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# Behavioral Differences Among Subjects With Prader-Willi Syndrome and Type I or Type II Deletion and Maternal Disomy

Merlin G. Butler, MD, PhD\*; Douglas C. Bittel, PhD\*; Nataliya Kibiryeveva, MD\*; Zohreh Talebizadeh, PhD\*; and Travis Thompson, PhD†

**ABSTRACT.** *Objective.* To determine whether phenotypic differences exist among individuals with Prader-Willi syndrome with either type I or type II deletions of chromosome 15 or maternal disomy 15 leading to a better understanding of cause and pathophysiology of this classical genetic syndrome.

*Methods.* We analyzed clinical, anthropometric, and behavioral data in 12 individuals (5 men, 7 women; mean age:  $25.9 \pm 8.8$  years) with PWS and a type I (TI) deletion, 14 individuals (6 men, 8 women; mean age:  $19.6 \pm 6.5$  years) with PWS and a type II (TII) deletion, and 21 individuals (10 men, 11 women; mean age:  $23.6 \pm 9.2$  years) with PWS and maternal disomy 15 (UPD). The deletion type was determined by genotyping of DNA markers between proximal chromosome 15 breakpoints BP1 and BP2. TI deletions are  $\sim 500$  kb larger than TII deletions. Several validated psychological and behavioral tests were used to assess phenotypic characteristics of individuals with PWS representing the 3 genetic subtypes.

*Results.* Significant differences were found between the 2 deletion groups and those with UPD in multiple psychological and behavioral tests, but no differences were observed in other clinical or anthropometric data studied. Adaptive behavior scores were generally worse in individuals with PWS and the TI deletion, and specific obsessive-compulsive behaviors were more evident in the TI individuals compared with those with UPD. Individuals with PWS with TI deletions also had poorer reading and math skills as well as visual-motor integration.

*Conclusions.* Our study indicates that individuals with TI deletion generally have more behavioral and psychological problems than individuals with the TII deletion or UPD. Four recently identified genes have been identified in the chromosome region between BP1 and BP2 with 1 of the genes (NIPA-1) expressed in mouse brain tissue but not thought to be imprinted. It may be important for brain development or function. These genes are deleted in individuals with TI deletion and are implicated in compulsive behavior and lower intellectual ability in individuals with TI versus TII. *Pediatrics* 2004; 113:565–573; *Prader-Willi syndrome, type I and type II deletions, maternal disomy 15, clinical differences.*

ABBREVIATIONS. PWS, Prader-Willi syndrome; UPD, maternal disomy 15; AS, Angelman syndrome; BP, breakpoint; TI, type I; TII, type II; IQ, intelligence quotient; CBC, Child Behavior Checklist; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; VMI, visual-motor integration; SIB, self-injurious behavior.

Prader-Willi syndrome (PWS) is a genetic disorder that results from the absence of normally active paternally expressed genes from the 15q11-q13 chromosome region.<sup>1–3</sup> A number of genes located in the 15q11-q13 region have been shown to be imprinted (active on only 1 member of the chromosome pair), and expression is dependent on the parent of origin of the chromosome 15. The major characteristics of this syndrome include infantile hypotonia with feeding problems, global developmental delay and mental deficiency, behavior problems, small hands and feet, hypogonadism and hyperphagia leading to marked obesity in early childhood, and a characteristic face.<sup>1,2,4</sup> The majority of individuals,  $\sim 70\%$ , have a paternally derived interstitial deletion of 15q11-q13,  $\sim 25\%$  have maternal disomy 15 (UPD), and the remaining 2% to 5% of individuals have imprinting defects.<sup>2,3</sup>

PWS and Angelman syndrome (AS), an entirely different clinical disorder, were the first examples in humans of genomic imprinting or the differential expression of genetic material depending on the parent of origin. The majority of AS patients have a maternally derived interstitial deletion of 15q11-q13. At least 1 dozen imprinted genes have been identified in the 15q11-q13 region, and the majority are paternally expressed (maternally imprinted or inactivated). The paternally expressed genes are candidates for PWS, whereas a single maternally expressed gene (UBE3A) is thought to cause AS.

The typical deletion responsible for PWS encompasses most of the 15q11-q13 region; however, recent studies have shown that the proximal deletion breakpoint may occur at 1 of 2 sites within either of 2 large duplicons centromeric to locus ZNF127.<sup>3</sup> The precise location of the breakpoints within the duplicons may vary,<sup>5</sup> but the breakpoints seem to be confined to a relatively small region of chromosome 15, which allows for the identification of 2 classes of deletion subjects. Breakpoint 1 (BP1) is proximal to D15S541/S1035 loci, and BP2 lies between loci D15S541/S1035 and D15S543.<sup>6</sup> The type I (TI) deletion involves BP1, which is close to the centromere, while the type II (TII) deletion involves breakpoint BP2 and is located

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~500 kb distal to BP1. Therefore, the TI deletion results in the loss of ~500 kb of genetic material in addition to what is missing in the TII deletion. Recently, Chai et al<sup>7</sup> reported 4 newly identified genes in the region between BP1 and BP2. BP3, located between loci D15S156 and D15S165, is the distal breakpoint in the 15q11-q13 region and is observed in both deletion subgroups.

Analyses of the genetic subtypes of PWS to date have compared deletion individuals and UPD individuals without grouping the deletion individuals into TI or TII. For example, hypopigmentation and homogeneous clinical presentations including dermatoglyphic patterns were more often seen in individuals with PWS and a deletion compared with those with normal chromosomes now recognized as having UPD.<sup>1,8</sup> In addition, we reported significantly higher verbal intelligence quotient (IQ) scores in PWS individuals with UPD compared with individuals with deletion.<sup>9</sup> PWS individuals from the UPD subgroup scored significantly higher than the deletion subgroup in 4 subcategories of verbal testing: information, arithmetic, vocabulary, and comprehension. Similarly, Dykens and others<sup>4,10–13</sup> also reported behavioral and cognitive differences in PWS individuals with the UPD individuals having fewer maladaptive behaviors measured by the Child Behavior Checklist's (CBC's) internalizing, externalizing, and total domain scores and more symptom-related distress noted using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS).

We further reported more self-injurious behavior in deletion individuals with PWS compared with those with UPD.<sup>14</sup> Conversely, visual processing of complex stimuli was significantly poorer in individuals with UPD compared with those with the deletion.<sup>15</sup> Gunay-Aygun et al<sup>16</sup> also reported a decrease in severity of some of the minor behavioral characteristics associated with PWS, particularly in individuals with UPD compared with individuals with deletions. Thus, analyses of individuals with PWS to date have included cognitive, psychological, behavioral, physiologic, and biochemical data and grouped into deletion or UPD subgroup categories. Herein, we report the first clinical study of individuals with PWS grouped by deletion size (TI vs TII) and compare their findings with individuals with UPD.

## METHODS

Individuals with PWS and their parents were recruited as part of a larger study on genotype/phenotype relationships. All individuals agreed to informed consent approved by the institutional review board before entry into the study. All individuals with PWS were diagnosed by a clinical geneticist (M.G.B.) and chromosome studies performed with fluorescent *in situ* hybridization showing a deletion of the 15q11-q13 region. In addition, DNA methylation and microsatellite analysis with 15q11-q13 probes were used following established protocols to confirm the deletion or UPD status.<sup>17–20</sup> The UPD status was confirmed by informative chromosome 15 microsatellite studies using DNA isolated from the parents and the patient. No individuals with imprinting defects were included in this study.

Individuals with deletions were further subdivided into TI or TII using microsatellite markers around and between BP1 and BP2. Additional molecular genetic testing confirmed the location of the distal breakpoint at BP3. The absence of the paternal D15S541/S1035 loci was classified as having the TI deletion and

identified by routine microsatellite analysis using an ABI 310 automated capillary sequencer with PWS subject and parental DNA isolated from peripheral blood (Fig 1). The TII deletion was classified as having the presence of these loci, which are located between BP1 and BP2 (Fig 2). The deletion subtype status was confirmed with quantitative polymerase chain reaction using established protocols<sup>6,20</sup> in individuals uninformative at these loci (data not shown).

We extensively analyzed clinical, anthropometric, physiologic, metabolic, cognitive, and behavioral data from a large clinical data set produced during a 5-year program project on PWS and obese comparison subjects. Twelve individuals with PWS and a TI deletion (5 men, 7 women; mean age: 25.9 ± 8.8 years), 14 individuals with PWS and a TII deletion (6 men, 8 women; mean age: 19.6 ± 6.9 years), and 21 individuals with PWS and UPD (10 men, 11 women; mean age: 23.6 ± 9.2 years) were analyzed for our study. No differences were found in the clinical or anthropometric data among the subjects with the deletion type or UPD, although differences were identified in behavior, academic, and intelligence parameters discussed below.

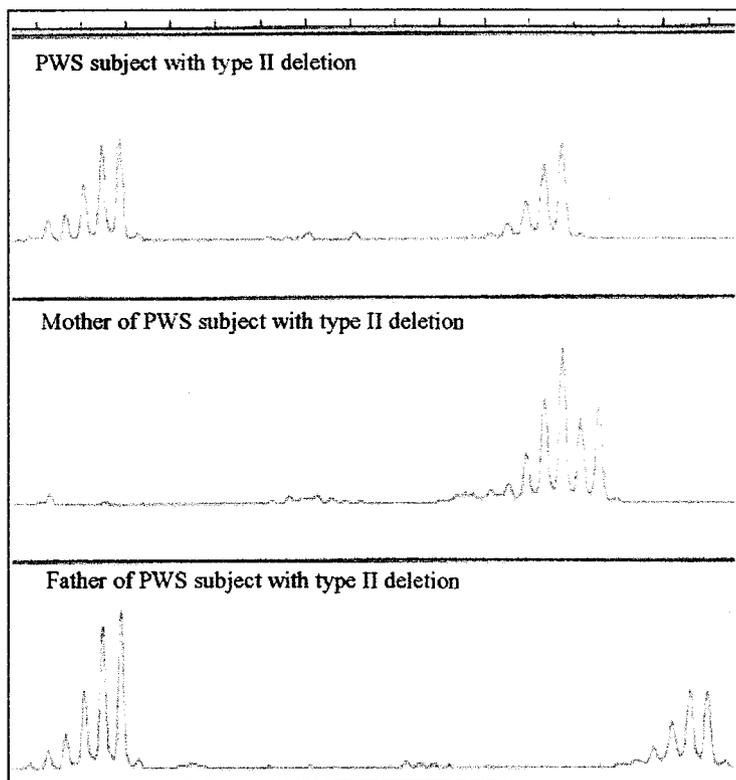
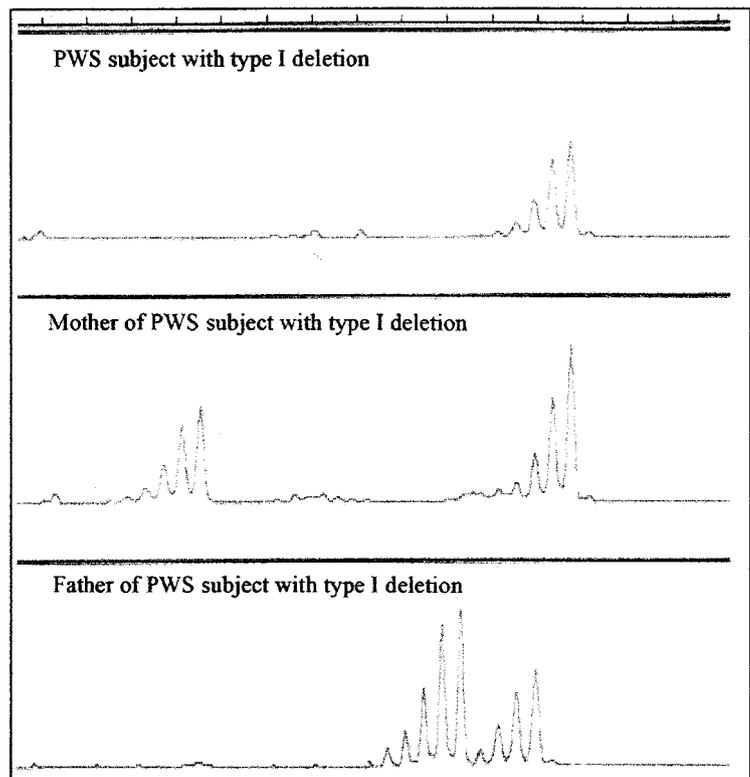
Several validated psychological and behavioral scales were used to assess phenotypic characteristics of individuals with PWS. The Y-BOCS<sup>21</sup> was used in our study and is the most widely used standardized scale for measuring obsessions and compulsions in psychiatric patients. A caregiver report form of the scale (used here) has been used with individuals with PWS and found to be sensitive to compulsivity.<sup>22,23</sup> Because it is difficult to assess obsessions among people with limited verbal capacity, we also used the Compulsive Behavior Checklist<sup>24</sup> designed for people with intellectual disabilities, focusing on compulsive behavior rather than obsessions.

The Reiss Screen for Maladaptive Behavior<sup>25</sup> is a caregiver report instrument for people older than 12 years that assesses psychiatric symptoms of people with developmental disabilities. The Scales of Independent Behavior<sup>26</sup> is designed to assess both adaptive and maladaptive behavior of individuals with cognitive disabilities and is used most widely with individuals with moderate to severe intellectual disabilities. The Wechsler Intelligence Scale was used to evaluate intellectual ability.<sup>27,28</sup> The Visual Motor Integrations Scale<sup>29</sup> is a measure of visual-motor integration (VMI) and has been shown to detect the ability to coordinate motor responses with specific visual demands. Academic skills were assessed using the Woodcock Johnson Psycho-Educational Battery-Revised.<sup>30</sup> Statistical analyses used throughout the study included mean and standard deviation, *t* test, and analysis of variance.

## RESULTS

Parameters classified into specific groups (maladaptive behavior, adaptive behavior, obsessive compulsive behavior, visual processing, academic achievement, and intelligence) were found to show significant differences after analyzing a large data set collected over a 5-year study on the genotype/phenotype relationships in individuals with PWS. Three PWS subject groups (TI, TII, and UPD) were analyzed in our study (see Tables 1–3). Significant differences in maladaptive behavior assessment parameters were found in the 3 PWS subject groups for self-injurious behavior (SIB) externalized and internalized maladaptive index; SIB hurtful to self frequency and severity, and Reiss self-injury. However, no significant correlations with age were found with these variables in the 3 PWS subject groups. Significant differences in adaptive behavior assessment parameters were found among the 3 groups for SIB broad independence score: SIB motor skills, SIB social interaction and communication, and SIB personal living skills. Significant differences were also observed in measurements of behavioral difficulties related to functional living skills. These differences seemed to manifest in reduced independence scores

**Fig 1.** Microsatellite pattern for D15S1035 locus from an individual with PWS and parental DNA isolated from peripheral blood using an ABI 310 automated capillary sequencer. Only 1 DNA signal pattern is seen in the individual with PWS and inherited from the mother, whereas no DNA signal was observed from the father, indicating a paternal TI deletion in the individual with PWS.



**Fig 2.** Microsatellite pattern for D15S1035 locus from an individual with PWS and parental DNA isolated from peripheral blood using an ABI 310 automated capillary sequencer. Two DNA signal patterns are seen from the individual with PWS, indicating inheritance of a D15S1035 allele from each parent. Genetic testing showed a deletion of the 15q11-q13 region in the individual with PWS but not for the D15S1035 locus, indicating a TII deletion.

for TI deletions compared with either TII or UPD. Generally, psychological, behavior, and academic achievement scores in individuals with PWS and TI deletions were significantly worse than in individuals with TII or UPD. Maladaptive difficulties were coupled with a reduction in independent behaviors, suggesting a requirement for closer supervision. Fig-

ures 3 and 4 show histograms of the behavior, visual processing, academic achievements, and cognitive data showing significant differences among our TI, TII, and UPD individuals.

Significant obsessive-compulsive behavior measures were found for Y-BOCS control over compulsion, Y-BOCS resistance to compulsion, CBC signifi-

**TABLE 1.** Analysis of Behavior Data in Individuals With PWS and TI or TII Deletions or UPD

Parameters	Test	Group	Mean	SD	N	P Value	
						vs TII Deletion	vs UPD
Maladaptive behavior	SIB externalized maladaptive index	TI deletion	-14.25	15.28	12	.019	.830
		TII deletion	-1.64	7.86	14	-	.033
		UPD	-11.88	10.73	21	-	-
	SIB hurtful to self frequency*	TI deletion	2.33	1.67	12	.328	.068
		TII deletion	3.21	1.53	14	-	.001
		UPD	1.05	1.50	21	-	-
	SIB hurtful to self severity*	TI deletion	1.50	1.24	12	.494	.097
		TII deletion	2.07	1.49	14	-	.003
		UPD	0.52	1.12	21	-	-
	Reiss self-injury*	TI deletion	0.50	0.67	12	.734	.285
		TII deletion	0.68	0.77	14	-	.048
		UPD	0.16	0.37	19	-	-
Adaptive behavior	SIB broad independence score	TI deletion	23.75	10.06	12	.027	.452
		TII deletion	37.86	15.07	14	-	.186
		UPD	29.62	13.78	21	-	-
	SIB motor skills	TI deletion	27.42	6.88	12	.007	.445
		TII deletion	43.71	14.24	14	-	.056
		UPD	33.14	14.45	21	-	-
	SIB social interaction and communication	TI deletion	37.25	15.01	12	.002	.057
		TII deletion	60.14	14.40	14	-	.264
		UPD	51.24	18.06	21	-	-
	SIB personal living skills	TI deletion	33.67	13.29	12	.001	.154
		TII deletion	57.36	12.77	14	-	.031
		UPD	43.86	16.90	21	-	-
Obsessive-compulsive behavior	Y-BOCS control over compulsion*	TI deletion	3.30	1.57	10	.021	.061
		TII deletion	1.86	1.17	14	-	.774
		UPD	2.16	1.12	19	-	-
	CBC significant interference with social*	TI deletion	0.70	0.48	10	.012	.082
		TII deletion	0.14	0.36	14	-	.518
		UPD	0.32	0.48	19	-	-
	CBC interruption response-halts and resumes*	TI deletion	2.40	0.97	10	.071	.987
		TII deletion	1.36	1.28	14	-	.045
		UPD	2.33	1.03	18	-	-
	CBC skin picking*	TI deletion	1.30	0.82	10	.891	.157
		TII deletion	1.50	1.34	14	-	.032
		UPD	0.53	0.90	19	-	-

SD indicates standard deviation.

\* Categorical variables analyzed by analysis of variance for descriptive purposes.

cant interference with social, Y-BOCS repeating compulsion (rereading and erasing), Y-BOCS washing compulsion (bathing/toilet), and CBC clean/tidy compulsion (data not shown). Although there were a variety of compulsive measurements, only a subset was significant (see Table 1). Generally, the TI deletion group had greater difficulty controlling compulsions. This seemed to be confirmed by several measurements related to the control or resistance to compulsive behavior. The difficulties associated with compulsions seem to present with greater problems for routine daily activities found in individuals with TI versus TII and UPD. The measurements of repetitive behaviors indicate that TI individuals scored more poorly.

Significant differences were also found in visual processing scores among the 3 subject groups based on VMI assessments for VMI (raw score), VMI (percentile), and VMI (standing score). Significant differences were found in academic achievement scores among the 3 groups using the Woodcock-Johnson Psycho-Educational Battery, which included Woodcock-Johnson reading cluster, reading comprehension, letter-word identification, Woodcock-Johnson math cluster, applied problems, and calculation (see Table 2). Significant academic achievement measure-

ments were the most strikingly different for TI deletions with poorer performances compared with individuals with TII or UPD. For example, in Woodcock-Johnson math cluster, individuals with TI performed more poorly than in individuals with either TII or UPD. These scores represented a convergent set of intellectual assessments that all suggested a reduction in scholastic aptitude by individuals with TI deletions compared with the other genetic subtypes. However, significant differences were observed in intelligence scores generated using the Wechsler Intelligence Scale, particularly with lower scores generated for both deletion types (TI and TII) compared with individuals with UPD. For these scores, observed significant differences were found between individuals with TII and UPD. Unlike the other intelligence scores, the object assembly scores were higher in individuals with TI and TII compared with individuals with UPD, in agreement with previous reports on deletion and UPD comparisons.

The following are assessment sets in which individuals with TII seemed to do better than individuals with TI or UPD: assessment of maladaptive and adaptive behavior (SIB externalized maladaptive index and SIB personal living skills) and for obsessive compulsive behavior (CBC interruption response-

**TABLE 2.** Analysis of Visual Processing, Academic Achievement, and Intelligence Data in Individuals With PWS and TI or TII Deletions or UPD

Parameters	Test	Group	Mean	SD	N	P Value	
						Vs TII Deletion	Vs UPD
Visual processing	Vineland Motor Inventory (raw score)	TI deletion	10.50	4.66	12	.045	.579
		TII deletion	15.93	7.25	14	-	.191
		UPD	12.52	4.72	21	-	-
	Vineland Motor Inventory (percentile)	TI deletion	1.00	0.00	12	.043	.994
		TII deletion	2.21	2.26	14	-	.024
		UPD	1.05	0.22	21	-	-
	Vineland Motor Inventory (standard score)	TI deletion	58.92	3.45	12	.007	.993
		TII deletion	64.08	8.69	13	-	.003
		UPD	57.14	3.88	21	-	-
Academic achievement	Woodcock-Johnson reading cluster*	TI deletion	43.27	27.43	11	.113	.040
		TII deletion	65.57	20.99	14	-	.927
		UPD	69.11	30.42	19	-	-
	Letter-word identification*	TI deletion	45.00	29.41	12	.023	.085
		TII deletion	69.29	21.37	14	-	.543
		UPD	63.75	28.50	20	-	-
	Reading comprehension	TI deletion	33.75	28.11	12	.048	.087
		TII deletion	60.50	22.85	14	-	.881
		UPD	55.85	30.64	20	-	-
	Woodcock-Johnson math cluster*	TI deletion	44.08	24.51	12	.031	.038
		TII deletion	63.07	17.52	14	-	.982
		UPD	62.90	23.31	20	-	-
	Applied problems	TI deletion	49.08	18.59	12	.087	.031
		TII deletion	62.93	14.65	14	-	.950
		UPD	64.65	15.69	20	-	-
	Calculation*	TI deletion	48.17	29.60	12	.047	.508
		TII deletion	67.71	17.37	14	-	.087
		UPD	54.58	23.47	19	-	-
Intelligence	Verbal IQ	TI deletion	62.91	9.34	11	.975	.058
		TII deletion	62.21	9.39	14	-	.020
		UPD	70.00	6.20	21	-	-
	Information (standard score)	TI deletion	2.64	1.50	11	.674	.031
		TII deletion	2.14	1.17	14	-	.001
		UPD	4.05	1.56	21	-	-
	Vocabulary (standard score)	TI deletion	3.18	1.72	11	.987	.068
		TII deletion	3.07	1.69	14	-	.030
		UPD	4.71	1.90	21	-	-
	Object assembly (standard score)	TI deletion	5.18	1.99	11	.992	.077
		TII deletion	5.29	2.55	14	-	.038
		UPD	3.43	1.83	21	-	-
	Comprehension (standard score)	TI deletion	3.18	1.78	11	.887	.090
		TII deletion	2.86	1.46	14	-	.017
		UPD	4.57	1.86	21	-	-

SD indicates standard deviation.

\* Variables analyzed by unpaired *t* tests only.

halts and resumes). For example, individuals with TII deletions had significantly better scores for 2 of the SIB measures, whereas 4 other measures were found to do more poorly. For visual processing, individuals with TI and UPD were similar, but individuals with TII were more different (performed better) than the other 2 genetic subtypes. These measurements suggest that individuals with TII deletions had better daily living skills than individuals with TI deletions or UPD. Intelligence as assessed by a number of subtests indicate that individuals with TI and TII did not differ from each other and were each lower than UPD for verbal IQ, which is in general agreement with our previous reports comparing UPD with deletion PWS individuals.

### DISCUSSION

The percentage of individuals with PWS and TI or TII deletions in our study was similar to that reported by others.<sup>5</sup> In addition, differences in the

behavioral, psychological, intellectual, and physical characteristics of individuals with PWS and uncharacterized deletions compared with individuals with UPD have been reported previously. However, we present the first assessment of clinical differences in individuals with PWS categorized as having TI or TII deletion. We examined a large existing data set of measures (eg, biochemical, morphologic, metabolic, behavioral, psychological) and most were not significantly different between the 2 deletion types, but significant differences were found for several behavioral and intelligence measures. The average age for our individuals with PWS would fall within the young adulthood range; therefore, the behavioral differences found may not apply to children with PWS.

Psychobehavioral phenotypic characteristics of individuals with PWS and TI or longer deletions (ie, BP1) were similar in several respects to individuals with uncharacterized deletions previously report-

**TABLE 3.** Behavior, Visual Processing, Academic Achievement, and Intelligence Parameters Found to be Significantly Different Among the Three PWS Subject Groups (TI deletion, TII deletion, or UPD) With the Two Subject Groups Listed Having Significant Differences

Parameter	Group
Maladaptive behavior	
SIB externalized maladaptive index	TI deletion vs TII deletion* TII deletion vs UPD*
SIB hurtful to self frequency	TII deletion vs UPD‡
SIB hurtful to self severity	TII deletion vs UPD†
Reiss self-injury	TII deletion vs UPD*
Adaptive behavior	
SIB broad independence score	TI deletion vs TII deletion*
SIB motor skills	TI deletion vs TII deletion†
SIB social interaction and communication	TI deletion vs TII deletion†
SIB personal living skills	TI deletion vs TII deletion‡ TII deletion vs UPD*
Obsessive-compulsive disorder	
Y-BOCS control over compulsion	TI deletion vs TII deletion*
CBC interference with social	TI deletion vs TII deletion*
CBC interruption response-halts and resumes	TII deletion vs UPD*
CBC skin picking	TII deletion vs UPD*
Visual processing	
Vineland Motor Inventory (raw score)	TI deletion vs TII deletion*
Vineland Motor Inventory (percentile)	TI deletion vs TII deletion* TII deletion vs UPD*
Vineland Motor Inventory (standard score)	TI deletion vs TII deletion† TII deletion vs UPD†
Academic achievement	
Woodcock-Johnson reading cluster	TI deletion vs UPD*
Letter-word identification	TI deletion vs TII deletion*
Reading comprehension	TI deletion vs TII deletion*
Woodcock-Johnson math cluster	TI deletion vs TII deletion*
Applied problems	TI deletion vs UPD*
Calculation	TI deletion vs TII deletion*
Intelligence	
Verbal IQ	TII deletion vs UPD*
Information (standard score)	TI deletion vs UPD* TII deletion vs UPD‡
Vocabulary (standard score)	TII deletion vs UPD*
Object assembly (standard score)	TII deletion vs UPD*
Comprehension (standard score)	TII deletion vs UPD*

\*  $P < .05$ .

†  $P < .01$ .

‡  $P \leq .001$ .

ed<sup>31-34</sup> but do differ from those with TII or shorter deletions (ie, BP2), the latter group resembling several features of individuals with UPD. Those with longer deletions had more compulsive behavior and more impairment of visual perception. Conversely, individuals with longer deletions did not display more self-injury than individuals with shorter deletions or UPD (eg, Scales of Independent Living, Reiss Self Injury Scale, Compulsive Behavior Checklist Skin Picking). Although both individuals with TI and TII deletion exhibited more SIB than individuals with UPD for several assessments, the differences were significant in only individuals with TII when compared with UPD. These differences may reflect the sample size with a larger number of individuals with TII and UPD studied compared with the number of individuals with TI. With larger sample sizes found in both the TII and UPD subject groups and thus higher degrees of freedom, higher  $t$  test values would meet the significance level for these parameters.

The disassociation of compulsivity and skin picking is consistent with our previous factor analytic study revealing that skin picking does not factor

with compulsivity using the Compulsive Behavior Checklist.<sup>35</sup> Moreover, we recently reported that plasma  $\gamma$ -aminobutyric acid levels are inversely correlated with skin picking in PWS but unrelated to compulsive behavior scale scores (T. Thompson, PhD, I. Feurer, PhD, W. MacLean, PhD, D. Schmidt, PhD, and M.G. Butler, MD, PhD, unpublished data, 2002). Several academic achievement scores differed between shorter and longer deletions, which may reflect a difference in intellectual functioning as well as differences in visual perception that may affect reading ability.

The longer deletion results in the loss of an additional 500 kb of DNA compared with the shorter deletion. DNA sequences contained in this region may contribute to the differences observed between individuals with PWS and TI and TII deletions, which is supported by the identification of 4 genes between BP1 and BP2.<sup>7</sup> Thus, individuals with the longer deletion are presumably missing the 4 genes compared with individuals with PWS and shorter deletions. One of these genes is NIPA-1, which is expressed in mouse brain tissue and is not thought to be imprinted but may be important for brain devel-

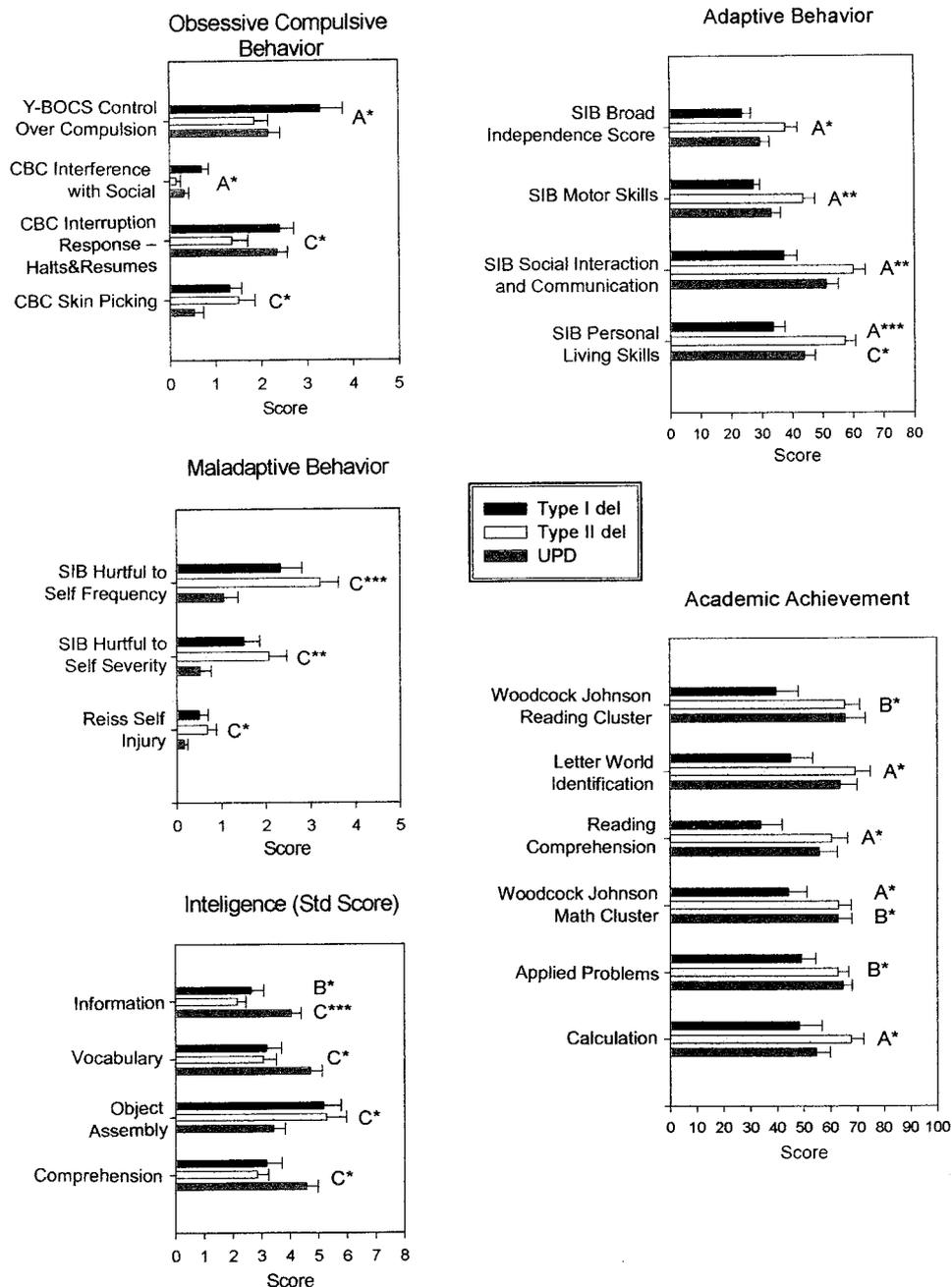


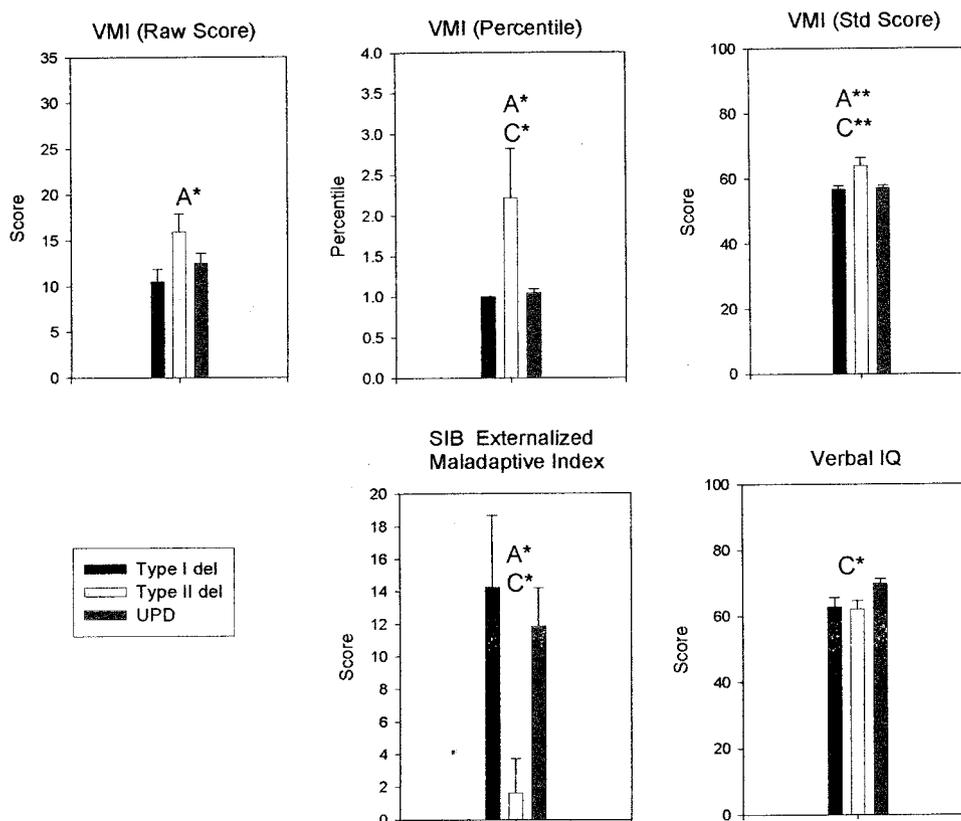
Fig 3. Histograms of maladaptive behavior, adaptive behavior, obsessive-compulsive behavior, academic achievement, and intelligence (standard score) data showing significant differences among the 3 PWS genetic subtypes (TI deletion, TII deletion, and UPD). A, TI deletion versus TII deletion; B, TI deletion versus UPD; C, TII deletion versus UPD; \* $P < .05$ ; \*\* $P < .01$ ; \*\*\* $P \leq .001$ .

opment or function.<sup>7</sup> These or other unidentified genes in the BP1 and BP2 region may be implicated in compulsive behavior and lower intellectual ability that were seen in our patients.

Our previous studies indicate that 2 maternal copies of the 15q11-q13 region may predispose to less skin picking, more visual perceptual abnormalities,<sup>15</sup> but a superior visual memory,<sup>36</sup> which may ameliorate the IQ deficit in individuals with UPD. In addition, the UBE3A gene, which is maternally expressed in Purkinje cells, hippocampal neurons, and mitral cells of the olfactory bulb in mouse models,<sup>37</sup> should also be considered as playing a role in 1 or more of these phenotypic features in PWS with UPD. Individuals with maternal disomy will have 2 expressed

alleles of the UBE3A gene, and this overproduction of gene product may have an impact on the behavior or clinical phenotype compared with the individual with TI or TII deletion with only 1 active allele of this gene.

Our results indicate that having a paternal copy of genes between BP1 and BP2 is beneficial to having 2 maternal copies as seen in individuals with UPD. One would anticipate no distinction between maternal and paternal alleles in this region if they are biallelically expressed; however, the 15q11-q13 region contains imprinted genes. This imprinting process may have an impact on the function of other genes in the region. In addition, paternally expressed genes outside the PWS critical region would not be



**Fig 4.** Histograms of visual processing (Vineland Motor Inventory), SIB externalized maladaptive index, and verbal IQ data showing significant differences among the 3 PWS genetic subtypes (TI deletion, TII deletion, and UPD). A, TI deletion versus TII deletion; B, TI deletion versus UPD; C, TII deletion versus UPD; \* $P < .05$ ; \*\* $P < .01$ ; \*\*\* $P \leq .001$ .

expressed in individuals with PWS and UPD but would be expressed in individuals with a deletion. Similarly, incorrect methylation may also play a role in this region. Hence, the above observations and speculations will require additional genetic testing and confirmation.

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# Behavioral Differences Among Subjects With Prader-Willi Syndrome and Type I or Type II Deletion and Maternal Disomy

Merlin G. Butler, Douglas C. Bittel, Nataliya Kibiryeve, Zohreh Talebizadeh and  
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