

Autistic-like Symptomatology in Prader-Willi Syndrome: A Review of Recent Findings

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Prader-Willi syndrome (PWS) is caused by either the structural loss of material or the absence of gene expression from the paternally inherited copy of chromosome 15 in the q11-q13 region. In addition to a well-described behavioral phenotype that includes hyperphagia, obsessive-compulsive symptoms, disruptive behavior, and an increased risk for mood disorders, recent evidence also suggests that some individuals with PWS have repetitive behavior and social deficits reminiscent of autism spectrum disorders. In particular, it appears as if those with maternal uniparental disomy (UPD) as the cause of PWS are at greater risk for autistic symptomatology than those with paternal deletions of 15q11-q13. These findings are particularly intriguing in light of data implicating maternal duplications and triplications of the same chromosomal interval in idiopathic autism, as well as evidence that functional alterations of genes in this region are associated with social deficits found in a variety of neurodevelopmental disorders. This paper will review the recent evidence for phenotypic similarities between autism and PWS and the risk of symptomatology for the UPD subtype.

Introduction

Prader-Willi syndrome (PWS) is caused by a structural or functional loss of the genetic contribution from a region of the long arm of chromosome 15 (q11-q13). Approximately 70% of cases are caused by a deletion from the paternal chromosome 15 (DEL), and approximately 25% are due to the inheritance of two copies of the maternal chromosome (maternal uniparental disomy [UPD]). In addition, approximately 5% of cases arise from genetic

mutations that lead to abnormal silencing of gene expression from the paternally transmitted chromosome. Autism is a genetically heterogeneous, behaviorally defined syndrome characterized by deficits in social reciprocity; delayed, absent, or deviant language development; and the presence of highly restricted interests and stereotypies. Individuals manifesting significant impairment in social functioning who do not display all features of the syndrome are diagnosed with either Asperger's syndrome or pervasive developmental disorder not otherwise specified (PDD-NOS). Collectively, autism, Asperger's syndrome, and PDD-NOS frequently are referred to as the autism spectrum disorders (ASDs), recognizing the heterogeneous nature of this set of disorders. Although there has been notable progress of late identifying genes that may contribute to increased risk for ASD [1,2], both the genetic architecture and molecular neurobiology of these syndromes remain largely a mystery [3].

It has long been noted that the genetic lesions underlying PWS may lead to a range of physical, cognitive, and behavioral manifestations. However, it has only recently been appreciated that individuals with the syndrome may be at increased risk for ASD. In particular, as reviewed later, it appears that those with maternal UPD are at greater risk for autistic symptomatology compared with individuals carrying paternal deletions of 15q11-q13. These findings are particularly intriguing for several reasons: first, increased copies of the maternal chromosome in the same genomic interval are the most common cytogenetic abnormality found in association with idiopathic autism (1% to 3% of cases) [4–6]; second, Angelman's syndrome, which is also caused by abnormalities in the 15q11-q13, also shares some phenotypic overlap with ASD [7]; and third, preliminary evidence suggests that gene regulation in this interval may be abnormal in the brains of individuals with a range of neurodevelopmental disorders, including autism and Rett and Angelman's syndromes [8,9]. In light of the relation of 15q11-q13 to autism, the phenotypic similarities between PWS and autism therefore may stem from some common genetic mechanism. Further detailed studies of the PWS behavioral phenotype, in addition to ongoing efforts to elaborate

the underlying biology of the disorder are likely to make an important contribution to the understanding of both normal and abnormal social development.

PWS Background

PWS is a neurodevelopmental disorder characterized primarily by hyperphagia and food preoccupations. Associated behaviors often include persistent hunger, obsessive thoughts about food, food-related compulsivity, food foraging, and increased likelihood of obesity. The physical phenotype also includes characteristic facial appearance, hypotonia, short stature, small hands and feet, and hypogonadism. Individuals with PWS typically also exhibit mild to moderate mental retardation and various internalizing and externalizing symptoms, of which food- and nonfood-related compulsivity are the most predominant characteristics [10–15].

PWS is caused by abnormalities of chromosome 15q11-q13 that result in the loss of the normal contribution from paternally inherited genes in this interval. Several of the transcripts in this region are imprinted, meaning that expression is dependent on the parent of origin of the chromosome. Consequently, the normal contribution of paternally expressed transcripts may be absent due to the physical loss of DNA from the father's chromosome, the inheritance of two copies of the maternal and no paternal chromosomes 15, or mutations that disrupt normal imprinting in this interval. In contrast, Angelman's syndrome, characterized by severe mental retardation, unusual gait and tremors, and sudden bursts of inappropriate laughter, results from abnormalities affecting the maternal contribution in the same interval, including deletions of the maternal chromosome, paternal UPD, imprinting mutations, and point mutations of a maternally expressed gene in this region, ubiquitin protein ligase E3A (UBE3A).

As noted, the majority of cases of PWS are the result of deletions, with most of the remainder resulting from maternal UPD. The DEL subtype may be further divided into type I and type II deletions [16]. The larger type I deletion is found in approximately 40% of individuals carrying deletions and involves a breakpoint that is closer to the centromere. The type II deletion is classified by a more distal centromeric breakpoint, which results in the loss of less genetic material [17].

Much of the early research on defining the PWS phenotype focused on identifying traits prevalent among the majority of individuals with the syndrome regardless of the underlying genetic mechanism. However, it has become increasingly clear that some of the variability seen in the clinical presentation among individuals with PWS may be a consequence of the nature of the specific genetic abnormality. Most research suggests that those with the DEL subtype are comparatively more severely affected across a number of domains, including the characteristic facial

appearance and hypopigmentation [18], intelligence [19], maladaptive behavior [20], and self-injurious behavior [21]. However, findings also suggest that individuals with UPD are at increased risk for developing atypical psychosis after adolescence (see [22] for a recent review) but are at similar risk for compulsive behavior [15,23•–25•].

Phenotypic characterization by deletion classification (type I vs type II) also has begun, with preliminary findings pointing to an increased risk for poor academic performance and maladaptive behavior for those with type I deletions [17,26]. However, not all studies have reached the same conclusions [24•]. We expect research over the next several years to clarify these initial findings.

PWS Compulsivity Versus Repetitive Behavior in Autism

Compulsive behavior has been of major interest to researchers investigating the PWS phenotype [12,14,15,20,27–29]. Individuals with PWS often exhibit specific behaviors that are repetitive and ritualistic in nature. In many instances, these behaviors are related to a preoccupation with food or food seeking, but non-food-related behaviors also are frequently seen. Older children and adults with PWS exhibit statistically significant elevations on the compulsivity subscale of the Yale-Brown Obsessive Compulsive Scale [12,14,30]. Compulsive/repetitive behavior is also common in early childhood among those with PWS. Dimitropoulos et al. [27] found that preschoolers with PWS displayed more types of compulsive behavior than children with Down syndrome. In PWS, the severity of repetitive behavior is related to severity of hyperphagia symptomatology, which may indicate a unique mechanism for repetitive behavior in this population [15].

Although systematic research shows similarities in compulsive behavior between PWS and obsessive-compulsive disorder (OCD), one difference that may be important is that those with PWS do not find these behaviors egodystonic or anxiety-provoking, and they actually may often be desired or enjoyable [31]. Furthermore, the types of behavior that are commonly seen in PWS (eg, hoarding, insistence on routines, ordering and arranging objects, and repeating rituals) differ from the typical behaviors seen in OCD, which most often involve obsessions regarding contamination, religion, and sexuality and compulsions such as checking and counting. Thus, although the number of compulsions and severity of behavior may be similar between OCD and PWS, individuals with PWS exhibit a distinct profile of behaviors that does not overlap with the most common compulsions exhibited in OCD.

In contrast, there is significant overlap in the types of repetitive behavior exhibited by individuals with PWS and those with ASD. Repetitive behavior is a central feature of ASD and is often expressed by ordering or arranging objects, repeating phrases, preoccupations with specific topics, preference for routine, and stereotypy. As with

PWS, not only do the types of behavior exhibited by individuals with ASD differ from those most common to OCD, but they also may not be bothersome and may even elicit pleasure for the individual [32–34]. Recent research has begun to examine the similarities between PWS and ASD by either direct comparison or by administering ASD diagnostic measures to individuals with PWS. For example, in a direct comparison to children and adolescents with ASD, Greaves et al. [23•] found similar levels of repetitive and ritualistic behavior between children with PWS and those with ASD, even with regard to the frequency and intensity of the exhibited behavior. Groups differed only by the prevalence of a few individual behaviors, including a higher proportion of children with PWS engaging in hoarding behavior compared with more children with ASD having strong preferences for certain foods, lining up objects, and seemingly very aware of minute details (eg, imperfections, flecks of dirt). We recently studied and compared 42 participants with autism and 32 participants with PWS and found similar increased rates of compulsive behaviors (eg, need for routine and ordering and arranging) [35]. In addition, total scores on the Developmental Behavior Checklist (DBC) [36], a validated instrument used to evaluate behavioral disturbance in individuals with intellectual disability, did not differ between groups; mean scores for both ASD and PWS were above the clinical cutoff for behavioral disturbance. Clinician-administered evaluations and surveys designed to assess ASD also indicate elevated repetitive behavior symptomatology in PWS, even when compared with controls matched for IQ, gender, and age [24•,25•,37•]. Collectively, these findings suggest that the behaviors of those with PWS may be more similar to those of ASD than OCD, and reconsidering repetitive behavior in PWS in terms of autistic-like symptomatology may be appropriate, except in cases in which behavior is clearly anxiety provoking and causes significant distress to the individual.

Prevalence of Autism Comorbidity in PWS

To date, there have been few systematic investigations of comorbid autism in PWS. In addition, in those studies that have been undertaken, results have not been completely consistent. Reddy and Pfeiffer [11] reported higher levels of psychopathology in PWS compared with controls with mental retardation, including both externalizing and internalizing behavior, conduct, anxiety, and attention, but found no significant differences with regard to autism. However, Descheemaeker et al. [25•] found that the mean score on the Pervasive Developmental Disorder Mental Retardation Scale was higher among PWS patients than among mentally retarded controls. However, the higher score on this dimensional measure of autistic symptomatology did not translate into a larger percentage of individuals with PWS meeting diagnostic criteria for an ASD as compared with mentally retarded controls

(19% of PWS and 15% of controls). Among individuals with PWS, higher IQ (> 70) and UPD genetic status were additional risk factors for increased autistic symptomatology. These PWS subtype data are consistent with other recent findings. Veltman et al. [37•] found significantly higher total scores on the Autism Screening Questionnaire (ASQ) [38] among individuals with UPD compared with those with DEL. However, as with the Descheemaeker et al. [25•] study, the rate of comorbid ASD diagnoses did not differ by genetic subtype. In contrast, in a review of all published PWS cases, Veltman et al. [39] found that overexpression of maternally imprinted genes in the 15q11-q13 region, such as in those with UPD, increases the risk of having comorbid ASD when compared with individuals with DEL or Angelman's syndrome. These findings must be interpreted with caution because of the difficulty equating rates of ASD diagnosis across studies in which ASD was not assessed using the same diagnostic criteria or gold standard diagnostic tools.

Collectively, these findings suggest that there may be increased ASD symptomatology in those with PWS compared with those with nonspecific mental retardation, even if the degree of ASD symptomatology is not enough to more frequently warrant a comorbid ASD diagnosis. However, the data are quite provocative, as they suggest that within-syndrome variability in autistic-like symptomatology may be related to genetic subtype. Clearly, more work needs to be done, as all studies to date have been underpowered, with relatively small samples and an overreliance on symptom checklists for making an ASD diagnosis. Further examination of these subtype differences is warranted using gold standard, clinician-administered diagnostic tools. In a preliminary study, our group has used such tools and found evidence in favor of greater autistic symptomatology and ASD diagnoses in those with a UPD versus DEL [35]. We have studied 17 participants with PWS (DEL = 11, UPD = 6), and only individuals with UPD (two of six) met criteria for ASD by the Autism Diagnostic Observation Schedule (ADOS). This rate of ASD is comparable to that predicted by Veltman et al.'s [37•] literature review. Moreover, 50% of our UPD sample met ASD criteria in the communication domain. In contrast, individuals with DEL did not meet criteria for ASD in any domain of functioning. Additional research incorporating both larger samples and validated diagnostic tools for assessing ASD are needed to further test the hypothesis that maternal UPD of chromosome 15 is a specific risk factor for autistic symptomatology.

Recent Evidence of Social Impairment

Clinical reports suggest that the social characteristics of those with PWS change after early childhood. In general, infants and toddlers with PWS initially appear to be happy, affectionate, and friendly but later develop significant behavior problems that include temper tantrums,

stubbornness, and food-related maladaptive behavior. Both clinical and research reports also suggest that older children and adults with PWS exhibit poor peer relationships, lack of friends, immaturity, weakness in coping skills, and preference for solitary activities [10,13,40,41]. Dykens and Cassidy [41] found that increasing age was associated with negative self-image and isolation in those with PWS, and almost 60% exhibited social inadequacies. This social impairment may be related to other maladaptive behaviors seen in PWS, including impulsivity, compulsivity, and temper outbursts, and perhaps also the lack of sexual maturity in adolescence [13,41]. Social and adaptive behavior have not received much empirical attention, as much of the behavioral research examining the PWS phenotype has focused primarily on other predominant maladaptive behaviors (eg, compulsivity) and not on examining the specific factors that contribute to social impairment. However, although individuals with PWS clearly do not exhibit the severity of deficits in social reciprocity found in autism proper, many of their social behaviors appear to be on the same continuum of social deficits found in ASD (eg, social withdrawal, poor peer relationships, lack of empathy).

In light of the 15q11-q13 findings in autism, researchers have started to examine social impairment in PWS more closely. Recent research suggests that individuals with PWS have significant social deficits compared with individuals with other forms of intellectual disability, and those with UPD subtype may be at increased risk for social impairment. Using a social attribution task (SAT) [42] that measures the ability to automatically employ a social template when asked to interpret an ambiguous visual display, Koenig et al. [43•] found strikingly similar social deficits between IQ- and age-matched participants with PWS and individuals with ASD; both the PWS and ASD groups were significantly impaired on this social perceptual task compared with matched controls. Five of the eight SAT indices distinguished PWS and ASD from the matched controls. Participants with PWS had significant difficulty trying to organize the task's visual information into a coherent social story, interpreting only 15% of the information correctly, as opposed to 40% for the control group. In addition, those with PWS and ASD made fewer attributions of feeling states and shared feeling states that result from social situations (eg, jealousy); these feeling state attributions were critical to understanding the social story in this task. These findings suggest that the social impairment exhibited by individuals with PWS represents a core deficit that is not merely a consequence of associated maladaptive behavior but rather reflects a specific difficulty interpreting social information.

The degree of social impairment also appears to differ by PWS genetic subtype. Milner et al. [24•] reported greater deficits in reciprocal social interaction in participants with UPD in comparison to both type I and type II DEL groups. They studied 49 individuals with UPD and

found greater social impairment on the ADOS, the ASQ, and the Autism Diagnostic Interview compared with other PWS subtypes. Interestingly, group differences were not found on the social domain of the Vineland Adaptive Behavior Scales. As the authors suggest, this discrepancy may indicate that the impairment concerns differences in autistic-like behavior rather than adaptive social behavior. These findings are consistent with other reports of increased social isolation in those with UPD compared with individuals with DEL [25•]. In a direct comparison of PWS and ASD, subscale analyses of the DBC [36] indicate that UPD is equivalent to ASD on autistic relating (eg, doesn't show affection, aloof, doesn't respond to others' feelings, unhappy) and the self-absorbed subscale (eg, loner, preoccupied with trivial items, runs away) [35].

This growing body of evidence suggests that more attention must be paid to the PWS social phenotype. Some of these impairments may be due to food seeking and perseveration; however, this recent research, albeit still rather small in quantity, suggests that there may be underlying social impairment that falls within the continuum of social reciprocity deficits in ASD.

Genotype-Phenotype Correlations

As noted, the current findings suggest that individuals with PWS are at increased risk of exhibiting autistic symptomatology. Two core deficits of ASD, social impairment and repetitive behavior, are evidenced in PWS. Furthermore, the extant literature suggests that those with UPD subtype may be at greater risk of social impairment than other genetic subtypes. Finally, as noted, maternal duplications and triplications in this same genomic interval have been associated with idiopathic autism.

At first blush, these findings would seem to offer the possibility of linking a specific genetic mechanism—that is, overexpression of maternal genes in this region—directly with ASD. Indeed, further study of both of the behavioral phenotypes associated with duplicated and triplicated maternal chromosomes, as well as ongoing intensive study of gene expression and regulation in the region may well begin to clarify this relationship. However, at present, there are divergent findings relating abnormalities in this genomic interval to social disability that make straightforward conclusions difficult. First, although there has been a reported preponderance of maternal duplications and triplications in this region associated with ASD, paternal abnormalities also have been identified [44]. Moreover, the 15q11-q13 interval has been implicated in social disability associated with the absence of a maternal contribution in this region [7]. Individuals with Angelman's syndrome display some overlapping features with those with severe forms of autism. A recent investigation of autism symptomatology in Angelman's syndrome found that 42% of participants met criteria for autism by ADOS evaluation [7]. In contrast to those who did not meet criteria for ASD, children who

met criteria rarely directed vocalizations to others, were not responsive to their names, and did not exhibit shared enjoyment in social interactions. Interpretation of these findings is complicated by the fact that children who met ASD criteria also scored significantly lower on cognition, language, and adaptive behavior, and that their average age was less than 4 years, thus raising the possibility of measurement problems in such a young and severely retarded group. It will be important to look carefully at social skills in older individuals with Angelman's syndrome before reaching any conclusions.

An understanding of the role of 15q11-q13 in social disability is further complicated by the identification of a putative association between common alleles of the nonimprinted gene (GABRB3) and autism, although these findings have not yet been convincingly replicated [45]. Finally, recent evidence points to dysregulation of gene expression in the 15q11-13 region in Angelman's syndrome, Rett syndrome, and autism [8,9]. In this case, reduced expression of UBE3A and GABRB3 was found in the brains of individuals with these syndromes, as well as in Rett mouse models. How such findings relate to the observation of an association of UPD and maternal duplications with ASD remains to be clarified.

In summary, although phenotypic research indicates autistic symptomatology is present in PWS and to a greater extent in those with maternal UPD subtype, several lines of evidence suggest that there may be overlapping biological mechanisms involved in PWS, Angelman's syndrome, Rett syndrome, and some cases of ASD that converge on chromosome 15. Further study of the contribution of 15q11-q13 to a range of disorders involving social and cognitive disability clearly is needed to fully understand the involved mechanisms.

Conclusions

Current findings suggest that individuals with PWS exhibit behavior characteristic of ASDs, including repetitive behavior and deficits in social relatedness. This phenotypic evidence suggests that overexpression of maternal genes in the region may be associated with increased social impairment in contrast to other causal mechanisms of PWS. Continued examination of autistic-like symptomatology in this population is warranted. However, future research should include methodology that incorporates direct comparison to ASD and gold standard diagnostic tools to assess ASD symptomatology. In addition, examining the PWS behavioral phenotype in relation to other neurodevelopmental disorders biologically linked to the 15q11-q13 region is critical to uncovering the genetic mechanisms involved. Understanding the behavioral and biological similarities and differences between these neurodevelopmental disorders will not only lead to more specified treatment options for individuals with these disorders but aid in illuminating a probable genetic pathway to ASDs.

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