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Maladaptive Behavior Differences in Prader-Willi Syndrome Due to Paternal Deletion Versus Maternal Uniparental Disomy

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Maladaptive behavior was compared across 23 people with Prader-Willi syndrome due to paternal deletion to 23 age- and gender-matched subjects with maternal uniparental disomy. Controlling for the higher IQs of the uniparental disomy group, deleted cases showed significantly higher maladaptive ratings on the Child Behavior Checklist's Internalizing, Externalizing, and Total domains as well as more symptom-related distress on the Yale-Brown Obsessive–Compulsive Scale. Across both measures, deleted cases were more apt to skin-pick, bite their nails, hoard, overeat, sulk, and withdraw. A dampening of symptom severity is suggested in Prader-Willi syndrome cases due to maternal uniparental disomy. Findings are compared to Angelman syndrome, and possible genetic mechanisms are discussed, as are implications for Prader-Willi syndrome and obsessive–compulsive behaviors.

Although Prader-Willi syndrome was only recognized 41 years ago (Prader, Labhart, & Willi, 1956), data have fast accumulated on the physical, behavioral, and genetic features of this common developmental disorder. The physical phenotype of Prader-Willi syndrome is now relatively well-described: infantile hypotonia, short stature, small hands and feet, characteristic facial appearance, hypopigmentation, and hypogonadism. Hyperphagia, perhaps the syndrome's most striking feature, begins in early childhood and is associated with persistent food-seeking and increased risks of obesity in affected individuals (Holm et al., 1993).

People with Prader-Willi syndrome also show a distinctive behavioral phenotype, which often includes significant levels of maladaptive behavior. Between 75% to 98% of the individuals in our samples show acting-out behaviors, such as temper tantrums, impulsivity, aggressivity, and stubbornness (Dykens & Cassidy, 1995; Dykens & Cassidy, in press; Dykens, Hodapp, Walsh, & Nash, 1992a). These problems are certainly not unique to individuals with Prader-Willi syndrome, yet

they do appear more often and more severely in people with this syndrome relative to individuals with mild to moderate mental retardation due to other causes (Dykens & Kasari, 1997).

Although hyperphagia, food preoccupations, and persistent food-seeking behavior are also central features of Prader-Willi syndrome, many people with this disorder show preoccupations and repetitive, compulsive-like behaviors that are not related to food. Frequent non-food compulsions include skin-picking, needing to tell or say things, ordering and arranging, sorting, hoarding, counting, and concerns with symmetry or exactness (Dykens, Leckman, & Cassidy, 1996). Indeed, 97% of a sample of 91 subjects with Prader-Willi syndrome showed persistent skin-picking, and 71% exhibited a mixture of compulsive behaviors, such as hoarding, ordering and arranging, redoing, and needing to tell or ask (Dykens & Cassidy, in press; Dykens et al., 1996). People with Prader-Willi syndrome appear to be at increased risk for obsessive–compulsive disorder (Dykens et al., 1996), and a blend of repetitive, compulsive-like behaviors are robust diagnostic predictors of Prader-Willi syndrome as opposed to other types of mental retardation (Dykens & Kasari, 1997; Dykens & Smith, in press).

Although the behavior of persons with Prader-Willi syndrome is, thus, increasingly well-understood, genetic advances now allow more refined differentiation of the Prader-Willi behavioral phenotype. It is now appreciated that about 70% of cases with Prader-Willi syndrome are associated with a paternally derived deletion on chromosome 15 [15(q11-q13)] (Ledbetter et al., 1981). The majority of remaining individuals have maternal uniparental disomy of chromosome 15, in which both copies of chromosome 15 are derived from the mother (Nichols et al., 1989). In contrast, when the deletion occurs on the maternally derived chromosome, or when there is paternal uniparental disomy, it results in Angelman syndrome, a dramatically different developmental disorder. Unlike Prader-Willi syndrome, people with Angelman syndrome typically have severe to profound mental retardation, limited expressive language, microcephaly, seizure disorders, an ataxic gait, and bouts of inappropriate laughter (Williams et al., 1995). Prader-Willi and Angelman syndromes, then, show the process of imprinting, whereby some genes are expressed differently, depending on whether they were inherited from the mother or the father. The genes relevant to Prader-Willi syndrome are active only when inherited from the father; the opposite is true for Angelman syndrome.

People with either the paternal deletion or maternal uniparental disomy share Prader-Willi syndrome's cardinal features, and researchers to date have found only a few phenotypic differences between these two genetic causes of Prader-Willi syndrome. Physically, individuals with deletions seem more apt to show typical facial features (Cassidy et al., 1997) as well as hypopigmentation (Butler, 1989; Cassidy et al., 1997; Gillessen-Kaesbach et al., 1995; Mitchell et al., 1996). Relative to those with deletions, people with maternal uniparental disomy have increased birth weights, a shorter course of gavage feeding in infancy, a later age of onset of hyperphagia, a later age of diagnosis, and their mothers show advanced maternal age (Cassidy et al., 1997; Gillessen-Karsbach et al., 1995; Gunay-Aygun & Cassidy, 1997; Mitchell et al., 1996). In essence, then, findings suggest a more mild expression of some physical symptoms among individuals with uniparental disomy and lend support for examining possible behavioral differences between these two genetic causes of Prader-Willi syndrome.

So far, the behavioral aspects of Prader-Willi syndrome have yet to be systematically compared across individuals with paternal deletion versus maternal uniparental disomy. Early observations

suggest a lower IQ among nondeleted individuals (Butler, Meaney, & Palmer, 1986), yet in more recent comparisons investigators found no significant IQ differences between 12 deleted versus 14 uniparental disomy individuals (Cassidy et al., 1997). Using informal clinical impressions, Gillessen-Kaesbach et al. (1995) suggested that there are no apparent differences between deleted versus uniparental disomy subjects in skin-picking, sleep disturbance, degree of mental retardation, or behavioral problems. Using retrospective ratings of patient charts, however, Cassidy et al. (1997) found increased rates of skin-picking and more frequent reports of an apparently high pain threshold among subjects with deletions.

Although behavior differences are inconsistently suggested, researchers have yet to measure behavior in a systematic way across deleted versus uniparental disomy groups. None of the previous researchers used standardized measures of behavior; instead, they relied on methodology that may not be sensitive enough to detect small differences across these two genetic subtypes of Prader-Willi syndrome. If behavioral differences exist across deleted versus uniparental disomy cases, they may, thus, be subtle, requiring a more systematic method of study than has previously been tried.

To this aim, we designed the present study to compare the maladaptive behavior of 23 individuals with Prader-Willi syndrome due to paternal deletion to 23 age- and gender-matched subjects with maternal uniparental disomy. We assessed the type and severity of maladaptive behavior with two standardized measures: the Child Behavior Checklist (Achenbach, 1991), which is used to examine a broad range of behavior problems, and the Yale-Brown Obsessive–Compulsive Scale (Goodman et al, 1989), which is used to assess obsessive–compulsive symptomatology typically seen in people with Prader-Willi syndrome.

Method

Subjects

Participants were 46 individuals with Prader-Willi syndrome (18 males, 28 females): 23 had paternal deletions and 23 had uniparental disomy. Participants were recruited during the 1996 and 1997 annual meetings of the national Prader-Willi Syndrome Association (n = 19) as well as from the Prader-Willi Syndrome Clinics at the University of California, Los Angeles (n = 15), University of Connecticut (n = 5), and Case Western Reserve University (n = 7). We assessed whether subjects recruited from the three clinics (n = 27) differed from participants recruited from the national Prader-Willi Syndrome Association meetings (n = 19). No evidence of an ascertainment bias was found; subjects from both sources had comparable ages, body mass indices (BMIs), IQs, and maladaptive behavior ratings.

Participants ranged in age from 6 to 42 years (M = 17, standard deviation [SD] = 9.42). The subjects' BMIs (weight in kg/[height in m]^2) ranged from 15.26 to 62.67 (M = 30.73 SD = 10.22). The majority of subjects (72%) were obese, as determined by age-appropriate BMI cut-off points for obesity.

The mean IQ of the sample was 67 (SD = 10.69). IQs were ascertained in two ways. For 20 subjects, seen in two of the university clinics, IQs were obtained through direct administration of a standardized measure, the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990). For the remaining participants, we used IQs derived through parental reports of previously administered standardized intelligence tests (either the Stanford-Binet Intelligence Scale: Fourth Edition or Wechsler-based or Kaufman-based tests).

All subjects had molecular genetic testing for Prader-Willi syndrome. Twenty-three subjects had Prader-Willi syndrome associated with chromosome 15 deletion [del 15(q11-13)], and 23 subjects had Prader-Willi syndrome associated with

maternal uniparental disomy. Genetic testing for Prader-Willi syndrome was conducted at either the University of California Los Angeles, University of Connecticut, or Case Western Reserve University, under the direction of one of the three investigators. For remaining subjects, copies of previous genetic testing results were obtained. These tests were conducted at other universities or diagnostic laboratories and were reviewed for accuracy by one of the three researchers. Current molecular genetic testing techniques for Prader-Willi syndrome allow identification of approximately 98% of persons with the Prader-Willi genotype (American Society, 1996).

Participants with uniparental disomy were individually matched on age and gender to subjects with deletions (pairs of subjects were matched within one year of their age). As uniparental disomy individuals are less common than deletion individuals, we first solicited uniparental disomy subjects, and then obtained appropriate age and gender matches for them from our larger roster of subjects with deletions. There were 8 males and 15 females in each of the deletion and uniparental disomy groups. Their average age was approximately 17 years (see Table 1).

Table 1
Subject Characteristics

	Paternal deletion		Maternal UPD[b]	
Characteristic	Mean	*SD*	Mean	*SD*
Age	16.81	9.78	17.00	9.27
BMI[a]	33.23	10.65	28.23	9.33
IQ	62.97	8.83	70.93	11.15

[a]Body mass index. [b]Uniparental disomy.

Procedure and Measures

Parents of offspring with Prader-Willi syndrome were invited to participate in an ongoing study of the behavioral features of children and adults with Prader-Willi syndrome. For the 27 clinic-based subjects, parents were asked to complete a packet of standardized questionnaires either prior to or during their clinic visit. The 19 families recruited at the annual Prader-Willi Syndrome Association meetings were given a packet of questionnaires to complete at their leisure and to return to us in the mail. We obtained responses to any missing items by interviewing parents directly or in follow-up telephone interviews.

Demographic questions. Parents were asked to supply their affected child's age, gender, height, weight, previous intelligence test results, names of current psychotropic and other medications, and genetic testing information (where and when testing was conducted, by whom, and the results). For families attending the clinics, subjects' heights and weights were also obtained during their clinic visits.

Child Behavior Checklist. On this widely used, standardized checklist parents are asked to rate 112 maladaptive behaviors on a 3-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true). The checklist contains three major factors; Internalizing Problems, Externalizing Problems, and Total problems, as well as nine clinical subdomains. Three subdomains comprise the Internalizing domain (Withdrawn, Somatic Complaints, Anxious/Depressed), and two subdomains are contained in the Externalizing domain (Delinquent Behavior, Aggressive Behavior). The four remaining clinical subdomains are Social Problems, Thought Problems, Attention Problems, and Other Problems. The checklist raw scores were used in all data analyses, though total Child Behavior Checklist raw scores were converted to *T* scores for one set of analyses. The checklist has been successfully used in previous studies involving people with mental retardation (Dykens & Cohen, 1996; Dykens & Kasari, 1997).

Yale-Brown Obsessive–Compulsive Scale. The informant-version of the Yale–Brown Obsessive–Compulsive Scale was used to assess both the types and severity of obsessive–compulsive symptoms. Twenty-seven behaviors were rated as

being present in the past week or ever, and data analyses were based on the ever or life-time ratings. The Yale–Brown Obsessive–Compulsive Scale was scored using four robust and recently delineated factors: Obsessions-Checking, Symmetry-Ordering, Contamination-Cleaning, and Hoarding (Leckman et al., 1997). Three miscellaneous compulsions were analyzed separately because they are not a part of the Yale–Brown Obsessive–Compulsive Scale factor structure but are highly pertinent to the Prader-Willi behavioral phenotype (skin-picking, food rituals, pulls out hair). Symptom severity was rated across three dimensions using a 5-point scale. Symptom severity items assessed the extent to which obsessions and compulsions were time-consuming, distressful, or caused impairments in social-adaptive functioning. The Yale–Brown Obsessive–Compulsive Scale has been shown to have excellent reliability and validity (see Taylor, 1995, for a review).

Results

Preliminary Deletion Versus Uniparental Disomy Comparisons

Body mass indices and medication status. Body mass indices were compared across deleted versus uniparental disomy groups in a one-way analysis of variance (ANOVA). As shown in Table 1, although the deleted group showed higher mean BMIs than did the uniparental disomy group, the difference was not significant. The proportion of subjects on psychotropic medication was comparable across genetic groups. Four participants with deletions and 5 with uniparental disomy were on medication at the time of the study. Among the deleted individuals, 3 were on serotonin reuptake inhibitors, and one was on a tricyclic antidepressant. Similarly, 3 subjects with uniparental disomy were taking serotonin reuptake inhibitors, one was on a neuroleptic and one was on a stimulant. The 9 participants on medication showed similar levels of Child Behavior Checklist and Yale–Brown Obsessive–Compulsive Scale scores as did subjects not on medication, as determined in one-way ANOVAs.

IQ. Significant IQ differences were found across the two genetic groups, $F(1, 45) = 6.71$, $p < .01$. As summarized in Table 1, participants from the deleted group had lower mean IQs than did those from the uniparental disomy group. Because IQs were obtained through two different means, we checked to ensure that the 20 clinic-based subjects who received direct testing with the Kaufman Brief Intelligence Test showed similar patterns of results as remaining subjects with previously administered standardized tests. Composite IQs from the Kaufman Brief Intelligence Tests were significantly lower for the 10 deleted individuals relative to the 10 uniparental disomy clinic individuals, $F(1, 19) = 5.38$, $p < .05$ (Ms = 61.80 and 71.80, respectively). The remaining 13 deletion and 13 uniparental disomy individuals also showed this pattern (Ms = 64.15 and 70.07, respectively), though the F was not significant. IQ was not significantly correlated with the Child Behavior Checklist or Yale–Brown Obsessive–Compulsive Scale scores in either deleted or uniparental disomy subjects. Even so, as mean IQs differed across the two genetic groups, IQ was used as a covariate in all between-group analyses.

Maladaptive Behavior Comparisons

Child Behavior Checklist major domains. We used analyses of covariance to compare the Internalizing, Externalizing, and Total Child Behavior Checklist domains across the two genetic groups, with IQ as the covariate. As shown in Table 2, the deleted group had significantly higher Internalizing, $F(1, 45) = 8.32$, $p < .01$, Externalizing, $F(1, 45) = 4.67$, $p < .05$, and Total Child Behavior Checklist mean raw

Table 2
Means and *SD*s for Child Behavior Checklist Domains Across Groups

Domain	Paternal deletion		Maternal UPD[a]	
	Mean	*SD*	Mean	*SD*
Internalizing	15.74	7.20	10.00	6.75
Externalizing	19.83	8.88	14.13	7.34
Total score	68.00	17.58	51.56	22.49

[a]Uniparental disomy.

scores, $F(1, 45) = 7.74$, $p < .01$, than did the uniparental disomy group.

To further explore these findings, we converted Child Behavior Checklist total raw scores to *T* scores, and using cut-points established by Achenbach (1991), we calculated the proportion of subjects who showed clinically elevated *T* scores. Of the deletion group, 83% had clinically elevated *T* scores, and 17% had scores in the borderline clinical range. In contrast, only 57% of the uniparental disomy group had clinically elevated *T* scores, 17% had scores of borderline clinical significance, and 26% had scores in the normal range. A 2 × 3 chi-square (genetic status by clinical, intermediate, normal *T* scores) was significant, χ^2 (2, $N = 46$) = 7.12, $p < .05$.

Child Behavior Checklist clinical domains. Significant Child Behavior Checklist between-group differences were further examined in a multivariate analysis of covariance (MANCOVA), with the nine Child Behavior Checklist clinical subdomains and IQ as the covariate. The MANCOVA was significant, $F(9, 35) = 2.94$, $p < .01$, with the deletion group showing consistently higher mean scores than did the uniparental disomy group. Using a Bonferroni-corrected value of $p < .005$, we found that two domains reached statistical significance: Withdrawn and Other. Table 3 shows the means and standard deviations (*SD*s) for the deletion and uniparental disomy groups across the nine domains.

To further specify how deletion and uniparental disomy individuals might differ, we conducted follow-up analyses with selected Child Behavior Checklist items that comprised the Withdrawn and Other domains. We examined frequently occurring behaviors, those that occurred in 50% or more of individuals in either the deletion or uniparental disomy group. As shown in Table 4, 5 behaviors occurred

Table 3
Means, *SD*s, and *F* Values for Child Behavior Checklist Clinical Domains Across Groups

Domain	Paternal deletion		Maternal UPD[a]		
	Mean	*SD*	Mean	*SD*	*F*
Withdrawn	5.61	2.81	3.26	2.30	10.59****
Somatic Complaints	4.08	3.33	2.39	1.92	4.72+
Anxious/ Depressed	6.04	3.51	4.35	3.79	2.56
Social Problems	8.35	2.64	7.47	3.20	3.14
Thought Problems	3.39	1.62	3.22	2.33	.880
Attention Problems	7.26	2.70	7.08	3.70	.544
Delinquent Behavior	5.17	3.31	3.69	2.67	1.92
Aggressive Behavior	14.65	6.73	10.43	6.32	4.42+
Other	13.43	3.70	9.65	4.48	9.28***

Note. Bonferroni-corrected value is $p < .005$.
[a]Uniparental disomy.
+$p < .05$. ***$p < .004$. ****$p < .002$.

Table 4
Proportion of Subjects (in %) by Group Showing Specific Child Behavior Checklist Behaviors by Domain

Domain/Behavior	Paternal deletion	Maternal uniparental disomy	χ^2
Withdrawn			
Underactive	96	74	4.21+
Rather be alone	65	52	.37
Secretive	60	52	.55
Withdrawn	52	17	6.13*
Sulks	50	13	6.57*
Other			
Skin-picks	100	69	8.25**
Overeats	96	65	6.77**
Speech problems	70	65	.75
Hoards	65	35	4.26+
Sleep more than others	61	65	.76
Bites nails	61	22	7.26**

Note. For Withdrawn domain, Bonferroni-corrected value is $p < .01$; for Other domain Bonferroni-corrected value is $p < .008$.
+$p < .05$. *$p < .01$. **$p < .008$.

frequently in the Withdrawn domain and 6, in the Other domain. Using Bonferroni-corrected p values for each domain, we found that 5 behaviors showed significant group differences. Relative to uniparental disomy individuals, subjects with deletions showed higher frequencies of withdrawal, sulks, nail-biting, skin-picking, and overeating.

Yale–Brown Obsessive–Compulsive Scale Symptoms. The four Yale–Brown Obsessive–Compulsive Scale factor scores were compared across deleted versus uniparental disomy groups in ANCOVAs, with IQ as the covariate. The Hoarding factor proved significant, $F(1, 43) = 4.12$, $p < .05$, with subjects with deletions showing significantly higher Hoarding scores than did the uniparental disomy group, (*M*s = .61 and .34, respectively). Remaining factors were not significant across groups.

We also used ANCOVAs to compare the three miscellaneous Yale–Brown Obsessive–Compulsive Scale items specific to Prader-Willi syndrome. The deleted group showed significantly higher scores in skin-picking, $F(1, 43) = 9.88$, $p < .01$ (*M*s = .96 vs. .65, respectively). There was a nonsignificant trend for subjects with deletions to have higher scores in "pulls hair out," $F(1, 43) = 3.14$, $p < .07$. Food ritual scores were comparable across groups.

Yale-Brown Obsessive–Compulsive Scale symptom severity. Analyses of covariance revealed significantly higher severity ratings in symptom-related distress among subjects with deletions as opposed to those with uniparental disomy, $F(1, 43) = 6.98$, $p < .01$, (*M*s = 1.65 vs. .69, respectively). No significant differences were found in the two remaining severity ratings--adaptive interference and time engaged in symptoms--although the deletion group showed slightly higher mean scores than did uniparental disomy individuals in both ratings (*M*s = 1.35 vs. .96 and 1.52 vs. 1.17, respectively).

Discussion

A dampening of symptom severity is suggested among Prader-Willi syndrome individuals due to maternal uniparental disomy versus paternal deletion. Controlling for higher IQs in the uniparental disomy group, we found that subjects with paternal deletions showed significantly higher total Child Behavior Checklist domain scores than did those with uniparental disomy. Further, significantly more subjects with deletions had Child Behavior Checklist scores that were in the clinically elevated range, again suggesting a more severe level of symptom expression in this group. Similarly, relative to individuals with uniparental disomy, the deletion group had more symptom-related distress on the Yale–Brown Obsessive–Compulsive Scale.

In addition to lower global ratings of maladaptive behavior, uniparental disomy subjects showed lower ratings in specific domains and behaviors on both the Child Behavior Checklist and Yale–Brown Obsessive–Compulsive Scale. These included externalizing and internalizing difficulties (e.g., withdrawal, sulks), as well as hoarding and a host of bodily related repetitive behaviors, such as skin-picking, nail-biting, and overeating. Across global and specific indices, then, findings suggest a milder behavioral expression among Prader-Willi individuals associated with maternal uniparental disomy relative to paternal deletion.

This pattern of findings mirrors recent findings in studies of Angelman syndrome, Prader-Willi's oppositely imprinted, genetic "sister syndrome." In contrast to Prader-Willi syndrome, most cases of Angelman syndrome are due to a maternally derived deletion in chromosome 15 (q11-q13), and only 5% of individuals are associated with paternal uniparental disomy of chromosome 15 (Williams et al., 1995). To date, 14 case reports of Angelman syndrome due to paternal uniparental disomy have been published (see Smith, Marks, Haan, Dixon, & Trent, 1997, for a

review). Relative to their counterparts with deletions, these individuals have better growth parameters, they walk at an earlier age, have milder ataxia, a lower frequency of seizures, and a greater facility with sign language (Smith et al., 1997).

Across both Prader-Willi and Angelman syndromes, then, a picture seems to be emerging of a milder phenotypic expression in individuals associated with uniparental disomy versus deletion. Although the reason for this difference is not yet known, several genetic mechanisms have been proposed to explain Angelman syndrome (Bottani et al., 1994; LaSalle & Lalande, 1995). One possibility is haploinsufficiency for deleted, nonimprinted genes within the large common deletion associated with Prader-Willi and Angelman syndromes. Another possible mechanism is that one or both of the common deletion breakpoints interrupt a gene whose consequence is an increase in phenotypic effect.

Among the most intriguing possibilities is the idea of imperfect imprinting, which suggests a dose-response effect. In particular, it may be that the process of switching off the expression of the relevant maternal genes in Prader-Willi syndrome (or paternal genes in Angelman syndrome) is incomplete, or "leaky." This partial expression of the gene(s) in two doses in uniparental disomy individuals versus one dose in deletion individuals could modify the manifestations of lack of gene expression. Thus, there would be a low level of expression from both chromosomes 15 in uniparental disomy and only one in deletion, possibly a significant difference.

A less severe behavioral expression in uniparental disomy individuals, however, is at odds with our clinical observation that, although Prader-Willi syndrome rarely co-occurs with autism, these comorbid individuals typically show maternal uniparental disomy and relatively low IQs Dykens & Cassidy, in press). These few cases may be associated with the increased risk of autism among persons with mental retardation in general (Dykens & Volkmar, 1997). Alternatively, some investigators have hypothesized that relationships exist between autism and other rare, recessive disorders in Prader-Willi syndrome uniparental disomy due to isodisomy (when the child has two copies of the same member of the maternal chromosome 15 pair) versus heterodisomy (when the child has both copies of the maternal chromosome 15 pair) (Rogan et al., 1994). Future research may thus show two subgroups of Prader-Willi individuals with maternal uniparental disomy, the majority of whom show a milder behavioral expression and the relatively few who show a more severe clinical presentation with lower IQs and co-occurring autism or autistic-like features.

Findings also provoke new avenues of work that further tie Prader-Willi syndrome to obsessive–compulsive disorder. In particular, subjects with deletions were much more prone to skin-pick, overeat, bite their nails, and, to some extent, pull out their hair. Although the association was less strong, hoarding also differed across groups. This blend of bodily related and hoarding symptoms may reflect deviant or exaggerated grooming or nesting behavior. In ethological models of obsessive–compulsive disorder, bodily related compulsions are cast as a type of grooming gone awry, and hoarding in this model is viewed as nesting gone awry (Swedo, 1989). Animal models of compulsive self-injury, including acral paw lick in dogs and self-biting in the rat, suggest an important role for serotonergic and dopaminergic mechanisms in fragmented grooming behavior (see King, 1994, for a review). Deviant grooming or nesting behaviors may also be mediated by oxytocin and other neuropeptides (Leckman et al., 1994), and preliminary studies suggest altered levels of both serotonin and hypothalamic oxytocin secreting neurons of people with Prader-Willi syndrome (Graham et al., 1995; Swaab, Purba, & Hofman, 1995).

Although speculative, it may be that certain bodily related and hoarding behaviors, and associated levels of serotonin or oxytocin, vary across genetic subtypes of Prader-Willi syndrome.

In addition to skin-picking, nail-biting, and hoarding, overeating emerged as more problematic in the deleted group relative to the uniparental disomy group. This discrepancy may relate to the modestly more elevated BMIs in the deletion relative to the uniparental disomy group as well as to previous reports of a later age of onset of hyperphagia in individuals with uniparental disomy (Gillessen-Kaesbach et al., 1995). Obsessions about food, noted on the Child Behavior Checklist and Yale–Brown Obsessive–Compulsive Scale, were similar across groups, suggesting a possible discontinuity in the uniparental disomy group between thinking about food and eating it. This discontinuity may be mediated by the better developed cognitive abilities of the individuals who have uniparental disomy as well as by their slight edge in controlling impulsive, externalizing behaviors over their counterparts with deletions.

Although provocative, findings are limited in that we did not systematically measure cognition in all participants. Although we directly tested 20 subjects, we relied on the records of other subjects, who were given different intelligence tests at different ages. As such, it may be that error associated with variable intelligence tests played a role in our IQ findings. Even so, all tests were well-standardized, with means of 100 and *SD*s of 15 or 16, and patterns of findings were similar across those with direct versus previously administered tests. Further, IQ appears fairly stable with advancing age in people with this syndrome (Dykens, Hodapp, Walsh, & Nash, 1992b). Another limitation is that we relied on parental reports of behavior. We were, however, re-assured that informant data in this study were quite consistent with our clinical observations and previous research findings about the Prader-Willi behavioral phenotype.

Despite these limitations, investigators should be encouraged to pay more careful attention to possible deletion versus uniparental disomy differences in cognition and in the profiles and developmental trajectories of a wide range of behavior. Although further work is needed, a dampening of symptom severity in people with maternal uniparental disomy has important implications for genetic counseling and intervention. Behavioral or developmental differences across deletion versus uniparental disomy groups may be subtle, and on first glance, these groups seem behaviorally more alike than different. Yet even small differences in maladaptive behavior or symptom severity are likely to have a significant impact on the quality of life of people with Prader-Willi syndrome and their families.

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