Behavioral features of individuals with Phelan McDermid (22q13.3 deletion) syndrome: An examination of autistic behavior, adaptive functioning and psychiatric symptoms

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Abstract

The 22q13.3 deletion syndrome is a neurodevelopmental disorder that includes general hypotonia, developmental delay, absent or poor speech, and autistic behavior. Despite advances in genetic testing, PMS remains under diagnosed because of difficulty identifying the behavioral phenotype. Results of the current study indicate that autism spectrum disorder (ASD) is a common occurrence among persons with PMS. The ASD criteria most frequently met by participants were deficits in reciprocal social interaction and play, and in verbal language and non-verbal communication. The comorbidity of PMS and ASD is characterized by more adaptive deficits in the areas of socialization and communication, as well as increased mental health risks. These findings add specificity to the behavioral phenotype of PMS and provide direction for future research.
Résumé

Le syndrome délétion 22q13.3 est un trouble neurodéveloppemental caractérisé par de l’hypotonie, des retards développementaux et du langage ainsi que par des comportements autistiques. Malgré les avancés en génétique, le PMS continue à être sous-diagnostiqué à cause de la difficulté à identifier le phenotype comportemental. Les résultats de cette étude suggèrent la présence de comorbidité entre le trouble du spectre de l’autisme et le PMS. Les manifestations de l’autisme les plus fréquents chez les participants étaient des déficits dans les interactions sociales ainsi que dans la communication verbale et non-verbale. La comorbidité entre le PMS et l’autisme est caractérisée par davantage de déficits adaptifs dans la sociabilité et la communication de même qu’un risque plus élevé de problèmes mentaux. Ces résultats améliorent la compréhension du phénotype comportementale du PMS et guident la recherche future.
Acknowledgements

I would like to begin by thanking my doctoral thesis supervisor, Dr. Steven Shaw, for his guidance, mentorship, and encouragement. I will forever be grateful for his ability to see through the fog of special circumstances and provide me with the space and peace of mind I needed to excel academically and professionally. I look forward to our future collaborations.

This project would not have been possible without the support of the many research assistants who dedicated their time to data collection, scoring, and data entry. Specifically, I would like to thank Tia Ouimet, Akanksha Sharma, Jessica Ganten, Shannon Morrison, Jennifer Chan, Seema Mahdavi, and Alice Kitz for their hard work and commitment to the project. I would also like to thank Anthony Claro for his editorial support. It takes a village to raise a dissertation.

I want to thank my friends and family for their unrelenting support and encouragement. During my doctoral studies I became a wife to Antonio, mother to Luca and Nina, and a dedicated professional to many children and families. These added roles and responsibilities provided me with the motivation and drive to succeed and grow personally, as well as professionally.

I am grateful to all the families affected by PMS that opened their lives and hearts to me.

Finally, this research was supported by a fellowship from the Fonds de recherche sur la société et la culture (FQRSC).
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Psychiatric symptoms

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Claims to Originality

Presently, Phelan McDermid Syndrome (PMS) is a largely underdiagnosed syndrome because of the lack of information regarding the unique clinical presentation of individuals with PMS. The current study represents a significant contribution to the literature by providing information about the occurrence of ASD among persons with PMS, specific profile of autistic behaviors, and the increased risk of adaptive and psychiatric impairments to individuals with comorbid PMS and ASD. This research also builds on the strengths of existing research that has employed the most comprehensive measure of autistic features (ADI-R), while also accounting for the limitations of previous studies (e.g., sample size, wide-age range, group comparisons, and all ADI-R items). The results of this study will contribute to differential diagnosis and service allocation for affected individuals. Moreover the current study is among the first to examine the presence of behavioral features among a large sample of children, adolescents and adults with PMS. A developmental understanding of the progression of autistic behavior, and related behaviors past puberty has implications for differential diagnosis and timing of interventions.
Introduction

The microdeletion syndrome 22q13.3, also called Phelan-McDermid syndrome (PMS), is a genetic disorder associated with cognitive, language, and social communicative impairments (Manning et al., 2004, Phelan et al., 2001). The phenotype of individuals with PMS includes delayed motor development, moderate to profound global developmental delay, hypotonia, delayed or absent speech, normal or accelerated growth, and minor dysmorphic facial features (Cusmano-Ozog, Manning, & Hoyme, 2007; Phelan et al., 2001). Many children with PMS demonstrate autistic-like behaviors which include poor eye contact, stereotypic behaviors, self-stimulation, and repetitive behaviors and interests (Cusmano-Ozog et al., 2007; Manning et al., 2004; Prasad et al., 2000).

Recent neurobiological findings support a relationship between PMS and autism. Specifically, SHANK3, which is one of the major genes affected in individuals with PMS, is also disrupted in many individuals with autism (Durand et al., 2007; Meyer, 2004). The SHANK3 gene produces proteins necessary to construct synapses in the brain and when disrupted, as in children with PMS and autism, results in severe cognitive delays, language delays, and social communicative deficits. Another possible link with autism is the clinical finding that children with PMS show regression or loss in skill (Manning et al., 2004; Wilson et al., 2003) similar to that which is reported in 20% to 40% of children with autism (Baird, 2004; Rogers, 2004).

The study of autistic behaviors among individuals with PMS is in its infancy and has relied heavily on case studies. The present study is among the first to explore the relationship between PMS and autism using a comprehensive measure
of autistic behavior on a large sample of individuals of varying ages. The overall objective of this project was to improve the description of the behavioral phenotype of PMS by highlighting the behavioral link between PMS and autism.

One of the specific aims of the study was to identify the proportion of children with PMS that had a previous diagnosis of autism spectrum disorder. A second aim was to identify a specific profile of autistic-like behaviors among individuals with PMS using items of the *Autism Diagnostic Interview-Revised* (ADI-R; Lord, Rutter, & Le Couteur, 1994). A third aim was to identify the proportion of children with PMS who show regression in skill using the ADI-R regression addendum. In order to further define the behavioral profile of PMS, individuals with PMS who had a previous diagnosis of autism were compared with individuals who did not have a previous diagnosis of autism on measures of adaptive functioning and psychiatric symptoms. Finally, the age effects for severity of autistic behavior, adaptive functioning and psychiatric symptoms were examined.

The present project provided vital information on the syndrome profile of autistic behavior and other behavioral features of PMS. Refining the behavioral phenotype of individuals with PMS will serve to increase awareness of PMS among educators and health care professionals and thus aid in the differential diagnosis of individuals with PMS and autism.
Review of Literature

22q13.3 Deletion Syndrome

The microdeletion syndrome 22q13.3, also referred to as Phelan-Mcdermid syndrome (PMS), is a genetic condition associated with severe cognitive deficits (Manning et al., 2004). There are over 400 diagnosed cases of PMS worldwide (22q13 Deletion Syndrome Foundation, 2008), almost all of which are young children. The first case of 22q13 deletion was described in 1985 (Watt et al., 1985). Several case studies followed, as well as a study including 7 individuals with PMS (Nesslinger et al., 1994). In 2001 Phelan et al. (2001) reported on a sample of 37 individuals with PMS and compared them to 24 individuals previously reported in the literature. Initial cases of PMS were diagnosed by routine chromosome analysis. A more reliable measure of the 22q13.3 deletion, the Fluorescence in situ Hybridization (FISH) test came into popular use in the early 1990s, as did molecular genetic testing methods. Currently microarray comparative genomic hybridization (CGH) is the first method of testing to detect the 22q13.3 deletion.

In nearly all cases PMS is due to the absence of genetic material on the long arm of the 22nd chromosome (Phelan et al., 2001). The 22q13.3 deletions are mostly de novo occurrences (i.e., arise spontaneously during development) but approximately 20% of cases result from familial translocations. Although rare, ring chromosome 22 and mosaic cases have also been reported (Jefferies et al., 2005; Phelan et al., 2001; Wilson et al., 2003). In general, ring chromosome occurs when both ends of chromosome 22 are lost (including segment 22q13.3) and the broken ends rejoin to form a ring. A Mosaic is the result of two
populations of cells with different genotypes present in one individual, who has
developed from a single fertilized egg. For unknown reasons, there appears to be
a higher frequency of females than males identified with abnormalities of 22q13
region (Bourgeron & Durand, 2008).

There are approximately 200 genes affected by the deletion of
cromosome 22q13.3 (e.g., ACR, RABL2B, SHANK3). The haploinsufficiency
SHANK3 gene has been associated with the core neurological deficits (i.e.,
intellectual disability, delayed expressive speech) identified in persons with PMS
(Jefferies et al., 2005; Wilson et al., 2003). Individuals whose ring chromosome
22 does not disrupt the SHANK3 gene may show less impairment in cognitive
and behavioral functioning than individuals with PMS and mutations of the
SHANK3 gene (Jefferies et al., 2005). The SHANK3 gene codes for a structural
protein of the post synaptic density (PSD). The PSD can be described as a
 cellular junction that allows for rapid, neural transmission. This SHANK3 protein
product is expressed in the cerebral cortex and cerebellum and is responsible for
proper brain and nervous system development in utero and after birth (Bonaglia et
al., 2001). However, haploinsufficiency of the SHANK3 protein resulting in
cognitive deficits, language delays, and social communicative deficits has also
been identified in individuals with autism (Durand et al., 2007). Although there is
much variability in the phenotypic presentation of individuals with PMS (see
Table 1), the size of the chromosomal deletion has not been associated with the
neurological symptoms (Jefferies et al., 2005; Wilson et al., 2003).
Table 1

*Physical Characteristics of PMS*

<table>
<thead>
<tr>
<th>Shown by more than half of the deletion population</th>
<th>Shown by less than half of the deletion population:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Hypotonia (poor muscle tone which can affect lungs, digestion, and swallowing): 97%</td>
<td>▪ Epicanthal folds (fold over inner corner of eye): 41%</td>
</tr>
<tr>
<td>▪ Normal to accelerated growth: 95%</td>
<td>▪ Syndactyly (webbing) between 2nd and 3rd toes: 38%</td>
</tr>
<tr>
<td>▪ Thin, flaky toenails: 78%</td>
<td>▪ Clinodactyly (curving of fifth finger towards fourth): 14%</td>
</tr>
<tr>
<td>▪ Large, fleshy hands: 68%</td>
<td>▪ Smooth and thin philtrum (upper lip) with loss of cupid’s bow</td>
</tr>
<tr>
<td>▪ Mild dysmorphic facial features</td>
<td></td>
</tr>
<tr>
<td>▪ Prominent, poorly formed ears: 65%</td>
<td></td>
</tr>
<tr>
<td>▪ Pointed chin: 62%</td>
<td>▪ High forehead</td>
</tr>
<tr>
<td>▪ Dolicocephaly (elongated head): 57%</td>
<td>▪ Fair skin</td>
</tr>
<tr>
<td>▪ Ptosis (droopy eyelids): 57%</td>
<td>▪ Puffy eyelids and deep set eyes</td>
</tr>
<tr>
<td>▪ Increased tolerance to pain: 86%</td>
<td>▪ Long eye lashes</td>
</tr>
<tr>
<td>▪ Tendency to overheat and lack of perspiration: 51%</td>
<td>▪ Full cheeks</td>
</tr>
<tr>
<td>▪ Vision impairments resulting in reliance on peripheral vision and poor depth perception.</td>
<td>▪ Wide nasal bridge</td>
</tr>
<tr>
<td></td>
<td>▪ Full eyebrows</td>
</tr>
<tr>
<td></td>
<td>▪ Seizures: 27%</td>
</tr>
<tr>
<td></td>
<td>▪ Strabismus (lazy eye)</td>
</tr>
<tr>
<td></td>
<td>▪ Anomalies of the spine</td>
</tr>
</tbody>
</table>

Neurological Features of PMS. In the language domain most individuals with PMS have absent or severely delayed speech. In contrast to expressive speech, receptive vocabulary is a relative strength (Phelan et al. 2001). Some affected individuals are able to follow directions, respond to commands, and communicate using gestures, signs, and pictures. Cognitively, the majority of individuals with PMS have global developmental delays. Approximately 75% of individuals with PMS fall within the severe range of intellectual disability (ID; Phelan et al., 2001). Specifically, the average intellectual quotient (IQ) of a group of individuals with PMS with a mean chronological age (CA) of 86 months was below 40 on the cognitive domain of the Battelle Developmental Inventory (Newborg et al., 1984; Phelan et al., 2001). The average cognitive age equivalent of the group was 9.3 months. The 25% that fell in the mild to moderate range consisted of the youngest of the individuals sampled. Another study found that a group of children with PMS (CA= 33 months) had a mean age Intelligence Equivalence of 19.7 months on a parent interview measure used to assess child’s functional developmental level (Wilson et al., 2003). These findings suggest that severity of intellectual disability is negatively associated with age so that as individuals with PMS age, they show more severe intellectual disability.

Behavioral features of PMS. There is a paucity of data on the specific behavioral features of PMS. Most of the information available is derived from semi-structured interviews with families at support group meetings. According to interviews, behavioral characteristics shared by individuals with PMS include mouthing or chewing non-food items (70%), teeth grinding, tongue thrusting, hair pulling, and aversion to clothes (Phelan et al., 2001). However, some parents
report that their children tend to outgrow some of these behaviors as do children with autism (Shattuck et al., 2007). The aim of the current study is to further the behavioral profile of individuals with PMS to improve diagnostic accuracy of PMS and increase the identification of individuals with comorbid PMS and ASD.

**Autistic behavior.** Prior to the development of the FISH test, some children with PMS who meet the Diagnostic and Statistic Manual of Mental Disorders- Fourth Edition (DSM-IV) criteria were diagnosed with autism (e.g., Goizet et al., 2000; Hensen et al., 1977; Prasad et al., 2000). In general, autistic disorder is an autism spectrum disorder characterized by impaired social interaction, communication, and by restricted and repetitive behavior that must be present before a child is three years old (DSM-IV; American Psychiatric Association, 1994). Autism or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) is characterized by impairment in two of the three DSM-IV criteria for autism spectrum disorder listed above.

Clinical and epidemiological studies indicate that genetic disorders are associated with 10% to 11% of ASD cases (Fombonne, Du Mazaubrun, Cans, & Grandjean, 1997; Gilleberg & Coleman, 1996). The genetic disorders associated with autism include fragile X syndrome, Angelman syndrome, Down syndrome, duplications of 15q11-q13, and PMS (see Cohen et al., 2005 for a review). Due to the present low prevalence rates of PMS, the exact percentage of autism cases attributed to this chromosomal abnormality is not known.

One review estimated that 10% of individuals with PMS show severe autism with no language, yet this rate is questionable given a paucity of empirical
### Table 2

**Autistic Behavior among Individuals with PMS**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansen, Brask, Nielsen, Rasmussen, and Sillesen (1977)</td>
<td>Case study</td>
<td>Unstructured</td>
<td>Deficits in social interaction, ritualistic behavior patterns, and severe language delay with echolalia (prior to 5 years old)</td>
</tr>
<tr>
<td>Rasmussen and Sillesen</td>
<td>Female 14 years old</td>
<td>Clinical Interviews</td>
<td>Severe lack of social interaction, shared attention, and absence of social initiation games; he also showed restricted and repetitive patterns of behavior and arm movements.</td>
</tr>
<tr>
<td>Assumpcao (1998)</td>
<td>Male 13 years old</td>
<td>DSM-IV</td>
<td>Delayed and abnormal functioning was noticed in social interaction, language, and symbolic play before her third birthday</td>
</tr>
<tr>
<td>Goizet et al. (2000)</td>
<td>Female 14 years old, PMS</td>
<td>DSM-IV</td>
<td>Delayed and abnormal functioning was noticed in social interaction, language, and symbolic play before her third birthday</td>
</tr>
</tbody>
</table>
Table 2 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacLean, Teshima, Szatmari, and Nowaczyk (2000)</td>
<td>Case study</td>
<td>Clinical Interview</td>
<td>– Deficits in social interaction, communication and significant repetitive behaviors</td>
</tr>
<tr>
<td>Male</td>
<td>Male</td>
<td>DSM III-R diagnostic criteria and ADI-R</td>
<td></td>
</tr>
<tr>
<td>11 years old</td>
<td>11 years old</td>
<td>Clinical Interview</td>
<td>– Difficulties in the areas of social interaction, communication, and behavior consistent with a pervasive developmental disorder</td>
</tr>
<tr>
<td>Ring 22</td>
<td>Ring 22</td>
<td>DSM-IV criteria and Childhood Autism Rating Scale (CARS)</td>
<td></td>
</tr>
<tr>
<td>Prasad et al. (2000)</td>
<td>Case studies</td>
<td>Clinical Interview</td>
<td>– 17 scored moderate to severe autistic PMS</td>
</tr>
<tr>
<td>Phelan (2001)</td>
<td>N = 18</td>
<td>CARS</td>
<td>– 6 showed lack of socialization and repetitive self-stimulatory actions</td>
</tr>
<tr>
<td>Manning et al. (2004)</td>
<td>N = 11</td>
<td>Unstructured Clinical Interview</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 (*continued*)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philippe et al. (2008)</td>
<td>N = 8</td>
<td>ADI-R PMS</td>
<td>– 0 met criteria for autistic disorder according to ADI-R criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– Met cut off on reciprocal social interaction, play and communication</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– 12 were previously diagnosed with autism</td>
</tr>
</tbody>
</table>
data (Cohen et al., 2005). As reported previously in Table 2, the majority of data on autistic behavior in PMS is derived from case studies describing autistic traits among children and adults or studies that rely on clinical descriptions and screening questionnaires (Assumpcao, 1998; Goizet et al., 2000; Hansen, Brask, Nielsen, Rasmussen, & Sillesen, 1977; MacLean, Teshima, Szatmari, & Nowaczyk, 2000; Prasad et al., 2000).

In one study, six out of 11 patients with PMS showed autistic-like behaviors, namely lack of socialization and repetitive self-stimulatory actions (Manning et al., 2004). However, this study included only 11 participants with PMS and relied on unstructured clinical interviews with parents for descriptions of autistic features. Another study reported that 17 of 18 participants with PMS, scored in the moderate to severe autistic range on the *Childhood Autism Rating Scale* (CARS; Schopler, Reichler & Rochen Renner, 1993; Phelan et al., 2001), a diagnostic screening tool. Similarly, 23 out of 27 individuals with PMS scored above the cut-off of 15 on the *Social Communication Questionnaire* (SCQ; Berument, Rutter, Lord, Pickles, & Bailey, 1999; Jefferies et al., 2005), suggestive of a clinical diagnosis of autism. Of the 23 who meet the cut-off for autism, 12 had been previously diagnosed with autism. Few studies have directly examined the autistic behavior among a large group of individuals with PMS using comprehensive diagnostic assessment tools such as the ADI-R. Along with Autism Diagnostic Observation Schedule (Lord et al., 1989), the ADI-R is also referred to as the “gold standard” in diagnostic evaluations of autism.
Only one study to date has assessed autism among children with PMS using a comprehensive measure of autism (ADI-R). None of the eight participants in this study met criteria for autistic disorder on the ADI-R (Philippe et al., 2008). Specifically, participants met the ADI-R cut-off for the domains of reciprocal social interaction, play and communication, but none met the cut-off in the area of repetitive behaviors and stereotyped patterns and thus did not meet DSM-IV criteria for autistic disorder. Significant difficulties were reported for the following individual ADI-R diagnostic algorithm items: articulation trouble, paucity of mimicry, absence of offers to share, failure to develop peer relationships, unusual sensory behaviors, resistance to change personal routines, and response to trivial changes in the environment. Despite the paucity of research and mixed methods, these findings suggest that while individuals with PMS may not qualify for a diagnosis of autistic disorder (adherence to all three DSM-IV core criteria), autism (adherence to two out three of the core DSM-IV criteria) is a significant aspect of the PMS phenotypic profile worthy of further investigation.

Recent neurobiological findings also support a relationship between PMS and autism. Specifically, recent findings show that deletions and duplications on chromosome 22q13.3 are found among individuals with autism (Vorstman et al., 2006). One study identified 22q13 abnormalities in 3 of 227 children diagnosed with autism (Durand et al., 2007). Moreover, SHANK3, which is one of the major genes affected in individuals with PMS, is also disrupted in approximately 1% of individuals with autism (Durand et al., 2007; Bonaglia et al., 2001; Moessner et al., 2007, Wilson et al., 2003). The SHANK3 gene produces proteins
necessary to construct synapses in the brain and when disrupted, like in children with PMS and autism, results in severe cognitive delays, language delays, and social communicative deficits (Durand et al., 2007; Jefferies et al., 2005). The haploinsufficiency of SHANK3 protein may also play a pivotal role in the developmental regression (skill loss) reported in children with PMS (see Wilson et al., 2003). Further study into the role of SHANK3 in the regression of skill among individuals with autism and individuals with PMS is required.

**Developmental Regression in PMS and Autism**

Children with PMS show regression in language and non-language skills (Cusmano-Ozog et al., 2007; Manning et al., 2004; Wilson et al., 2003). A total of 17 out of 48 parents interviewed (semi-structured) reported that their child with PMS experienced significant skill regression (Wilson et al., 2003). Specifically, parents observed their child to show progress in a trained skill over a few weeks or months, and then experience a sudden and complete loss of skill. This regression occurred in the absence of a neurodegenerative condition such as EEG evidence of increased seizure activity. The skill loss was reported to be permanent for some individuals and slow to recover for others.

A total of four out of 11 individuals with PMS were identified with regression in skills (Manning et al., 2004). Two of the four individuals showed loss of motor skills and two others showed loss of language. Children with PMS develop limited language such as babbling or limited vocabulary before they show language regression (Cusmano-Ozog et al., 2007). Moreover, the language lost among individuals with PMS may be limited to monosyllabic repetition (Goizet et al., 2000; Philippe et al., 2008).
A recent study revealed that two of eight individuals with PMS who used at least five words by 15 to 18 months, lost these words for many months, and then recovered those words lost (Philippe et al., 2008). This was the only study to date that used a standardized measure, the ADI-R, to assess for regression in skill among individuals with PMS, albeit with a small sample size. More studies are needed to identify the prevalence of developmental regression in individuals with PMS using a standardized measure such as the ADI-R to validate anecdotal reports. It is unknown whether the PMS regression is similar to autistic regression in terms of type, onset, duration, and relationship to illness. This information would also add to the behavioral profile of individuals with PMS and further clarify the link between autism and PMS.

Although autism is not the only condition in which regression occurs, it is the most common (Luyster et al., 2005; Shinnar et al., 2001). Over the past 40 years the phenomenon of developmental regression in autism has been documented to occur at a rate of 15% to 50%, with conservative estimates at 25% (Lord, Shulman, & DiLavore, 2004). See Table 3 for a chronological listing of studies that report prevalence rates of regression among children with autism. Although the rate of regression in autism may be variable across studies, regression (i.e., word loss and non-language skill loss) is specific to children with autism when compared to atypical developmental trajectories other than autism (i.e., Down syndrome and idiopathic developmental delay) and typical development (Lord et al., 2004; Luyster et al., 2005; Werner & Dawson, 2005, Werner, Dawson, Munson, & Osterling, 2005). As a group, children with autism are more likely than dysphasic children to have a history of regression of language
Table 3

*Prevalence of Developmental Regression in Autism*

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Description</th>
<th>Diagnostic Criteria</th>
<th>Regression Rate (~%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creak (1964)</td>
<td>N = 100 Infantile Psychosis</td>
<td>Maternal Interview</td>
<td>25% - Developmental setback</td>
</tr>
<tr>
<td>Wolff and Chess (1964)</td>
<td>N = 14 Early Infantile Autism</td>
<td>Maternal Interview</td>
<td>50% - Developmental setback</td>
</tr>
<tr>
<td></td>
<td></td>
<td>School Records</td>
<td></td>
</tr>
<tr>
<td>Lotter (1966)</td>
<td>N = 32 Autistic Disorder</td>
<td>Medical records</td>
<td>31% - Developmental setback</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parent Interview</td>
<td></td>
</tr>
<tr>
<td>Wakabayashi (1974)</td>
<td>N = 116 Infantile Autism</td>
<td>Medical records</td>
<td>22% - “Retrogressive shift with speech</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>disappearance”</td>
</tr>
<tr>
<td>Kurita (1985)</td>
<td>N = 261 Infantile Autism</td>
<td>Clinical Charts</td>
<td>37% - Speech/Gesture Loss</td>
</tr>
<tr>
<td>Taylor et al. (2002)</td>
<td>N = 278 Autism</td>
<td>Clinical Notes</td>
<td>25% - Loss of speech or any behavior</td>
</tr>
<tr>
<td>Hoshino et al. (1987)</td>
<td>N = 80 Autism (divided into 2</td>
<td>Questionnaire</td>
<td>49% - Loss of expressive or receptive</td>
</tr>
<tr>
<td></td>
<td>acquired + 1 natal groups)</td>
<td></td>
<td>language, social behavior or self care skills</td>
</tr>
</tbody>
</table>
Table 3 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Description</th>
<th>Diagnostic Criteria</th>
<th>Regression Rate (~%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kobayashi and Murata (1998)</td>
<td>N = 179 Autistic Disorder</td>
<td>Maternal Interview</td>
<td>30% - Loss of words and/or loss of social interest</td>
</tr>
<tr>
<td>Davidovitch et al. (2000)</td>
<td>N = 40 Autism</td>
<td>Questionnaire</td>
<td>48% - Developmental regression</td>
</tr>
<tr>
<td>Fombonne and Chakrabarti (2001)</td>
<td>N = 96 Autism</td>
<td>ADI-R</td>
<td>16% - Definite or probable loss of skills in 1/7 language and non-language domains.</td>
</tr>
<tr>
<td>Goldberg et al. (2003)</td>
<td>N = 132 Autism</td>
<td>ADI-R + RSF Home</td>
<td>33% - Language Only, or Other Skills or Full Regression</td>
</tr>
<tr>
<td>Lord et al. (2004)</td>
<td>N = 96 Autism (n = 28 PDD)</td>
<td>ADI-R</td>
<td>25% - Word loss (combined Autistic and PDD group)</td>
</tr>
</tbody>
</table>
and behavior (Tuchman, Rapin, & Shinnar, 1991). When the early development of autistic symptoms is assessed, the presence of regression is consistently identified in a small, yet significant, proportion of children sampled. Although skill loss is not universal to ASD, it is a valid phenomenon in early development that may serve as an important clinical marker for this group of disorders.

Regression of skills for children with autism is most often associated with loss of language that occurs after a period of apparently normal development or following a period of slightly delayed development (Bernabei, Cerquiglini, Cortesi, & D’Ardia., 2007). Regression of skills for children with autism include loss of words, loss of nonverbal communication skills, decreased interest in the social environment, decreased cognitive function, and several other behaviors (Kobayashi & Murata, 1998; Kurita, 1985; Rogers & DiLalla, 1990; Tuchman & Rapin, 1997; Wilson, Djukic, Shinnar, Dharmani, & Rapin, 2003).

There is lack of consensus concerning the prevalence, measurement, development, and nature of the regression. The variability in the study of language regression can be explained to a large extent by lack of commonly shared diagnostic criteria of word loss and the lack of standardized tools for the assessment of regression in childhood (Bernabei, Cerquiglini, Cortesi, & D’Ardia, 2007). Most of the research on regression has been based on medical records, clinical notes, unstructured interviews, or originally developed questionnaires that rely on retrospective reports of parent’s recall of their child’s early development. The validity of retrospective assessment has always been a concern in the study of regression and in many other areas of developmental research. Specifically, over
time, parental reports of their child’s development may lose accuracy (Lord et al., 2004). However, the recent use of home videotapes to code skills and symptoms from infancy has confirmed the validity of retrospective parental reports of developmental regression (Rogers, 2004).

In response to the need for more standardized and reliable diagnostic criteria for regression, researchers have worked on the following assessment methods: a) improved interview techniques, which involve having parents recall events based on specific timelines or anchor points of important historical events such as birthdays, births, deaths (e.g., Early Development Interview; Werner & Dawson, 2005; Werner et al., 2005; b) the use of behavioral data from the coding of home videotapes of children’s 1st and 2nd birthdays (Goldberg et al., 2003; Werner & Dawson, 2005); and c) detailed behavioral questionnaires of children’s early development and symptom progression such as the ADI-R, the Regression Supplement Form (RSF; Goldberg et al., 2003), and the Early Development Questionnaire (EDQ; Ozonoff Williams, & Landa, 2005). However, the ADI-R is the only comprehensive clinical diagnostic instrument designed to assess skill loss in autism among children.

**Patterns of Adaptive Behavior among Individuals with PMS and Autism**

Some individuals with PMS develop some daily living skills and lose them over time. However, many individuals with PMS never adequately develop the skills necessary to adapt and function independently in their environment. Specifically, individuals with PMS show significant impairment in adaptive functioning (Phelan et al., 2001) as do the majority of individuals with autism with intellectual disability (Perry et al., 2009). According to the DSM-IV, the
three criteria required for an identification of intellectual disability are the following: a significantly below average IQ, concurrent significant impairment in two or more areas of adaptive behavior, and evidence that the limitations emerged prior 18 years of age (American Psychiatric Association, 1994). Adaptive behaviors are the personal, daily and social skills required to live independently and cope with changes in the environment. Specific adaptive behavioral domains include communication (receptive, expressive, and written), daily living (personal, domestic, and community), socialization (interpersonal, play, leisure, and coping skills), and Motor/Physical Skills (fine and gross). Adaptive behavior measures, such as the Vineland Adaptive Behavior Scale (VABS-II), are commonly used in the process of evaluation for intellectual disability and planning interventions for individuals with special needs (Sparrow, Cicchetti, & Balla, , 2005).

Specifically children with PMS show severe difficulties with eating, dressing, and toilet training (Phelan et al., 2001). However, not all individuals show impairments in these areas, deficit levels vary across individuals and may only be slow to progress. The fine and gross motor delays include the following skills: rolling, sitting (average 18 months), crawling (range 10 months to not at all), and walking occurs usually with unsteady gate at an average age of 27 months and ranges from 16 months to not at all (Prasad et al., 2000). Motor and self-care skill deficits may be related to the hypotonia (low muscle tone) experienced by most individuals with PMS.

Few studies have assessed the adaptive functioning of individuals with PMS using standardized measures. Of 56 patients with PMS assessed using the
Developmental Profile-II (DP-II; Alpern, Boll, & Shearer, 2000) and the Scales of Independent Behavior-Revised (SIB-R; Bruininks, Woodcock, Weatherman, & Hill, 1996) all were reported to have lower adaptive functioning compared to their chronological age (CA; Wilson et al., 2003). However, their adaptive functioning was comparable to their intellectual functioning as estimated by the Intelligence Equivalence (IE) Index of the DP-II. The IE, which is calculated from the academic scale of the DP-II, has shown moderate to high correlations with standard measures of intelligence (Malhi & Singhi, 2005). Another study used the VABS to assess for adaptive functioning found that 15 out of 20 individuals with PMS showed severe deficits (standard scores less than 40) and 5 out of 20 (the youngest of the sample) showed mild to moderate deficits with scores between 40 and 70 (Phelan et al., 2001). The highest age equivalent on the VABS was 18 months for a sample of 20 individuals, well below the group’s mean CA of 7 years 2 months. Moreover, these individuals with PMS showed significantly below average Daily Living skills (i.e., eating, dressing, and toilet training) beyond what would be expected given their developmental level (Phelan et al., 2001). Finally, case studies of patients with PMS showed weaker communication skills than socialization and daily living skills (Bonaglia et al., 2001; Bonaglia et al., 2006; Goizet et al., 2000)

Whether some individuals with PMS show similar patterns of adaptive functioning as do individuals with autism is unclear. An assessment of adaptive functioning in children with PMS who meet criteria for autism would help determine whether an “autistic profile” of adaptive behavior emerges among this syndrome. Recognition of an autistic profile of adaptive skills among individuals
with PMS may assist in distinguishing individuals comorbid with ASD and PMS and individuals with PMS only.

The abundant research on the adaptive functioning of children and adults with autism suggests that individuals with autism consistently show lower adaptive functioning than CA and IQ matched individuals with ID without autism (Burack & Volkmar, 1992; Carpentieri & Morgan, 1996; Lord & Schopler, 1989a; Perry et al., 2009), and typically developing children (Rodrigue, Morgan & Geffken, 1991). Children with autism show a distinctive profile of adaptive functioning as measured by the VABS. Specifically, children with autism show severe deficits in the domain of socialization (e.g., Carpentieri & Morgan, 1996; Liss et al., 2001; Loveland & Kelley 1991; Rodrigue, et al., 1991; Volkmar et al. 1987), moderate deficits in the domain of communication (Carpentieri & Morgan, 1996; Stone et al., 1999; VanMeter, Fein, Morris, Waterhouse, & Allen, 1997; Vig & Jedrysek, 1995), and relative strength in Daily Living and Motor skills (Bolte & Poustka, 2002; Carter et al., 1998; Malhi & Singhi., 2005).

The adaptive functioning profiles of children with autism also show greater variability among adaptive domains than children with ID, particularly for children with autism with an intellectual quotient (IQ) lower than 50 (Burack & Volkmar, 1992; Rodrigue et al., 1991; VanMeter et al., 1997). Variability in patterns of adaptive behavior functioning among children with autism can also be understood in the context of age. Specifically, older individuals with autism show more deficits than their younger counterparts in the areas of Daily Living, Socialization and Fine Motor skills (Carter et al., 1998; Lord & Schopler, 1989b; Pandey et al., 2008). Similarly, younger children (five to 12 years old) with
autism produce higher scores in the area of Daily Living than CA matched children with ID (Jacobson & Ackerman, 1990), while adults with autism show lower scores in the Daily Living domain than adults with ID. A study that did not include pre-pubescent participants did not find any age-related differences in the pattern of adaptive behavior across groups (Schatz & Hamdan-Allen, 1995). These results shed light on the developmental course of adaptive behaviors in autism. As individuals with autism age past puberty they make fewer gains in adaptive skills than children with other developmental disorders.

Knowledge of age-related changes of adaptive behaviors is in PMS is unclear. One study by Phelan et al., suggested that younger individuals with PMS show less severe impairment in adaptive functioning than older individuals (2001). However, the younger and older groups were uneven in sample size; 5 younger to 20 older individuals thus limiting the validity of group comparisons. Studies are needed that assess age-related differences in adaptive functioning among a large sample of children, adolescents and adults affected by PMS to highlight the developmental course of adaptive skills. Moreover, no studies have looked at differences in adaptive functioning among individuals with PMS with and without autism. Such studies would determine whether comorbid PMS and autism put individuals with PMS at higher risk of severe adaptive deficits. These studies would help identify critical period of growth and decline in skills for this population that may help target intervention and inform program planning.

**Psychiatric Symptoms among Children with PMS and Autism**

Individuals with developmental disorders such as PMS and autism will experience a myriad of social emotional difficulties over the course of their lives.
Approximately 40% of a sample of 545 children with intellectual disability (ID; IQ < 80) ages four to 18, experience severe behavioral or psychiatric disorder (Einfeld & Tonge, 1996; McCarthy, 2007; Tonge & Einfeld, 2000). Other research indicates that children with ID have approximately three to four times higher levels of psychopathology than typically developing children (Einfeld et al., 2006; Dekker, Koot, van der Ende, & Verhulst, 2002). Moreover, children with autism have a higher overall frequency of psychopathology than children with ID without autism (Brereton, Tonge, & Einfeld, 2006).

Specifically, 41% of children with autism met criteria for an impairing co-morbid psychiatric disorder based on a mental health interview (Dekker & Koot, 2003). Moreover, 72% of the children and adolescents with autism met criteria for at least one DSM-IV Axis I disorder; clinical disorders, including major mental disorders, as well as developmental and learning disorders (Leyfer et al., 2006).

Among the most common of co-morbid psychiatric difficulties in children with autism are symptoms of anxiety and depression (Howlin, 2000; Kim, Szatmari, Bryson, Streiner, & Wilson, 2000; Lainhart, 1999; Simonoff, Pickles, Charman, Chandler, & Baird, 2008; Tantam, 2000). In addition, youths with mood or anxiety disorders exhibited higher autism scores (Pine, Guyer, Goldwin, Towbin, & Leibenluft, 2008). Autism symptom scale scores also showed an association with level of impairment (on the Children’s Global Assessment Scale), and attention deficit/hyperactivity disorder (Shaffer et al., 1983).

Research on autism has consistently indicated higher prevalence of attention-deficit/hyperactivity disorder (Gadow, DeVincent, Pomeroy, 2006; Leyfer et al., 2006), catatonia, and repetitive behaviors, tics, and Tourette’s syndrome relative to
children with ID who do not have autism (Carcani-Rathwell, Rabe-Hasketh, & Santosh, 2006; Lee & Ousley, 2006; Wing & Shah, 2006).

Although there is an abundance of evidence to suggest a high frequency of psychopathology among individuals with ID with and without autism, few measures have been developed to assess for dual diagnosis in children with ID. Dual diagnosis refers to the presence of psychiatric conditions among individuals with significant intellectual deficits. According to parent reports on the Child Behavior Checklist (CBCL), children with autism show a clinically significant level of affective (26%), anxiety (25%), attentional (25%), conduct (16%), oppositional (15%), and somatic problems (6%) (Kanne, Abbacchi, & Constantino, 1992; Lecavalier, 2006). The CBCL was developed for the general population to measure behavioral problems and is used to assess comorbidity in individuals with developmental disorders including autism. However, it has yet to be tested for reliability and validity in autism and other developmental disorders.

The Reiss Scales for children’s Dual Diagnosis (RSCDD; Reiss & Valenti-Hein, 1994) is a 60-item behavioral ratings questionnaire specifically designed to assess psychopathology in children and validated for such use. The RSCDD screens for the presence and severity of psychopathology in children with intellectual disability. This measure was designed to reflect essential criteria outlined in the DSM-III-R. The informant ratings produce 10 Psychometric Scales (e.g., depression, anxiety disorder, autism), 10 rare behaviors (e.g., crying spells, hallucinations) and a Total score which is a sum of all items. The Reiss Scales for children’s Dual Diagnosis indicates that children previously diagnosed with
autism show high scores on the Autism, Psychosis, and Withdrawal/Isolation Reiss scales (Reiss & Valenti-Hein, 1994). Moreover, high scores on the Reiss scales were associated with severity of ID and age.

A total of 583 children and adolescents with autism were screened using the Reiss child scales (Reiss, 1994). Individuals with mild to moderate ID had Total scores that were approximately one standard deviation higher than those with severe or profound MR. Significant differences were also revealed between lower and higher functioning groups on the Anger/Self Control, Anxiety Disorder, Autism, Conduct Disorder, and Somatoform behavior scales. In addition, children ages 11 to 21 years had significantly higher levels of Depression, Poor Self Esteem, and Withdrawal/Isolated psychometric relative to children between the ages of 4 and 10 years. Similarly, when compared to older children (> 4 years old) with developmental delay (DD), younger children with DD scored significantly lower on the Total score, and 8 of the 10 subscales of the RSCDD (Feldman, Hancock, Rielly, Minnes, & Cairns, 2000). These findings support previous reports that young children with ID show lower rates of psychopathology than adolescents and adults with developmental disorders (Reiss, 1985).

Children with autism show increased levels of psychiatric behavior (Brereton, Tonge, & Einfeld, 2006). There is evidence that individuals with PMS show similarly high levels of maladaptive behavior. Specifically, older individuals with ring chromosome 22 show significant behavioral disturbances such as severe hyperactivity, inattention, poor impulse control, and excited mood (Reeve et al., 1985; Sovner, Stone, & Fox, 1996). Moreover, hyperactivity and
excitable mood may put individuals with ring 22 chromosome at increased risk of developing atypical bipolar disorder such as rapid-cycling disorder and chronic mania (Goodwin & Redfield, 1990; Sovner et al., 1996). However, these studies were based on case studies of individuals with ring chromosomes, limiting the generalizability of the results (also see De Mas, 2002).

A recent study, which involved 36 individuals with simple 22q13.3 deletions (no ring 22), provided evidence for unstable mood, depressive symptoms, and overactivity based on the Children’s Interview for Psychiatric System (P-ChIPS; Weller, Weller, Fristad, Rooney, & Schecter, 2000), a parent interview that assesses 20 different DSM-IV Axis –I disorders (Shaw, Rahman, Sharma, 2011). The total sample also had elevated scores on the RSCDD. Specifically, individuals with PMS showed significant problems in the areas of Psychosis, Depression, Withdrawal, Attention-Deficit, and Autism. The sample scored highest on the Psychosis scale, significantly higher than the second highest score (i.e., Depression psychometric scale). Yet when the sample was split at the median age of 7 years 4 months, age related differences emerged. Individuals younger than the median age showed higher levels of autism than any other scale, while children older than the median showed higher levels of psychosis than any other scale of the RSCDD.

However, a study that included a developmental assessment of 56 patients with the PMS indicated that individuals with PMS showed fewer problematic behaviors (Wilson et al., 2003) than other children with moderate to severe intellectual disability (Hill & Bruininks, 1984). These results were based on a measure of self-harm, repetitive habits, withdrawal, uncooperative behavior,
socially offensive behavior, destruction of property, disruptive behaviors and harm to others. The mean CA of these patients was 33.9 months, which is much younger than the individuals with PMS reported to show significant behavioral disturbances in other studies (Philippe et al., 2008; Shaw, Rahman, & Sharma, 2011; Sovner et al., 1996).

A study that included individuals with telomeric 22q deletion (simple deletions and ring chromosomes) who ranged in age from one to 36 years, identified significant behavior disturbances in all of the 32 individuals sampled (Luciani et al., 2003). Specifically, these individuals showed behavioral disorders such as hyperactivity, sleep troubles, aggressive outbursts, or confusional states based on clinical observation and caregiver reports (Philippe et al., 2008). Moreover, the severity of behavior disturbance increased with age, regardless of the type of chromosomal abnormality (simple versus ring 22).

Research on the behavioral features of individuals with PMS is emerging. A well-defined behavioral phenotype specific to PMS will impact the underdiagnosis of affected individuals. The current study will contribute to expanding the behavioral profile of PMS by using standardized measures to examine autistic behavior, adaptive functioning, and psychiatric symptoms among a large sample of young and older individuals with PMS.

Research Objective and Goals

This study is the first to assess children previously diagnosed with PMS on standardized measures of autistic behavior, adaptive functioning and psychopathology concurrently. The overall objective of the study was to improve the description of the behavioral phenotype of PMS and to investigate a
behavioral link between PMS and autism. To achieve this objective the following goals were developed; a) to identify the percentage of individuals who have been previously diagnosed with ASD; b) to identify the percentage of children with PMS who show developmental regression (ADI-R); c) to identify a specific profile of autistic-like behaviors (ADI-R), adaptive behaviors (VABS-II), and psychiatric abnormalities (RSCDD) among children with PMS; and d) to examine the relationship between autistic behavior, adaptive functioning and maladaptive behavior to chronological age. Individuals with PMS who had been previously diagnosed with autism were compared with their non-autistic counterparts to assess for the impact of autism diagnosis on the behavioral presentation of individuals with PMS.

**Hypotheses of Current Study**

The current study includes the following hypotheses:

1. **Occurrence of autism among individuals with PMS.** At least 10% of children with PMS will have a previous diagnosis of ASD (Cohen et al., 2005). Moreover, it is expected that significantly more males would have a previous diagnosis than girls (Fombonne, 2003; Kanner, 1943; Wing, 1981)

2. **Profile of autistic behaviors in PMS.** Individuals with PMS will present with a specific subset of autistic behaviors. Specifically, the majority (50% or more) of individuals with PMS will show definite abnormality (code of 2 or 3) on ADI-R items related to reciprocal social interaction and play (e.g., offering to share, failure to develop peer relationships) and communication (e.g., Articulation/Pronunciation, Reciprocal Conversation, Spontaneous Imitation of Actions). Less than 50% of individuals with PMS will show definite
abnormality in the area of restricted and repetitive behavior (Philippe et al., 2008).

3. **Developmental regression among individuals with PMS.** Some proportion of individuals with PMS will show skill loss in the areas of language, non-verbal communication and motor skills (Wilson et al., 2003). Moreover, regression in skill will be reported more frequently among individuals with PMS and autism compared with individuals with PMS without autism.

4. **Adaptive functioning among individuals with PMS with and without autism.** Individuals with PMS and autism will show significantly lower levels of adaptive functioning on the VABS-II in the areas of socialization and communication than individuals with PMS without autism (Carpentieri & Morgan, 1996; Liss et al., 2001).

5. **Psychiatric behavior among individuals with PMS with and without autism.** Individuals with PMS and autism will show significantly higher levels of psychiatric behaviors on the RSCDD scales of attention-deficit, depression, anxiety, and withdrawal than children with PMS without autism (Carcani-Rathwell, Rabe-Hasketh, & Santosh, 2006; Lee & Ousley, 2006; Wing & Shah, 2006; Shaw et al., 2011).

6. **Age-related patterns of autistic symptoms, adaptive functioning, and psychiatric symptoms among individuals with PMS.** Younger individuals with PMS and autism will be more likely to demonstrate autistic behaviors on the ADI-R (Shattuck et al., 2007) and less deficits in adaptive functioning on the VABS-II than older individuals with PMS (Pandey et al., 2008). Younger individuals with PMS will also show higher levels of autism than any other
scale, while older children will show higher levels of psychosis than any other scale on the RSCDD (Shaw, Rahman, & Sharma, 2011).

**Method**

**Participants**

The current study includes a sample of 46 individuals with PMS ages 2 to 27 years with autism \( n = 21 \) and without autism \( n = 25 \) and their families. This sample represents approximately 10% of the known population of individuals diagnosed with PMS world-wide. A large age range was used to allow for an investigation of age-related changes in behavior. Older individuals provide vital information regarding the progression or deterioration of behavior with age, particularly with regards to changes in adaptive skill and the emergence of psychiatric symptoms post puberty.

The inclusion criteria for the current study were that participants had to have a of 22q13.3 deletion syndrome (e.g., FISH, CGH), and participants had to have received a diagnosis on the autism spectrum (e.g., autistic disorder, autism or PDD-NOS) from a medical, psychological, or educational professional, as reported by parents. Moreover, families of participants had to be English speaking in order to be interviewed with the ADI-R, which at the time of testing was only available for scoring in English. Exclusionary criteria for the current study included total blindness or deafness and a diagnosis of chronic epilepsy, Rett’s disorder, or childhood disintegrative disorder because their confounding effects on the assessment of autistic skill loss. However, none of the individuals who showed interest in the study fit the exclusionary criteria. As well, none of the participants presented with ring 22 or a mosaic presentation of PMS. Socio-
demographic characteristics such as chronological age and gender characteristics for participants with PMS with and without autism are presented in Table 4 (see pp. 49).

**Recruitment**

Participants were recruited through advertisements placed on the PMS deletion foundation website (http://www.22q13.org/), the PMS deletion foundation support group directory, and a 22q13.3 deletion foundation Yahoo chat group. Participating families were from various locations in Canada and the United States and Europe. Seventy-four families showed interest in the study by e-mailing the principal investigator for an information sheet and consent form. Forty-six families agreed to participate by completing the provided consent form. Of the 46 families who participated, all completed the demographic ADI-R interview \((n = 46)\), two did not return the VABS-II \((n = 44)\) and three did not return the RSCDD questionnaires \((n = 43)\).

**Materials**

**Demographic Questionnaire.** Although the other measures used to collect data (ADI-R) included rudimentary background questions, a Demographics Questionnaire was needed to obtain other more detailed information (see Appendix A). A Demographics Questionnaire was created in order to collect relevant information such as diagnostic history (e.g., 22q13.3 deletion syndrome and autism), family characteristics (i.e., people living in the household) and family history of mental health issues. Medical information was also collected in order to determine whether the child was taking medications or
suffered from any illness such as chronic epilepsy, and hearing or visual impairments.

**Autistic behavior.** The *Autism Diagnostic Interview-Revised* (ADI-R) was used to assess the presence of autistic behaviors among individuals with PMS (Lord et al., 1994). The ADI-R is a semi-structured parental interview designed to assess behaviors related to autism; to evaluate general functioning prior to onset of autism; and regression in both language and non-language skills.

The ADI-R focuses on behaviors that are rare in non-affected individuals; thus it does not provide scales (i.e., dimensions reflecting a continuum of some unitary underlying skill, trait, or ability) nor does it provide useful norms. The results are categorical (i.e., does or does not meet criteria). The ADI-R can be used to survey the needs of clinical population for which a relatively high rate of autism might be expected (i.e., children with severe language disorders, marked cognitive impairment, and those with neurological conditions commonly associated with autism (e.g., PMS, Fragile X syndrome).

The ADI-R contains 93 items that take approximately 1.5 to 2.5 hours to administer. The ADI-R assesses the following three domains of functioning based on criteria specified in the DSM-IV: a) Reciprocal Social Interaction and Play (RSIP), b) Language and Communication (LC), and c) Restricted Repetitive and Stereotyped Patterns of Behavior (RRSB). Some items provide qualitative data on age of developmental milestones (e.g., first walk) and age of onset of first developmental abnormality. The remaining items were coded with the following conventions: “0” if “behavior of the type specified in the coding is/was not present”; “1” if behavior of the type specified is/was present in an abnormal form.
(or “lack of behavior”), but not sufficiently severe, frequent, or marked to meet
criteria for “2”; “2” indicating “definite abnormality of the type specified
meets/met criteria given for that coding”; “3” indicating “severe abnormality of
the type specified and a more severe manifestation of “2” (ADI-R Manual; Rutter
et al., 2005, p. 10). For analyses purposes, scores of 3 were recoded to 2 on the
diagnostic algorithm forms, as recommended by Lord et al. (1994). All ADI-R
items/behaviors are coded for the “Current” time period which includes behavior
occurring in the last three months (see Rutter et al., 2005). The current behavior
algorithm form focuses on present functioning and is generally used for treatment
and educational planning. For the purposes of the current study, all behaviors
coded outside of the current period (last three months) have been labeled “past”
behavior (i.e., “ever”, “most abnormal 4 to 5 years”, “at 5 years”). The diagnostic
algorithm form used for autism diagnostic classification is based on
developmental history and thus only includes codes for “past” behavior.

According to the ADI-R scoring conventions (consistent with DSM-IV
criteria), a classification of autistic disorder is likely if a participant scores (on
diagnostic behavior algorithm) above the specified cut-off on all three of the
domains, and if deficits are reported to have presented before the age of 3 years
(Rutter et al., 2005, p. 34). If only two of the three main domain cut-offs are met
and deficits are reported to have presented behavior before the age of 3, then a
classification of autism or PDD-NOS is likely (Rutter et al., 2005, p. 34).

The ADI-R has demonstrated validity when used with subjects whose
mental age is 2 years 0 months or older (Lord, Storoschuk, Rutter, & Pickles,
1993). Although diagnostic validity is constrained, the ADI-R can be used
BEHAVIORAL FEATURES OF INDIVIDUALS WITH PMS

reliably to produce satisfactory detailed descriptions of behavior of children who do not meet the mental age cut-off. According to the ADI-R manual, when psychometric testing is not available, the Vineland Adaptive Scales can be used as a screening tool to assess developmental level (Rutter, Le Couteur, & Lord, 2003, p. 3). Given the severe level of impairment among individuals with PMS, it is more appropriate to use the ADI-R scores for descriptive rather than diagnostic purposes.

**Developmental regression.** The ADI-R also includes questions that address regression in skill among a variety of developmental areas (e.g., spoken language, nonverbal communication, social interest and responsiveness, play). Additional questions address whether skills development prior to loss age of onset for different types regression, and duration of loss. Skill loss can only be identified when the minimum requirement for use of skill (i.e., 5 or more words used spontaneously and consistently for a period of at least 3 months) and duration of loss (i.e., substantial or complete loss lasting at least 3 months) is established.

**Adaptive functioning.** The *Vineland Adaptive Behavior Scales-II* (VABS-II) Parent/Caregiver Rating Survey Form assesses personal and social skills required for daily living (Sparrow, Cicchetti, & Balla, 2005). The VABS-II can be used to measure adaptive functioning among individuals with intellectual disabilities, autism, or other special needs populations. The VABS-II can be completed by caregivers in 25 to 60 minutes (depending on the age of the child) and consists of 60 items. Each item is rated “2” (behavior is usually or habitually performed), “1” (sometimes or partly performed), or “0” (never performed). Raw
scores are converted to standard scores \((M = 100, \ SD = 15)\) are summed and an Adaptive Behavior Composite can be obtained. Age equivalents are also provided for the following domains and their associated subdomains: Communication (Receptive, Expressive, Written), Daily Living Skills (Personal, Domestic, Community); Socialization (Interpersonal Relationships, Play and Leisure Time, Coping Skills); and Motor Skills (Fine, Gross).

According to the VABS-II manual this instrument has demonstrated a high degree of internal reliability (split half coefficients ranged from .90 to .97 for domains and .98 to .99 for the Adaptive Behavior Composite), high criterion-related validity, and high construct validity (also see Bildt, Kraijer, Sytema, & Minderaa, 2005).

**Psychiatric symptoms.** The Reiss Scales for Children's Dual Diagnosis (RSCDD) screens for the presence and severity of psychopathology in children with intellectual disability (Reiss, 1994) ages 4 to 21 years. The instrument consists of 60 items that can be completed in approximately 20 minutes by caregivers or professionals. Each item includes an explanation and example of an abnormal behavior. Answer choices of no problem (0 points), problem (1 point), and major problem (2 points) are listed beneath each of the 60 descriptive items for circling by the parent. The Psychometric Scales include Anger/Self-Control, Anxiety Disorder, Attention-Deficit, Autism/Pervasive Developmental Disorder, Conduct Disorder, Depression, Poor Self-Esteem, Psychosis, Somatoform Behavior, and Withdrawn/Isolated. The item content of the Psychometric Scales was developed to reflect the definitions of psychiatric disorders in the DSM-III-R (American Psychiatric Association, 1988). A Total Score is also produced.
Meeting the specified cut-off standard on the RSCDD scales will indicate clinically elevated symptoms. Meeting the cut-off standard of the Total Score on the RSCDD indicates the presence of Dual Diagnosis; combined presence of intellectual disability and psychiatric symptoms.

The RSCDD measure was designed to reflect essential criteria outlined in the DSM-III-R and has demonstrated a high degree of internal reliability (Cronbach's alpha of 0.91 to 0.92) and good factor-content validity, and factor loadings of 0.42 to 0.83 (Havercamp & Reiss, 1997; Prout., 1993; Reiss & Valenti-Hein, 1994). Along with the ADI-R, the RSCDD will provide a complete spectrum of maladaptive behaviors that occur with PMS and autism.

**Procedure**

Study packets were mailed to interested families who returned consent forms. Packets included the Demographics Questionnaire, the VABS-II, and the RSCDD. Upon receipt of the packet, participants were asked to call the principal investigator to schedule an appointment for the ADI-R interview. Twenty-six families completed the ADI-R in person at a biennial 22q13.3 deletion foundation conference in Greenville, South Carolina and twenty families completed the ADI-R over the phone with the principal investigator following the conference.

**Results**

All data was entered in the Statistical Package for the Social Sciences (SPSS). Table 4 includes information on gender, and the mean, standard deviation, and range for chronological age.
BEHAVIORAL FEATURES OF INDIVIDUALS WITH PMS

Table 4

*Frequency of Gender and Mean, Standard Deviation and Range for Chronological Age (in years) across Autism and No Autism Groups*

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>M (SD)</th>
<th>Range</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>21</td>
<td>9.8 (6.2)</td>
<td>2.1-27.0</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Non-Autism</td>
<td>25</td>
<td>8.4 (5.2)</td>
<td>2.1-22.1</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Total Sample</td>
<td>46</td>
<td>9.9 (5.7)</td>
<td>2.1-27.0</td>
<td>15</td>
<td>31</td>
</tr>
</tbody>
</table>

*Note:* The groups did not contain an equal number of boys and girls. However, there is some evidence that there is an overrepresentation of girls identified with PMS (Bourgeron & Durand, 2008).
Description of PMS Sample

**Percentage of autism diagnosis.** It was hypothesized that at least 10% of children with PMS will have a previous diagnosis of ASD (Cohen et al., 2005). The total sample included 46 participants with simple 22q13.3 deletion syndrome, 46% of which had a previous diagnosis of autism as reported by parents. The remaining 54% did not have a previous diagnosis of autism. A one-way analysis of variance was performed with group (autism, no autism) as the independent variable and the age measures as the dependent variables. The analysis revealed no significant group effect for chronological age, $F(1, 44) = .77, p = 0.39, \eta_p^2 = .02$, indicating that the autism and no autism groups are comparable in chronological age.

**Gender differences in autism diagnoses.** It was hypothesized that more males would have a previous ASD diagnosis than females and that boys would show a higher frequency of autistic behaviors on the ADI-R. A chi-square test revealed no significant difference between the frequency of males and females across groups, $\chi^2(1, 46) = 1.85, p = .17, \eta_p^2 = .17$. Although 60% of males with PMS and autism are males (40% females), gender is not significantly related to previous autism diagnosis.

**Acquisition of developmental milestones.** Tables 5 and 6 include the details of the mean, standard deviations, and range for age of first developmental abnormality and milestones for the PMS autism and PMS no autism group. Milestones are based on ADI-R items related to age of first developmental abnormality, independent walking, first single words, first phrases, and toilet
Table 5

*Mean, Standard Deviation and Range for Walking and Language Developmental Milestones (in months) across Autism and No Autism Groups*

<table>
<thead>
<tr>
<th>Group</th>
<th>Independent Walking</th>
<th>First Single Words</th>
<th>First Phrases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>M</td>
<td>Range (SD)</td>
</tr>
<tr>
<td>Autism</td>
<td>21</td>
<td>26</td>
<td>10-48 (12)</td>
</tr>
<tr>
<td>Non-Autism</td>
<td>22</td>
<td>27</td>
<td>12-88 (18)</td>
</tr>
<tr>
<td>Total Sample</td>
<td>43</td>
<td>26</td>
<td>10-88 (15)</td>
</tr>
</tbody>
</table>
Table 6

Mean, Standard Deviation and Range for Toilet Training Developmental Milestones (in months) across Autism and No Autism Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Daytime Bladder</th>
<th>Night Bladder</th>
<th>Bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>M</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>(SD)</td>
<td>(SD)</td>
<td></td>
</tr>
<tr>
<td>Autism</td>
<td>4</td>
<td>65</td>
<td>48-78</td>
</tr>
<tr>
<td></td>
<td>(13)</td>
<td>(13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0)</td>
<td>(0)</td>
<td></td>
</tr>
<tr>
<td>Total Sample</td>
<td>6</td>
<td>65</td>
<td>48-78</td>
</tr>
<tr>
<td></td>
<td>(10)</td>
<td>(10)</td>
<td></td>
</tr>
</tbody>
</table>
Table 7

Analysis of Variance for Onset of First Abnormality and Developmental Milestones

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>.01</td>
<td>44</td>
<td>.01</td>
<td>.01</td>
<td>.99</td>
<td>.01</td>
</tr>
<tr>
<td>Walking</td>
<td>12.94</td>
<td>41</td>
<td>12.94</td>
<td>.06</td>
<td>.82</td>
<td>.01</td>
</tr>
<tr>
<td>Single Words</td>
<td>63.82</td>
<td>31</td>
<td>63.82</td>
<td>.14</td>
<td>.72</td>
<td>.01</td>
</tr>
<tr>
<td>Phrases</td>
<td>48.06</td>
<td>12</td>
<td>48.06</td>
<td>.08</td>
<td>.78</td>
<td>.01</td>
</tr>
<tr>
<td>Toilet-Bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>3.00</td>
<td>4</td>
<td>3.00</td>
<td>.02</td>
<td>.89</td>
<td>.01</td>
</tr>
<tr>
<td>Toilet-Bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night</td>
<td>529.20</td>
<td>3</td>
<td>529.20</td>
<td>1.80</td>
<td>.27</td>
<td>.38</td>
</tr>
<tr>
<td>Bowel</td>
<td>226.71</td>
<td>5</td>
<td>226.71</td>
<td>1.24</td>
<td>.32</td>
<td>.20</td>
</tr>
</tbody>
</table>
training. A total of 16 participants across groups showed developmental abnormality from birth. The age of onset for first abnormality for the autism group is 7.88 months and 7.86 months for the no autism group. The most frequent early abnormal symptoms reported for the total sample were related to hypotonia, feeding difficulties, and reflux across groups. Three out of 46 participants were reported to not have achieved independent walking, 13 never achieved functional single word speech (i.e., spontaneous use of words used on a daily basis for at least three months), 32 never achieved phrase speech (i.e., spontaneous use of phrases including two or more words and usually including a verb used on a daily basis for at least three months), 40 never achieved toilet training for bladder in the daytime, 41 never achieved toilet training for bladder at nighttime, and 39 never achieved toilet training for bowels. Of the total sample, 37 participants were non-verbal and 9 were verbal. For the purpose of the ADI-R, verbal is defined as “the functional use of spontaneous, echoed, or stereotyped language that, on a daily basis, involves phrases of three words or more that at least sometimes includes a verb and are comprehensible to other people” (Rutter et al., 2003, p. 8).

**Group differences in developmental milestones.** As previously presented in Table 7, analyses of variance revealed no significant difference between groups for age of onset of first developmental abnormality and achievement of developmental milestones. Furthermore, a chi square test (Fisher exact test) revealed no significant difference between the frequency of verbal and non-verbal participants across groups, $\chi^2(1, N = 46) = 2.48$, $p = .15$, Cramer's $V = 0.23$. 
**Occurrence of Autism among Individuals with PMS**

Table 8 includes the frequency of participants who met the cut-off for each of the three ADI-R domains and details of the mean, standard deviation, range and mode for the total raw scores on the ADI-R domains.

**Percentage of individuals who met criteria for autism on ADI-R.**

Based on the ADI-R Diagnosis Algorithm, 67% of the total sample met ADI-R criteria for autistic disorder, 24% met criteria for autism, and 9% did not meet criteria for autism spectrum disorder. These results indicate that the ADI-R may over-represent the cases of autistic disorder among individuals with PMS. A total of 11 of 31 participants who met criteria for autistic disorder, were only one value above the cut-off for the RRSB domain. An additional 10 participants who met criteria for autism, were at the cutoff (3) for RRSB domain. The raw scores for the RSIP and LC domains were more widely distributed and not centered around the respective domain cut-off scores.

**Differences in ADI-R interview method.** A one-way analysis of variance was performed with interview method (in person, phone) as the independent variable and the ADI-R domain total raw scores as the dependent variables. The analysis revealed no significant group effect for interview method, indicating that individuals interviewed with the ADI-R in-person and by phone were comparable on ADI-R total raw scores across the domains of RSIP, $F(1, 44) = 3.22, p = .09, \eta^2_p = .08$; LC (verbal), $F(1, 44) = .06, p = .81, \eta^2_p = .01$; LV (non-verbal) $F(1, 44) = 1.07, p = .31, \eta^2_p = .03$; RRSB $F(1, 44) = .43, p = .52, \eta^2_p = .01$.
Table 8

*Descriptive Statistics and Cut-Off Values for ADI-R Domain Raw Scores across Groups*

<table>
<thead>
<tr>
<th>ADI-R Domains</th>
<th>RSIP</th>
<th>LC (Verbal)</th>
<th>LC (Non-Verbal)</th>
<th>RRSB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>AUT</td>
<td>N-AUT</td>
<td>TOT</td>
<td>AUT</td>
</tr>
<tr>
<td>n</td>
<td>21</td>
<td>25</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>(SD)</td>
<td>(5.85)</td>
<td>(6.97)</td>
<td>(6.78)</td>
<td>(7.07)</td>
</tr>
<tr>
<td>Range</td>
<td>8-30</td>
<td>4-28</td>
<td>4-30</td>
<td>11-21</td>
</tr>
<tr>
<td>Mode</td>
<td>25</td>
<td>11</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Cut-Off Values</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Frequency (cut-off)</td>
<td>20</td>
<td>22</td>
<td>42</td>
<td>2</td>
</tr>
</tbody>
</table>

*Note.* AUT=Autism; N-AUT=No Autism; TOT=Total Sample.
**Group differences in ADI-R total raw score by group.** A multivariate analysis of variance was conducted to assess group differences for the total raw scores of the three ADI-R domains. Results of the analysis revealed a significant group differences for the RSIP domain, $F(1, 44) = 5.16, p = .03, \eta_p^2 = .13$. There were no significant group effects on the remaining ADI-R domains of LC (verbal), $F(1, 7) = .53, p = .49, \eta_p^2 = .07$, LC (non-verbal), $F(1, 35) = .62, p = .44, \eta_p^2 = .02$, and RRSB, $F(1, 44) = 2.99, p = .09, \eta_p^2 = .08$, indicating that the groups differed most on behaviors related to RSIP, and were more similar in their level of impairment in the domains of CL and RRSB.

To further examine group differences in ADI-R domain raw scores, Pearson correlations were performed for RSIP and LC domain raw scores and the VABS-II overall adaptive composite scores (ABC) scores by group (see Table 9). The correlations revealed negative associations between the VABS-II domains of Communication, Socialization, Daily Living, and Motor Skills for the no autism group only. Thus, a higher raw score (indicative of more impairment) for the ADI-R domains of communication and sociability is related to lower overall adaptive functioning for only the PMS no autism group.
Table 9

Correlations between ADI-R Domain Raw Scores and VABS-II Adaptive Behavior Composite (ABC)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RSIP</th>
<th>Verbal(^a)</th>
<th>Non-Verbal(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMS (no autism)</td>
<td>24</td>
<td>-.664**</td>
<td>-.776*</td>
</tr>
<tr>
<td>PMS (autism)</td>
<td>20</td>
<td>-.344</td>
<td>-</td>
</tr>
<tr>
<td>Total Sample</td>
<td>44</td>
<td>-.590**</td>
<td>-.769*</td>
</tr>
</tbody>
</table>

Note: Higher ADI-R domain raw scores are indicative of more impairment in behavior. Higher ABC scores are indicative of less impairment in adaptive functioning.

\(^a\)Autism verbal \(n = 2\); No autism verbal \(n = 7\).

\(^b\)Autism non-verbal \(n = 18\); No autism non-verbal \(n = 17\).

\(*p < .05\), two tailed.

\(**p < .01\), two-tailed.
Profile of Autistic Behavior in PMS

In order to assess the profile of autistic behaviors, percentages of definite or severe abnormality scores for each of the three ADI-R domains were calculated. Behavioral descriptions given by the caregiver are coded by the interviewers as 0 (no abnormality), 1 (possible abnormality), 2 (definite autistic-like abnormality), and 3 (severe autistic-like abnormality). Scoring conventions of the ADI-R specify that codes of 3 be treated as codes of 2 and given equal weight (2 points) on diagnostic algorithm form (see Rutter, Le Couteur, & Lord 2005, p. 10). Thus, for the analyses, the total number of 2 and 3 codes per item was divided by the total number of items coded for each of the three ADI-R domains. Unlike previous research (Philippe et al., 2008) the current study used all ADI-R items, not only those scored on the diagnostic algorithm in order to provide qualitative information on the range of autistic behaviors characteristic of PMS.

Percentage of individuals with definite abnormalities in RSIP: It was hypothesized that individuals with PMS would present with a specific subset of autistic behaviors. Specifically, it was expected that the majority (50% or more) of individuals with PMS would show abnormalities on ADI-R items related to RSIP, and LC and not in the area of RRSB (Philippe et al., 2008). As seen in Figure 1, for “past” behavior in the RSIP domain of the ADI-R, the majority (50% or more) of participants showed definite abnormality for behavior related to Showing and Directing Attention, Offering to Share, Seeking to Share Enjoyment, Appropriateness of Social Responses, Imitative Social Play, Interest in Children, Group Play with Peers, and Social Disinhibition (see Figure 1).
Percentage of individuals with definite abnormalities in LC: Within the LC domain certain items (e.g., social chat, reciprocal conversation, pronunciation) are relevant only for verbal subjects \((n = 9)\). As seen in Figure 2, for “past” behavior in the LC domain, the majority of participants showed definite abnormality for behaviors related to Comprehension of Simple Language, Articulation/Pronunciation (verbal only), Reciprocal Conversation (verbal only), Pronominal Reversal (verbal only), Pointing to Express Interest, Nodding, Head Shaking, Spontaneous Imitation of Actions, Imaginative Play, and Imaginative Play with Peers (see Figure 2).

Percentage of individuals with definite abnormalities in RRSB: As seen in Figure 3, for “past” behavior in the RRSB domain less no participants showed definite abnormality (codes of 2 or 3) for any items, suggesting lower incidence behavior within the RRSB domain for individuals with PMS (see Figure 3).
Figure 1. Reciprocal social interaction and play (RSIP). This figure illustrates the percentage of codes “2” or “3” on items in the RSIP domain.
Figure 2. Language and communication (LC). This figure illustrates the percentage of codes “2” or “3” on items in the Language and Communication domain.
Figure 3. Restricted repetitive and stereotyped patterns of behavior. This figure illustrates the percentage of codes “2” or “3” on ADI-R items in the RRSB domain.
Developmental Regression among Individuals with PMS

The following two ADI-R items were used to assess regression in skill: #11 Loss of language after acquisition (language) and #20 Loss of skills (non-language). These items were coded as “1” when “No Loss” was reported by caregivers and “2” when “Definite Loss” (duration of at least 3 months) had been reported. Percentages were calculated to identify the proportion of individuals who were reported as having lost (coded “2”) language and other skills.

Percentage of developmental regression. A proportion of individuals with PMS were hypothesized to show skill loss in the areas of language, non-verbal communication and motor skills (Manning et al., 2004; Philippe et al., 2008; Wilson et al., 2003). Language loss on the ADI-R includes loss of the following skills: five or more meaningful words, communicative intent, syntactical skills, and articulation. Of the total sample of 46 participants, 22% or 10 were reported to have experienced loss in language skills, 50% of which were associated the loss with illness. None of the families associated loss with impaired consciousness/epileptic attacks or other definite evidence of meningeval or encephalitic involvement. The mean age of onset for language loss was 62 months ($SD = 45$) with a range of 13 to 172 months. Approximately seven individuals with language loss were reported to never have regained the skills lost and the remaining three individuals regained skills within 24 months. Eight of the ten individuals with reported language loss were also reported to have experienced loss in other (non-language) skills.
Other skill loss includes purposive hand movements, motor skills, self-help skills (e.g., feeding, dressing), constructive or imaginative play, and social engagement and responsiveness. Of the total sample, 37% or 17 were reported to have experienced other skill loss, 4% of which were associated with illness. None of the families associated loss with impaired consciousness/epileptic attacks or other evidence of meningeval or encephalitic involvement. Within the other skill loss domain, four participants showed definite motor skill loss. The mean age of onset for other skill loss was 62 months ($SD = 47$), with a range of 24 to 148 months. Of the 17 individuals with reported other skill loss, two showed continued progressive deterioration, nine were reported to never have regained skills lost, two were reported to have regained skills within two years, and three more regained other skills within eight and half years.

**Group differences in developmental regression by group.** Skill loss was hypothesized to be more frequent among individuals with PMS and autism compared to individuals with PMS without autism. A chi-square test (Fisher exact test) revealed no significant difference between the frequency of language skill loss across groups, $x^2(1, 46) = .97, p = .99$, Cramer’s $V = .20$, and other skill loss across groups, $x^2(1, 46) = 1.89, p = .17$, Cramer’s $V = .05$, indicating that language and other skill loss is not significantly related to autism diagnosis for individuals with PMS.

**Adaptive Functioning among Individuals with PMS with and without Autism**

**Mean of VABS-II raw scores by domain.** Table 10 includes the details of the mean, range and standard deviation for the VABS-II sub-domain age
Table 10

_Mean, Standard Deviation, and Range of Age Equivalents (AE) in Months for VABS-II Sub-domains for Total Sample (N = 44)_

<table>
<thead>
<tr>
<th>Domain</th>
<th>Mean AE</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Communication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receptive</td>
<td>22.84</td>
<td>24.66</td>
<td>1-132</td>
</tr>
<tr>
<td>Expressive</td>
<td>16.86</td>
<td>16.97</td>
<td>1-91</td>
</tr>
<tr>
<td>Written</td>
<td>31.93</td>
<td>16.74</td>
<td>22-93</td>
</tr>
<tr>
<td><strong>Daily Living Skills</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal</td>
<td>25.39</td>
<td>12.12</td>
<td>5-59</td>
</tr>
<tr>
<td>Domestic</td>
<td>29.00</td>
<td>26.00</td>
<td>7-101</td>
</tr>
<tr>
<td>Community</td>
<td>23.27</td>
<td>22.81</td>
<td>1-118</td>
</tr>
<tr>
<td><strong>Socialization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpersonal Relations</td>
<td>16.77</td>
<td>20.88</td>
<td>1-120</td>
</tr>
<tr>
<td>Play and Leisure Time</td>
<td>19.95</td>
<td>19.86</td>
<td>1-91</td>
</tr>
<tr>
<td>Coping Skills</td>
<td>24.52</td>
<td>19.70</td>
<td>1-103</td>
</tr>
<tr>
<td><strong>Motor Skills (N= 16)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross</td>
<td>24.93</td>
<td>10.74</td>
<td>4-47</td>
</tr>
<tr>
<td>Fine</td>
<td>27.45</td>
<td>14.86</td>
<td>4-68</td>
</tr>
</tbody>
</table>
equivalents for the total sample ($N = 44$). Table 11 includes details of the mean and standard deviation for the VABS-II domain standard scores (DSS) by group.

**Group differences in VABS-II domain standard scores.** Individuals with PMS with autism were hypothesized to show significantly lower levels of adaptive functioning on the VABS-II in the domains of socialization and communication than children with PMS without autism. Two multivariate analyses of variance (MANOVA) were conducted on the dependent variables of adaptive functioning (Stevens, 2002, p. 245). One MANOVA was conducted on the dependent measures that were hypothesized to show group differences (i.e., Communication, Socialization). A second MANOVA was conducted on the remaining dependent variables (Daily living Skills, Motor Skills). The first analysis revealed a significant difference between groups for Communication DSS, $F(1, 44) = 5.45, p = .02, \eta^2_p = .12$, and Socialization DSS, $F(1, 44) = 4.336, p = .04, \eta^2_p = .09$. Individuals with autism showed lower Socialization DSS, indicating lower adaptive functioning than individuals with PMS without autism in the areas of socialization and communication. There was no significant difference between groups on the DSS for the Adaptive Behavior Composite, $F(1, 42) = 3.77, p = .06, \eta^2_p = .12$; Daily Living Skills, $F(1, 42) = 2.60, p = .11, \eta^2_p = .06$; Motor domains of the VAB-II, $F(1, 42) = .71, p = .42, \eta^2_p = .05$. 

Table 11

Mean and Standard Deviation of Standard Scores for VABS-II Domains and Adaptive Behavior Composite by Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Communication</th>
<th>Daily Living</th>
<th>Socialization</th>
<th>Motor Skills</th>
<th>Adaptive Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism</td>
<td>24</td>
<td>54.42</td>
<td>17.39</td>
<td>55.25</td>
<td>16.84</td>
</tr>
<tr>
<td>Autism</td>
<td>20</td>
<td>43.70</td>
<td>11.92</td>
<td>47.70</td>
<td>13.60</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample</td>
<td>44</td>
<td>49.55</td>
<td>15.93</td>
<td>51.82</td>
<td>15.74</td>
</tr>
</tbody>
</table>
Psychiatric Symptoms among Individuals with PMS with and without Autism.

**Frequency of psychiatric symptoms by group.** Details of the frequency of individuals that met the cut-off value for each of the Psychometric Scales and total score by group is presented in Table 12. An individual is considered positive for dual diagnosis if one or both of the following conditions are met: The total score is 29 or higher or at least two of the ten Psychometric Scales have scores at or above the specified cut-off value of 5 or 6 (Reiss & Valenti-Hein, 1984). Dual diagnosis refers to the combined presence of intellectual disability and psychopathology. A total of 12 participants (six in the autism group and six in the no autism group) met criteria for dual diagnosis. Meeting criteria on the Psychometric Scales indicates clinically elevated psychiatric symptoms. The most frequent psychiatric symptom (above cut-off value) among the autism group \((n = 19)\) was Attention-Deficit. The most frequent psychiatric symptom among the no autism group \((n = 24)\) was Psychosis. The most frequent psychometric symptom among the total sample \((N = 43)\) was Psychosis, followed by Attention–Deficit, Withdrawal, and Anger/Self-Control.

**Mean of RCSDD raw scores by domain.** Details of the means and standard deviations for RSCDD Psychometric Scales are presented in Table 13.

**Group differences in RSCDD domain raw scores.** Individuals with PMS and autism were hypothesized to show a higher frequency of psychiatric behaviors on the RSCDD scales of Attention-Deficit, Depression, Anxiety
### Table 12

*Frequency of Individuals with PMS that Met Cut-off Values for the Psychometric Scales and Total Score by Group*

<table>
<thead>
<tr>
<th>Psychometric Scale</th>
<th>Frequency Met Cutoff Autism</th>
<th>Frequency Met Cutoff No Autism</th>
<th>Frequency Met Cut-Off Total Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anger/Self Control</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Attention-Deficit</td>
<td>7</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Autism/Pervasive</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Depression</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Poor Self Esteem</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Psychosis</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Somatoform Behavior</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawal/Isolated</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Total Score</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

*Note: Autism n = 19; No Autism n = 24; Total Sample N = 43*
Table 13

Mean and Standard Deviation for RSCDD Psychometric Scale Raw Scores by Group

<table>
<thead>
<tr>
<th>Behavior Scales</th>
<th>PMS- No Autism (n = 24)</th>
<th>PMS-Autism (n = 19)</th>
<th>Total Sample (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>Anger/Self Control</td>
<td>2.79</td>
<td>2.06</td>
<td>3.21</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>0.54</td>
<td>1.38</td>
<td>0.84</td>
</tr>
<tr>
<td>Attention-Deficit</td>
<td>2.96</td>
<td>2.16</td>
<td>4.84</td>
</tr>
<tr>
<td>Autism/Pervasive</td>
<td>1.75</td>
<td>1.80</td>
<td>2.63</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>0.58</td>
<td>1.21</td>
<td>1.58</td>
</tr>
<tr>
<td>Depression</td>
<td>0.75</td>
<td>0.79</td>
<td>2.47</td>
</tr>
<tr>
<td>Self Esteem</td>
<td>0.37</td>
<td>0.82</td>
<td>0.63</td>
</tr>
<tr>
<td>Psychosis</td>
<td>3.08</td>
<td>1.93</td>
<td>2.89</td>
</tr>
<tr>
<td>Somatoform Behavior</td>
<td>0.42</td>
<td>1.10</td>
<td>0.37</td>
</tr>
<tr>
<td>Withdrawal/Isolated</td>
<td>1.88</td>
<td>2.54</td>
<td>3.79</td>
</tr>
</tbody>
</table>
Disorder, and Withdrawal/Isolated than individuals with PMS without autism.

Two MANOVAs were conducted to assess group differences on RSCDD Psychometric Scales (Stevens, 2002, p. 245). One MANOVA was conducted on the dependent measures that were hypothesized to show group differences (i.e., Attention-Deficit, Depression, Anxiety Disorder, Withdrawal/Isolated). A second MANOVA was conducted on the remaining dependent variables (i.e., Anger/Self-Control, Autism/Pervasive, Conduct Disorder, Poor Self Esteem, Psychosis, Somatoform Behavior). The first analysis revealed a significant difference between groups, $F(1, 44) = 4.14, p < .01$. Specifically, group differences were identified on the psychometric scale of Attention-Deficit, $F(1, 44) = 8.14, p < .01$, $\eta_p^2 = .17$, Depression, $F(1, 44) = 14.48, p < .01, \eta_p^2 = .26$, and Withdrawal/Isolated, $F(1, 44) = 5.42, p = .03, \eta_p^2 = .12$. The first analysis revealed no significant difference between groups on the scale of Anxiety Disorder, $F(1, 42) = .53, p = .47, \eta_p^2 = .01$. These results indicate that individuals with PMS and autism showed more behaviors related to Attention-Deficit, Depression and Withdrawal/Isolated compared to the PMS with no autism group. The second analysis revealed no significant difference between groups for the remaining Psychometric Scales: Anger/Self Control, $F(1, 42) = .32, p = .58, \eta_p^2 = .17, \eta_p^2 = .01$; Autism/Pervasive, $F(1, 42) = 1.98, p = .17, \eta_p^2 = .05$; Conduct Disorder, $F(1, 42) = 3.64, p = .06, \eta_p^2 = .08$; Poor Self Esteem, $F(1,42) = .53, p = .47, \eta_p^2 = .01$; Psychosis, $F(1, 42) = .14, p = .71, \eta_p^2 = .01$; Somatoform/Isolated, $F(1,42) = .02, p = .90, \eta_p^2 = .01$. 
To further examine group differences in RSCDD psychometric scale raw scores, Pearson correlations were performed for RSCDD raw scores for the Attention-Deficit, Depression and Withdrawal/Isolated Psychometric Scales and the VABS-II overall adaptive composite scores (ABC) scores by group (see Table 14). The correlations revealed no significant associations for the autism group and no autism group.

**Age-related Patterns of Autistic Behavior, Adaptive Functioning, and Psychiatric Symptoms in PMS**

**Correlations between ADI-R domain standard scores and chronological age.** Younger individuals with PMS were hypothesized to be more likely to demonstrate autistic behaviors on the ADI-R domains than older individuals with PMS (Shattuck et al., 2007). Pearson correlations were performed for chronological age and ADI-R *current behavior* domain raw scores. For individuals 10 years, 0 months or older many items on the *current behavior* algorithm are no longer applicable in the RSIP and LC domains. Thus, correlations were calculated for individuals younger than 10 years, 0 months across groups (see Table 15). The correlations revealed no significant association for chronological age and ADI-R domain raw scores for individuals younger than 10 years old with and without autism.

**Correlations between VABS-II scores and chronological age.** Younger individual with PMS and autism were hypothesized to show less deficits in adaptive functioning on the VABS-II than older individuals with PMS and autism (see Pandey et al., 2008). Pearson correlations were performed for chronological
age and VABS-II subdomain standard scores for the autism and no autism groups (see Table 1). The correlations revealed significant negative associations between the VABS-II domains of Communication, Daily Living, Socialization, Motor Skills, ABC and chronological age (CA) for the autism group and no autism group. Specifically, as individuals with PMS with and without autism age past puberty they make fewer gains in adaptive skills (see Figures 4-8).
Table 14

*Pearson Correlations between VABS-II ABC and RSCDD Psychometric Scales*

<table>
<thead>
<tr>
<th>Psychometric Scale</th>
<th>No Autism (n = 24)</th>
<th>Autism (n = 19)</th>
<th>Total Sample (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention-Deficit</td>
<td>-.198</td>
<td>.307</td>
<td>-.116</td>
</tr>
<tr>
<td>Depression</td>
<td>-.041</td>
<td>-.310</td>
<td>-.298</td>
</tr>
<tr>
<td>Withdrawal/Isolated</td>
<td>-.242</td>
<td>-.030</td>
<td>-.234</td>
</tr>
</tbody>
</table>
Table 15

*Correlations between Chronological Age and ADI-R Domain Raw Scores for Individuals Younger than 10 Years Old*

<table>
<thead>
<tr>
<th>ADI-R Domain</th>
<th>Language Communication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RSIP</td>
</tr>
<tr>
<td>Chronological Age</td>
<td>n</td>
</tr>
<tr>
<td>PMS (no autism)</td>
<td>16</td>
</tr>
<tr>
<td>PMS (autism)</td>
<td>12</td>
</tr>
<tr>
<td>Total Sample</td>
<td>28</td>
</tr>
</tbody>
</table>

*Note:* Higher ADI-R domain raw scores are indicative of more impairment in behavior.

<sup>a</sup>Autism verbal n = 0; No autism verbal n = 4.  
<sup>b</sup>Autism non-verbal n = 12; No autism non-verbal n = 12.  
*p < .05, two tailed.*
Table 16

*Correlations between Chronological Age and VABS-II Domain Standard Scores*

<table>
<thead>
<tr>
<th>VABS-II Domain</th>
<th>Communication</th>
<th>Daily Living</th>
<th>Socialization</th>
<th>Motor Skills(^a)</th>
<th>ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronological Age</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMS- No Autism</td>
<td>24</td>
<td>-.628**</td>
<td>-.703**</td>
<td>-.662**</td>
<td>-.703</td>
</tr>
<tr>
<td>PMS- Autism</td>
<td>20</td>
<td>-.562**</td>
<td>-.728**</td>
<td>-.771**</td>
<td>-.196</td>
</tr>
<tr>
<td>Total Sample</td>
<td>44</td>
<td>-.574**</td>
<td>-.699**</td>
<td>-.683**</td>
<td>-.568*</td>
</tr>
</tbody>
</table>

*Note:* ABC = Adaptive Behavior Composite; \( N = 44 \). Higher VABS-II scores are indicative of less impairment in adaptive functioning.

\(^a\)Motor Skills autism \( n = 8 \); Motor skills no autism \( n = 8 \).

*\( p < .05 \), two tailed. **\( p < .001 \).*
Figure 4. VABS-II Communication domain and chronological age. This figure illustrates the results of a Pearson correlation for VABS-II Communication domain standard score and chronological age in years ($r = -.574$).
Figure 5. VABS-II Daily Living Skills domain and chronological age. This figure illustrates the results of a Pearson correlation for VABS-II Daily Living Skills domain standard score and chronological age in years ($r = -.699$).
Figure 6. VABS-II Socialization domain and chronological age. This figure illustrates the results of a Pearson correlation for VABS-II Socialization domain standard score and chronological age in years ($r = -.683$).
Figure 7. VABS-II Motor Skills domain and chronological age. This figure illustrates the results of a Pearson correlation for VABS-II Motor Skills domain standard score and chronological age in years ($r = -.568$).
Figure 8. VABS-II Adaptive Behavior Composite and chronological age. This figure illustrates the results of a Pearson correlation for VABS-II Adaptive Behavior Composite standard score and chronological age in years ($r = -0.673$).
Psychiatric symptoms in younger versus older individuals with PMS. Individuals with PMS younger than 7 years 4 months were expected to show higher levels of autism than any other scale, while children 7 years 4 months and older would show higher levels of psychosis than any other scale of the RSCDD (Shaw, Rahman, & Sharma, 2011). The results of an analysis of variance revealed no significant difference between younger and older groups on any of the RSCDD Psychometric Scales (see Table 17). To further assess age-related patterns of psychiatric symptoms, Pearson correlations were performed for chronological age and RSCDD domain raw scores for the autism and no autism groups (see Table 18). The correlations revealed no significant association for chronological age and RSCDD domain raw scores.
Table 17

Analysis of Variance for RSCDD Psychometric Scales by Younger and Older Groups

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>$\eta^2_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anger/Self Control</td>
<td>3.91</td>
<td>1</td>
<td>3.91</td>
<td>.67</td>
<td>.42</td>
<td>.02</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>.931</td>
<td>1</td>
<td>.931</td>
<td>.51</td>
<td>.48</td>
<td>.01</td>
</tr>
<tr>
<td>Attention-Deficit</td>
<td>10.06</td>
<td>1</td>
<td>10.06</td>
<td>1.90</td>
<td>.18</td>
<td>.04</td>
</tr>
<tr>
<td>Autism/Pervasive</td>
<td>.80</td>
<td>1</td>
<td>.80</td>
<td>.18</td>
<td>.67</td>
<td>.01</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>1.15</td>
<td>1</td>
<td>1.15</td>
<td>.37</td>
<td>.55</td>
<td>.01</td>
</tr>
<tr>
<td>Depression</td>
<td>.15</td>
<td>1</td>
<td>.15</td>
<td>.05</td>
<td>.82</td>
<td>.01</td>
</tr>
<tr>
<td>Self Esteem</td>
<td>.28</td>
<td>1</td>
<td>.28</td>
<td>.21</td>
<td>.65</td>
<td>.01</td>
</tr>
<tr>
<td>Psychosis</td>
<td>5.96</td>
<td>1</td>
<td>5.96</td>
<td>2.26</td>
<td>.14</td>
<td>.05</td>
</tr>
<tr>
<td>Somatoform</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior</td>
<td>.01</td>
<td>1</td>
<td>.01</td>
<td>.01</td>
<td>.94</td>
<td>.01</td>
</tr>
<tr>
<td>Withdrawal/Isolated</td>
<td>1.39</td>
<td>1</td>
<td>1.39</td>
<td>.17</td>
<td>.681</td>
<td>.01</td>
</tr>
</tbody>
</table>

Note: Younger = 7.3 years and younger. Older = 7.4 years and older.
Table 18

*Pearson Correlations between Chronological Age and RSCDD Psychometric Scales*

<table>
<thead>
<tr>
<th>Psychometric Scale</th>
<th>No Autism (n = 24)</th>
<th>Autism (n = 19)</th>
<th>Total Sample (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anger/Self Control</td>
<td>-1.55</td>
<td>.027</td>
<td>-.041</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>-.143</td>
<td>.129</td>
<td>.145</td>
</tr>
<tr>
<td>Attention-Deficit</td>
<td>.174</td>
<td>-.214</td>
<td>.025</td>
</tr>
<tr>
<td>Autism/Pervasive</td>
<td>.073</td>
<td>.346</td>
<td>.241</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>-.124</td>
<td>.022</td>
<td>.000</td>
</tr>
<tr>
<td>Depression</td>
<td>-.153</td>
<td>.139</td>
<td>.098</td>
</tr>
<tr>
<td>Self Esteem</td>
<td>-.075</td>
<td>.005</td>
<td>-.012</td>
</tr>
<tr>
<td>Psychosis</td>
<td>-.077</td>
<td>-.100</td>
<td>-.087</td>
</tr>
<tr>
<td>Somatoform Behavior</td>
<td>-.078</td>
<td>.269</td>
<td>.112</td>
</tr>
<tr>
<td>Withdrawal/Isolated</td>
<td>.034</td>
<td>-.148</td>
<td>-.023</td>
</tr>
</tbody>
</table>

* *p < .05, two tailed*
Discussion

The overall objective of the current study was to improve the description of the behavioral phenotype of PMS by providing information about the overlap between PMS and autism.

Is ASD a Significant Occurrence among Individuals with PMS?

The findings of this study suggest that individuals with PMS may qualify for an ASD diagnosis with greater frequency than previously reported (Cohen et al., 2005; Philippe et al., 2008). Based on review literature, it was predicted that at least 10% of children with PMS would have a previous diagnosis of autism (Cohen et al.). Of the total sample, 46% of individuals with PMS had a previous diagnosis of an autism spectrum disorder. These results are consistent with a study of 11 patients with PMS, 54% of which exhibited autistic-like behaviors (Manning et al., 2004).

Also males were predicted to have a higher prevalence of autism than females (Fombonne, 2003; Saemundsen, Magnússon, Smári, & Sigurdardóttir, 2003). Although 60% of males with PMS had a previous diagnosis of autism and 39% of females with PMS had a previous diagnosis of autism, results indicated that gender was not significantly related to previous autism diagnosis. However, there were approximately twice as many females in the sample than males. A larger sample with a more proportional frequency of males and females would better address the relationship between gender and autism diagnosis among individuals with PMS.
Of the total sample, 67% met ADI-R criteria for autistic disorder (met three of the three criteria), 24% met criteria for autism (met 2 of the 3 criteria), and 9% did not meet criteria for autism spectrum disorder. This proportion is significantly higher than predicted based on past research involving the use of the ADI-R with families affected by PMS (Philippe et al., 2008). The results of a study that examined autism in 8 individuals with PMS indicated that none of the participants met the ADI-R criteria for autistic disorder, while 75% of individuals met ADI-R criteria for autism (met cut-off on two of the three domains). The discrepancy in results may stem from the larger sample size employed by the current study. With a total of 8 participants, the Philippe et al. (2008) study may not have had sufficient power to accurately estimate the frequency of autism in this syndrome.

The ADI-R may have over represented the cases of autistic disorder among individuals with PMS because of the moderate to profound developmental delay characteristic of this population. Approximately 75% of individuals with PMS fall within the severe range of intellectual disability (ID) with intellectual age equivalents reported between 10 and 19 months (Phelan et al., 2001; Wilson et al., 2003). Moreover, over 70% of individuals in the current study were non-verbal; that is, never achieved two-word phrase speech. There is limited research to date on the diagnostic validity of the ADI-R with young non-verbal children (Gray et al., 2008). Thus, the results of the ADI-R should be interpreted with caution when used to diagnose very young children, particularly those with a mental age below two years and those who are non-verbal (Rutter et al., 2003). As
such, the use of the ADI-R in the current study was for descriptive rather than for diagnostic purposes (Philippe et al., 2009).

**What is the Profile of Autistic Behavior that Best Characterizes Individuals with PMS?**

The PMS autism group showed significantly more impairment in reciprocal social interaction on the *diagnostic algorithm items* than the PMS only group. Although similar in their level of communication skills and frequency of repetitive behaviors, severity of impairment in social interaction may help distinguish individuals with PMS comorbid with autism and individuals with PMS only. However, factor-analytic studies of the ADI-R items reveal that studies that include only algorithm items have diagnostic and psychometric utility, while studies examining all ADI-R items contribute significantly to further defining the “broader autism phenotype” (e.g., Snow, Lecavalier, & Houts, 2008).

Consistent with previous research, a detailed analysis of *all ADI-R items* across domains for the total sample indicated that the majority of individuals with PMS show significant abnormality in the area of Reciprocal Social Interaction and Communication and not in area of Repetitive Behaviors (Philippe et al., 2008). Specifically, significant ADI-R items in the Reciprocal Social Interaction and Play domain included Showing and Directing Attention, Offering to Share, Seeking to Sharing of Enjoyment with Others, Appropriateness of Social Responses, Imitiative Social Play, Interest in Children, Failure to develop peer relationships (Friendships), Group Play with Peers, and Social Disinhibition. Significant items on the ADI-R items in the Language and Communication
domain included Comprehension of Simple Language, Articulation/Pronunciation (verbal only), Reciprocal Conversation (verbal only), Pronominal Reversal (verbal only), Pointing to Express Interest, Nodding, Head Shaking, Spontaneous Imitation of Actions, Imaginative Play, and Imaginative Play with Peers. The high frequency of certain autistic features and low frequency of others, particularly within the Restricted Repetitive, and Stereotyped Patterns of Behavior domain, could further assist professionals in recognizing PMS among children and adults with developmental delay, as well as alert physicians to individuals with autism who may warrant genetic testing for PMS.

Many participants in the current study met cut-off for the Restricted Repetitive, and Stereotyped Patterns of Behavior (RRSB), but none of the individuals showed definite abnormalities on ADI-R items in this area. Case studies of individuals with PMS and autism screening measures used in other studies have indicated the presence of repetitive behaviors (Manning et al., 2004). The current study and other studies that used the ADI-R, a comprehensive autism diagnostic tool, suggest that the nature of repetitive behaviors among PMS may be distinct from autistic disorder (Philippe et al., 2008).

Repetitive behaviors encompass a heterogeneous group of behaviors. The presence of complex or higher level behaviors (e.g., verbal rituals, circumscribed interests) better distinguish children with and without autism than repetitive motor or lower level behaviors such as repetitive use of objects, head banging (Evans et al., 1997; Frith & Done, 1990; Thelen, 1979; Turner, 1996). Moreover, individuals with lower cognitive functioning are more likely to demonstrate
increased motor and sensory behaviors (Bodfish, Symons, Parker, & Lewis, 2000; Turner, 1999).

Some research supports a two factor model of repetitive behavior may better distinguish between subtypes of autism, and “reduce the effects of behavioral heterogeneity in neurobiological and genetic studies of autism” (Cuccaro et al., 2003, pp. 16). In another study 5 of the 34 RRSB items loaded on the RRSB factor suggesting a need for more items within this domain to facilitate better assessment of this core feature of autism (Snow et al., 2008). The same authors also suggest the use of a “dimensional” (core features measured qualitatively) rather than “categorical” (meeting specific cut-offs) approach in the assessment of autism in genetic groups, as well as consideration of verbal skills in the evaluation of autism to appropriately address the concern of varying functioning levels (Snow et al., 2008).

Taken together, research on the ADI-R highlights the benefits of combining the social and communication domains, deconstructing the RRSB domain, and examining the ADI-R qualitatively to broaden the autism phenotype to include subtypes and improve efficiency of diagnosis.

**Do Individuals with PMS Regress in their Development of Language and Other Skills?**

Results of the current study indicate that developmental regression is a significant aspect of the behavioral profile of individuals with PMS. Specifically, 22% of participants were reported to show *language skill loss* and 37% experienced *other skill loss*. These results are consistent with studies of
individuals with PMS, where a proportion of affected individuals were reported to show skill loss in the areas of language, non-verbal communication and motor skills (Manning et al., 2004; Philippe et al., 2008). In a large scale study of individuals with PMS, 35% of children were reported to have experienced regression, without mention of the specific skills lost (Wilson et al., 2003). The current study is the first to identify the type, onset, and duration of skill loss, as well as the relationship of loss to illness for a large group of individuals with PMS.

Specifically, the types of language loss reported in the current study were regression of single words and communicative intent. Types of other skill loss reported for the total sample were loss of purposeful hand movement, motor movement, as well as self-help, play, and social relatedness skills. A total of eight of the ten participants with PMS and language loss also experienced other skill loss. Language regression is rarely unaccompanied by other skill loss in children with autism (Goldberg et al., 2008). In a large sample of individuals with autistic language regression, 76% also had a definite regression in their social skills and 59% had regressed in play skills (Goldberg et al., 2003). However, the link between language development and other skill loss is still unclear and requires further study.

**Is the Regression Observed in PMS Distinct from Autistic Regression?**

The onset of loss, duration of regression, and relationship to illness suggest that the regression among individuals with PMS may be distinct from the broad autism phenotype. Firstly, individuals with PMS and autism did not differ
in their frequency of skill loss as compared to individuals with PMS only. Secondly, the age of onset of loss was not comparable to that observed in individuals with autism. The majority of individuals with autism tend to experience regression prior to their second birthday (Luyster et al., 2005; Rogers 2004). In the current study individuals with PMS (with and without autism) showed regression in language and other skills on average by 62 months; only two individuals showed language loss before 24 months and none showed other skill loss before 24 months.

Duration of loss among individuals with PMS also differs from the duration reported for autistic regression. The majority (75%) of individuals with autistic regression reported at least some reacquisition of language and other skills (e.g., direct gaze, orient to name, and several social interactive behaviors). Skills had a tendency to be regained when the children were between three and half and five years of age, with language returning before other skills (Goldberg et al., 2003). In the current study, 70% of individuals with language loss were reported to never have regained the skills lost. The remaining 30% of individuals regained skills within 24 months. Among individuals with other skill loss, 53% never regained skills, two were reported to have regained skills within two years, and three more regained other skills within eight and half years.

The high prevalence of enduring loss among individuals with PMS may be related to the high frequency of illness related triggers of regression and significant medical issues common to this syndrome. There is little support for the link between autistic regression and physical/medical illness (Baird et al 2008;
Kurita, Kita, & Miyake, 1992). However, a total of 50% of cases of language regression among our sample were related to illness not including seizures or evidence of mengingeal or encephalitic involvement. The illnesses associated with skills were of various types such as influenza, ear infection, severe reflux, bladder or bowel problems, and minor/day surgery.

Detailed studies on regression in PMS, may indicate medical, environmental (e.g., move, change of caregiver or school), family (e.g., birth of a sibling), and social emotional triggers. The results of such studies may assist clinicians to differentiate individuals with PMS at risk for permanent skill loss from those with temporary regression or no history of a regressive episode.

What is the Pattern of Adaptive Functioning that Best Characterizes Individuals with PMS?

In addition to delay and regression of major developmental milestones (see Tables 5 and 6), individuals with PMS show significant delays in their development of adaptive skills (Carpentieri & Morgan, 1996; Liss et al., 2001; Philippe et al., 2008). One study indicated that 15 out of 20 individuals with PMS had severe deficits (standard scores less than 40) in overall adaptive skills with the remaining participants falling in the mild to moderate range (standard scores between 40 and 70; Phelan et al., 2001). Overall adaptive skill level reported in the current study is slightly higher. Specifically, only 21% of participants were reported to have overall adaptive skills in the severely impaired range.

The discrepancy in results may be related to sample size (i.e., improved statistical power) and methodological difference such as the administration of the
VABS-II. In the study by Phelan et al. (2001) the VABS (Sparrow, Balla, & Cicchetti, 1984) was given as a parent interview by a trained professional. The revised version, VABS-II, used in the current study is designed as a questionnaire that parents can complete with minimal instruction. Without the guidance of a trained professional, there is an increased chance of reporting error (i.e., overestimate of skills). Moreover, unlike the current study, the majority of participants (78%) in the Phelan et al. included individuals who had been previously cited in the PMS literature (i.e., case studies). Thus, their sample may represent a group of individuals with more severe impairment and subsequently lower adaptive skills.

**Do Individuals with PMS and Autism Show Greater Deficits in Adaptive Functioning than Individuals with PMS only?**

Results of the current study suggest that comorbid PMS and autism are linked to more adaptive skill deficits. Moreover, individuals with PMS and autism share a similar pattern of adaptive skill deficits as do individuals with autism; significant deficits in sociability (RSIP) and communication (LC) as compared to PMS no autism counterparts. There was a significant relationship between overall adaptive functioning and severity of autistic symptoms across RSIP and LC domains only for the no autism group, which had higher overall adaptive skills than the PMS autism group. The relationship between specific areas of adaptive functioning and autistic symptomology among individuals with autism has been related to level of intellectual functioning (e.g., Carpentieri & Morgan, 1996; Liss et al., 2001; Vig & Jedrysek, 1995). Further studies are...
needed with individuals with PMS that include a measure of ID or an IQ (non-verbal) matched comparison group (see pp. 101-102).

**What is the Pattern of Psychiatric Symptoms that Best Characterize Individuals with PMS with and without Autism?**

Persons with intellectual disabilities such as those with PMS have a higher probability of experiencing mental health problems (Dekker, Koot, van der Ende, & Verhulst, 2002; Einfeld, 1996; Einfeld, 2005) than typically developing individuals. Individuals with PMS have been shown to experience elevated scores on the RRCDD in the areas of Psychosis, Depression, Withdrawal, Attention Deficit, and Autism (Shaw, Rahman, & Sharma, 2011). The results of the current study also indicate that individuals with PMS are at risk of suffering from problems related to psychosis, attention-deficit, depression and withdrawal.

Results indicate that the PMS autism group were reported to share a similar pattern of psychiatric symptomology as individual with autism reported in other studies (Carcani-Rathwell, Rabe-Hasketh, & Santosh, 2006; Lee & Ousley, 2006; Shaw, Rahman, & Sharma, 2011; Wing & Shah, 2006). Specifically, the results of the current study indicate that individuals with comorbid PMS and autism show more behaviors related to Attention-Deficit, Depression and Withdrawal/Isolated as compared to the PMS no autism group. Thus, they may be at greater risk of developing mental health problems than individuals with PMS only. There was no relationship between overall adaptive functioning and psychiatric symptomology for the autism group. So how might the similarities in
psychopathological risk between individuals with PMS and autism be understood?

There is some evidence that individuals with autism present with more psychiatric symptoms (e.g., mood disorders, fears and anxiety, ADHD) than children with ID (Brereton, Tonge, & Einfeld, 2006). The increased risk among the autism group is not well understood. However, there is support for the influence of IQ (Howlin, 1998; Wing, 1982), language (DeMyer, Hington, & Jackson, 1981; Lord, Bristol, & Schopler, 1993) and increased biological vulnerability (e.g., link with familial depression) (Bolton, Pickles, Murphy, & Rutter, 1998). Moreover, Bereton, Tonge, & Einfeld (2006) point out that “cognitive and perceptual disturbances caused by autism may also lead to increased mental health problems because of stress experienced by these children in their interactions with others and the consequently disturbed responses of others towards them” (pp. 868).

The presence of mental health issues among young people with ID may contribute to parental burden and the need for respite and placement in residential care (Howlin, 1998). The current study may increase awareness of clinicians and community workers to the specific symptoms and increased risk of psychopathology among individuals with comorbid PMS and autism.

**Are there Age-related Changes in Autistic Behavior, Adaptive Skills, and Psychiatric Symptoms among Individuals with PMS?**

**Autistic behavior.** Results of the current study did not lend support for the improvement of autism symptomatology over time for individuals with PMS.
Specifically, there was no significant relationship between chronological age and current autistic behaviors across domains of RSIP, LC, and RRSB suggesting that for individuals with PMS autistic features persist in severity until at least age 10 years. These results are in contrast to autism research that clearly indicates symptoms improvement over time (Boelte & Poustka, 2000; Gilchrist, Green, Cox, Burton, Rutter, and LeCouteur 2001; Piven, Harper, Palmer, & Arndt, 1996; Seltzer et al., 2003). Due to constraints of the measure, only current behavior algorithm scores for individuals younger that 10 years old were included in the current study’s analysis. Many of the above mentioned studies observed changes in autistic symptomology for individuals older than 10 years. Longitudinal studies that include the repeated use of the ADI-R with the same individuals across a five to ten year span will provide valuable information into the developmental course of core autistic behaviors for this population.

Recent research has highlighted the importance of including measures of intellectual functioning in the study of change in autistic symptoms (Esbensen, Seltzer, Lam, & Bodfish, 2009). Although the present study did not include a measure of intellectual functioning, it is possible that autistic symptoms do not improve over time because of the severe impairment (i.e., cognitive and adaptive skills) that characterizes the majority of the population (Phelan et al., 2001).

Adaptive functioning. Results of current study indicate that as individuals with PMS with and without autism age past puberty they make fewer gains in adaptive skills regardless of autism diagnosis. Previous PMS research suggests that younger individuals with PMS show mild to moderate deficits in
adaptive functioning compared to older individuals who scored in the severe range of disability (Phelan et al., 2001). Unlike previous reports (Phelan et al. 2001), the current study included a large sample with a wide age range thus providing a more representative sample and improved generalization of results.

Although autism diagnosis does not appear to impact the developmental course of adaptive skills for individuals with PMS, the onset of puberty appears to play a role. Specifically, standard scores tend to decline for individuals older than approximately 12 years old (see Figure 4, 5, and 6). These results suggest a critical period for development of communication, socialization, and daily living that may inform intervention and program planning.

The psychometric properties of the VABS-II could have influenced changes over time. Specifically, older individuals are assigned more items reflecting a greater range of skill resulting in a wider range of possible scores. Moreover, items exclusive to older individuals are more cognitively complex or socially demanding, which may result in lower scores. Nonetheless, individuals with PMS do not seem to progress in their adaptive skills compared to normative samples of typically developing individuals, and persons with intellectual delay and other behavioral difficulties including ADHD (Sparrow, Cicchetti, & Balla, 2005). Replication of these results is needed, given the paucity of research on adaptive skill development in PMS.

**Psychiatric symptoms.** The severity of psychiatric symptoms does not appear to vary according to age among the current sample of individuals with PMS, regardless of autism diagnosis. These results are in contrast to previous
studies indicating that for individuals with autism behavioral disturbance becomes more severe with age (Goodwin & Redfield, 1990; Luciani et al., 2003; Reeve et al., 1985; Sovner, Stone, & Fox, 1996). Much of the research on maladaptive behaviors in individuals with PMS are based on case studies, often of individuals with ring chromosome 22, which limits the generalizability of results to the broader PMS population. Moreover, the behaviors reported in the study by Luciani et al. were based on clinical observations rather than results from a standardized instrument.

Another study that included the RSCDD in the assessment of a sample of 36 individuals with PMS indicated that individuals younger showed higher levels of autism than any other scale, while older children showed higher levels of psychosis than any other scale of the RSCDD (Shaw, Rahman, & Sharma, 2011). These results were not replicated by the current study. The Shaw et al. (2011) study consisted of families attending the 22q13 support group meeting. These families are likely to have higher socioeconomic status than affected families who were not in attendance. These families may have attended the conference because they required support because their children were experiencing a significant level of behavioral difficulties. Approximately 40% of the current study’s sample included individuals beyond the PMS support group. Thus, the results of the current study may be a better representation of the range of mental health risk among individuals with PMS.
Limitations of the Study

The results of the current study need to be considered in the context of methodological limitations. Although this study included a large sample size as compared to previous PMS behavioral and neurological studies (e.g., Manning et al., 2004; Phelan et al., 2001; Philippe et al., 2008), an even larger sample size (n=100) would have allowed for more powerful statistical analyses. For example a factor analyses of autistic behaviors (ADI-R items) would have provided information about which behaviors and related factors best represent the profile of autism among this population (see Frazier, Youngstrom, Kubu, Sinclair, Rezai, 2008). Multiple regression analyses could provide information on the predictive value of gender, age, adaptive skill deficits, receptive and expressive language, developmental level or intellectual skills on severity of autistic behavior.

The autism diagnoses were based on parental report of a previous diagnosis by educational or clinical psychologist or psychiatrists. Many of the families did not provide diagnostic reports. Moreover, the reports received reflect the different diagnostic practices in use in the past 20 years. However, it is encouraging that many of the differences expected between groups based on autism diagnosis were supported by the data.

Direct observation of behavior was not feasible given the geographical location of the participating families. The validity of retrospective assessment has always been a concern in the area of developmental psychopathology. The major concern is accuracy. Over time parental reports of their child’s development lose accuracy (Lord et al., 2004; Rogers, 2004). With regards to autistic behavior, the
recent use of home videotapes to code skills and symptoms from infancy has confirmed the validity of retrospective parental reports of autistic behavior (Rogers, 2004). However, best practices in the assessment of children necessitate multiple sources of information including a developmental history and observational data (American Educational Research Association, 1999).

The use of the RSDDC to assess for dual diagnosis was also limited to parental reports and did not include items that address a broad range of behavioral and emotional disturbance. Given the time demands of the ADI-R, the RSDDC (60 items) seemed more feasible for families than the more comprehensive measures. Other measures of psychopathology for individuals with intellectual delay are available that include options for teacher or educator reports, as well as separate versions for children and adults (e.g., 96-item: Developmental Behavior Checklist; Einfeld & Tonge, 2002). Teachers and support staff generally spend more time with children than parents. They also have the opportunity to observe skills (e.g., social, motor, daily living skills) that parents don’t have the same access to. Including educators would likely mean a decrease in the potential for response bias and an increased likelihood of obtaining a more comprehensive picture of behavior and skill level.

This study did not control for factors such as ethnicity, nationality, level of parental education, or social economic status. Participants were recruited through advertisements placed on the Phelan-McDermid Syndrome Foundation website, the PMS deletion foundation support group directory, and a PMS deletion foundation Yahoo chat group. Many of the parents in these families were well
educated, residents of the continental United States, Caucasian, participants in other research studies, and extremely knowledgeable of PMS. They were also active in obtaining information and services that address their child’s wide range of behavioral, educational and medical needs. These families had the time to participate in the study, which may be an indication of higher socio-economic status. Moreover, all the participants in the study had experienced severe enough developmental, behavioral or medical issues to warrant genetic testing. There may be less affected individuals with PMS who have not been tested. Taken together, the generalizability of results may be limited because the families included in this study may not fully representative of the population of individuals with PMS.

**Future Directions for Research**

Further research is needed to look at the influence of language development, intellectual functioning and other biological and environmental factors that may influence the manifestation of autistic behavior and related behavioral impairments across the lifespan of individual with PMS.

Measures of intellectual functioning that have been shown to relate to autistic behaviors and psychiatric symptomology were not available. Many parents who participated in the current study reported that they could not obtain IQ scores for their children. This is likely because obtaining a valid measure of intellectual functioning using standard measures of intelligence with individuals with severe developmental delay is extremely difficult. However, developmental measures with IQ equivalents (e.g., The Developmental Profile II; Alpern, Boll, &
Shearer, 2000; Psychoeducational Profile – Revised; Schopler, Reichler, Bashford, Lansing & Marcus, 1990) or non-verbal measures of intelligence (e.g., Universal Nonverbal Intelligence Test; Bruce & McCallum, 1998; Leiter International Performance Scale—Revised; Roid, & Miller 1997) are available for use with individuals who have severe delays in cognitive functioning and language development. These measures could be used in future research to obtain information on the impact of ID on autistic behavior and the appropriateness of using the ADI-R with this population.

The role of language development in developmental regression is unclear. However, level of meaningful speech prior to loss has been shown to be predictive of outcome (Rutter, Greenfeld, & Lockyer, 1967). A study of regression among a group of individuals with PMS and another group of individuals with autism, matched on expressive vocabulary prior to skill loss, may indicate that regression in social communication and play skills is related more to language delay than a shared autistic phenotype.

Another focus for future studies is the link between developmental regression and SHANK3, which is one of the major genes affected in individuals with PMS and 1% of individuals with autism (Durand et al., 2007; Wilson et al., 2003). The haploinsufficiency or lack of SHANK3 gene has been associated with the cognitive impairments, expressive language and social communication deficits in both PMS and autism (Durand et al.; Jeffries et al., 2005; Wilson et al., 2003). Specifically, the SHANK3 gene is responsible for production of a protein essential for neural synaptic development. A lack of SHANK3 protein, typically
results in neural signal unable to travel along neural pathways and damage to neural network supporting a particular learned skill. A study of skill development and periods of regression among individuals with autism with and without deficits for SHANK3 may aid in the identification of a major cause of regression among a subgroup of individuals with autism, PMS and other neurodevelopmental disorders.

Further research is needed to assess the direct influence of cognitive level on symptom progression. There is a higher correlation between estimates of intellectual functioning and adaptive behavior for children with autism as compared to children with ID without autism (e.g., Carpentieri & Morgan, 1996; Liss et al., 2001; Vig & Jedrysek, 1995). Moreover, IQ appears to be a better predictor of adaptive functioning than severity of autistic symptoms for lower functioning compared with higher functioning individuals with autism (Bolte & Poustka, 2002; 2009; Liss et al., 2001). In order to better understand the link between autistic symptomology and adaptive functioning for individual with PMS, future studies are necessary that include groups of individuals with PMS and autism matched on IQ. This design would help in understanding and predicting adaptive strengths and weaknesses and in identifying limiting factors that may be useful for service planning and educational programming for individuals with PMS.

Further studies are needed that examine the influence of biological and genetic factors on psychiatric symptoms. There are genetic linkage studies that have identified genes (loci within 22q13: GPR24; PICK1; Sult4A1 and BZRP)
that increase the susceptibility to schizophrenia, affective and mood disorders (Badner & Gershon, 2002; Condra et al., 2007; Fujii et al., 2006; Severinsen et al., 2006). Longitudinal studies are also vital for the identification “risk” and “resilience” factors that may influence the developmental course of psychopathology among individuals with PMS with and without autism. These investigations will surely impact the early identification of those at risk, and improve the availability of health and educational services to families in need.

Compared to other neurodevelopmental disorders (e.g., Fragile X, Williams syndrome) PMS is a relatively newly identified syndrome. As a result, many of the individuals diagnosed are school-aged. Longitudinal studies will provide valuable information into the developmental course of core autistic behaviors for this population.

Prospective studies are needed that repeat the ADI-R (current behavior algorithm) over adolescence and into adulthood for individuals with PMS. Moreover, prospective studies that track the behavior of children with PMS into adolescence and adulthood would allow for the study of the developmental progression of psychiatric symptoms and the identification of affected children at risk for ADHD, schizophrenia, and mood disorder. Early identification is especially important because of the availability of effective psychological and pharmacological treatment for a variety of mental health issues.

**Conclusion**

The current study found that autistic behavior is a significant aspect of the PMS behavioral phenotype and that deficits in sociability and communication best
distinguish individuals comorbid with PMS and autism and PMS only.

Developmental regression, often associated with autism, is prevalent among our sample. However, skill loss appears to be distinct from autistic regression in relation to onset, duration and relationship with illness. Furthermore, co-morbid PMS and autism is characterized by more adaptive skills deficits in the areas of Communication and Socialization and the presence of psychiatric symptoms including Attention-Deficit, Depression, and Withdrawal.

In summary these results add to the emerging behavioral profile of individuals with PMS by highlighting the importance of including autistic behavior in the PMS phenotypic profile. The recognition and awareness of the comorbidity of autism and PMS will facilitate differential diagnosis, appropriate and timely interventions, as well assist parents in their efforts to access educational and community services and resources that are typically reserved for individuals with autism.
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BEHAVIORAL FEATURES OF INDIVIDUALS WITH PMS


Appendix A

Demographic Form

Please answer the questions you are comfortable responding to and feel free to leave blank the questions you don’t wish to answer or cannot recall an answer.

Date (month/day/year):_____________

1. Study ID #:

2. Interviewer:

3. Person filling out questionnaire (mother, father, other):

4. Gender of the child:

5. Location of the child (city, province/state, country):

6. Child’s birth date (month/day/year):

7. Ethnicity of the child:

8. Primary language spoken in the home:

9. Other languages spoken in the home:

10. Has the child been diagnosed with 22q13.3 Deletion Syndrome?
   
   a. If yes, please specify the genetic diagnosis (e.g., 22q13.3, ring 22, mosaic presentation):
   
   b. Who diagnosed the child (psychiatrist, psychologist, etc.)?
   
   c. What diagnostic method was used (e.g., Fluorescence In Situ Hybridization; FISH test)?
   
   d. When was the child diagnosed?
e. Does the child receive any special services for this disorder (please list)?

11. Has your child been diagnosed with an Autism Spectrum Disorder (ASD) or autism (e.g., autistic disorder, pervasive developmental disorder, Rett’s syndrome, Childhood disintegrative disorder etc)?

   a. If yes, who diagnosed the child (psychiatrist, psychologist etc.)?

   b. Which ASD?

   c. What diagnostic tools were used (ADOS, ADI-R, etc.)?

   d. When was the child diagnosed?

   e. Does the child receive any special services for this disorder (please list)?

12. Who are the people CURRENTLY living in our household (including yourself and the child)? Please include the people who eat, sleep and share your home on a regular basis. You can write on the back of this sheet if you need more space.

<table>
<thead>
<tr>
<th>Name</th>
<th>Sex</th>
<th>Birth date or age</th>
<th>Relation to child?</th>
<th>How long has he or she lived with the child?</th>
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13. Does the child have any illnesses or conditions for which he/she received regular care (e.g. asthma, diabetes, seizures, chronic epilepsy)?

14. Significant hospitalizations or surgeries?

15. Names of current medications?

16. Medications taken in the past?

17. Any Drug or major food allergies?

18. Is your child hearing or seeing impaired?

19. What other medical, psychiatric, or educational diagnosis has your child received?

20. Immunizations (Yes/No):
   a. DPT:
   b. OPV:
   c. HIB:
   d. MMR:
   e. Hepatitis:
   f. Varacella:
   g. Other:______

21. Reaction to vaccine:

16. Complications during pregnancy, labor and/or delivery:

17. Drug or alcohol use during pregnancy (e.g. including prescription medications):

19. Allergies (i.e. food, medicine, or environmental):
22. Any family history of mental health issues?
   i) Intellectual Disabilities:
   ii) Autism:
   iii) Learning Disabilities:
   iv) Bipolar Disorder:
   v) ADHD:
   vi) Depression:
   vii) Schizophrenia:
   viii) Alcohol Abuse:
   ix) Other________

23. Have you participated in any or Dr. Steven Shaw’s research projects in the past?

If so, please specify if possible:

Would you like to be contacted by Dr. Steven Shaw’s laboratory for future research studies (yes or no)?

Thank you for completing this form and for your participation in our study.

Amira Rahman, M.A.
Principal Investigator McGill University
Ph.D. Candidate-School/ Applied Child Psychology