# AUTISM SPECTRUM SYMPTOMS IN PRADER-WILLI SYNDROME: COMPARISONS ACROSS GENETIC SUBTYPE

By

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## *Introduction*

Prader-Willi Syndrome (PWS) is a rare genetic neurodevelopmental disorder caused by the lack of expression of paternal genetic material from a region on the long arm of chromosome 15 (q11-q13). Occurring in 1 in 15,000 birth, PWS and its oppositely imprinted "sister," Angelman syndrome, made molecular genetic history as the first human disorders to show the effects of genomic imprinting.

In particular, chromosome 15 (q11-q13), known as the Prader-Willi/Angelman Critical Region (PWACR), contains genes that are subject to imprinting, an epigenetic phenomenon that results in the expression and silencing of genes based on the parent of origin. The PWACR contains several paternally imprinted genes that are silenced on the maternal chromosome, and thus if the paternal copies are missing, they are not expressed. The most common causes of PWS are the deletion of paternally derived genetic material in this region, which causes 70% of cases, and maternal uniparental disomy (UPD), the inheritance of two copies of the maternal chromosome (Cassidy, et al., 1997; Ledbetter, et al., 1981; Mascari, et al., 1992). In UPD, which causes 25% of cases, the genes remain intact, but due to imprinting the presence of only maternally derived genetic material results in a lack of expression of paternal genes. The remaining 5% of cases are caused by abnormal mutations resulting in silencing of the paternal PWACR, including imprinting center mutations.

These genetic abnormalities result in a host of physical, behavioral, cognitive, and psychiatric features, including hypogonadism and small stature, growth hormone deficiency, and the early childhood onset of hyperphagia and food-seeking. Without sustained dietary and other environmental controls, hyperphagia leads to high risks of morbid obesity. PWS is also characterized by mild to moderate intellectual disability, irritability, mood problems, and obsessive-compulsive traits, including needs for sameness, repetitive questioning, hoarding and skin-picking (Dykens, Cassidy, & King, 1999; Dykens & Kasari, 1997; Dykens, Leckman, & Cassidy, 1996; Holland, et al., 2003; Holm, et al., 1993).

The existence and severity of such phenotypic features seem to have some correlation with the genetic subtypes of PWS. Studies comparing individuals with UPD to those with deletion indicate that with respect to some features of PWS, such as distinctive facial features and the tendency to skin-pick, individuals with UPD may be less affected

than their counterparts with deletion (Dykens, et al., 1999). While some findings also suggest that individuals with UPD may, on average, have higher IQs and superior verbal abilities to those with deletions, these results vary across study samples (Cassidy, et al., 1997; Dykens, et al., 1999; Roof, et al., 2000).

Adding to the phenotypic picture of PWS, recent research has shown that individuals with PWS may also be at increased risk for certain symptoms and behaviors commonly associated with autism spectrum disorders (ASD), such as deficits in social skills and the presence of restricted and repetitive behaviors (Descheemaeker, Govers, Vermeulen, & Fryns, 2006; Greaves, Prince, Evans, & Charman, 2006; Koenig, Klin, & Schultz, 2004). ASDs, including Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), are neurodevelopmental disorders characterized by impairments in social interaction, communication, and the presence of restricted and repetitive behaviors.

Few studies have gone beyond behavior in assessing the presence of ASD traits in those with PWS. However, one recent study employing electroencephalography (EEG) and eye-tracking suggests that face processing may be abnormal in PWS (Halit, Grice, Bolton, & Johnson, 2008). Numerous studies using varying methodologies have demonstrated that face processing is abnormal in ASD (Dalton, et al., 2005; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001). Another recent EEG study also points to abnormal face processing in PWS (Key, Jones, & Dykens, In Preparation). The authors made comparisons based on genetic subtype of PWS, and found that the neural responses to faces of individuals with UPD more closely resembled patterns of response in ASD as compared to individuals with deletion. Furthermore, this response pattern was associated with increased autism symptomatology. One brain imaging study using positron emission topography showed functional abnormalities in the anterior cingulate and superior temporal regions in PWS versus typically developing controls (Mantoulan, et al., 2011). These brain regions are involved in social cognition and emotion regulation, and have been shown to be abnormal in ASD as well (Boddaert, et al., 2004; Kennedy & Courchesne, 2008; Wallace, Dankner, Kenworthy, Giedd, & Martin, 2010).

This growing body of literature in behavioral genetics and psychophysiology supports the notion that PWS confers increased risk for ASD, and such risks may vary by

genetic subtype. Unlike most other genotype-phenotype correlations in PWS where individuals with UPD are often less affected than their counterparts with deletion, risks for ASD appear to be greatest in individuals with UPD (Milner, et al., 2005; Veltman, Craig, & Bolton, 2005; Veltman, et al., 2004). While the exact causal mechanisms of idiopathic ASD are unknown, it is widely accepted that the disorder has a genetic basis (see Geschwind, 2011 for review). Numerous studies have been conducted in order to hone in on possible genetic underpinnings of ASD, and the most common cytogenetic abnormalities found to be associated with the disorder are maternal duplications and triplications in the chromosome 15q11-q13 region (Bolton, et al., 2001; Cook, et al., 1997; Vorstman, et al., 2006). Additionally, there is a significant amount of phenotypic overlap between ASD and Angelman Syndrome, PWS's "sister syndrome" which is caused by the lack of expression of maternally derived genes in the PWACR (Peters, Beaudet, Madduri, & Bacino, 2004). Given these facts, in concert with recent findings indicating that individuals with UPD are at increased risk for ASD symptomatology as compared to those with deletions, a compelling case can be made that the overlap of symptoms found in ASD and PWS results from a shared genetic mechanism. The present study sought to replicate and expand previous findings of increased risk for ASD in UPD versus deletions. In doing so, we used the largest sample to date of well-characterized individuals with PWS. Unlike previous work, we also used multiple, gold-standard methodologies to establish ASD symptoms and diagnoses, including caregiver report and direct observation with a standard interview.

## *Methods*

### *Participants*

Participants were drawn from a larger longitudinal study on phenotypic behavior in relation to genetics in PWS. In all, 80 individuals (38 males, 42 females) with PWS aged 4-52 years (M = 16.21, SD = 9.26) were included in the study. Of these, 46 had PWS caused by deletion, and 34 had PWS caused by UPD. PWS genetic subtype was verified via obtaining copies of participants' previous genetic testing results, which included FISH and DNA methylation studies. If these were not available or inconclusive, we conducted additional genetic testing to confirm the PWS genetic subtype. Participants were excluded if PWS was caused by an abnormality other than deletion or UPD, and also if they did not receive

Module 3 of the Autism Diagnostic Observation Schedule (Lord, et al., 1989). As shown in Table 1, mean ages did not significantly differ between groups. Males and females were equally distributed across the two genetic subtypes.

Table 1. Demographics

| | UPD | Deletion | Statistic | *p* value |
|---|---|---|---|---|
| Sample Size | 34 | 46 | - | - |
| Subject Age | 14.82 (7.85) | 17.23 (10.13) | $F(1,78) = 1.33$ | 0.252 |
| Gender (M:F) | 15:19 | 23:23 | $X^2(1) = 0.27$ | 0.602 |
| Full Scale IQ | 72.44 (19.85) | 68.54 (16.08) | $F(1,78) = 0.94$ | 0.335 |
| Verbal IQ | 82.09 (19.33) | 74.15 (14.31) | $F(1,78) = 4.46$ | 0.038* |
| Nonverbal IQ | 68.18 (20.95) | 69.74 (18.40) | $F(1,78) = 0.13$ | 0.724 |

*significant at the .05 level

*Procedures and Measures*

Participants and their primary care providers completed a battery of questionnaires and diagnostic interviews during a visit to Vanderbilt University. Some questionnaires were mailed to participants' care providers beforehand, and were mailed back at their convenience. Informed consent was obtained from all participants per Vanderbilt University's Institutional Review Board.

*Demographic questionnaire.* Parents completed questions regarding their offspring's height, weight, medical and psychiatric histories, medications, and family composition.

*Kaufman Brief Intelligence Test, Second Edition (K-BIT2; Kaufman & Kaufman, 2004).* The KBIT-2 is a brief intelligence test that provides a verbal intelligence score, nonverbal intelligence score, and full-scale IQ. The verbal scale consists of two subtests that assess vocabulary knowledge and the ability to identify terms from a short description,

respectively. The nonverbal score is derived from one subtest that tests the ability to complete picture matrices.

*Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989).* The ADOS is a semi-structured, standardized assessment of communication, social interaction, and play or imaginative use of materials designed to assess and diagnose ASD. An examiner observes behavior throughout a semi-structured interview and play setting, and scores individual behaviors. In the past, these scores fed into three larger domain scores assessing the degree to which the individual showed impairment in reciprocal social interaction, communication, and the presence of repetitive and stereotyped behaviors. A Communication + Social Interaction total score was calculated from the Reciprocal Social Interaction and Communication domain scores. In order for a diagnosis of ASD to be made, individuals needed to meet or exceed a cutoff on all three of these scores. The scoring system of the ADOS was recently revised in order to improve diagnostic validity, such that the scores of individual behaviors now feed into two domain scores: a Social Affect score and a Restricted and Repetitive Behavior score (Gotham, Risi, Pickles, & Lord, 2007; Gotham, Pickles, & Lord, 2009). The sum of these scores is also used to create calculate an overall Severity Score, which quantifies the individual's level of autistic impairment. Thresholds which indicate likely autism diagnoses are applied to this score, and are broken down into three diagnostic groups, in order of severity: autism, autism spectrum, and non-spectrum. This revised system was used in this study. Only Module 3 of the ADOS, which is used to assess individuals with good verbal ability, was utilized in the current study. The assessments were performed by one of three trained and experienced examiners.

*Social Communication Questionnaire (SCQ; Berument, Rutter, Lord, Pickles, & Bailey, 1999).* The SCQ (formerly known as the Autism Screening Questionnaire, or ASQ) is a 40-item screening instrument whose content parallels the diagnostic algorithm of the Autism Diagnostic Interview – Revised (ADI-R), a parent or caregiver interview which complements the ADOS (Lord, Rutter, & Le Couteur, 1994). Respondents indicate the presence or absence of behaviors and features associated with autism in a yes or no format. A score of (1) indicates the presence of a behavior or feature, and a score of (0) indicates its

absence. Items are assigned to one of three domains: reciprocal social interaction, communication, and stereotyped behavior. Items are also added up to compute a total score.

## *Results*

As shown in Table 1, the UPD group scored significantly higher on a measure of verbal intelligence than did the deletion group. Therefore, verbal IQ is covaried in the following analyses. More detail on the following analyses can be found in Tables 2, 3 and 4.

### *ADOS Results*

A series of analyses of covariance (ANCOVA) was performed to assess whether the UPD group differed from the deletion group with regards to the domain scores and total severity scores created utilizing the revised ADOS diagnostic algorithms. The groups differed significantly on the social affect score ($F(1,77)=4.296$, $p=0.042$), restricted and repetitive behavior total (RRB) ($F(1,77)=4.52$, $p=.037$), and total Severity Score ($F(1,77)=5.23$, $p=0.025$). For each, the UPD group scored significantly higher than the deletion group, indicating greater autistic symptomatology.

A severity score of 1-3 on the ADOS represents a "nonspectrum" classification. A score of 4-5 represents an "ASD" classification on the ADOS, or an individual who is likely on the spectrum, but is less severely affected than if they were to receive an "autism" classification, which is assigned to individuals with scores of 6 and above. There were no significant differences by group in diagnosis based on the thresholds applied to the Severity Score. This was true both when the groups were compared on the basis of these three classifications, and when the autism and autism spectrum classifications were collapsed to create one overarching autism group. In the UPD group, 13 individuals met ADOS criteria for an "autism" classification, 4 for an "ASD" classification, and 17 were classified as "nonspectrum." In the deletion group, 10 individuals reached the threshold for an "autism" classification, 6 for an "ASD" classification, and 30 were classified as "nonspectrum."

*SCQ Results*

An additional series of ANCOVAs was performed to measure group differences with regards to the domain and total scores of the SCQ. The UPD group scored significantly higher than the deletion group ($F(1,77)=4.661$, $p=.034$) on the total score, indicating overall greater autistic symptomatology. The two groups also showed a significant difference on the reciprocal social interaction (RSI) subscale of the SCQ ($F(1,77)=7.752$, $p=.007$), with the UPD group again scoring higher than the deletion group. A total score of 15 or higher on the SCQ indicates a possible ASD diagnosis. As with the ADOS results, the UPD and deletion groups did not differ on diagnostic status. However, the result was trending, such that individuals with UPD were more likely than individuals with deletions to reach the threshold of ASD classification ($\chi^2(1)=3.418$, $p=.064$). In the UPD group, 13 individuals reached the threshold of a possible ASD diagnosis, while 21 did not. In the deletion group, 9 individuals met criteria for a possible ASD diagnosis, while 37 did not.

Table 2. ASD Battery Subtype Comparisons

| | UPD | Deletion | Statistic | *p* value |
|---|---|---|---|---|
| *ADOS* | | | | |
| Social Affect | 5.91 (4.41) | 4.96 (4.39) | F(1,77) = 4.30 | 0.042* |
| RRB | 1.85 (1.88) | 1.28 (1.54) | F(1,77) = 4.52 | 0.037* |
| Severity Score | 4.44 (3.16) | 3.63 (2.84) | F(1,77) = 5.23 | 0.025* |
| *SCQ* | | | | |
| RSI | 3.76 (3.25) | 2.35 (2.17) | F(1,77) = 7.75 | 0.007* |
| Communication | 4.15 (2.58) | 3.96 (2.26) | F(1,77) = 1.05 | 0.309 |
| RRB | 3.38 (2.24) | 2.63 (2.14) | F(1,77) = 1.90 | 0.172 |
| Total Score | 11.76 (7.19) | 9.30 (5.26) | F(1,77) = 4.66 | 0.034* |

* significant at the .05 level

*Correlates*

In both the UPD and deletion groups, verbal and full-scale IQ were significantly negatively correlated with the Social Affect total and Severity Score of the ADOS, such that lower IQs were related to greater autism symptomatology (See Tables 3 and 4). In the deletion group,

nonverbal IQ was also significantly negatively correlated with Social Affect total and Severity Score. Also in the UPD group, verbal, nonverbal, and full-scale IQ were negatively correlated with the Communication total of the SCQ. In the deletion group, verbal, nonverbal, and full-scale IQ was negatively correlated with the Reciprocal Social Interaction total of the SCQ. In the UPD group, gender was correlated with the Restricted and Repetitive Behaviors total and Severity Score, such that being male was related to greater autism symptomatology in these domains. Also in the UPD group, age was significantly negatively correlated with the Restricted and Repetitive Behavior domain score of the SCQ. There were no significant correlations in the deletion group between age and autism symptoms.

Table 3. UPD Correlations

| | ADOS Social Affect | ADOS RRB | ADOS Severity Score | SCQ RSI | SCQ Comm | SCQ RRB | SCQ Total |
|---|---|---|---|---|---|---|---|
| Age | .145 | -.006 | .086 | -.080 | -.003 | -.417* | -.179 |
| Gender | -.291 | -.487** | -.406* | .156 | .075 | -.168 | .037 |
| VIQ | -.490** | -.335 | -.470** | -.146 | -.380* | .115 | -.160 |
| NVIQ | -.330 | -.214 | -.287 | -.065 | -.370* | -.173 | -.219 |
| FSIQ | -.425* | -.250 | -.381* | -.119 | -.406* | -.057 | -.217 |

RRB = Restricted and Repetitive Behavior
RSI = Reciprocal Social Interaction
Comm = Communication
* significant at the .05 level
** significant at the .01 level

Table 4. Deletion Correlations

| | ADOS Social Affect | ADOS RRB | ADOS Severity Score | SCQ RSI | SCQ Comm | SCQ RRB | SCQ Total |
|---|---|---|---|---|---|---|---|
| Age | .155 | .062 | .163 | .212 | .143 | -.149 | .073 |
| Gender | .261 | .071 | .240 | .142 | -.058 | -.154 | -.075 |
| VIQ | -.422** | -.239 | -.407** | -.342* | -.235 | -.025 | -.252 |
| NVIQ | -.353* | -.187 | -.345* | -.365* | -.213 | .031 | -.225 |
| FSIQ | -.394** | -.230 | -.388** | -.379** | -.252 | -.022 | -.273 |

RRB = Restricted and Repetitive Behavior
RSI = Reciprocal Social Interaction
Comm = Communication
* significant at the .05 level
** significant at the .01 level

## *Discussion*

This study is the largest to date comparing ASD symptoms across deletion versus UPD subtypes of PWS. Similar to previous work, this study identified increased social deficits in persons with UPD (Veltman et al., 2004; Milner et al., 2005). Unlike previous studies, however, we also found that those with UPD are at heightened risk for autistic-like restricted and repetitive behaviors. Findings expand our current understandings of the PWS phenotype and suggest areas of future research on interventions in this population.

While significant differences in ASD symptoms were found between genetic subtypes, these differences did not translate into discrepant rates of autism diagnoses between groups. Although this could be due to insufficient power, the studies conducted by Veltman and colleagues (2004) and Milner and colleagues (2005) also failed to find higher rates of ASD diagnoses in UPD versus deletion, in spite of significant differences in ASD symptomatology. In a review of the literature, Veltman et al. (2005) found that

approximately 37.7% of individuals with UPD received an ASD diagnosis, while only 18.5% of those with deletions received such a diagnosis, amounting to a significant difference. However, these analyses were based on the conglomeration of published case studies and case series that used widely different sample sizes, methods for assessing autism symptoms, and criteria for determining autism diagnoses.

It is unclear why those with UPD have consistently higher autism symptoms, but not necessarily formal ASD diagnoses. Some of this discrepancy may relate to the challenges of making autism diagnoses in those with known genetic syndromes. Moss and colleagues (2008) assessed autism spectrum systems in a sample of individuals with Cornelia de Lange and Cri du Chat syndromes, and noted that the autism symptom profiles in these syndromes was atypical compared to that of idiopathic autism. The same research group also assessed the phenomenology of autistic-like repetitive behaviors in several well-studied genetic syndromes, including PWS, and found that each syndrome carried with it a specific phenotypic profile (Moss, Oliver, Arron, Burbidge, & Berg, 2009). While these types of syndrome-specific profiles serve as the basis for the fruitfulness of behavior genetics research, they can make diagnosis difficult. Making reliable psychiatric diagnoses is also challenging in people with intellectual disabilities in general, which further clouds diagnoses in PWS (Dykens, 2000).

The discrepancy in ASD symptoms versus diagnoses in UPD may also relate to the higher verbal IQ scores in this group compared to their counterparts with deletions. Strikingly, differences between the two genetic subtypes in ASD symptomatology were made even more apparent when covarying for verbal IQ in analyses. Previous work has shown that relative to individuals with deletions, those with UPD have higher verbal

reasoning abilities, but not necessarily as well-developed visual-spatial abilities (Dykens et al., 1999; Roof et al., 2000). Thus, individuals with UPD may be utilizing their more advanced verbal abilities to mask some of their ASD-like deficits, especially in regards to social interaction.

Correlation analyses showed that IQ was negatively associated with several domains of autism symptoms in both PWS subtypes. As discussed above in regards to higher verbal IQ in UPD, this could be due to the ability of those with higher IQ to mask some of their maladaptive autistic behaviors. Furthermore, those with lower cognitive abilities may be more affected in general, and thus it would be unsurprising if they were also at higher risk for ASD. In the UPD group, restricted and repetitive behaviors as measured by the SCQ were negatively correlated with age.

Finally, although those with UPD show heightened social and repetitive behavior symptoms associated with autism, perhaps focusing solely on the autism diagnostic schema is not the best means to describe these impairments. Indeed, those with UPD are at markedly high risk for developing psychosis, especially in later adolescence or young adulthood (Boer, et al., 2002; Vogels, Matthijs, Legius, Devriendt, & Fryns, 2003). Our finding that ASD-like restricted and repetitive behaviors lessen with age in the UPD group may be a sign of this transition. As with ASD, psychotic disorders are associated with impaired social cognition and obsessive-compulsive traits. It is possible that these traits in PWS represent some form of prodromal psychosis, which resembles ASD in childhood and early adolescence. Data on secondary psychiatric conditions in people with ASD in general consistently find increased rates of co-occurring depression and anxiety disorders, but virtually no overlap with psychosis or schizophrenia (Leyfer, et al., 2006; Tsatsanis, 2003).

While comorbidity of psychosis in idiopathic ASD is rare, this does not preclude their co-occurrence in PWS. If ASD and psychosis often co-occur in PWS, this would represent a marked deviation from co-morbidities in ASD in the general population, highlighting PWS as a model for studying these co-morbidities.

While maternal duplications and triplications of genetic material in the PWACR are the most common cytogenetic abnormality linked to ASD, these still only account for 1-3% of cases (Cook et al., 1997; Bolton et al., 2001; Vorstman et al., 2006). Indeed, many factors are associated with risk for the development of autism, including environmental ones. Thus, while PWACR abnormalities are robustly associated with ASD, the PWS diagnosis does not translate directly into formal autism diagnoses.

This study had both strengths and limitations. First, it had an ample sample size of participants with genetically confirmed PWS. However, one weakness lies in the fact that we did not have adequate power to separately analyze those with Type I versus Type II paternal deletions. Individuals with Type I deletions are missing more genetic material than those with Type II deletions. Thus, those with Type I deletions may be at risk for greater psychopathology and worse outcomes than their counterparts with Type II deletions (Butler, Bittel, Kibiryeva, Talebizadeh, & Thompson, 2004). Second, data were derived from parents or care providers as well as a trained clinician using a widely accepted diagnostic interview. However, these tools focus primarily on diagnoses, and do not provide fine-tuned assessments of social dysfunction.

In this vein, future research should begin to more finely assess the phenomenology of social deficits and compulsive behavior in PWS as compared to ASD, and the phenomenology of these deficits in individuals whose PWS is caused by UPD versus those

with deletions. Only one study has assessed the quality of social impairment in PWS generally (Koenig et al., 2004). Using a social attribution task, the authors found that social deficits in PWS can be characterized by an inability to recognize social cues, interpret social situations, and organize visual information into a coherent social story. They also found that individuals with PWS and ASD used less affective terms in describing the scene as compared to IQ matched controls. These findings need replication, and further studies should make comparisons based on PWS subtype. Such clinical and behavioral research also demands complementary work in psychophysiology and imaging as well. Very few studies of this ilk have compared PWS to ASD, and none have assessed ASD-like abnormalities by genetic subtype in PWS.

Behavioral genetics research such as the kind performed in this study has immense potential for helping to map out the genetic risk factors for disorders like ASD, where causes are complex and poorly understood. Comparing overlapping phenotypic traits with syndromes of known genetic etiology, like PWS, reinforces findings in the field of ASD genetics, a literature that is marked by significant variability in findings. Additionally, behavioral genetics research in PWS allows for a richer picture of both the PWS genotype and phenotype, and can be an invaluable tool to help guide more effective therapies and treatments. Furthermore, greater understanding of the genetic underpinnings of social deficits and obsessive-compulsive traits has wide ranging implications for treatment and research in myriad forms of psychopathology, such as schizophrenia, social anxiety disorder, obsessive-compulsive disorder, and more.

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