THE JOURNAL OF
CHILD PSYCHOLOGY AND PSYCHIATRY

Journal of Child Psychology and Psychiatry 49:9 (2008), pp 1001–1008 doi:10.1111/j.1469-7610.2008.01913.x

Behavior in Prader-Willi syndrome: relationship to genetic subtypes and age

Elisabeth M. Dykens and Elizabeth Roof

Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, USA

Background: Some behavioral features of Prader-Willi syndrome (PWS) are associated with the major genetic subtypes of this disorder. While most agree that those with maternal uniparental disomy (UPD) have a distinctive cognitive and psychiatric profile, findings are more controversial regarding possible differences among persons who vary in paternal deletion size. **Methods:** Caregivers of 88 persons with PWS aged 5 to 51 years (M = 22 years) were administered measures of problem behavior, compulsivity, hyperphagia, and adaptive skills. The sample was well characterized as having relatively large, Type I (n = 26) or smaller, Type II (n = 29) deletions, or UPD (n = 33). **Results:** No significant behavioral differences were found between the Type I versus Type II deletion groups. Within each genetic subtype, however, differences emerged in how advancing age related to behavior. Although age did not emerge as a significant correlate of behavior in the Type II or UPD groups, in the Type I group age was consistently associated with lower problem behaviors, adaptive skills, and externalizing symptoms. **Conclusion:** Although differences between deletion subtypes were not found, significant within-subtype differences emerged in relationships between age and behavior. Negative associations between age and behavior in the Type I group only may relate to non-imprinted genes that are deleted in Type I but not Type II cases, including CYFIP1. Altered expression of CYFIP1 is seen in other developmental disabilities, including 15q disorders, and haploinsufficiency of CYFIP1 in Type I PWS cases may be associated with age-related phenotypic effects. Findings underscore the importance of a life-span perspective in phenotypic research. **Keywords:** Prader-Willi syndrome, genetic subtypes, age, CYFIP1.

Prader-Willi syndrome (PWS) results in intellectual disabilities, life-threatening hyperphagia, specific cognitive strengths, and salient problem and compulsive behaviors such as tantrums, skin-picking, hoarding, and concerns with exactness and routine (Dykens, 2006; Whittington & Holland, 2004). Recently, a flurry of research has tested the assumption that phenotypic features of PWS differ across the major genetic subtypes of this disorder. The majority of persons with PWS (70%) have paternal deletions of 15q11-q13, and approximately 25% have maternal UPD, or when both copies of chromosome 15 are inherited from the mother, the few remaining cases have imprinting center defects or translocations. Individuals with PWS thus lack a paternally imprinted 15q11-q13 contribution.

Relative to persons with paternal deletions, those with UPD generally have better-developed expressive language (Roof et al., 2000; Whittington et al., 2004), but somewhat poorer visual memory and puzzle-solving skills (Dykens, 2002; Verdine, Troseth, Hodapp, & Dykens, in press). Individuals with UPD may be less apt to skin-pick (Dykens, Cassidy, & King, 1999; Symons et al., 1999), but they are at higher risk than their deletion counterparts for autism spectrum disorders, most likely because of duplication and over-expression of maternally expressed genes in the 15q11-q13 region (Veltman, Craig, & Bolton, 2005). Similarly, young adulthood persons with UPD are at high risk for psychiatric disorders, primarily psychosis or affective psychosis (Boer et al., 2002; Vogels et al., 2003).

Individuals with paternal deletions can be further divided according to deletion size. Both subtypes share a breakpoint (BP3), and deletions between BP3 and BP1 are classified as Type I deletions, and are 500mb larger than breakpoints between BP3 and BP2, designated as Type II deletions. The larger Type I deletions are seen in approximately 40% of deletion cases. To date, four non-imprinted genes have been identified that are deleted in Type I cases, but present in those with smaller, Type II deletions (Chai et al., 2003). Three of these genes are widely expressed in the CNS: NIPA1 is associated with spastic paraplegia; NIPA2 may be implicated in transporter or receptor function; and CYFIP1 interacts with and is a primary target of FMRP, the protein associated with fragile X syndrome. CYFIP1 likely enables FMRP to carry out its functions in transporting and regulating mRNAs (Chai et al., 2003).

Reports have been contradictory about behavioral differences between those with Type I versus Type II deletions. Comparing 12 participants with Type I to 14 with Type II deletions, Butler et al. (2004) found that the Type I group had lower reading, math, and adaptive behavior scores, and higher externalizing behaviors and severity of compulsions. Building on this same cohort, Hartley et al. (2005) reported higher depression-physical scores in 14 individuals with Type I versus 20 with Type II deletions. Adding

Conflict of interest statement: No conflicts declared.

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to this sample, Zarcone et al. (2007) compared 16 persons with Type I to 26 with Type II deletions, and reported more washing/cleaning compulsions in those with Type I deletions, as well as more rereading and rewriting compulsions among those with Type II deletions.

Although these findings collectively suggest 'important differences between the two deletion subtypes' (Zarcone et al., 2007, p. 478), they have not been replicated by others. Milner et al. (2005) found no significant differences in compulsivity or autistic symptoms between 14 persons with Type I and 32 with Type II deletions, although the Type I group had lower motor adaptive behavior scores. Varela, Kok, Setian, Kim, and Koiffmann (2005) compared clinic data from 11 PWS patients with Type 1 to 32 with Type II deletions. No differences were found, although the Type I group had a later onset of speech.

This two-part study sheds light on the inconsistent behavioral findings across Type I versus Type II deletion subtypes. Using a relatively large sample, we first compare compulsivity and behavioral problems in groups with Type 1 or Type II deletions, and maternal UPD. Using a new measure (Dykens, Maxwell, Pantino, Kossler, & Roof, 2007), we also assess hyperphagia across subtypes.

Part two addresses the idea that variability in the PWS phenotype extends beyond genetic subtypes to include other participant factors. Although correlates of behavior have been examined in PWS in general, this study does so within each subtype, including IQ, gender, degree of obesity (BMI), and age. Beyond age as a risk factor for psychosis in UPD, it remains unknown whether age or other factors are differentially associated with behavior within each of the three PWS genetic subtypes.

Method

Participants

Eighty-eight individuals (43 males, 45 females) with PWS aged 5 to 51 years (M = 22.41, SD = 11.74) participated in the study. Of these, 26 had Type I deletions, 29 had Type II deletions, and 33 had maternal UPD. As shown in Table 1, mean ages did not significantly differ across groups. Males and females were equally distributed across the three genetic subtypes.

Participants had a mixture of previous genetic testing, including FISH and methylation studies, to identify their deletion or UPD status. If UPD was well documented, genetic studies were not repeated. For those with deletions, Type I versus Type II designations were identified with extracted DNA that was subjected to routine microsatellite analyses using microsatellite markers around and between BP1 and BP2 (e.g., D15S541, D15S542, D151035). An absence of the paternal D15S541/S1035 allele indicated a Type I

Table 1 Behavioral or descriptive measures across PWS Type I or Type II deletions, or maternal UPD subtypes

	Type I		Type II		UPD		
	M	*SD*	*M*	*SD*	*M*	*SD*	F or X^2 and p
N	26 (13M, 13F)		29 (17M, 12F)		33 (13M, 20F)		
Age	24.85	13.28	23.88	11.99	19.20	9.68	2.00
BMI	31.46	7.98	32.28	10.78	30.23	10.28	.31
IQ	63.88	14.17	60.64	10.35	64.96	13.07	1.03
% Hospitalized	45%		45%		39%		.07
% Psychiatric Hospital	20%		26%		55%		6.37*
CBCL Maladaptive							
Total	60.40	27.77	68.96	24.51	70.75	31.73	1.02
External	16.96	10.74	18.14	8.91	19.91	10.17	.64
Internal	13.32	7.25	15.03	9.42	14.56	10.11	.25
Y-BOCS							
Number compulsions	4.32	3.06	3.69	2.37	3.94	2.94	.34
Severity compulsions	2.32	1.93	3.44	2.31	2.78	1.83	2.09
Symmetry/Ordering	2.85	2.01	2.86	1.81	2.42	1.75	.56
Cleanliness/Washing	.42	.64	.24	.57	.45	.90	.73
Checking/Obsessions	.73	.91	.75	.83	.53	.76	.67
Hoarding	1.20	.82	1.38	.82	1.25	.95	.31
Skin picking	85%		97%		70%		7.94**
Rectal picking	4%		14%		37%		10.71**
Hyperphagia Questionnaire							
Drive	10.64	2.98	11.55	3.22	11.75	3.42	.82
Behavior	12.88	4.60	13.44	4.89	13.15	4.79	.07
Severity	4.57	1.69	4.64	1.42	4.70	1.72	.04
Vineland Adaptive Behavior							
Communication	54.36	21.20	64.84	27.38	67.00	22.14	.99
Daily Living Skills	52.00	11.75	61.62	26.87	63.88	18.85	1.20
Socialization	60.27	14.59	64.85	27.73	67.41	18.52	.47
Composite	52.94	15.14	60.53	23.61	63.47	18.52	1.05

Note: ** $p < .01$.

deletion, and the presence of these two paternal alleles, located between BP1 and BP2, indicated a Type II deletion. For approximately 12 persons, parental DNA was also obtained to clarify deletion or UPD status using methylation-specific multiplex ligation-dependent probe amplifications or MLPA (for detailed descriptions see Kim et al., 2007).

Approximately half of the sample (47%) was recruited for an ongoing study at Vanderbilt University, and 53% were administered behavioral surveys via the mail. No significant differences emerged across these two recruitment sources in age, genetic subtypes, or behavioral scores; as such, no evidence of an ascertainment bias was found.

Many participants (68%) were taking psychotropic medications. The frequency of psychotropic medication use did not significantly differ across the Type I (69%), Type II (75%) or UPD (61%) subgroups, X^2 (2) = 2.54. Medication status was not significantly associated with any of the behavioral measures.

Procedures and test battery

Participants' primary care providers, typically mothers, completed questionnaires during their visit to Vanderbilt, or they mailed them in at their convenience. Informed consent was obtained from all participants as per Vanderbilt University's Institutional Review Board. Saliva and/or blood samples were obtained from offspring, and DNA was extracted and amplified for genetic testing. Parents reported previous IQ test scores, and the 41 participants seen in person were also administered the Kaufman Brief Intelligence Test-2 (K-BIT2; Kaufman & Kaufman, 2004). The correlation between parent-reported and K-BIT IQ scores was .87, indicating excellent agreement.

Demographic questionnaire. Parents completed questions regarding their offspring's previous IQ test scores, height, weight, medical and psychiatric histories, medications, genetic testing, and family composition.

Child Behavior Checklist (CBCL; Achenbach, 2001). The widely used CBCL asks parents to rate 112 problem behaviors: (0) not true; (1) somewhat or sometimes true; and (2) very true or often true. The CBCL contains an Internalizing Domain (anxious/depressed, somatic complaints, withdrawn subdomains), Externalizing Domain (non-compliant and aggressive behavior subdomains) and three additional subdomains (social, thought, attention, and other problems). Raw scores were used in data analyses.

Yale–Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989). The informant version of the Y-BOCS consists of 30 symptoms that are rated as occurring ever or in the last week. Informants also rate time spent engaged in compulsive behaviors, and the degree of distress and adaptive impairment associated with symptoms (0 = none to 5 = extreme). The Y-BOCS has been used in previous PWS studies.

The Y-BOCS was scored using factors that reflect clusters of symptoms in people without intellectual disabilities (Leckman et al., 1997, see Table 1). Consistent with factor analytic studies in PWS, we also summed the number of compulsions, but separately examined skin-picking, as it appears distinct from other behaviors (Feurer et al., 1998). Rectal-picking was also examined separately.

Hyperphagia Questionnaire. This 13-item questionnaire (Dykens et al., 2007) probes symptoms of hyperphagia in PWS. Previous factor analyses identified three robust factors: Hyperphagic Drive (e.g., how persistent in asking for food); Hyperphagic Behaviors (e.g., stealing food), and Hyperphagic Severity (e.g., extent that food interferes with everyday functioning). Items are rated by care providers on a 5-point scale (1 = not a problem to 5 = a severe and/or frequent problem). Data analyses used raw scores for each factor.

Vineland Adaptive Behavior Scales-II (Sparrow, Cicchetti, & Balla, 2005). Identifying the performance of behaviors required for person or social self-sufficiency, the Vineland yields standard scores for an Adaptive Behavior Composite, and Communication, Daily Living Skills, and Socialization. The Vineland was administered to 41 parents who were seen at Vanderbilt. Although based on smaller numbers, the Vineland provides a meaningful point of comparison to previous PWS subtype studies.

Results

Part I: Between-subtype analyses

CBCL, Y-BOCS, Hyperphagia. ANOVAs compared scores on the CBCL, Y-BOCS and Hyperphagia Questionnaire across the three genetic subtypes. None were significant. Table 1 shows the means and SDs for each group. As age was somewhat lower in the UPD group, we re-ran analyses controlling for age; findings remained the same. We also ruled out an effect of medication on the lack of group differences.

Picking behaviors. As shown in Table 1, skin-picking was highly prevalent, and Chi-square analyses revealed more skin-picking in deletion versus UPD groups. This pattern was reversed for rectal-picking, which was more common in cases with UPD.

Hospitalizations. Rates of medical hospitalizations were similar across groups. As no participants aged 16 years or younger had a psychiatric admission, we limited psychiatric analyses to 63 individuals older than 16 years of age. Of the 20 adults with Type I deletions, 20% had been psychiatrically hospitalized, similar to the rate (26%) seen in 23 adults with Type II deletions. In contrast, 55% of the 20 adults with UPD had been psychiatrically hospitalized, $X^2(2) = 6.37$, $p < .05$. Of the 9 adults with UPD who were not psychiatrically hospitalized, 6 were taking anti-psychotic medications, and 3 (aged 21, 21, and 23 years) were not on any psychotropic agents.

Vineland Adaptive Behavior. Although the Type I group had lower adaptive scores than others, no significant differences were found across subtypes (see Table 1).

Part II: Within-subtype analyses

Four participant variables were examined within each genetic subtype – IQ, gender, BMI, and age – in relation to the behavioral measures. Given the number of analyses performed, we adopted a more conservative $p < .01$ level.

IQ and gender. Few IQ or gender effects were found. An inverse relationship emerged in the Type I group between IQ and the Y-BOCS Total and Compulsive Behavior scores (*r*s = –.58 and –.78, respectively, *p*s < .01 and .001). In the Type II deletion group, females had higher Hyperphagic Drive scores than males ($M = 13.36$, $SD = 3.00$ versus $M = 10.31$, $SD = 2.82$), $t(25) = 2.69$, $p < .01$.

BMI. As expected, age and BMI were significantly correlated for the sample as a whole, $r = .41$, $p < .001$, and as such, BMI correlations were corrected for age. In the Type II group, BMI was negatively associated with the number of compulsive behaviors on the Y-BOCS, $r = –.48$, $p < .01$. In the UPD group, negative correlations emerged between BMI and the CBCL Thought and Attention Domains (*r*s = –.41 and –.45, respectively, *p*s<.01). Examining CBCL items that comprise these two domains, correlations were found between the BMI and repetitive, compulsive-like behaviors, $r = –.50$, $p < .01$, being nervous, tense, and high strung, $r = –.47$, $p < .01$, and having difficulties concentrating ($r = –.41$, $p < .01$).

Age. In the UPD group, age was positively correlated with the Y-BOCS hoarding factor ($r = .44$, $p < .01$). All remaining age correlations were negative, and were only found in the group with Type I deletions.

In the Type I group only, advancing age was associated (*p*s < .01) with reduced Hyperphagic Severity ($r = –.48$), CBCL Total and Externalizing Domains (*r*s = –.44 and –.50, respectively), and five CBCL subdomains: Aggressive Behavior ($r = –.59$), and Social, Thought, Attention and Other problems (*r*s = –.59, –.44, –.47, –.51, respectively). All findings held up even when a high-scoring, young participant was removed from analyses. To exemplify these negative correlations, Figure 1 shows the scatterplots between age and the CBCL Externalizing domain for each subtype. In contrast to the negative correlation in Type I cases, Figure 1 depicts the lack of age-related patterns in the Type II or UPD groups. Non-significant age correlations in these groups ranged from –.19 to .25.

To further specify age findings in the Type I group, we examined the items that comprised the five CBCL subdomains that showed significant relations to age.

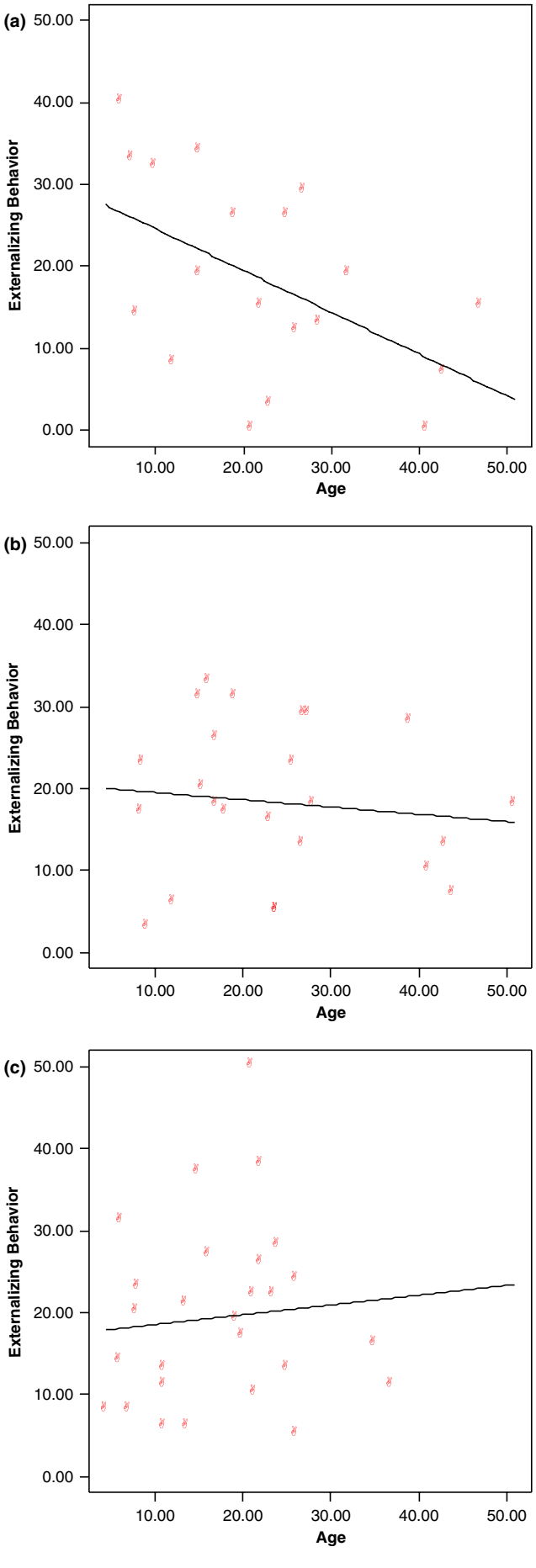

Figure 1 (a) Type I cases; (b) Type II cases; (c) UPD cases

Significant, negative correlations ($p < .01$) were found between age and impulsivity ($r = -.67$), being accident prone ($r = -.61$), sudden mood swings or changes ($r = -.53$), whining ($r = -.53$), temper tantrums ($r = -.51$), clumsiness ($r = -.49$), showing off or clowning ($r = -.48$), being restless or overly active (–.48), being argumentative (–.47), and talking too much (–.47). None of these items were correlated with age in the Type II or UPD groups.

Age in the Type I group was also negatively related to the Vineland Adaptive Behavior Composite score ($r = -.59$), albeit at the $p < .05$ level, as well as with the Daily Living Skills and Socialization Domains (rs = –.60 and –.59, respectively, ps < .05).

To further demonstrate age findings, we used the median age for the sample as a whole (21 years) to split participants into child–adolescent versus adult age groups. *T*-tests were conducted between age groups on those CBCL domains showing significant age correlations. As shown in Table 2, compared to younger Type I individuals, adults with Type I deletions had significantly lower mean CBCL and Vineland scores. Table 2 shows the lack of significant age group comparisons in Type II deletion or UPD groups.

Discussion

In contrast to prior studies, we did not find compelling behavioral differences across PWS paternal deletion subtypes. Within-subtype correlate analyses, however, revealed consistent group differences, primarily related to age and those with Type I deletions. Findings have implications for future research linking PWS to other disorders, and underscore the need for longitudinal studies on how phenotypes evolve and change across the lifespan.

On average, the two deletion subtypes were remarkably similar in the number and severity of their maladaptive, compulsive and hyperphagic behaviors, even when controlling for possible confounds due to age or medication status. Perhaps the contradictory deletion subtype findings in previous reports relate to differences across studies in sample sizes, ages of participants, or behavioral measures. The present study confirmed reduced skin-picking in those with UPD, but with an unexpected twist involving increased rectal-picking in this group. While skin-picking has long been observed in PWS, rectal-picking has yet to be widely studied, in part because families or researchers are less apt to discuss this symptom. If left untreated, however, rectal-picking may lead to serious medical complications (Bhargava et al., 1996). Studies are needed on how picking and other compulsive behaviors in PWS relate to environmental cues, and to altered genes or RNAs in the 15q11-q13 region involved with the regulation of both serotonin and GABA (Kishore & Stamm, 2006; Lucignani et al., 2004).

Within-subtype analyses revealed consistent differences in correlates of behavior, especially age. In contrast to those with UPD or Type II deletions, the Type I group had a markedly different pattern of negative correlations between age and problem behaviors. In the Type 1 group only, advancing age was negatively correlated with the CBCL Total and Externalizing Domains, and five CBCL subdomains, including such behaviors as temper tantrums, aggression, impulsivity, clumsiness, restlessness, talking too much, mood swings, and being argumentative. Compared to the lack of age-related findings in the Type II or UPD groups, a 26-point difference in total CBCL scores was seen across child–adolescent versus adult age groups of those with Type I deletions.

Table 2 Means, SDs, *t* and *p*s for behavioral measures showing significant age correlations in child-adolescent (< 21 years) versus adult (> 22 years) age groups for Type I, Type II and UPD subtypes

	Type I		Type II		UPD	
	< 21 years	> 22 years	< 21 years	> 22 years	< 21 years	> 22 years
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Age	12.65 (4.80)	33.78 (9.79)	13.39 (4.28)	32.42 (9.00)	13.11 (5.88)	28.57 (6.21)
CBCL						
Total	74.73 (29.09)*	49.14 (21.52)	66.54 (22.51)	71.06 (26.52)	66.68 (33.13)	77.16 (29.53)
External	21.54 (12.43)*	13.36 (7.91)	19.85 (9.62)	16.75 (8.35)	19.00 (11.34)	21.23 (8.46)
Aggressive behavior	17.27 (9.45)**	8.50 (4.74)	15.61 (7.27)	11.75 (6.17)	14.14 (7.81)	14.85 (5.74)
Thought problems	8.82 (3.57)**	5.35 (2.44)	9.31 (3.01)	7.94 (3.62)	7.47 (4.38)	10.92 (4.68)*
Social problems	11.18 (3.82)**	5.00 (2.22)	8.53 (3.12)	7.25 (4.46)	8.37 (4.04)	8.38 (3.71)
Attention problems	8.36 (2.94)*	5.57 (2.87)	8.54 (3.17)	8.81 (3.29)	9.05 (4.19)	9.92 (4.64)
Other problems	15.91 (6.65)**	8.42 (4.66)	13.54 (4.01)	13.93 (6.53)	12.05 (7.23)	14.46 (6.30)
Vineland ABS						
Adaptive composite	60.00 (6.78)**	41.83 (14.11)	64.16 (19.51)	56.43 (23.85)	63.12 (17.82)	60.66 (13.27)

Note: For Type I group only, CBCL total t (24) = 2.53, $p < .05$; External t (24) = 2.00, $p < .05$; Aggressive behavior t (24) = 3.03, $p < .01$; Thought problems t = 2.88, $p < .01$; Social problems t (24) = 5.08, $p < .001$; Attention problems t (24) = 2.38, $p < .05$; Other problems t (24) = 3.30, $p < .01$; Adaptive Behavior Composite t (12) = 2.48, $p < .01$. For the UPD group, thought problems t (29) = −2.07, $p < .05$.

Unlike their PWS counterparts, acting out behaviors and moodiness seem turned down several notches as persons with Type I deletions get older. We previously reported behavioral mellowing in adults with PWS (Dykens, 2004), but did not have complete deletion subtyping of these participants. Mellowing in Type I cases could reflect the trend for adolescents with intellectual disabilities in general to show fewer aggressive behaviors over time (Ruiter, Dekker, Verhulst, & Koot, 2007). Such reasoning, however, does not explain why those with Type I deletions had age-related changes while others with the same syndrome did not.

As well, negative age correlations in the Type I group were not limited to behavior problems. Hyperphagic severity was also negatively associated with advancing age in this group, though not necessarily their food-seeking behaviors or BMIs. In addition, although based on smaller numbers, adaptive behavior scores were negatively correlated with age only in the Type I group, and mean adaptive behavior composite scores in adults with Type I deletions were 19 points lower than younger persons with this subtype.

Although it is unclear why the Type I group showed age-related changes across several behavioral domains, a reasonable explanation involves the four genes that are deleted in these individuals but present in others with PWS. Compared to those with Type II deletions, expression of these four genes is reduced in Type I cases (Bittell et al., 2006), and one of these genes, CYFIP1, is a primary target of the protein involved in fragile X syndrome, FMRP. Interestingly, CYFIP1 has recently been linked to other types of 15q11-q13 disorders, and to an unusual variant of fragile X syndrome. Examining persons with maternal duplications of 15q11-q13 and autism, Nishimura et al. (2007) reported that CYFIP1 was selectively over-expressed in these cases. As excess CYFIP1 was also found in fragile X cases and autism (due to the lack of FRMP as a binding partner), Nishimura et al. (2007) propose that CYFIP1 is a common molecular link between co-occurring fragile X syndrome and autism, and 15q duplications and autism. Using a different cohort, Nowicki et al. (2007) reported altered CYFIP1 in 13 individuals with fragile X syndrome and a Prader-Willi phenotype. These cases had fragile X mutations, along with obesity, severe hyperphagia, obsessive-compulsive behaviors, symptoms of autism spectrum disorder, and other sporadic PWS features. Compared to a group with classic fragile X syndrome or typical controls, these fragile X-PWS phenotype cases had reduced levels of CYFIP1 mRNA. Altered CYFIP1 is thus a common finding in several developmental disorders that on first glance show obvious phenotypic differences, but have some overlapping features that may be more apparent over time.

In addition to age, the BMI also emerged as a significant correlate of behavior, and was negatively associated in Type II and UPD groups with repetitive, compulsive behaviors, and with being nervous, tense, and high strung. These inverse relationships are consistent with earlier studies showing increased compulsivity, distress, anxiety, agitation, hoarding, and disordered thinking in those with lower BMIs (Dykens & Cassidy, 1995; Dykens, 2004; Hartley et al., 2005; Whitman & Accardo, 1987). Reasons for these counterintuitive findings may relate to altered profiles of hormones or neuropeptides such as ghrelin that are implicated in the aberrant satiety in PWS (Cummings et al., 2002). These relationships may also be associated with the physiological and psychological stress of maintaining a lower weight. Due to a low resting metabolic rate and hypotonia, persons with PWS typically require fewer calories than others to lose or maintain weight. Chronic, very low caloric restriction or sudden weight loss may contribute to increased psychopathology or compulsivity, especially in those already at risk for these problems due to maternal UPD.

This study had several strengths and weaknesses. It is the largest PWS cohort reported to date with Type I or Type II deletions, and the study used standardized measures to assess behavior problems, compulsivity, and adaptive skills. The study is also the first to compare hyperphagia across genetic subtypes. Even so, we had reduced power for the adaptive behavior analyses, and these findings should be interpreted more cautiously. The study itself was cross-sectional, which is of particular concern as age emerged as a key factor in the within-subtype analyses. Longitudinal studies are under way, and these data are needed to clarify age-related shifts in behavior and neurobiological functioning in PWS.

A further limitation is that we did not administer psychiatric interviews, and psychiatric diagnoses would have helped on two fronts. First, autism or autistic behaviors were frequently noted in cases with altered CYFIP1 and 15q duplications, fragile X syndrome, and a fragile X-PWS phenotype. While none of the PWS Type I cases in the present study had previous autism spectrum diagnoses, studies are needed to document symptoms of autism in Type I and other PWS subtypes over the course of time. Second, persons with UPD are at risk for psychosis or affective illness, and we did not directly assess thought or mood disorder. Adults with UPD did, however, have higher CBCL Thought Problem scores than young UPD cases, and we also found a twofold increase of psychiatric hospitalizations in adults with UPD relative to adults with deletions. Only three of 20 adults with UPD were not hospitalized nor on psychotropic medication. Further studies are needed on risk factors for severe psychopathology in PWS, including age, genetic subtype, family psychiatric history, BMI, and life stressors.

Future studies may also need to go beyond the Type I versus Type II classification, as it does not accurately capture unique deletions or breakpoints

that are only now being identified via high resolution array and other techniques (Butler, Kibiryeva, Fischer, & Bittell, 2007; Kim et al., 2007). These techniques can shed new light on the role of altered genes, copy number variations, or gene–gene interactions in the PWS phenotype. Emerging behavioral or molecular data that link fragile X syndrome, PWS, and other 15q disorders demonstrate the complexities of phenotypic work ahead, as does the fact that phenotypes change over time. To date, however, researchers have been less concerned with the evolution of phenotypes, and instead focused on discrete developmental periods, between-syndrome comparisons, or in the case of PWS, on comparisons across genetic subtypes regardless of age. Neurocognitive and behavioral effects of PWS and other syndromes are, however, differentially expressed across the lifespan. Future research on these trajectories may provide important new clues about gene function, and when interventions are more or less apt to be successful.

Acknowledgements

This research was supported by NICHD grant R01HD135681 to EMD, and P30HD15052 to the Vanderbilt Kennedy Center, the Vanderbilt General Clinical Research Center, and a pilot grant from the Prader-Willi Syndrome Association (USA). The authors thank the families for their enthusiastic participation, Merlin Butler, M.D., and Douglas Bittel, Ph.D., for their subtyping of deletion cases, Elizabeth Pantino and Rebecca Kossler for assistance in data collection, and Robert Hodapp, Ph.D, for his helpful comments on previous drafts of this manuscript.

Correspondence to

Elisabeth M. Dykens, Vanderbilt Kennedy Center for Research on Human Development, Department of Psychology and Human Development, Vanderbilt University, 230 Appleton Place, Nashville, TN 37203, USA; Email: elisabeth.dykens@vanderbilt.edu

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Manuscript accepted 12 February 2008