order to ensure adequate reporting of evidence. In summary, given the recent surge of new studies since the last review, the ten years since the last prevalence estimate, and the arrival of the PRISMA checklist to ensure adequate reporting, an up-to-date systematic review was not only warranted, but necessary. This updated systematic review will serve to inform professionals of the most recent evidence and to identify existing knowledge gaps.

My descriptive study aimed to address a few of the relevant knowledge gaps identified in my systematic review, including a focus solely on children with PWS and the use of diagnosis based on clinical best estimate to compare various ASD symptoms and assessments in the PWS population. Although sample size limited formal group comparisons, the UPD genetic subtype showed relatively higher ASD symptomatology than the DEL subtype, which is consistent with our systematic review. The review also identified the most commonly used assessments when investigating ASD in PWS, including the ADOS, the SCQ, and the SRS. My study was also able to describe the social-communicative phenotype of a sample of children with PWS, measuring both ASD symptoms and broader aspects of social behaviour. Additionally, we were able to identify areas of social functioning that are relatively strong within the PWS population, which could help inform future intervention strategies by using relative strengths to help address problem behaviours and social impairments.

Research Questions:

This thesis reviewed the literature surrounding ASD in PWS, and described ASD symptoms in children with PWS. It sought to answer the following specific research questions:

- What ASD symptoms are associated with PWS, and what symptoms differ between PWS-ASD and PWS+ASD?
- What is the estimated prevalence of ASD in PWS, based on studies that have used relevant ASD assessments?
- What characterizes social behaviour in children with PWS, both ASD-related and in general?
- What are the potential limitations to using ASD assessments and their respective ASD cut-off scores for diagnosis in children with PWS?

Outline:

This thesis comprises three articles, which have been, or will be, submitted to peer-reviewed journals for publication. The first is a systematic review reporting on: (1) studies investigating core ASD symptoms in individuals with PWS, and (2) a prevalence estimate of individuals with PWS who meet criteria for ASD, either based on clinical diagnosis or passing clinical-cut points on relevant ASD assessments. This review serves as the background and rationale for the work of this thesis. The second article is the protocol for the cross-sectional study that was originally designed to compare children with PWS (both UPD and DEL) to children with ASD. However, based on sample-size restraints, we instead performed a descriptive study, which constitutes the third article. This study used various measures to help describe the social-behavioural phenotype in children with PWS.

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Chapter 2

Bennett JA, Germani T, Haqq AM*, Zwaigenbaum L*. *co-senior authors. Autism Spectrum Disorder in Prader-Willi Syndrome: A Systematic Review. Accepted for publication by *American Journal of Medical Genetics, Part A*

Introduction

Background

Prader-Willi syndrome (PWS) is a genetic disorder that results from a lack of expression of paternally-derived genes on chromosome 15q11-13. Two mechanisms account for most cases: deletion (DEL) of that region from the paternal chromosome (~70% of cases) or maternal uniparental disomy (UPD), where both chromosomes have genetic material from the mother (~25% of cases). A small minority of cases (<5%) are caused by imprinting defects. Prevalence of PWS is estimated to be between 1 in 10 000 to 1 in 30 000 [Cassidy et al. 2012]. PWS is characterized by hypotonia and difficulty feeding during infancy, followed by hyperphagia, insatiable hunger, morbid obesity, and short stature during development. Intellectual disability (average IQ: 60-70) and challenging behaviours (e.g., tantrums, self-injurious behaviors, obsessive compulsive traits) as well as atypical social behaviors are common [Cassidy et al. 2012].

Indeed, some of the behavioral features of PWS arguably overlap with those found in individuals with autism spectrum disorder (ASD), a neurodevelopmental disorder defined by impairment in social communication and highly repetitive or restricted behaviours and interests [American Psychiatric Association (APA), 2013] . ASD is associated with several common co-morbidities including intellectual disability (31% with IQ ≤70) [Center for Disease Control and Prevention (CDC) 2014] and challenging behaviours such as tantrums and self-injurious behaviour [Hodgetts et al. 2013; Horner et al. 2002]. ASD prevalence in the United States is reported by the CDC [2014] to be as high as 1 in 68 children, with the prevalence in boys (1 in 42) over four times higher than that in girls (1 in 189).

Despite a growing recognition of a potential relationship between PWS and ASD, only one systematic review on the topic has been published to date [Veltman et al. 2005]. In this review, prevalence of ASD in individuals with genetically confirmed PWS was estimated at 25.3% (38 of 150; range: 0-36.5%) based on a total of five studies. In studies that stratified by genetic subtype, prevalence of ASD was estimated at 18.5% (18 of 97) in DEL and 37.7% (20 of 53) in UPD. Indeed, the prevalence of ASD in the UPD subtype has been found to be consistently higher by the majority of studies investigating ASD in PWS [Dimitropoulos and Schultz 2007; Dykens et al. 2011], possibly due to the dosage effect postulated as the cause for the association of ASD with chromosome 15 duplications. Two other narrative literature reviews investigating the occurrence of ASD in PWS have been published in the past decade [Dimitropoulos and Schultz 2007; Dykens et al. 2011]; however, a recent surge of research into the occurrence of ASD in those with PWS warrants further study and critical analysis using a systematic approach to provide an up-to-date synthesis. An updated systematic review of the literature investigating ASD in PWS would also provide the opportunity to update prevalence estimates of ASD in PWS and its major genetic subtypes (UPD and DEL).

Aims and Rationale of Review

The aim of this review was to summarize findings related to symptoms of ASD in individuals with PWS, since the last systematic review published by Veltman et al. in 2005. The current review was done using a systematic approach, incorporating the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist [Moher et al. 2009] to ensure adequate reporting of evidence. The PRISMA checklist is endorsed by nearly 200 journals in the health sciences in order to improve the reporting quality of systematic reviews, and includes 27 recommendations for items to be included (e.g. Title: Identify the report as a

systematic review, meta-analysis, or both). In addition, the secondary purpose of the review was to update the prevalence of ASD in those with PWS to give clinicians and researchers a more accurate representation of how frequently to expect ASD in PWS patients.

Materials and Methods

Information sources

Two reviewers independently searched the following databases and years: Medline (1946 to present); CINAHL (1937 to present), PsychINFO (1887 to present), Embase (1974 to present) and Web of Science (1898 to present). The searches are inclusive up to February 1, 2015. A hand-search of the references of relevant articles was also performed. Study language included English and Spanish, based on the reviewers' language abilities.

Search and Selection Criteria

The following terms were used to search for articles: ((Prader-Willi syndrome OR PWS OR Prader-Labhart-Willi syndrome) AND (autism* OR autistic* OR Asperger* OR Pervasive Developmental Disorder* OR ASD OR PDD)). To be included for review, studies had to meet at least one of the following two criteria: (1) explicitly report core ASD symptoms (social communication impairment and restricted or repetitive behaviours and interests) in individuals with PWS, and (2) report a prevalence of individuals with PWS who met criteria for ASD, either based on clinical diagnosis or on scores exceeding clinical cut-points on relevant ASD symptom measures. Studies were excluded if they were case reports or were primarily focused on secondary aspects of ASD rather than the core symptoms (e.g. face processing, sleep impairments). Studies that reported on any other disorder on chromosome 15, genetic findings, and intervention studies were also excluded. Two independent reviewers (JB and TG)

participated in the screening and full text article review. Any disagreements between the two reviewers were taken to a third party (LZ) for resolution.

Data collection process

A critical review form from McMaster University [Law et al. 1998] was modified to include all necessary data, including study objective and rationale, presence or absence of control group, outcome measures, prevalence, and results.

Study demographics were recorded and compiled in Table 1, including sample size and mean age of the PWS group (overall and by genetic subtype, where available) and comparison groups. Cognitive and ASD assessments were also recorded, including assessments used to support a diagnosis of ASD or those that assessed one of: social communication or repetitive and restricted behaviours.

Results

In total, 1023 articles were identified (Figure 1). After removal of duplicates, 764 articles were screened based on abstract and title. The vast majority of articles were excluded for a number of reasons, including: focus on genetics; animal models; investigating other 15q11-13 defects (not PWS); intervention studies; and case reports. The initial screen by JB and TG resulted in 27 full-text articles to be reviewed for eligibility. For the entire systematic review, seven articles were excluded either because of a lack of focus on core ASD symptoms or failure to report prevalence of ASD in those with PWS [Bruining et al. 2014; Cotton and Richdale 2006; Cotton and Richdale 2010; Dimitropoulos et al. 2009; Feldman and Dimitropoulos 2014; Halit et al. 2008; Key et al. 2013]. For the study aim of investigating ASD core domains in PWS, an additional five articles were not included in the analysis [Akefeldt and Gillberg 1999; Beardsmore et al. 1998; Descheemaeker et al. 2002; Hou et al. 1998; Reilly et al. 2014]. For the

study aim of investigating the prevalence of ASD in PWS, seven articles that met criteria for the systematic review were not included in the analysis: three articles didn't use an ASD assessment tool [Buono et al. 2010; Greaves et al. 2006; Koenig et al. 2004]; two studies did not report number of individuals with PWS who passed cut-off for ASD [Ogata et al. 2014; Song et al. 2015]; and two studies used data on participants that had already been reported in a previous study [Milner et al., 2005; Moss et al., 2009; Oliver et al., 2011; Veltman et al., 2004] In summary, a total of 20 articles were identified that either measured core ASD symptoms in PWS (n=15) and/or included data that could be used to calculate the prevalence of individuals with PWS who met criteria for ASD (n=13) (See Figure 1).

Studies that reported ASD symptoms in individuals with PWS are summarized in Table 1. Notably, each of these except one [Ali et al. 2013] had a mean sample age of >10 years. Fewer than half of the studies included non-PWS ASD comparison groups. Most studies had a relatively small sample size, which would decrease power to detect meaningful differences; however, this might be anticipated, given the rarity of the disorder. As well, only one study was longitudinal in design [Descheemaeker et al. 2002]; the rest were cross-sectional. While blinding of research participants is not possible in cross-sectional studies, only one of the studies reported blinding the data collectors/assessors or those analyzing the data [Milner et al. 2005]. This lack of blinding increases risk of detection bias. The most common cognitive assessments were the Wechsler Intelligence scales (e.g. Wechsler Preschool and Primary Scales of Intelligence [Wechsler 2002], Wechsler Intelligence Scales for Children [Wechsler 2003]). ASD assessments varied widely, although the Autism Screening Questionnaire [Berument et al. 1999], which was later renamed the Social Communication Questionnaire [Rutter et al. 2003a], was the most commonly used.

Synthesis of Results: ASD Core Domain

Overall ASD Symptomatology

ASD Symptomatology

Studies investigating overall ASD symptomatology in individuals with PWS used various comparison/control groups. A recent descriptive study with no control group [Ali et al. 2013] found that 4 of 15 (26.7%) individuals with PWS had mild to significant ASD features, based on cut-offs from the Childhood Autism Rating Scale [Schopler et al. 1980]. Notably, all four individuals were the UPD genetic subtype. Another study [Descheemaeker et al. 2006] compared ASD symptomatology between individuals with PWS (n=59) and other individuals with non-specific intellectual disability (n=59) using the Pervasive Developmental Disorder-Mental Retardation Scale [Kraijer 1999]. The results showed that higher IQ is not protective against ASD symptoms in PWS, whereas in non-specific intellectual disability, ASD symptoms increase as IQ decreases. Using the Pervasive Developmental Disorders Autism Society Japan Rating Scale [Adachi et al. 2006], Ogata et al. [2014] compared ASD symptoms in children (mean age 9 years; range 6-12 years) to adolescents (mean age 16 years; range= 13-19 years). They found no difference in ASD symptoms between genetic subtypes in children with PWS (n=22) but did find significant differences between genetic subtypes in adolescents with PWS (n=23). Consistent with previous findings, the UPD subtype showed significantly higher autistic symptomatology in adolescents with UPD. The data from the Ogata et al. [2014] study was followed up by Song et al. [2015], which directly compared ASD symptomatology in individuals with PWS (n=30) and individuals with Asperger Disorder (n=31) between three age groups: 6 to 8 years, 9 to 12 years, and 13 to 15 years. The results found that individuals with PWS age 6 to 12 showed less prominent ASD traits than same-age individuals with Asperger's, whereas individuals age 13 to

15 showed similar ASD traits. This finding, that ASD traits in PWS are more pronounced with age, was also reported by Lo et al. [2013]. They reported that, within their sample of 66 individuals with PWS age 7 to 17 years (mean age 11.0 years), none of the individuals below age 10 (n=22) met the cut-off for ASD on the Autism Screening Questionnaire [Berument et al. 1999], whereas 24 individuals age 10 and over met the cut-off. However, this study lacked a comparison or control group.

Restricted or Repetitive Behaviors and Interests (RRBs)

Several studies have characterized RRBs in individuals with PWS, comparing to both those with ASD and those with various other disorders. Greaves et al. [2006] found similar levels and significant overlap among the RRBs found in PWS (n=80) and ASD (n=89) using the Childhood Routine's Inventory [Evans et al. 1997]. Significant differences were found in that individuals with PWS tend to "collect or store objects" more often, whereas children with ASD "have a strong preference for certain foods", "line up objects in lines or symmetrical patterns", and "seem very aware of details at home". In a more recent study Flores et al. [2011] compared RRBs across two ASD samples (n=207) and one PWS sample (n=45) using the Repetitive Behavior Scale-Revised [Lam and Aman 2007]. This study found a higher trend of RRBs in the ASD group compared to the PWS group. Specifically, 16 of the 43 items were endorsed by the ASD groups significantly more often than by the PWS group, whereas no significant differences were found between those with the DEL and UPD subtypes of PWS. Furthermore, Flores et al. [2011] separated individuals with PWS by those who scored ≥15 (5/24 with DEL, and 7/20 with UPD)) on the Social Communication Questionnaire (SCQ) and those who scored <15 (a score of ≥15 being indicative of ASD). They found similar rates of RRBs in those with ASD and those

with PWS who scored ≥15 on the SCQ; not surprisingly, given that individuals with more autistic traits will likely have more RRBs.

Oliver et al. [2011] and Moss et al. [2009] examined RRBs and ASD characteristics (using the Repetitive Behavior Questionnaire [Moss and Oliver 2008] and the Autism Screening Questionnaire [Berument et al. 1999], respectively) across seven different genetic syndromes, including PWS (n=189). Oliver et al. [2011] found that individuals with PWS had significantly lower levels of stereotyped behaviours such as hand stereotypy, lining objects, and repetitive behaviors, when compared to all other groups. Moss et al. [2009] also found that the PWS group had the lowest mean score on the Autism Screening Questionnaire compared to the Fragile X, Cornelia de Lange, and Angelman syndrome groups as well as to the intellectual disability group.

It is important to emphasize that while broad categories of behavioral symptoms may be shared in common between individuals with ASD and those with PWS, specific aspects of these behaviors may differ between groups. For example, Buono et al. [2010] compared self-injurious behaviours (SIBs) among those with PWS, ASD and Down syndrome using the Self-Injurious Behavior Scale [Buono et al. 2006]. Whereas individuals with ASD were found to be more prone to participate in "body-hand-hitting" and "body-object hitting", skin-picking was the most common SIB in PWS [Buono et al. 2010]. Also see [Dykens et al. 1999; Dykens et al. 2011].

Social Communication Impairment

Prior to 2013, few studies had specifically investigated ASD-related social communication (SC) impairment in children with PWS. Veltman et al. [2004] compared 32 individuals with UPD to 31 with DEL using the Autism Screening Questionnaire [Berument et al. 1999]. Overall scores, as well as those for the social interaction subdomain, were found to be

significantly higher in individuals with the UPD subtype. A follow-up study published one year later [Milner et al. 2005] added more participants (UPD=49, DEL=47) and included the gold standard [Falkmer et al. 2013] of ASD assessment tools, the Autism Diagnostic Observation Schedule [Lord et al. 2006] and the Autism Diagnostic Interview-Revised [Rutter et al. 2003b]. Milner et al. [2005] found significantly more ASD-related social communication impairments in individuals with the UPD subtype when compared with those with the DEL subtype on all three assessments. One other early study found that individuals with PWS showed significantly lower social attribution abilities (i.e. the ability to attribute ambiguous visual display to social cues), compared to individuals with similar intellectual ability, but that social attribution abilities did not differ when compared to individuals with pervasive developmental disorder [Koenig et al. 2004].

More recent studies have confirmed these findings of social communication impairment in individuals with PWS using various measures. Dimitropoulos et al. [2013] used the Social Responsiveness Scale [Constantino and Gruber 2005] and Social Competence Inventory [Rydell et al. 1997] to directly compare social communication impairments between both subtypes of PWS and ASD. Results between the UPD and ASD groups were found to be similar, and both groups showed significantly more impairment than did the DEL group. Delayed development of theory of mind [Lo et al. 2013] and pretend play [Zyga et al. 2014], common findings in ASD ([Baron-Cohen 2000] and [Baron-Cohen 1987], respectively), were recently reported in children with PWS, with either UPD or DEL.

ASD Prevalence

Overall prevalence of ASD was estimated based on percentage of individuals who met criteria for ASD, either based on clinical diagnosis or on scores exceeding clinical cut-points on

reported ASD symptoms measures. An overall prevalence of ASD in PWS, as well as prevalence based on genetic subtype, is shown in Table 2. Using the binomial model, a z-test was used to compare the outcome proportions to determine whether our results differed from the results found by Veltman et al. [2005]. Our overall prevalence estimate (26.7%, 95% CI= 23.6% - 29.8%; n= 786) was found to be not significantly different (p=.719) from the results obtained by Veltman et al. [2005] (prevalence= 25.3%, 95% CI= 18.4 - 32.3%; n= 150). The prevalence of ASD in those with UPD based on our updated review (prevalence= 35.3%, 95% CI=28.5% - 42.1%; n=190) was significantly higher (p<.001) than the prevalence of ASD in those with DEL (prevalence= 18.5%, 95% CI= 13.7% - 23.3%; n= 254). Veltman et al. [2005] also had similar findings for both subtypes (p = .741 and .992 for UPD and DEL subtypes, respectively).Because the measures used by different studies were heterogeneous, symptom severity of ASD in individuals with PWS could not be synthesized as a whole.

Interestingly, only one study commented on use of growth hormone therapy in its cohort [Akefeldt and Gillberg 1999]. While this study found that it had no impact on ASD symptoms, other studies [Festen et al. 2008; Siemensma et al. 2012] have found cognitive benefits of growth hormone therapy in individuals with PWS, although these findings are not consistent [Haqq et al. 2003]. To date, no studies have reported altered behavior in cohorts on growth hormone therapy. Given that cognitive function has been found to negatively correlate with RRBs in PWS [Dykens et al. 2011], it may be worth including growth hormone therapy as a stratification variable in future studies to further address whether use of GH affects ASD symptom severity in PWS.

Discussion

Summary of Evidence

In total, 15 studies were identified that met inclusion criteria for measuring ASD symptomatology in PWS. These studies found multiple similarities regarding the presence of RRBs and social communication impairment between ASD and PWS; the UPD genetic subtype showed more ASD symptomatology than did the DEL subtype. Thirteen studies were included to measure overall prevalence of ASD in PWS, based on either clinical diagnosis or meeting ASD cut-off on a psychometrically-sound ASD assessment tool. The prevalence estimate of ASD in PWS in this systematic review (26.7%) did not differ from the estimate provided in the systematic review published 10 years ago [Veltman et al. 2005]. This group also found that the estimated prevalence of ASD in the UPD genetic subtype of PWS (35.3%) was higher than the estimated prevalence of ASD in the DEL subtype (18.5%).

This review is the first systematic review published on the topic of ASD in PWS since the development of the PRISMA checklist [Moher et al. 2009] to ensure adequate search strategies, data collection, and reporting techniques. For example, the Veltman et al. [2005] review did not indicate which studies were excluded after full review and did not mention any potential financial conflicts of interest. Furthermore, this review is the first in a decade to report a prevalence estimate for ASD in PWS. By more than doubling the number of studies included and having greater than five times the number of individuals with PWS included in the estimate, we were able to confirm the previous findings with greater confidence, as demonstrated by a narrower 95% confidence interval. Before the last review was written [Dykens et al. 2011], all publications investigating ASD symptoms in PWS had taken place in the United States or select Western European countries (United Kingdom, Netherlands, Belgium, and Italy). Since that

review, publications have emerged from other countries, including Egypt [Ali et al. 2013] and Japan [Ogata et al. 2014; Song et al. 2015], confirming the presence of ASD symptomatology in more diverse samples of those with PWS.

Limitations

Due to the rarity of PWS, the majority of studies have used a cross-sectional design. Cross-sectional studies are useful in gaining a quantitative view of a disorder and estimating prevalence, but are limited in their ability to examine development over time, which is particularly relevant given that cross sectional studies indicate higher levels of ASD symptoms in older children with PWS. Only one study [Flores et al. 2011] attempted to stratify its PWS sample into those who did and did not meet criteria for ASD. This technique might be more informative than simply treating PWS cohorts as homogenous for ASD symptoms. Furthermore, few studies incorporated relevant comparison groups (e.g. ASD), limiting our ability to examine similarities and differences in symptom expression. Another obvious limitation is a lack of psychometrically sound assessments to verify ASD within the PWS population. Since these assessments have been validated in non-syndromic ASD samples, they cannot be easily generalized to other populations, especially those with PWS and other genetic disorders. Given that many PWS symptoms likely overlap with idiopathic ASD symptoms (although may differ qualitatively; as in SIB), it is likely that the prevalence estimate obtained is higher than the true prevalence, given that these measures may lack specificity in a PWS sample.

Future Directions

Future studies are required to determine which ASD assessment tools are valid for children and adolescents with PWS. This will require clinical diagnosis of individuals with PWS combined with the use of well-validated assessment tools to verify which assessments capture

potentially unique ASD impairments within paediatric populations with PWS. Furthermore, one major knowledge gap identified in this review is the lack of studies investigating ASD symptoms in younger children with PWS. Despite the common finding that ASD symptoms become more pronounced with age in PWS, none of the identified studies had a mean age less than eight. As per DSM-5 [APA, 2013], ASD is characterized by the presence of core impairments in early development, but these deficits may not fully manifest until social demands exceed limited capacities, or may be masked by learning coping strategies later in life. Therefore, it is critical that future studies identifying ASD symptoms in younger patients with PWS be done.

Early diagnosis of ASD can translate to early interventions, which in turn result in improved outcomes [Anagnostou et al. 2014b; Dawson 2008]. Specifically, early behavioural intervention has shown promise to achieving maximal outcomes among very young children with ASD [MacDonald et al. 2014]. Therefore, uncovering the spectrum of social-communicative deficits found in PWS is imperative to inform intervention strategies. If social deficits are similar between PWS and ASD, evidence-based interventions for children with ASD may be generalizable to children with PWS. However, if the impairments found in children with PWS are distinct from the difficulties in social reciprocity classically shown in ASD, this would suggest these children should be treated using more tailored strategies. Given the current prevalence of ASD in PWS as demonstrated in this study, it would be prudent for clinicians to evaluate for social deficits in children with PWS.

Conclusions

The overarching conclusion of these papers is that the prevalence of ASD in PWS individuals is much higher than is found in typically developing individuals, and those with the UPD subtype are more likely to have symptoms of ASD than are those with the DEL subtype.

These findings were repeated using multiple assessment tools assessing for both RRBs and social communication impairment. Furthermore, the populations studied have been sampled from across multiple populations, including the United States, multiple European countries, Egypt, and Japan. Overall, the evidence has shown that the prevalence of ASD within the PWS population merits s further research to address diagnosis and intervention. Finally, future studies to elucidate the possible shared genetic and neurotransmitter defects contributing to the pathogenesis of PWS and ASD are further required.

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Contributions

Study searches and selection were carried out by JB and TG. Writing the systematic review was carried out by JB. Edits and review were carried out by TG, AH, and LZ. Expert clinical knowledge was provided by AH and LZ.

Conflict of Interest Disclosure

The authors declare no conflict of interest, financial or otherwise.

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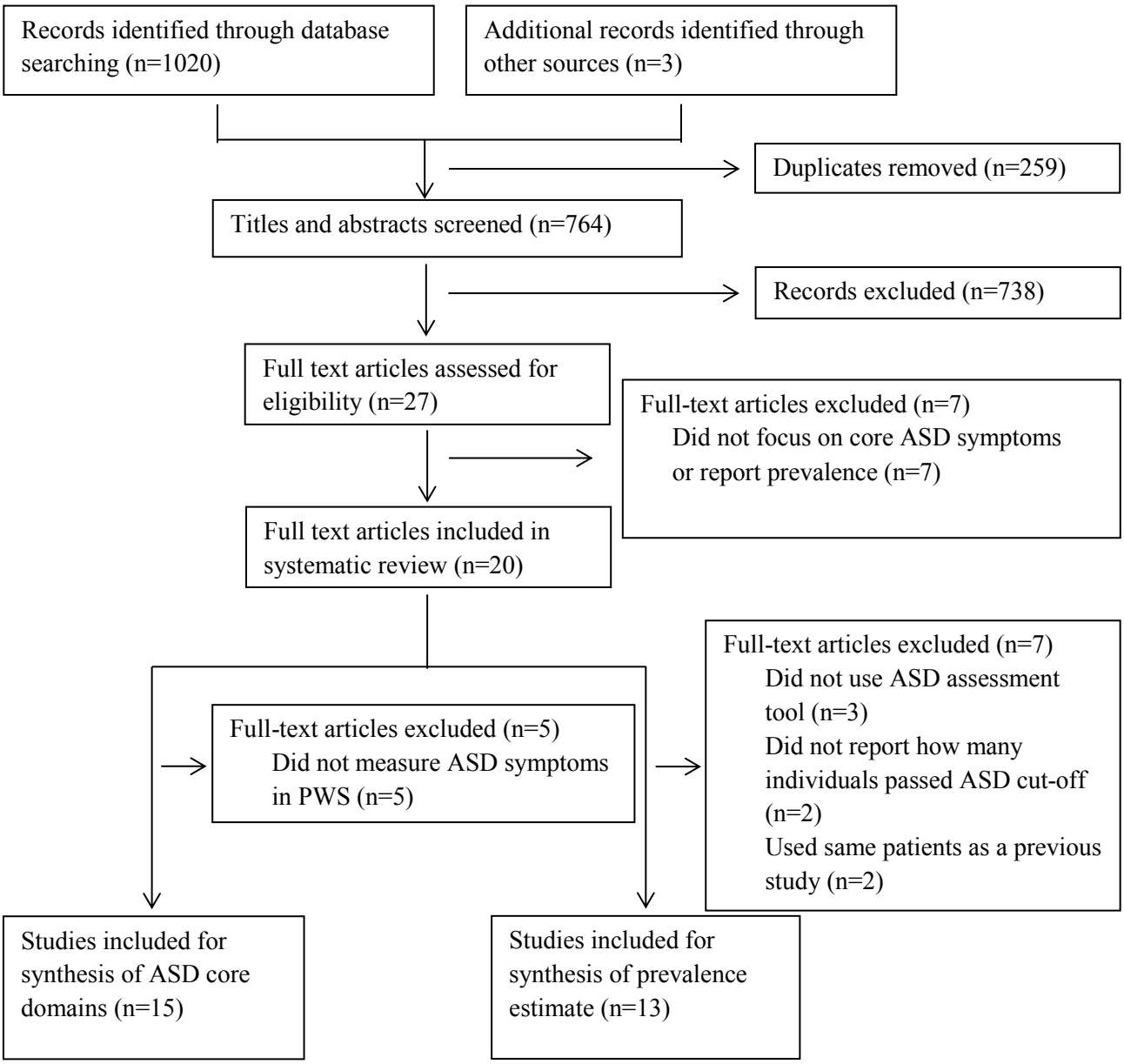
Figure 1: Literature review flow diagram



1: *Studies investigating ASD in PWS*

	PWS Group				***Comparison Group***			***Assessment Tool***	
thor,	*N (% male)*	*Mean Age (SD; Range)*	*DEL*	*UPD*	*Description*	*N (% male)*	*Mean Age (SD; Range)*	*Cognitive*	*ASD symptom measure*
4	15 (53)	8.0 (2.19;6.0-13.0)	10	5	-	-	-	WISC	Childhood Autism Rati
2010	10 (60)	14.3 (7.1;1.0-47.0)	nr	nr	Down ASD	25 (64) 49 (59)	15.3 (10.6;1.0-47.0) 13.1 (8.5;1.0-47.0)	-	Self-Injurious Behaviou Schedule
maeker,	59 (53)	21.2 (nr;2.0-51.0)	40	19	Non-specific MR	59 (53)	22.1 (nr;2.0-51.0)	WISC/WAIS	PDD-MR scale
poulos,	39 (36)	16.7 (6.8^{+} ;7.0 - 30.0)	20	19	ASD	19 (84)	14.2 (4.2;7.0-30.0)	WISC/WAIS/ WASI	SRS, Social Competency Inventory
2011	45 (44)	10.6 (7.7;3.0-37.0)	24	20	ASD	207 (82)	9.9 (5.0^{+};3.2-33.8)	-	Repetitive Behaviour Scale-Revised; SCQ
, 2006	80 (49)	10.4 (4.0;3.6-18.5)	nr	nr	ASD	89 (84)	9.9 (4.8;3.0-17.9)	Vineland	Childhood Routines Inv
2004	18 (72)	19.9 (9.0;nr)	15	3	PDD IQ Match	21 (95) 17 (65)	15.7 (7.25;nr) 20.8 (6.8;nr)	Kaufmann Brief Intelligence Test	Social Attribution Task
3	66 (55)	11.0 (nr;7.0-17.0)	25	41	-	-	-	WISC	Dutch ToM Test-R, DI
2005	96 (53)	16.3 (12.7^{+};3.3-50)	47	49	-	-	-	WAIS/WASI/ Raven/Mullen	ADOS, ADI, ASQ
009	189 (53)	17.0 (17.0;4.0-51.0)	nr	nr	HID AS CdC CdLS FXS LS SMS	56 (64) 104 (56) 58 (36) 101 (41) 191 (100) 56 (100) 42 (41)	18.3 (10.0;6.0-38.0) 13.4 (8.0;4.0-45.0) 17.2 (12.2;4.0-44.0) 17.5 (9.9;4.0-40.0) 16.6 (8.8;6.0-47.0) 16.2 (10.3;4.0-51.0) 15.5 (8.9;4.0-38.0)	Wessex	ASQ, Repetitive Behaviour Questionnai
2014	22 (64)	9.0 (nr;6.0-12.9)	16	6	PWS Adolescents	23 (65)	15.8 (nr;13.0-19.0)	WISC	PARS
2011	See Moss, 2009								
015	30 (60)	10.6 (2.8;6.0-15.0)	21	9	Asperger's	31 (77)	10.5 (3.1;6.0-15.0)	WISC [#]	PARS
, 2004	63 (?)	14.3 (12.3^{+};1.7-48.3)	31	32	-	-	-	Vineland	ASQ
014	14 (57)	10.1 (2.1;7.0-13.0)	4	10	ASD	10 (100)	10.4 (1.97.0-13.0)	WISC	SRS, ADOS

utism Diagnostic Interview; ADOS= Autism Diagnostic Observation Schedule; AS= Angelman syndrome; ASQ=Autism Screening Questionnaire (later renamed SCQ=S nication Questionnaire); CdLS= Cornelia de Lange syndrome; DISCO= Diagnostic Interview for Social and Communication Disorders; FXS= Fragile X syndrome; HID= ellectual disability of heterogeneous cause; LS= Lowe syndrome; MR= Mentally Retarded; PARS= PDD Autism Society Japan Rating Scale; PDD=Pervasive Developme r; SMS= Smith Magenis syndrome; SRS= Social Responsiveness Scale; ToM= Theory of Mind; VCFS= Velo-Cardio-Facial syndrome; WAIS= Wechsler Adult Intelligen Wechsler Abbreviated Scale of Intelligence; WISC= Wechsler Intelligence Scale for Children

p differences existed in this measure; + = SD was reported across multiple groups, but not combined; the more conservative SD was reported

Table 2. *ASD in PWS prevalence*

First author, year of publication	***N (% male)***	***# DEL***	***# UPD***	***ASD symptomatology assessment***	***Total***	***%***	***DEL***	***%***	***UPD***	***%***
Ali, 2014	15 (53)	10	5	Childhood Autism Rating Scale	4	26.7	0	0	4	80
Akefeldt, 1999	44 (64)	-	-	Clinical Diagnosis	1	2.27	-	-	-	-
Beardsmore, 1998	23 (39)	-	-	PAS-ADD	0	0	-	-	-	-
Descheemaeker, 2002	53 (57)	-	-	Clinical diagnosis	4	7.55	-	-	-	-
Descheemaeker, 2006	59 (53)	40	19	PDD-MR scale	11	18.6	6	15	5	26.3
Dimitropoulos, 2013	39 (36)	20	19	SRS, Social Competency Inventory	22	56.4	7	35	15	78.9
Flores, 2011	45 (44)	24	20	Repetitive Behaviour Scale-Revised; SCQ	12	26.7	5	20.8	7	35
Hou, 1998	66 (68)	48	18	ADI	10	15.2	6	12.5	4	22.2
Lo, 2013	66 (55)	25	41	Dutch ToM Test-R, DISCO	24	36.4	7	28	14	34.1
Moss, 2009	189 (53)	-	-	ASQ, Repetitive Behaviour Questionnaire	77	40.7	-	-	-	-
Reilly, 2014,***	110 (54)	56	36	Parent report about clinical diagnosis	14	12.7	7	12.5	4	11.1
Veltman, 2004	63 (nr)	31	32	ASQ	23	36.5	9	29	14	43.8
Zyga, 2014	14 (57)	-	-	SRS, ADOS	8	57.1	-	-	-	-
TOTALS	786	254	190	-	210	26.7	47	18.5	67	35.3

nr = not reported

* = data for genetic subtype obtained from correspondence with authors

** = genetic subtype not know for every individual

Chapter 3

J.A. Bennett, A.M. Haqq*, and L. Zwaigenbaum*. *co-senior authors. Development of Social Communication in Children with Prader-Willi Syndrome: A Direct Comparison to Autism Spectrum Disorder- Study Protocol. To be submitted for publication to *Journal of Comorbidity*

Introduction

Background

Prader-Willi syndrome (PWS) is a genetic disorder that results from a lack of expression of the paternal contribution of chromosome 15q11-13. The two main causes of PWS are a deletion (DEL) of that region from the paternal chromosome (~70% of cases) or maternal uniparental disomy (UPD), where both chromosomes have genetic material from the mother (~25% of cases) [Dimitropoulos and Schultz 2007]. PWS is characterized by hypotonia and difficulty feeding during infancy, followed by hyperphagia, insatiable hunger, morbid obesity, and short stature in later childhood [Cassidy et al. 2012]. Additionally, cognitive disabilities and problem behaviours are common. The prevalence of autism spectrum disorder (ASD) in people diagnosed with PWS has been reported to be as high as 38% for individuals with the UPD subtype and 18% for those with the DEL subtype [Bennett et al. 2015]. These rates far exceed the prevalence of ASD in the general population of about 1.5% (1 in 68) [Center for Disease Control and Prevention (CDC) 2014].

ASD is a neurodevelopmental disorder characterized by two main symptoms: impairment in social communication, and highly repetitive or restricted behaviours and interests. Unlike for PWS, there is currently no genetic test that can confirm a diagnosis of ASD. The restricted or repetitive behaviours and interests in PWS have been well characterized [Dykens et al. 2011; Flores et al. 2011; Greaves et al. 2006]; however, despite a growing interest in the field, the profile of social-communication deficits in children with PWS is poorly understood. Recent studies have compared these deficits in adolescents and adults with ASD to same-age peers with PWS [Dimitropoulos et al. 2013; Key et al. 2013], yet no studies have investigated these deficits in children under the age of 10. Furthermore, no research focusing on ASD-related social

communication impairments in children with PWS have used both gold-standard ASD assessment tools [Falkmer et al. 2013], the Autism Diagnostic Observation Scale-2 (ADOS-2) [Lord et al. 2012] and the Autism Diagnostic Interview-Revised (ADI-R) [Rutter et al. 2003b], to compare children with PWS to their peers with idiopathic ASD.

The earlier intervention begins for children with ASD, the better the long-term outcomes [Anagnostou et al. 2014b; Dawson 2008]. Specifically, early behavioural intervention has shown promise to achieving optimal outcomes among very young children with ASD [MacDonald et al. 2014]. Therefore, delineating the pattern of social-communicative deficits found in PWS, relative to those of individuals on the autism spectrum, is imperative to inform intervention strategies. If these deficits are similar, evidence-based interventions for children with ASD may be generalizable to children with PWS. However, if the impairments found in children with PWS are distinct from the difficulties in social reciprocity classically shown in ASD, this would suggest these children should be treated using more tailored strategies.

Major Knowledge Gaps

A systematic review of 20 studies investigating ASD in PWS [Bennett et al. 2015] resulted in the identification of the following evidence gaps:

- No studies have a mean age less than eight years old
- No studies have compared children with PWS who meet diagnostic criteria for ASD (PWS+ASD) to children with PWS who do not meet diagnostic criteria for ASD (PWS-ASD)
- No studies have used the gold-standard ASD assessment tools to investigate severity and specific features of social communication development in children with the UPD and DEL subtypes and compared them directly to children with ASD

Study Aims

The aim of this research is to:

(1) Compare overall severity of social communication impairment between children with PWS+ASD, children with PWS-ASD, and children with idiopathic ASD using the gold standard ASD assessment tools

(2) Compare social communication development between children with UPD, DEL, and ASD using gold-standard assessment tools

(3) Assess the specific profile of social communication impairment in children with PWS+ASD by comparing which symptoms are more common in children with PWS+ASD compared to children with PWS-ASD

Hypotheses

We hypothesize that:

(1) Social communication development in children with PWS+ASD will be significantly different from children with PWS-ASD, but not different from children with idiopathic ASD

(2) Social communication development in children with UPD will differ from children with DEL, but will not differ from children with idiopathic ASD

(3) Specific differences will be found between children with PWS+ASD and PWS-ASD

Materials and Methods

Participants

Males and females 3 to 10 years of age, who are diagnosed with PWS or ASD, will be included in this research project. Children with PWS will be recruited from: (1) the Pediatric

Endocrinology and Genetics Clinics at the Stollery Children's Hospital, and under the care of Dr. Andrea Haqq, and (2) organizations, such as the Foundation for Prader-Willi Research (FPWR-Canada and USA) and provincial PWS chapters. The comparison group of children diagnosed with ASD will come from pre-existing data available from a multi-site inception cohort of children with ASD in Canada, the 'Pathways in ASD' study, a longitudinal study (n=500) of children with ASD followed from initial diagnosis (age 2.0 to 4.11 years) through to middle school years (age 10.0). The comparison group of children with ASD from this study will be selected, matched 1:1 to PWS participants based on age, gender, and full-scale IQ. Approval has been received from the Research Ethics Office at the University of Alberta.

A sample size calculation determined that 20 children from each PWS subtype (DEL and UPD) are necessary to detect a minimum effect size of d=0.9. This effect size was chosen based on a group comparison between the average T-scores from the Social Responsiveness Scale in a similar study looking at ASD-related social impairment in adolescents [Dimitropoulos et al. 2013]. This study found a significant difference (effect size d= 0.8) between t-scores for the PWS-deletion subtype group (mean=70.60, SD=14.2) and the ASD group (mean=79.79, SD=8.9), and a significant difference (effect size =0.9) between the PWS-deletion group and the PWS-UPD group (mean=82.32, SD=10.8), but no difference between the PWS- UPD subtype group and the ASD group.

Assessment

ASD symptom measures will include two gold standard ASD assessments (ADOS-2 and ADI-R) as well as other tools to assess social, communication, and cognitive function. Qualified and experienced individuals, who have obtained research reliability where necessary (e.g., ADOS-2), will complete all assessments. Additionally, the data collectors and data analysts will be blinded

to genetic subtype to avoid detection bias and analysis bias, as the UPD genetic subtype has shown to have more ASD symptomatology than the DEL subtype [Bennett et al. 2015].

The ADOS-2 [Lord et al. 2012] is a semi-structured assessment that provides an opportunity for the researcher to observe a number of behaviours specific to ASD. Based on the coding algorithm, it provides a score for both social affect and restricted and repetitive behaviours. Both of these can be translated into a severity score comparable both between multiple children and within the same child over time. The ADOS-2 has been tested and validated for infants aged 12 months to adulthood, and consists of five modules based on age and verbal fluency. Module 1 is designed for individuals with no speech or single words, Module 2 is for individuals with phrase speech, and Module 3 is for individuals with fluent speech and typically less than 14 years of age. Additionally, the toddler module is for toddlers ages 12-36 months, and Module 4 is for individuals with fluent speech who are more mature.

The scores from each ADOS-2 are entered into an algorithm, which was devised to maximize discrimination between ASD and intellectual disability. The psychometric properties of the ADOS-2 are quite strong: internal consistency alpha= 0.51-0.92; test-retest reliability= 0.68-0.92; and inter-rater reliability= 0.79-0.97.

The ADI-R [Rutter et al. 2003b] is a semi-structured interview mapping onto DSM-5 diagnostic criteria for ASD. Parents are asked to describe their child's current behaviours related to autistic traits, as well behaviours that occurred at earlier ages. Complementing the ADOS-2, the ADI-R is considered a gold-standard diagnostic assessment, and has excellent specificity and reliability for individuals with a mental age greater than or equal to 2 years [Falkmer et al. 2013]. The psychometric properties for the ADI-R are also considered to be strong: internal consistency alpha= 0.69-0.95; test-retest reliability= 0.82-0.97; and inter-rater reliability= 0.59-0.87.

The Social Responsiveness Scale-2 (SRS-2) [Constantino and Gruber 2012] is a questionnaire completed by a primary caregiver and/or a teacher that provides an overall score of social impairment as well as five ASD-specific subdomains (Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted and Repetitive Behaviours and Interests [RRB]). It is designed to measure ASD-related social impairment in individuals from age 2.5 to adulthood. Psychometric properties of the SRS-2 include: internal consistency alpha= 0.95-0.97; test-retest reliability= 0.72-0.95; and inter-rater reliability= 0.61-0.91.

The Social Skills Improvement System- Rating Scales (SSIS-RS) [Gresham and Elliot 2008] is a parent questionnaire that collects information about general social skills from ages 3-18, including communication, cooperation, assertion, responsibility, empathy, engagement, and self-control. It has been widely used in the ASD population and found a valid research tool for measuring social skills [Anagnostou et al. 2014a]. The psychometric properties of the SSIS-RS are also quite strong: internal consistency alpha: 0.70-0.95; test-retest reliability= 0.71-0.87; and inter-rater reliability= 0.56-0.59.

The Vineland Adaptive Behavior Scales-II (Vineland-II)[Sparrow et al. 2005] is a parent interview that quantifies the adaptive behaviours/daily living skills currently held by the individual, including two subdomains that measure socialization and communication ability. It has been validated for all ages and specifically for individuals with ASD. Psychometric properties of the Vineland-II are also sufficiently strong: internal consistency alpha= 0.72-0.90; test-retest reliability= 0.88-0.92; and inter-rater reliability= 0.78-0.80.

The Wechsler Preschool and Primary Scale of Intelligence-IV (WPPSI-IV) and Wechsler Intelligence Scale for Children-IV (WISC-IV) are individually administered measures of cognitive abilities, which yield full-scale IQ. The WPPSI-IV has been validated in children from

age 2 to 7 years, and the WISC-IV has been validated in children from age 6 to 16 years [Wechsler 2002; Wechsler 2003]. Children with PWS will be matched to children with idiopathic ASD by full-scale IQ, using with WISC-IV.

Notably, all of the ASD assessments include a subscale indexing 'communication', although some measure different aspects (e.g., the SRS-2 measures social communication, whereas the Vineland-II measures written, expressive, and receptive communication). This overlap speaks to the complexities of measuring communication, and perhaps helps explain the changing of the criteria for ASD from 'impaired communication' and 'impairment in social reciprocity' in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition- Text Revision (DSM-IV-TR) to 'impairment in social communication' in the DSM-5.

The ADOS-2 and ADI-R were selected based on having the highest sensitivity and specificity for ASD of any assessments, when used in combination [Falkmer et al. 2013]. Additionally, the ADOS-2 provides comparison scores for the social affect domain and restricted or repetitive behaviours domain, which are sensitive to age and verbal level. The SRS-2 will add further depth into measuring social communication with its four subdomains. Furthermore, it is a popular tool to measure ASD symptoms that has been used in the PWS population; however its validity within this population is still unknown. The SSIS-RS investigates social skills, such as engagement, empathy, and responsibility, which have never been researched in a PWS population. Identification of relative strengths or weaknesses of social skills in children with PWS could aid in creation of behavioural interventions tailored to the needs of children with PWS. Furthermore, the SSIS-RS was not designed as an ASD assessment tool, and will provide a measure of social skills outside of the ASD perspective. The Vineland-II will identify adaptive behaviours and could help serve the same purpose as the SSIS-RS in tailored intervention.

Additionally, comparison of adaptive skills to children with ASD will provide further insight on the symptomatology in children with PWS.

Clinical best estimate (CBE) is considered gold standard for diagnosis of ASD [Huerta and Lord 2012]. Although Lord and Bishop [2010] argue that a multi-disciplinary team may not always be feasible, assessing multiple areas of functioning should always be considered. This team is very fortunate to have support from clinical psychologist, a developmental pediatrician, and certified psychometrists to aid in the assessment of these children. Therefore, after the completion of assessments, the team will meet to discuss the findings and determine whether a diagnosis of ASD is warranted.

Analyses

After controlling for age, gender, and full-scale IQ, an ANCOVA will be used to compare social communication development scores between children with PWS+ASD, PWS-ASD, and idiopathic ASD. Post-hoc analyses will reveal if the PWS-ASD group is significantly different from the PWS+ASD and idiopathic ASD groups, in line with our hypothesis. An ANCOVA will also be applied to the assessment scores from the children with UPD, DEL, and idiopathic ASD. Post-hoc analyses will then reveal if the DEL group is significantly different from the UPD and idiopathic ASD groups. Chi-square tests based on individual scores from the assessments will help determine if any ASD traits are more common in PWS+ASD versus PWS-ASD or PWS+ASD versus idiopathic ASD.

Significance

Characterization of ASD-related social-communication deficits in young children with PWS will provide critical information on the relationship between the two disorders. If there are significant ASD-like symptoms present throughout childhood that compare to those of idiopathic

ASD, practitioners and parents will have invaluable information to support earlier identification of specific social-communication deficits in PWS. Earlier identification can translate to earlier intervention, leading to a better prognosis for children with PWS and improvements in quality of life for their families. Behavioural interventions are the front-line defense in young children with ASD, with increasing evidence to support its use. Indeed, a recent study found that the greatest improvements were made in children with ASD when behavioural intervention started before age two [MacDonald et al. 2014]. Nevertheless, if the results show that social communication skills in PWS children differ from those of idiopathic ASD, this will help inform the implementation of specific interventions that can begin in early life and focus on the unique special needs of children with PWS.

Impact

The implications of this study include improved identification strategies and potential targets for behavioural intervention. This study will be the first to compare children with PWS+ASD to children with PWS-ASD in order to determine which assessments are most appropriate for identifying ASD within a PWS population. It could also help identify warning signs for physicians with patients with PWS, leading to better identification and potentially improved behavioural outcomes. Furthermore, the identification of strengths and weaknesses in social skills and adaptive skills could help tailor strategies for future interventions for children with PWS. Early identification and treatment of social communication impairment in PWS will improve outcomes for children with PWS and their families.

Dissemination

Our end of project Knowledge Translation plan will take into account the perspectives of parents, clinicians, and researchers in order to ensure relevance and rapid clinical uptake of the

research findings. This will first be achieved locally as study findings are condensed into checklists that will be presented to physicians working with children with PWS (e.g., at the Stollery Children's Hospital). These clinical checklists will give clinicians warning signs to watch out for in young children with PWS. This will facilitate proper referral to intervention as early as possible to achieve optimal outcomes. Furthermore, using video obtained during the ADOS-2, we can create a video library toolkit to show physicians the nuances between the behavioural issues that are present in most children with PWS and the subtle social-communication impairments found in those with co-occurring ASD.

Conflict of Interest

The authors declare no conflict of interest.

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Chapter 4

J.A. Bennett, S. Hodgetts, M.L. Mackenzie, A.M. Haqq*, and L. Zwaigenbaum*. *co-senior authors. Investigating Autism-Related Social Communication Impairment in Children with Prader-Willi syndrome: A Descriptive Study. Submitted for publication to the Journal of Neurodevelopmental Disorders.

Introduction

Prader-Willi syndrome (PWS) is a genetic disorder caused by the absence of expression of the paternal contribution of chromosome 15q11-13. The majority of cases are due to deletion (DEL; 65-75%) or uniparental disomy (UPD; 20-30%), with a small minority (1-3%) due to rare imprinting center defects [Cassidy et al. 2012]. The phenotype of PWS includes hypotonia and failure to thrive during infancy, followed in early childhood by hyperphagia and an insatiable appetite which can lead to morbid obesity if left unchecked [Cassidy et al. 2012]. Cognitive disability and problem behaviours are also common and, for some families, represent greater challenges than the food-seeking behaviours [Dykens et al. 2007].

Although variable, the phenotype of PWS overlaps to some degree with autism spectrum disorder (ASD), a neurodevelopmental disorder characterized by the presence of symptoms in two core domains: social communication impairment and restricted or repetitive behaviours and interests [American Psychiatric Association (APA) 2013]. Indeed, the prevalence of ASD in PWS has been estimated at 26.7% based on exceeding clinical cut-points on relevant ASD assessments, with ASD in the UPD genetic subtype (35.3%) almost twice as common as the DEL subtype (18.3%) [Bennett et al. 2015]. This may be partially due to a genetic finding that overexpression of chromosome 15 is associated with higher rates of ASD [Vorstman et al. 2006]. The estimated prevalence of ASD in PWS is significantly higher than the current prevalence estimate of about 1.5% for ASD in the general population . To receive an ASD diagnosis, symptoms in both domains must be present during the early developmental period; however, they may not be fully recognized until a child is older and social demands exceed their capacity [APA 2013]. Nevertheless, early social communication impairment (including reduced gazing towards faces and directed vocalizations [Ozonoff et al. 2010], and reduced orienting to name

[Zwaigenbaum et al. 2005]) in children who later receive a diagnosis of ASD has been reported as early as 12 months. Indeed, ASD diagnosis can be reliably made by 18 to 24 months in a clinical setting. Studies have demonstrated that early intervention in ASD yields more favorable outcomes [Anagnostou et al. 2014b]. Therefore, early identification of ASD in children with PWS, and participation in early intervention programs might improve outcomes for these affected children.

Despite a recent increase of research investigating symptoms of ASD in PWS, no studies have focused on young children with PWS. Eight years of age is the youngest mean age in a study investigating ASD in individuals with PWS [Ali et al. 2013]. Expression of ASD in PWS may change over development, with two studies reporting more prominent symptoms in adolescents and adults with PWS compared to younger children. Lo et al. [2013] reported that none of the 22 children with PWS, ages 7-9, exceeded cut-off for ASD on the Diagnostic Interview for Social and Communication Disorders (DISCO); however, 24 of 44 of the individuals ages 10-17 years old exceeded cut-off for ASD. Additionally, Akefeldt and Gillberg [1999] reported lower average scores (3.4; SD=4.4) in the toddlers with PWS (mean age= 2.1 years; range= 0.8-3.7 years) compared to the older individuals (19.1; SD=10.7) with PWS (mean age 18.4 years; range= 4.2-36.3 years) on the Autism Spectrum Screening Questionnaire (ASSQ) [Ehlers et al. 1999]. However, this tool was designed to assess children ages 6 to 17 years old with normal intelligence to mild mental retardation, raising concerns about the validity of the ASSQ in this sample.

Assessments commonly used to investigate ASD symptomatology and adaptive functioning in individuals with PWS include the Social Responsiveness Scale [Dimitropoulos et al. 2013; Zyga et al. 2014], Social Communication Questionnaire [Moss et al. 2009; Veltman et al. 2004], and

Vineland Adaptive Behavior Scales [Dimitropoulos et al. 2013; Milner et al. 2005]. A recent systematic review [Bennett et al. 2015] found that few studies investigating ASD in PWS have included the Autism Diagnostic Observation Schedule (ADOS) [Lord et al. 2006] or the Autism Diagnostic Interview-Revised (ADI-R) [Rutter et al. 2003b]. These assessments are considered gold standard measures of ASD symptoms based on excellent sensitivity and specificity in differentiating ASD from other developmental disorders [Falkmer et al. 2013]. However, because ASD consists of such a broad spectrum of subtle symptoms which can be missed by assessment, clinical best estimate (CBE) from a healthcare professional who is familiar with ASD is considered gold standard in ASD diagnosis [Huerta and Lord 2012].

The primary objective of this study was to characterize ASD symptoms in children ages 3 to 12 with PWS using the gold-standard ADOS, 2nd edition (ADOS-2) [Lord et al. 2012], and other standardized ASD assessment tools. As a secondary objective, we used multiple assessments to investigate different aspects of social-communication impairment, and to compare the agreement between these ASD assessment tools in a PWS population with a co-occurring ASD diagnosis based on CBE.

Methods

This cross-sectional study was conducted in Edmonton, Alberta, Canada. Individuals aged 3 to 12 with PWS were recruited for this study from local and regional care providers, as well as provincial PWS groups. Ethical approval was received from the local Research Ethics Board at the University of Alberta. Parents gave informed consent for their children prior to participation in this study.

Assessments

Qualified and experienced individuals, who had obtained research reliability where necessary (e.g., ADOS-2), administered all assessments. Additionally, the data collectors and data analysts were blinded to information about genetic subtype to avoid detection and analysis bias. After all of the assessments were completed, a developmental paediatrician with significant expertise in ASD reviewed all study findings, and met with parents and children as needed, in order to determine whether a diagnosis of ASD was warranted.

Autism Diagnostic Observation Schedule-2

The Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2)[Lord et al. 2012] is a semi-structured assessment that provides an opportunity to observe a number of behaviours specific to ASD. Items are generally scored from 0 to 3, with '0' representing a continuum of behaviour not generally associated with ASD, a code of '1' generally indicating mild impairment of a nature observed in persons with ASD, and a code of '2' indicating definite impairment in that area. A code of '3' represents more profound impairment, although for the purpose of the scoring algorithm, scores of '3' are converted to '2'. Based on the coding algorithm, the ADOS-2 provides a total score for social affect (SA) and restricted and repetitive behaviours (RRB) symptoms. Both of these domains have separate cut-off which must be reached to qualify for ASD, and both domain raw scores can be translated into a severity score on a scale of 1 to 10, which is comparable between children of any age. There is also an overall severity score, with scores ≥4 indicative of ASD. Because severity of SA symptoms is rated based on ten algorithm items and RRB severity, four items, the overall severity score is more heavily weighted towards the SA domain. Additionally, since the RRB domain only consists of four algorithm items, if all items are scored '0', severity is 0, whereas any item scored '1' leads to a severity rating of 5.

Thus, the RRB severity scores is highly sensitive to scoring on individual items, and must be interpreted with caution. The ADOS-2 has been tested and validated for people aged 12 months to adulthood, and serves as a diagnostic instrument to assist in the diagnosis of ASD. One of five modules is administered, based on age and verbal fluency, although only Modules 1-3 were administered in our study. Module 1 is designed for individuals with no speech or single words, Module 2 is for individuals with phrase speech, and Module 3 is for individuals with fluent speech and typically less than 14 years of age. Additionally, the toddler module is for toddlers ages 12-30 months without phrase speech, and Module 4 is for individuals with fluent speech who are more mature.

Social Communication Questionnaire

The Social Communication Questionnaire (SCQ) [Rutter et al. 2003a] is a 40-item parent questionnaire used to screen for autistic symptomatology, its content derived from a the Autism Diagnostic Interview- Revised (ADI-R), a semi-structured interview used in ASD diagnosis [Rutter et al. 2003b]. The SCQ, which uses a yes/no parent response form, was chosen over the ADI-R to be more time-feasible for parents and researchers (10 minutes for the SCQ vs 2 hours for the ADI-R). Questions were selected from the ADI-R that most strongly discriminated ASD diagnosis. Raw scores of 15 or greater are indicative of ASD. However, a study released after the publication of the SCQ indicates that a cut-off of 12 greatly improves the sensitivity of the assessment when used in combination with the ADOS, particularly for younger children [Corsello et al. 2007].

Social Responsiveness Scale-2

The Social Responsiveness Scale, 2nd edition (SRS-2)[Constantino and Gruber 2012] is a questionnaire completed by a primary caregiver and/or a teacher that provides an overall rating of social impairment as well as scores on five ASD-specific subdomains: (1) Social Awareness, (2) Social Cognition, (3) Social Communication, (4) Social Motivation, and (5) RRBs. It is designed to assess individuals from age 2.5 years to adulthood. Total scores on the SRS-2 are standardized as T-scores, based on age and gender, and are further separated into four levels: <60 (Within normal limits; generally not associated with ASD); 60 to 65 (Mild range; indicates deficiencies in reciprocal social behaviour that may lead to mild to moderate interference with everyday social interactions); 66 to 75 (Moderate range; indicates deficiencies in reciprocal social interaction that lead to substantial interference with everyday social interaction, and are typical for children with ASD of moderate severity); and >75 (Severe range; indicates deficiencies in reciprocal social interaction that lead to severe interference with everyday social interaction, and are strongly associated with a clinical diagnosis of ASD).

Social Skills Improvement System-Rating Scales

The Social Skills Improvement System- Rating Scales (SSIS-RS)[Gresham and Elliot 2008] is a parent questionnaire that collects information about general social skills of children between the ages of 3 and 18. The SSIS-RS provides percentiles for social skills (where higher scores indicate more advanced social skills) as well as problem behaviours (where higher scores indicate increased problem behaviours), normed by gender and age. There is also a subscale to indicate ASD symptoms (demonstrated by below average, average, or above average). Although the SSIS-RS has never been used in a PWS population, it has been widely used in the ASD population and determined to be a valid research tool for measuring social skills [Anagnostou et

al. 2014a]. Furthermore, this questionnaire also assesses non-ASD related social impairments that might be present in PWS.

Vineland Adaptive Behavior Scales-II

The Vineland Adaptive Behavior Scales, 2nd edition *(*Vineland-II)[Sparrow et al. 2005] is a parent interview that quantifies their child's current adaptive behaviours. It provides a composite score, plus subscores in the following domains: (1) daily living skills, (2) socialization, (3) communication, and (4) motor skills. Resulting scores are based on a standardized scale with a mean of 100, and standard deviation of 15. It has been validated for all ages and specifically for individuals with ASD [Carter et al. 1998].

Wechsler Preschool and Primary Scale of Intelligence-III/ Wechsler Intelligence Scale for Children-IV

The Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III)[Wechsler 2002] and Wechsler Intelligence Scale for Children, 4th edition (WISC-IV)[Wechsler 2003] are individually administered measures of cognitive abilities that yield full-scale IQ. The WPPSI-III has been validated in children from age 2 to 7 years, and the WICS-IV has been validated in children from age 6 to 16 years. Both the WPSSI-III and WISC-IV have been used previously to assess samples with PWS and samples with ASD [Dimitropoulos et al. 2013; Song et al. 2015; Zyga et al. 2014].

Analytic Approach

Each child was described based on the findings from the ADOS-2, the three questionnaires (SCQ, SRS-2, and SSIS-RS), and the Vineland-II. Any noticeable patterns or positive test results were described in relation to the decision by the multidisciplinary team using CBE to determine

whether a diagnosis of ASD was warranted. Descriptive statistics were calculated for each assessment, including mean, standard deviation, standard error of the mean, and range. Furthermore, the questions which were endorsed at a relatively high frequency from each questionnaire were reported in order to show behaviours/impairments that were the most common in our cohort: for the ADOS-2, any category in which at least 60% of children scored at least '1' was reported, as well as any category for which less than 20% scored above '0'; for the SCQ, any question that that was endorsed by at least 50% of the parents was reported; for the SRS-2, which uses a scale of 0 to 3, any question that had a sample mean of at least 1.5 was reported, and comparison across domains was made to determine whether any domain was significantly more impaired than others; for the SSIS-RS, which uses a scale of 0 to 3, any question that had a mean of one or less (which implies impairment in general social skills) was reported, as well as any question that had a mean of at least two (which implies strength in general social skills). We included the items which were not found to occur regularly on the ADOS-2 because it is an observational assessment in which trained psychometrists are able to distinguish between ASD-like symptoms and other symptoms, and on the SSIS-RS because it measures social skills in general, rather than probing for specific ASD symptoms (like the SCQ and SRS-2). All data analyses were performed using SPSS version 22. Experiment-wise alpha was set at $p<.05$ for all statistical analyses, which were completed using non-parametric tests due to the small sample size and associated non-normal distribution of study measures across our sample.

Results

Demographics

There were a total of 10 participants, all of whom resided in western Canada (Alberta (n=8); British Columbia (n=1); Saskatchewan (n=1)). The cohort included seven females and three

males, with a mean age of 6.77 years old (SD= 2.85). Interestingly, only two participants were the DEL subtype; the other eight were the UPD subtype. Each participant completed all of the assessments. Table 3 provides a summary of the study results, including the mean, standard error of the mean, and standard deviation, as well as the minimum and maximum scores attained for all measures. The average full scale IQ (FSIQ) was 63.38 (SD=17.42), which falls into the expected range for individuals with PWS described by Cassidy et al. [2012]. A negative correlation between age and FSIQ was found (Spearman's rho=-.815, p=.004).

Assessments

Table 4 gives detailed results for every participant on each of the ASD assessments, including an indication of which scores exceeded clinical cut-offs. Figure 1 illustrates the relative scores as measured between the four ASD assessments. The results from the SCQ, SSIS-RS, and ADOS-2 were multiplied by 5, 4, and 15, respectively, in order to show all four assessments based on a standard cut-off score of 60.

In total, three of ten children scored above cut-off for ASD on the ADOS-2. However, two of those three children (P8 and P9) scored zero in the RRB domain, which would indicate that ASD is not present, because meeting clinical cut-off on the ADOS-2 requires the individual to exceed cut-offs on both symptom domains. Table 5 lists the nine items on which at least 50% of the children received non-zero scores, as well as the six items on which 20% or fewer scored greater than zero.

Additionally, five of ten children scored above the revised cut-off of 12 for ASD on the SCQ. Table 6 lists the eight questions on which at least 50% of parents responded that a specific ASD symptom was present. Six of the eight questions fall under the category of restricted or repetitive behaviours.

On the SRS-2, five children exceed cut-off for ASD, and four of those children also exceeded cut-off on the SCQ. The eight questions with a mean score of greater than 1.5 are listed in Table 7. With respect to the separate domains, social motivation showed the least impairment (T-score= 56.10), while the RRB domain showed the most impairment (T-score= 65.80). A non-parametric Kruskal-Wallis Test was used to compare the mean scores across all of the domains, and did not reveal significant difference between any of the means.

Six of ten children had above average ASD symptoms on the SSIS-RS ASD subscale. These six children also exceeded cut-off on the SCQ and/or the SRS-2. Table 8 lists the five questions on which the sample of children received an average score of one or less, as well as the eleven questions on which the children received an average score of two or more. Only one item from the problem behaviour questions had an average score over two; this score was inversed (from 2.4 to 0.6) and placed in the average score of one or less column to indicate impairment.

Lastly, despite the sample means on all assessments indicating impairments close to the prescribed cut-offs for ASD, CBE determined that *none of the ten children in our sample presented with ASD.*

Case Profiles

Profiles of each participant (P) are described below. For confidentiality reasons, age and gender could not be revealed, although the participants are ordered from youngest (P1) to oldest (P10) to give a sense of relative age. Based on informal discussion, parents of these children reported numerous concerns, including impaired speech development, oppositional behaviour (tantrums/meltdowns), shyness, and lack of social skills in general. Each profile aims to describe the unique or extreme findings from each child, as well as any patterns that emerged across participants.

P1

P1 was the youngest individual in our study. Their assessment results were not indicative of ASD; however, the Restricted or Repetitive Behaviours and Interests (RRB) sections on both the ADOS-2 and SRS-2 confirmed mild impairment in this symptom domain. The SSIS-RS percentiles and Vineland-II scores were average, with the exception of the Vineland-II motor skills domain, which was more than one standard deviation below the normative standard. Based on these results, it is not surprising that CBE determined that this child did not have co-occurring ASD.

P2

Along with P1, P2 was the only other individual who did not exceed cut-off for ASD on any of the assessments. Again, the SSIS-RS and Vineland-II results were all close to normative standard, with the exception of motor skills on the Vineland-II. CBE determined that this individual did not have ASD.

P3

P3 was an interesting case, whose results from the three ASD questionnaires (SCQ, SRS-2, and SSIS-RS) were the lowest in the entire sample. However, their ADOS-2 results exceeded cut-off, albeit by one point. This individual also had among the most favourable scores on the SSIS-RS and Vineland-II, scoring above the normative standard on all domains except Vineland-II socialization and Vineland-II motor skills domains, both of which were less than one standard deviation below normative standard. Despite the ADOS-2 results, the relative strengths in other areas were consistent with CBE that this individual did not have ASD.

P4

Both the SCQ and SSIS-RS ASD subdomain scores for P4 exceeded cut-off for ASD, while the SRS-2 score was one point below cut-off. The SRS-2 domains that elevated the overall scores included social awareness, social cognition, and RRBs. Additionally, this individual also scored below the sample mean on the social skills subdomain of the SSIS-RS (18th percentile), and higher on the problem behaviours subdomain (90th percentile). However, their Vineland-II scores were close to average, with the exception of motor skills, which fell more than two standard deviations below the standard. After review of these findings, and their lack of consistency with the ADOS-2 score, which was quite low, CBE determined that this individual did not meet criteria for ASD.

P5

The results from P5 were similar to P4; low ADOS-2 scores, plus exceeding cut-off for ASD on two of the three questionnaires. The SCQ score was three points below cut-off and the SRS-2 overall score was only two points above cut-off; SRS-2 social communication was the only domain to exceed cut-off. This individual also scored low on the social skills domain of the SSIS-RS (14th percentile), and very high on the problem behaviours domain (98th percentile). Additionally, the Vineland-II scores were all below the sample mean, with motor skills the most affected. As with P4, observation of the child's social interactions during the ADOS-2 helped CBE determine that this individual did not have ASD.

P6

P6 was the youngest individual to exceed cut-off on all three questionnaires, and the ADOS-2 score was only one point below cut-off. The SRS-2 scores were especially high, with the overall

score one point below the severe range. These scores were largely driven by the RRB and the social cognition subdomains, both of which fell in the severe range; comparatively, the social motivation subdomain only showed mild impairment. Additionally, the SSIS-RS social skills (8th percentile) and problem behaviours (97th percentile) were both indicative of significant social impairments. Despite the high scores on the questionnaires, this individual scored very well on the communication and daily living skills domains on the Vineland-II, although they scored over one standard deviation lower on the socialization and motor skills domains. Despite relatively high impairment implicated by all three questionnaires, CBE found that the impairments could be attributed to intellectual disability and other symptoms common the PWS phenotype, and this individual did not meet criteria for ASD.

P7

Like P6, P7 also exceeded cut-off for ASD on all three questionnaires and fell one point short on the ADOS-2. This individual had the most unfavourable scores across the SSIS-RS, including 2nd percentile for the social skills domain, >99th percentile for the problem behaviours domain, and the highest raw score on the ASD subdomain. Their SCQ score was also the second-highest in the sample. Interestingly, all of the subdomains on the SRS-2 were extremely similar (scores ranged from 65-67), with the exception of social cognition, which was below cut-off. This is in contrast to P4 and P6, whose social cognition was among the most impaired. Similar to P6, CBE determined that this individual did not meet criteria for ASD.

P8

P8 was the only participant to exceed cut-off on all three questionnaires and the ADOS-2. Interestingly, the ADOS-2 overall score was comprised solely of sections pertaining to the social

affect; their RRB severity score was zero, indicating that P8 did not technically qualify for ASD on the ADOS-2. However, scores from the SRS-2 did show severe impairments in the RRB subdomain, and their overall SRS-2 score fell one point below the cut-off for the severe range. Additionally, their SSIS-RS social skills (4th percentile) and problem behaviours (96th percentile) were very indicative of social impairment, and the ASD subscale score was very high as well. This participant scored over two standard deviations below the normative standard on communication domain of the Vineland-II, and had slightly higher scores in the other three domains. Despite having exceeded the cut-off on every assessment, CBE determined that other factors such as cognitive delay, speech impairment, and oppositional behaviours could explain the social communication impairments, and this individual did not have ASD.

P9

P9, like P3, was a very interesting case. They too had among the lowest scores on the SSIS-RS ASD domain, the SCQ, and the SRS-2, and yet scored above cut-off for ASD on the ADOS-2. Interestingly, like P8, they showed no impairments in the RRB domain on the ADOS-2, but unlike P8, the RRB subdomain on the SRS-2 did not exceed cut-off. The only other subdomain that exceeded cut-off for ASD was social motivation on the SRS-2, albeit by one point. Not surprisingly, CBE determined that this individual did not have ASD.

P10

P10 presented with the highest scores on the SCQ and the SRS-2, yet did not exceed cut-off on the ADOS-2. Their SSIS-RS ASD score was also well above cut-off, and the SSIS-RS social skills (2nd percentile) and problem behaviours (98th percentile) also showed significant impairment. This individual also had the lowest adaptive behaviour composite score on the

Vineland-II, with the socialization and communication scores almost three standard deviations below standard. Despite the apparent impairment in socialization and communication, CBE decided that severe intellectual disability was the main cause for impairment, indicating that P10 did not have ASD.

Assessment Agreement and Validity based on Clinical Best Estimate

The three questionnaires (SRS-2, SCQ, and SSIS-RS) all had over 50% agreement; a total of six children exceeded cut-off on the SSIS-RS, and five of those six children exceeded cut-off on both the SRS-2 and SCQ, although not the same children. Cohen's kappa for the SCQ/SRS-2 and SSIS-RS was calculated to be 0.80 (SE= 0.19), and kappa for the SCQ and SRS-2 was calculated to be 0.60 (SE= 0.25). However, agreement between the three questionnaires and the ADOS-2 was extremely poor. Cohen's kappa for the ADOS-2 and SCQ/SRS-2 was calculated to be -0.20 (SE=0.28), and for the ADOS-2 and the SSIS-RS, kappa was calculated to be -.30 (SE=0.28). The kappa for all of the assessments, when compared to CBE was 0, since none were able to positively predict ASD.

Discussion

To date, this study comprises the youngest mean age of any study investigating ASD in PWS. Our main finding was that ASD symptomatology and social skills in children with PWS is highly heterogeneous. In total, eight of ten children exceeded cut-off for ASD on at least one of the assessments, although only one child exceeded cut-off on all four. Findings from the SCQ, SRS-2, and ADOS-2 indicate that, overall, the presence of RRBs (though not statistically significant) may be the most commonly occurring ASD-related impairment (see Tables 3 and 5). The SSIS-RS further demonstrated that children with PWS on average have lower social skills and higher problem behaviours than typically developing children. Since no children in our study were

diagnosed with ASD based on expert clinical judgement (i.e., CBE), it was not possible to speculate about which assessments are most appropriate in a PWS sample. However, given that only three children exceeded cut-off for ASD on the ADOS-2, compared to five and six on the SCQ/SRS-2 and SSIS-RS respectively, it appears that the specificity for the ADOS-2 may be more appropriate than that of the SCQ, SRS-2, and SSIS-RS. This seems logical, given that the ADOS-2 should be administered by individuals who are very familiar with ASD and have obtained research reliability. Additionally, the ADOS-2 is considered a diagnostic instrument, whereas the questionnaires are considered screening tools to help determine if clinical ASD assessment is warranted. Nevertheless, the ADOS-2 is not a replacement for clinical judgement, which is ultimately the gold standard for diagnosing ASD. Although no conclusions can be drawn, the findings from this study suggest future areas of investigation such as assessment of the validity of ASD assessments used.

Lack of agreement between ASD assessment measures has been reported in studies investigating ASD in Fragile-X syndrome [Hall et al. 2010]; these studies indicate poor agreement between the ADOS-2 and SCQ (Cohen's kappa=0.33 for girls, 0.13 for boys). Additionally, using a combination of the ADI-R, ADOS, and DSM-IV criteria, Harris et al. [2008] found that in a group of 63 males with Fragile X syndrome, 15 participants (24%) met criteria for ASD on all three assessments, while an additional 28 individuals (44%) met criteria on only one or two of the assessments. These studies support our findings showing lack of agreement between various ASD assessments in PWS and question the validity of using ASD assessments in genetic syndromes without having previously validated them specifically in the genetic disorder. One simple explanation for these findings is that each genetic syndrome manifests its own set of complex behaviors which are not typical in the general population, and some of which may

overlap with ASD. The overlap in phenotype places individuals with a genetic syndrome closer to ASD cut-off scores than typically developing individuals. For example, avoidance of eye gaze in Fragile-X syndrome (FXS) was once commonly attributed to phenotypic overlap with ASD [Moss and Howlin 2009]. However, current research now distinguishes these two conditions; FXS eye gaze is related to being overly sensitive to sensory stimuli, hyperarousal, and social anxiety, whereas eye gaze avoidance in ASD is attributed to general lack of understanding of social situations [Cornish et al. 2008; Cornish et al. 2007]. Another plausible explanation for higher scores on ASD assessments is that some degree of intellectual disability is present in most individuals with PWS. Indeed, the SCQ manual [Rutter et al. 2003a] mentions that non-ASD individuals with lower IQ (50-69) obtained higher scores on the SCQ (11.40; SD=5.87), which is quite similar to the results in our study (mean IQ= 63.38; mean SCQ score= 11.90). The SRS-2 manual [Constantino and Gruber 2012] gives similar caution to its use in individuals with an IQ less than 70. Both overlapping phenotype and intellectual disability may affect the ability for these assessments to reliably detect ASD in PWS.

While under-diagnosis of ASD in the PWS population may have negative implications for lack of appropriate treatment and intervention, the topic of over-diagnosis is complex and warrants thoughtful consideration. Some parents do not wish for further diagnoses for their children, and over-diagnosing ASD may cause unnecessary stress for these parents. Additionally, over-diagnosis of ASD would lead to intervention that may not be necessary, placing extra strain on the health care system, especially in provinces such as Alberta where provincial funding pays for interventions and treatments. However, even if these children do not meet diagnostic criteria for ASD, their high scores on ASD assessments implies the presence of social communication impairments and thus they would likely benefit from the interventions.

In our study, sample means on ASD assessments in children with PWS were less indicative of ASD than have been previously reported in adolescents and adults with PWS. For example, Zyga et al. [2014] and Dimitropoulos et al. [2013] both used the SRS in samples with a mean age over 10 years of age, and found average scores of 82.18 and 76.31, respectively. Both of these scores fall in the severe range on the SRS-2, whereas the average score from our population was 62.70, which falls in the mild range. Dimitropoulos et al. [2013] and Milner et al. [2005] also used the Vineland-II in their samples of adolescents and adults with PWS, and reported average composite scores of 65.15 and 62.60, respectively. Meanwhile, our sample had an average score of 80.40, over one standard deviation above results from these previously published studies. Lastly, Zyga et al. [2014] reported that 8 of 14 adolescents (57.14%) met criteria for ASD on the ADOS, whereas only 3 of 10 (30%) from our cohort met criteria (actually only 1 of 10 (10%), considering that P8 and P9 did not pass cut-off on the RRB domain). These findings display interesting differences in ASD symptoms and adaptive functioning between age groups (children vs adolescents and adults). However, other potential confounders, such as growth hormone treatment or exposure to other interventions, cannot be ruled out.

Although there were many social impairments found in PWS (see Tables 5 to 8), some relative strengths were also identified. For example, results from the ADOS-2 revealed that the vast majority of children had good eye contact (80%), shared enjoyment in interactions (90%), and functional play with objects (100%). Additionally, the SSIS-RS identified many areas of strength that could be used when implementing behavioral intervention, such as starting conversations with peers and adults as well as trying to make others feel better, comforting others, and showing concern for others. The two highest mean scores for individual items on the SSIS-RS were saying please and thank you; this indicates that social skills can be successfully taught to

children with PWS. Although many impairments were found in this study, the relative strengths of these children may be harnessed to help them overcome or compensate for these impairments. Additionally, interventions that have been successfully implemented in the ASD population may help in PWS also. For example, skin-picking, a common finding in PWS, could be treated using differential reinforcement of incompatible behavior (DRI) [Wong et al. 2014]. DRI reinforces a behavior which makes it impossible to perform the undesired behavior; in the case of skin picking, a parent or interventionist could reinforce the child keeping their hands clasped or arms folded when not using them. Additionally, by identifying an antecedent action, the parent or interventionist could know what typically triggers skin-picking, so that they can avoid those triggers when possible [Wong et al. 2014]. These select few examples of techniques that have shown success in ASD might be beneficial as part of behavioral intervention for children with PWS.

Our cohort of children had a wide range of adaptive skill levels. Even though the mean adaptive behaviours composite score on the Vineland-II was more than one standard deviation below the normative standard, some children scored slightly above the normative standard in some areas. The adaptive score domain most affected in PWS was motor skills; decreased motor functioning in children with PWS is an expected finding given that hypotonia is a core symptom in the early years of PWS. However, decreased motor skills could imply that children with PWS are less able to perform motor activities at the same level as their peers, both gross and fine, which could also contribute to their overall social-communication impairment. Indeed, Rubin et al. [2015] found that children with PWS exhibit altered stress hormone responses to exercise, when compared to obese and lean controls. If children with PWS lack motor abilities or coordination to participate

in social games such as tag or kickball, these individuals with PWS may be missing out on various social activities, giving them fewer chances to develop social skills.

One interesting trend we identified using simple linear regression was a strong, negative correlation between age and full-scale IQ (Spearman's rho=-.815, p=.004). A search for literature reporting IQ trajectory in young children with PWS yielded no studies that have investigated this finding. However, a recent randomised control trial in children age 3 to 14 years old with PWS found that four years of continuous growth hormone treatment prevented deterioration of certain cognitive skills and significantly improved other cognitive skills [Siemensma et al. 2012]. Although the mediating factors responsible for this IQ/age relationship are unclear, the age at which growth hormone treatment is initiated might be one plausible factor. This decline in IQ over time might also be more accurately described as a delay in developmental progression rather than a decline in cognitive abilities. Thus, children with PWS might acquire cognitive abilities less readily than typically-developing children. Further investigation of the relationship between age and IQ in children with PWS is warranted.

Limitations

Limitations to this study include a limited sample size and cross-sectional design. This study was originally designed to make group comparisons between UPD, DEL, and an ASD comparison group, but lacks an adequate sample size. Although descriptive studies are able to provide a wealth of information regarding smaller samples in order to generate hypotheses and ideas, they lack the statistical power to compare results to other groups, such as an ASD comparison group. A longitudinal design would be helpful in the future to discriminate possible factors involved in the negative correlation between age and IQ, and to determine if ASD symptoms in PWS are exacerbated with age. Additionally, the genetic subtype of PWS was not taken into

consideration, once again due to a smaller sample size. It has been found that the UPD genetic subtype has more ASD symptoms than the DEL subtype [Dimitropoulos and Schultz 2007; Dykens et al. 2011], implying that our sample may have shown less ASD symptomatology if there were a greater proportion of individuals with DEL (our sample had eight UPD and two DEL). Notably, one of two (50%) DEL did not exceed cut-off on any of the ASD assessments, whereas seven of eight (88%) UPD exceeded cut-off on at least one of the ASD assessments.

Within the DEL subtype, there are two types of deletions: the longer type 1, and relatively shorter type 2. Some studies have found differences between type 1 and type 2, with type 1 typically showing greater overall impairment as well as ASD-related impairments [Dykens and Roof 2008; Milner et al. 2005]. However, we were unable to classify between the two types in our study, as the sample population had not received the necessary genotyping as part of the initial diagnosis in order to distinguish between the two deletion types.

Future Directions

Further research is necessary to identify the most appropriate tools to assess ASD in PWS. This will require further studies with increased sample size to confirm our suspicions that the ADOS-2 is the most accurate assessment tool to identify ASD in PWS. Larger sample sizes are also needed to further explore, and potentially verify, our findings of the strong, negative correlation between age and IQ in children with PWS, and if any treatments or interventions have proven successful in maintaining IQ throughout childhood and into adolescence, including growth hormone.

Our finding that eight of ten children exceeded cut-off for ASD on at least one assessment suggests that behavioural intervention in young children with PWS may be justified, based on

functional impairments implied by the relatively high assessment scores and not just based on presence or absence of ASD diagnosis. Indeed, behavioural intervention in children with ASD has been found to be most effective when started at a young age [MacDonald et al. 2014]. Identification of ASD in PWS, however, may not be as important as determining what can be done to help children with PWS achieve optimal outcomes from an early age. Identification of common behavioural issues, such as the high scores on RRB domains found in our sample, could lead to more tailored interventions for children with PWS. These interventions would be informed by the significant body of research that has focused on evidence-based interventions for children with ASD, and could focus on using their relative social strengths, such as good eye contact and shared enjoyment in social situations.

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Table 3. *Results from assessments, given as mean (SE; SD) and range*

	Mean (SE; SD)	Min-Max
Age	6.77 (2.85)	3.42-11.75
# (%) male	3 (30)	-
# (%) UPD	8 (80)	-
FSIQ	64.70 (5.05; 15.96)	40-92
ADOS-2 Severity score	3.00 (0.42; 1.33)	1-5
ADOS-2 SA Severity score	3.50 (0.56; 1.78)	2-7
ADOS-2 RRB Severity score	4.70 (0.80; 2.54)	0-7
SCQ raw score	11.90 (2.20; 6.95)	5-21
SRS-2 Overall T-score	62.70 (3.98; 12.56)	43-85
SRS-2: Social Awareness T-score	61.60 (4.16; 13.16)	43-81
SRS-2: Social Cognition T-score	61.00 (4.83; 15.27)	40-94
SRS-2: Social Communication T-score	61.70 (4.04; 12.78)	43-86
SRS-2: Social Motivation T-score	56.10 (2.47; 7.81)	43-67
SRS-2: RRB T-score	65.80 (4.20; 13.28)	48-88
SSIS-RS: Social Skills percentile	23.10 (7.02; 22.18)	2-64
SSIS-RS: Problem Behaviours percentile	80.00 (7.06; 22.32)	42-99
SSIS-RS: ASD raw score	19.00 (2.53; 8.01)	8-31
Vineland-II Composite standard score	80.40 (3.57; 11.29)	60-96
Vineland-II: Communication standard score	85.20 (4.60; 14.56)	59-100
Vineland-II: Daily Living Skills standard score	86.50 (3.60; 11.38)	68-101
Vineland-II: Socialization standard score	83.20 (4.79; 15.14)	57-108
Vineland-II: Motor standard score	77.20 (2.59; 8.19)	67-91

n=10 for all assessments
SE = Standard Error (of the mean)
SD= Standard Deviation (of the sample)
FSIQ=Full-scale IQ (based on WPPSI/WISC scores)
SRS-2= Social Responsiveness Scale-2
SCQ=Social Communication Questionnaire
SSIS-RS= Social Skills Improvement System- Rating Scales
ADOS-2= Autism Diagnostic Observation Schedule-2

dividual participant score profiles

	FSIQ	ADOS Module	ADOS-SA	ADOS-RRB	ADOS-Overall	SCQ	SRS-AWR	SRS-COG	SRS-COM	SRS-MOT	SRS-RRB	SRS-Overall	SSIS-SS	SSIS-PB	SSIS-ASD
	92	2	2	6	2	6	54	56	55	51	62	56	25	53	11
	63	2	2	5	1	6	43	54	48	57	56	52	50	56	16
	77	2	4	6	***4***	5	49	40	43	43	48	43	64	42	8
	82	2	2	6	2	***14***	66	63	57	47	64	59	18	90	***21***
	69	2	2	6	2	9	57	53	64	54	58	***62***	14	98	***20***
	56	2	3	6	3	***13***	68	77	71	64	82	***75***	8	97	***26***
	65	3	4	5	3	***20***	67	55	65	67	66	***65***	2	99	***31***
	47	1	6	0	***5***	***14***	81	67	73	64	80	***75***	4	96	***21***
	56	3	7	0	***5***	6	50	51	55	60	54	55	44	71	8
	40	3	3	7	3	***26***	81	94	86	54	88	***85***	2	98	***23***

= ADOSS-2 Social Affect Severity Score; ADOS-RRB= ADOS-2 Restricted or Repetitive Behaviour Severity Score; SCQ= SCQ Raw Sco
S-2 Social Awareness Subscale; SRS-COG= SRS-2 Social Cognition Subscale; SRS-COM= SRS-2 Social Communication Subscale; SRS-
ial Motivation Subscale; SRS-RRB= SRS-2 Restricted or Repetitive Behaviours Subscale; SSIS-SS= SSIS-RS Social Skills Percentile; SSI
roblem Behaviours Percentile; SSIS-ASD= SSIS-RS ASD Subscale Raw Score; CBE= Clinical Best Estimate

cores of >3 are associated with ASD
s of ≥12 are associated with ASD
res of <60 are not associated with ASD, 60-65 are associated with mild to moderate impairment in social responsiveness, 66-75 are associa
impairment in social responsiveness and ASD , and >75 are associated with severe impairment in social responsiveness and ASD
verall score for the following age ranges represents average amount of ASD behaviours; any score above or below these ranges indicate ab
age ASD symptoms, respectively: age 3-5 years: 4-16; age 5-12 years: 3-14
oes not qualify for ASD diagnosis, Y=does qualify for ASD diagnosis

t exceed cut-off for ASD are ***bolded and italicized****

ndividuals were ordered from youngest (ID=1) to oldest (ID=10) in order to give a sense of participant age (range= 3-12 years); however, i
onfidentiality (due to the rarity of PWS), participant age and gender could not be revealed.

Table 5. *ADOS-2 strengths and weaknesses*

Relative Impairments (≥60% with a score >0)	Frequency*	Question
	6 of 9**	Speech Abnormalities Associated with Autism (Intonation/Volume/Rhythm/Rate)
	7 of 9	Conversation
	3 of 3	Reporting of Events
	6 of 7	Pointing
	10 of 10	Quality of Social Response
	8 of 10	Imagination/Creativity
	6 of 10	Unusually Repetitive Interests or Stereotyped Behaviours
	3 of 3	Comment on Others' Emotions/Empathy
	3 of 3	Insight into typical social situations and relationships
Relative Strengths (≤20 with a score >0)	Frequency*	Question
	2 of 10	Eye contact
	0 of 7	Response to name
	1 of 10	Shared enjoyment
	0 of 7	Response to joint attention
	0 of 7	Functional play with objects
	1 of 10	SIBs

*not all items are scored on every module; Module 1 was completed by one individual, Module 2 by six individuals, and Module 3 by three individuals

** Although four of the six participants received a score of seven, which refers to a stutter, stammer, or other fluency disorder not specific to ASD, and is changed to a score of 0 for the ASD algorithm

Table 6. *SCQ questions endorsed by at least 50% of parents*

Frequency	Question:	Category
90% Yes	Has s/he ever used odd phrases or said the same thing over and over in almost exactly the same way (either phrases that s/he has heard other people use of one that s/he has made up)?	RRB
60% Yes	Has s/he ever got her/his pronouns mixed up (e.g. saying *you* or *s/he* for *I)*?	Communication
80% Yes	Has s/he ever said the same thing over and over in exactly the same way or insisted you say the same thing over and over again?	RRB
70% Yes	Has s/he ever had things that s/he seemed to have to do in a very particular way or order or rituals s/he insisted that you go through?	RRB
50% Yes	Has s/he ever had any interests that preoccupy her/him and might seem odd to other people (e.g. traffic lights, drainpipes, timetables)?	RRB
60% Yes	Has s/he ever had any special interests that were unusual in their intensity but otherwise appropriate for her/his age and peer group (e.g. trains, dinosaurs)?	RRB
50% Yes	Has s/he ever seemed to be unusually interested in the sight, feel, sound, taste, or smell of things or people?	RRB
60% No	Does s/he have any particular friends or a best friend?	Social

RRB=Restricted or repetitive behaviours

Table 7. *SRS-2 questions with a mean score ≥ 1.5*

Mean Score*	Question	SRS-2 Domain
2.1	Doesn't recognize when others are trying to take advantage of them	COG
1.5	Is aware of what others are thinking or feeling	AWR
1.5	Plays appropriately with children their age	COM
1.6	More difficulty than other children their age with change in routine	RRB
1.9	Doesn't care that they're not on the same 'wavelength' as others	AWR
2	Regarded by other children as odd or weird	RRB
1.8	Hard time getting mind off something once they start thinking about it	RRB
1.7	Good personal hygiene	AWR
1.5	Separates easily from caregivers	MOT
1.5	Focuses attention to where others are looking or listening	AWR
2	Knows when they are talking too loud/making too much noise	AWR
2.1	Knows when they are too close to someone/in their personal space	COM
1.5	Is inflexible, has a hard time changing their mind	COM

AWR= Social Awareness; COG= Social Cognition; COM= Social Communication; MOT= Social Motivation; RRB= Restricted or Repetitive Behaviours

* Each question was rated on a scale from 0 to 3, with 0 being not true and 3 being almost always true; the mean score from all ten children is reported

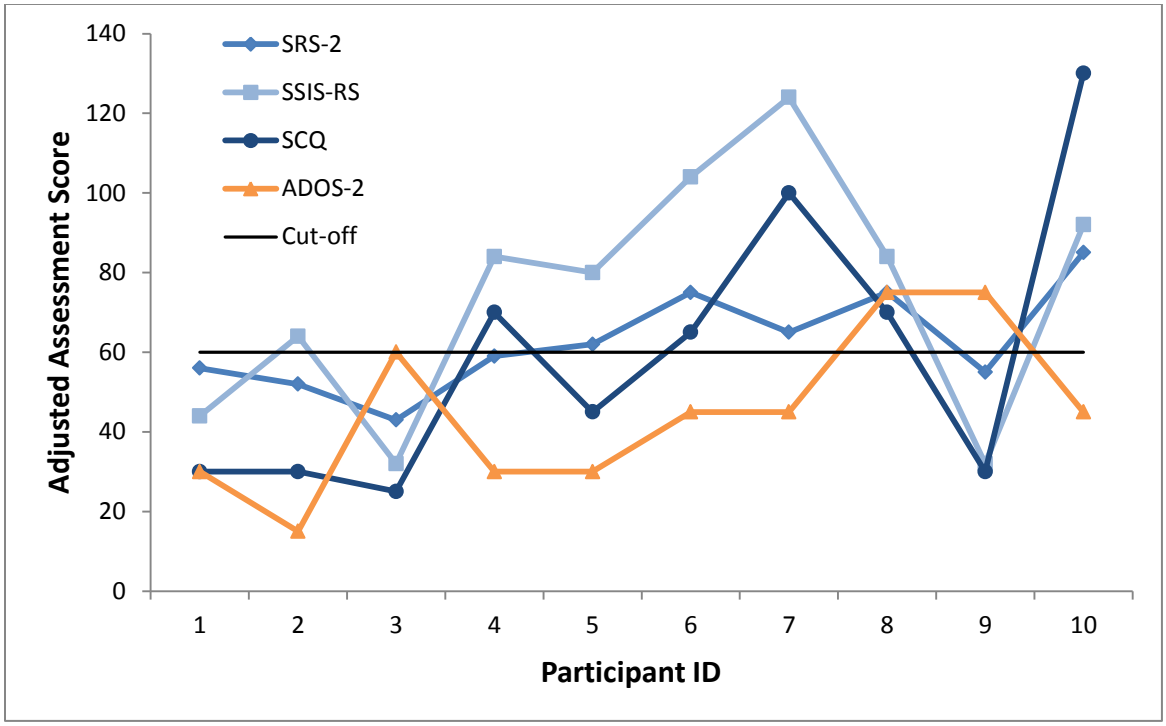
Table 8. *SSIS-RS results*

Relative Impairments (mean score ≤ 1)	Mean Score*	Question
	0.8	Stands up for others who are treated unfairly
	1	Takes responsibility for their own actions
	1	Takes responsibility for their own mistakes
	0.9	Stays calm when disagreeing with other
	0.6**	Refrains from repeating the same thing over and over again
Relative Strengths (mean score ≥ 2)	Mean Score*	Question
	2.3	Express feelings when wronged
	2.5	Says thank you
	2.1	Asks for help from adults
	2	Tries to make others feel better
	2.1	Says when there is a problem
	2.4	Starts conversations with peers
	2.6	Says please
	2.1	Tries to comfort others
	2	Interacts well with other children
	2.1	Shows concern for others
	2.3	Starts conversations with adults

* Each question was answered on a scale from 0 to 3, with 0 meaning never and 3 meaning always; the mean score from all ten children is reported

** This question was changed to its negative to be able to group with the other relative impairments; the actual question is “Repeats the same thing over and over”, with a mean score of 2.4

Figure 2: *Comparison of adjusted scores on three questionnaires and ADOS-2*



In order to convert to comparable scores, ADOS-2 severity scores were multiplied by 15, SCQ scores were multiplied by 5, and SSIS-ASD raw scores were multiplied by 4. This converted all scores to have an ASD cut-off score of 60 (although for the SSIS-RS, it took the average cut-off between the two age groups). These conversions were conducted to illustrate relative scoring on the questionnaires in comparison with the ADOS-2.

Chapter 5: Conclusion

Integration of findings:

My systematic review included 13 studies that found that 26.7% (210 of 786) of individuals with PWS exceeded the cut-off associated with ASD on an ASD symptom measure, although the range reported in the studies varied widely, from 0-57%. Our descriptive study used four assessments that measure ASD-related symptoms, with a different proportion of children exceeding cut-off on each assessment: ADOS-2 (30%), SRS-2 (50%), SCQ (50%), and SSIS-RS (60%). Overall, eight of ten children (80%) exceeded cut-off on at least one ASD assessments, and one child (10%) exceeded cut-off on all four. With the exception of the ADOS-2, these rates are generally higher than those found in studies included in the systematic review, although the relatively high proportion of UPD to DEL (8:2) in our study may have influenced our findings. Indeed, a study by Dimitropoulos et al. [2013] found that 78.9% of individuals with UPD exceeded cut-off on the SRS. Despite these findings, based on clinical best estimate to confirm diagnosis, none of the ten children were found to meet DSM-5 diagnostic criteria for ASD. This finding emphasizes the need for validation of ASD assessments in the PWS population; that is, to compare classification by ASD symptom measures to expert judgement by CBE. As well, even though 8 of 10 children exceeded cut-off on at least one questionnaire, the average scores from our descriptive study implied noticeably less impairment than other studies with adolescents with PWS, both with respect to ASD symptoms (SCQ and SRS-2) and adaptive behaviours (Vineland-II). This finding lends preliminary support to the hypothesis that ASD symptomatology is less severe in children with PWS than adolescents and adults [Lo et al. 2013; Song et al. 2015]. However, interpretation of these findings must be done with caution because of the small sample size and limited age range, which did not allow formal comparison between

groups. Moreover, there may be selection biases that favour longer-term follow-up of individuals with PWS with more severe social-emotional and/or behavioural impairment.

Challenges of Researching Rare Diseases:

One of the major difficulties in my research was identification of participants. Parents were generally interested in participating (only one parent of the ten I contacted said they were not interested); when I expanded recruitment to British Columbia, five additional parents contacted me. However, four of the five children either already had a diagnosis of ASD (n=2), or were unable to complete the study visit during the recruitment window (n=2). Given that the prevalence of PWS in the general population is estimated at 1 in 10 000 to 1 in 30 000 [Cassidy et al. 2012], it is not surprising that our sample size was limited. Future studies could involve international collaboration among multiple centers in order to recruit sufficient numbers of PWS participants.

As previously mentioned, eight of ten children in our study exceeded cut-off on at least one ASD assessment; however, none of them were diagnosed with ASD based on CBE. The lack of agreement between findings on ASD assessments versus CBE highlights the importance of establishing psychometrically validated tools for measuring ASD symptoms within a rare disease. Key features of the tools including reliability, reproducibility and validity are all valid concerns in the PWS population. It is challenging for researchers to validate such assessment tools, due to sample size constraints. Furthermore, within PWS children, there is a spectrum of behaviors and challenges, such as RRBs and low adaptive functioning, which may overlap with ASD to varying degrees. It is difficult to confirm a true diagnosis of ASD in children with PWS due to overlapping behavioral symptoms between PWS and ASD. This again underscores the need for trained health care professionals with ample experience with ASD to be included in

making a diagnosis of ASD in individuals with PWS. Even when CBE is used, however, it may be difficult for professionals who are not familiar with the behavioral complexities of PWS to distinguish between the variable PWS phenotype and true ASD symptomatology.

Researchers can take different approaches when investigating ASD in genetic syndromes. Some studies approach ASD as a categorical diagnosis (looking for presence/absence), whereas other studies focus on autistic symptomatology as a continuum across multiple domains [Dykens et al. 2004]. The latter approach may be more informative when investigating ASD in genetic syndromes as it takes account of the heterogeneity of symptoms found on the autism spectrum. For example, instead of investigating rates of categorically defined ASD in PWS, comparison of specific areas of social communication or RRBs between UPD and DEL may help researchers understand that genetic contribution of duplication of maternal chromosome 15q11-13 in ASD.

One priority for future research is to design an ASD assessment that has high sensitivity and specificity for ASD in the PWS population to ensure accurate diagnosis. Although creating a new assessment may not be feasible, calibrating current assessments such as the SRS-2 or the SCQ by adjusting cut-offs or changing a few questions may be sufficient to better identify ASD in PWS. Although assessments with high sensitivity and high specificity would be ideal, DiGuiseppi et al. [2010] commented on the difficulty of achieving both sensitivity *and* specificity in rare genetic syndromes (e.g. Down syndrome). They hypothesize that, in children with intellectual disabilities, social communication development is commonly delayed, and may be mistaken for ASD symptomatology in ASD assessments. Furthermore, they suggest that clinically significant executive functioning deficits, commonly found in individuals with Down syndrome, might also adversely affect social and communicative functioning. Interestingly, a recent study shows that a majority of children with PWS also show clinically-significant

impaired executive function [Hutchison et al. 2015]. These two potential confounders (intellectual disability and impaired executive function) lead to difficulties in the design of accurate ASD assessments with both high sensitivity (correctly identifying all cases of ASD in individuals with PWS) and high specificity (not falsely identifying an individual with PWS who does not have ASD). By correctly identifying children with co-occurring ASD and PWS, these individuals have the best opportunity at optimal outcomes by receiving diagnosis early enough to receive the necessary early intervention and treatment.

Importance of understanding ASD in PWS:

The most challenging aspect of ASD diagnosis is the lack of consistent definitive markers or precursors to indicate its presence or absence. Understanding the ASD phenotype in PWS may be helpful in understanding the genetic contribution of chromosome 15q11-13 to ASD. For example, Bruining et al. [2014] used responses from the ADI-R from a number of genetic syndromes (including 22q11.2 deletion, Down's syndrome, PWS, supernumerary marker chromosome 15, tuberous sclerosis complex, and Klinefelter syndrome) to compare behavioural specificity associated with each syndrome. They found that when all six syndromes were analyzed simultaneously, 63% of cases could be predicted based on behavioural patterns from the ADI-R. In addition, the prediction probabilities for PWS were most similar to that of supernumerary marker chromosome 15, which is logical given that they are both genetic syndromes associated with chromosome 15. Further understanding of the PWS phenotype in relation to ASD could potentially add to the existing knowledge regarding the potential contribution of chromosome 15q11-13 to the ASD phenotype.

Other biological factors are important to consider when comparing ASD to PWS. For example, research has found irregularities in the oxytocin pathway in both ASD and PWS [Francis et al.

2014]. Magel2, a gene commonly found mutated in ASD and lost altogether in individuals with PWS, plays a role in the oxytocin pathway, and may be a common factor in the phenotype of ASD and PWS. Meziane et al. [2015]studied the effects of the Magel2 gene in knockout mice, finding that Magel2 inactivation resulted in deficits in both social recognition and social interaction, as well as learning disabilities. Additionally, the oxytocin system in these knockout mice showed functional and anatomical modifications that change from birth to adulthood that were not present in the wildtype mice. However, when the knockout mice were administered oxytocin during the first postnatal week, this prevented the social and learning disabilities exhibited by the knockout mice who had not received the oxytocin treatment. Perinatal oxytocin treatment partially normalized the oxytocin system function as well. Although these findings have not been replicated in humans, they show one common pathway that could partially explain the presence of ASD symptoms in PWS. Future studies investigating the use of oxytocin treatment postnatally in infants with PWS may be warranted.

Furthermore, brain imaging studies may reveal a common association with atypical connectivity. Lukoshe et al. [2014] compared age- and sex-matched children with PWS to typically developing children and found lower cortical complexity in children with PWS, which they suggest may partially explain developmental delay. Furthermore, Zhang et al. [2013] found that children with PWS showed functional connectivity alterations in brain regions implicated in eating as well as reward (such as the prefrontal cortex), when compared to sibling controls of similar age and sex. Meanwhile, a recent review of connectivity in ASD [Rane et al. 2015] found that decrease white matter and long-range neural coherence are most commonly found in ASD. Rane et al. [2015] also found ten studies reporting lower resting-state connectivity in the

prefrontal cortex. However no studies have compared imaging between ASD and PWS, which could help reveal similarities or differences between these two disorders.

Future Directions

In order to make comparisons between children with ASD and the UPD and DEL subtypes, as well as between those with PWS who meet criteria for ASD (PWS+ASD) and those with PWS who don't meet criteria for ASD (PWS-ASD), studies with larger sample sizes are required. A sample-size calculation should be made based on a pre-determined decision as to what difference between the two groups would be clinically relevant. Additionally, research including longitudinal follow-up from the early stages of life could help clinicians understand the development of ASD in PWS, in order to be able to identify early warning signs of ASD in infants and toddlers with PWS (e.g. lack of orientation to name or poor eye contact can be noticed in the first year of life for infants who later go on to develop ASD [Zwaigenbaum et al. 2005]).

As mentioned previously, other future studies should investigate the validation of current ASD assessments or creation of new valid assessments for the PWS population. Even if early warning signs of ASD can be identified in infants and toddlers with PWS, not all children will be identified in the first few years of life; repeated assessments may be required to monitor the progression of ASD symptoms. These assessments can help parents and clinicians identify new difficulties or unmet social demands so that interventions and treatments can be modified accordingly.

Lastly, future studies should investigate possible shared biological pathways that might account for shared phenotypes between ASD and PWS. Using imaging studies to compare functional brain connectivity between individuals with PWS and ASD may provide useful insights.

Additionally, future research should investigate the overlapping shared genetic pathways between ASD and PWS. These studies could potentially identify ASD patients who have a specific genetic syndrome and alternatively, by studying rare syndromes, more of the pathophysiology of ASD may be uncovered. Finally, the oxytocin pathway appears to be a logical candidate for future research, both for understanding genetic causes of ASD and for potential treatment. The correlation found in our descriptive study between age and full-scale IQ also warrants investigation into potential treatments to help stabilize the cognitive abilities of children with PWS as they grow. Growth hormone treatment has been suggested [Siemensma et al. 2012], although further research is required to determine whether these effects are long-lasting. Other treatment possibilities may include the use of behavioral intervention to help with the social communication deficits found in children with PWS. Our finding that children with PWS have many relative strengths for social skills in general, such as saying please and thank you, may indicate that more social skills need to be taught to children directly.

Concluding Remarks

My thesis investigated ASD-related symptomatology in PWS. I first conducted a systematic review of the literature investigating ASD symptomatology in PWS, which comprised my second chapter (AJMG, in press). Several knowledge gaps identified in this review included: (1) a lack of studies investigating ASD symptoms in children with PWS; and (2) the need for detailed studies comparing children with PWS+ASD to PWS children without ASD, to aid in earlier recognition of ASD in PWS. These findings led to the creation of my third chapter, a cross-sectional comparative study between children with UPD, DEL, and ASD, as well as a comparison between children with PWS+ASD and PWS-ASD. However, sample size and time constraints led to modifications in study design, resulting in the descriptive study (chapter four).

The descriptive study provided me with first-hand clinical experience in the assessment and diagnostic challenges involved in assignment of an ASD diagnosis. Although firm conclusions cannot be drawn from the descriptive study, due to the limited sample size, the detailed description of both the children and the assessments provides preliminary data for future studies. Three future studies implicated from this research include: (1) longitudinal studies starting at an early age in order to identify unique ASD symptomatology in infants and toddlers with PWS; (2) validation of ASD assessments within the PWS population, or the creation of new, validated ASD assessments; and (3) investigation of shared biology between ASD and PWS, including potential treatment.

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