THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY
Journal of Child Psychology and Psychiatry 52:5 (2011), pp 580–587 doi:10.1111/j.1469-7610.2011.02365.x

TPH2 G/T polymorphism is associated with hyperphagia, IQ, and internalizing problems in Prader–Willi syndrome

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Background: Prader–Willi syndrome (PWS) is a genetic, neurodevelopmental disorder characterized by intellectual disabilities, growth hormone dysregulation, hyperphagia, increased risks of morbid obesity, compulsive behaviors, and irritability. As aberrant serotonergic functioning is strongly implicated in PWS, we examined associations between the PWS phenotype and polymorphisms in tryptophan hydroxylase 2 (TPH2), the rate-limiting enzyme in the biosynthesis of serotonin in the brain. **Methods:** Ninety-two individuals with PWS aged 4 to 50 years (M = 21.97) were genotyped for the TPH2 G703-T polymorphism. IQ testing was conducted in offspring, and parents completed questionnaires that tapped their child's compulsivity, hyperphagia, and other behavior problems. **Results:** As expected, the frequency of G/T or T/T polymorphisms in participants with PWS (39%) was similar to rates found in the general population (38%). Compared to those with a homozygous (G/G) genotype, individuals with a T allele had significantly higher hyperphagic behavior, drive, and severity scores, and they also had a younger age of onset of hyperphagia. Those with a T allele also had higher IQ scores than their counterparts. Females with a T allele had significantly higher internalizing symptoms, primarily anxiety and depression, than all others. **Conclusions:** TPH2 G/T polymorphisms, and presumed loss of enzyme function, were associated with specific aspects of the PWS phenotype. Aberrant serotonergic functioning is strongly implicated in hyperphagia in PWS, and females with TPH2 T alleles may be at higher risk for affective or mood disorders. Findings hold promise for examining other serotonin-altering genes in PWS, and for future serotonin-altering treatment trials. **Keywords:** Behavior problems, genetics, intelligence, internalizing disorder, neurochemistry, Prader–Willi syndrome.

Prader–Willi syndrome (PWS) is a relatively rare genetic disorder well known for its genetic and phenotypic complexities. Seen in approximately 1 in 15,000 births, PWS is characterized by mild to moderate levels of intellectual disability, growth hormone dysregulation, hyperphagia, and increased risks of morbid obesity (Cassidy & Driscoll, 2009). The PWS behavioral phenotype includes high rate of repetitive, compulsive behaviors, as well as irritability, negative and labile moods, impulsivity, and tantrums (Dykens, Summar, & Roof, 2005). These problems, coupled with hyperphagia, necessitate that affected individuals receive lifelong supervision and supports.

PWS is caused by a lack of paternally derived imprinted material on chromosome 15q11-q13. In approximately 70% of cases, PWS is due to a paternal deletion at 15q11-q13, and deletions can be further characterized according to size, with Type I deletions being about 500 kb larger than Type II deletions. Approximately 25% of PWS cases are due to maternal uniparental disomy (mUPD), or when both copies of chromosome 15 are inherited from the mother, and 5% to translocations or imprinting center mutations.

Genetic causes of PWS aside, a growing literature on biomarkers suggests that genetic variation outside of the PWS critical region may greatly influence phenotypic expression in PWS. Based on converging clinical and genetic findings, for example, aberrant serotonergic functioning is strongly implicated in PWS. Individuals with PWS are prone to disorders or symptoms regulated by serotonin, including aberrant appetite and sleep, affective illness and mood disorders, and compulsive behaviors that are similar to those seen in autism spectrum disorders or obsessive-compulsive disorder (Clarke et al., 2002; Dykens, Cassidy, & Leckman, 1996). More severe symptoms or disorders (e.g., psychosis) are typically manifest in those with mUPD (e.g., Soni et al., 2007; Vogels, Matthijs, Legius, Devriendt, & Fryns, 2003). Treatment with selective serotonin reuptake inhibitors (SSRIs) is widely used and, in some people, reduces irritability, moodiness, outbursts, and compulsions (Dykens & Shah, 2003).

The PWS critical region is also implicated in the production of serotonin. A small nucleolar RNA (snoRNA), HBII-52 (SNORD115), located in the

Conflict of interest statement: No conflicts declared.

15q11-q13 region, has been shown to regulate the processing of the mRNA of the serotonin 2C receptor, located elsewhere on the genome (Kishore & Stamm, 2006). Several mouse models of PWS exist, including mice deleted for HBII-52 (Ding et al., 2008), or with altered 2C receptor mRNA functioning (Morabito et al., 2010). As with other PWS models, these mice are hyperphagic but not obese. Sahoo et al. (2008) reported a boy with features consistent with the diagnosis of PWS who had a small deletion of only the snoRNA HBII-85 (SNORD116) and part of HBII-52 (SNORD115) region, strongly implicating these clusters in the PWS phenotype. Lack of HBII-52 expression in PWS may lead to altered processing of serotonin 2C receptor mRNA, which may impact the efficacy of SSRIs in this population. Treatments with SSRIs are not consistently beneficial in PWS, with some persons showing a worsening of target symptoms (Dykens & Shah, 2003). This variability in treatment response suggests that the PWS phenotype may also be influenced by genes that are known to alter serotonin production among people in general.

Although many genes are involved in the production of serotonin, we selected tryptophan hydroxylase (TPH2) for initial study, as it is the first-step and rate-limiting enzyme in the biosynthesis of serotonin in the brain. While TPH1 is expressed mostly in cells of the gut, TPH2 is expressed predominantly in the brainstem and is responsible for the production of serotonin in the brain (Walther & Bader, 2003). Polymorphisms in TPH2 are implicated in depression, anxiety, and aggression, as well as in the regulation of mood, attention, appetite, and sleep; all of these processes are disrupted in PWS (Cassidy & Driscoll, 2009).

Associations have been reported between sequence variants (single nucleotide polymorphisms, SNPs) in the TPH2 promoter (G-703T; dbSNP accession number rs4570625) and children with obsessive-compulsive disorder (OCD) (Mössner et al., 2006), autism (Coon et al., 2005), and ADHD (Walitza et al., 2005), and in adult depression or bipolar disorder (Harvey et al., 2004; Zhang et al., 2005). Other investigators have examined the effects of the TPH2, G-703T polymorphisms on broader personality traits or emotional reactivity. Compared to those homozygous for the G allele, Brown, Peet, Williamson, Dahl, and Harin (2005) identified increased amygdala activation in response to angry or fearful faces in healthy adults with the T allele. Canli, Congdon, Gutknecht, Constable, and Lesch (2005) subsequently demonstrated increased amygdala activation in participants with the T allele versus G/G allele in response to faces depicting both negative and positive affect. The TPH2-703 T allele may thus modulate emotional arousal in general, and is implicated in disorders involving emotional dysregulation.

This study identified TPH2 G/T allele status in a large cohort of 92 participants with genetically confirmed PWS, and compared salient features of PWS across those with or without polymorphisms in this allele. We predicted that the frequency of polymorphisms in the TPH2 G/T allele in PWS would be similar to those found in the general population. We also hypothesized that, compared to participants who are homozygous for the G/G allele, those with a loss of TPH2 enzyme function, or with a G/T or T/T allele, would show significantly more behavioral, mood, or emotional problems. Finally, although gender differences are rarely reported in PWS, gender by genotype differences may exist as females in the general population are more prone to mood disorders (Kessler et al., 2003). Significant gender effects of the TPH2 T/G allele have been identified in the emotional startle response (Armbruster et al., in press), susceptibility to depression (Utge et al., 2010), and panic disorder (Maron et al., 2007). As such, we reasoned that females with PWS may be more vulnerable to the effects of the T polymorphism and reduced serotonin production.

Methods

Participants

The sample included 92 individuals (47 males, 45 females) with PWS aged 4 to 51 years (*M* age = 21.97, *SD* = 11.66) and their parents. Based on Center for Disease Control (CDC) guidelines, most adults (62%) with PWS were classified as obese (see Table 1), and the mean BMI for adults aged 21 years and older was 34.66 (*SD* = 9.24). The mean BMI among children and adolescents aged 4 to 20 years was 27.52 (*SD* = 8.04), with 67% classified as obese using CDC age-and gender-percentiles.

Families were recruited and gave their written, informed consent either as part of an ongoing longitudinal study on behavior in PWS, or through a survey on medications and interventions commonly seen in PWS (e.g., SSRIs, growth hormone treatment, food restrictions). Survey participants (60% of sample) were somewhat older than those followed longitudinally

Table 1 Characteristics of 92 participants with PWS

		M	*SD*
Age		22.66	(11.66)
K-BIT-II IQ		65.01	(12.52)
BMI adults (*n* = 47)		34.66	(9.24)
% Normal	8%		
% Overweight	30%		
% Obese	62%		
BMI children (*n* = 45)		27.52	(8.04)
% Normal	21%		
% Overweight	12%		
% Obese	67%		
Genetic subtypes			
Deletion	58% (21% Type I, 32% Type II, 5% unknown)		
mUPD	38%		
Other	4%		

(*M* ages = 24.30 versus 19.85 years, t (91) = −1.93, p = .07), but did not significantly differ on any of the behavioral or cognitive measures.

Participants had genetic testing that confirmed their PWS diagnosis and genetic subtype (see Table 1). The study included slightly more cases of mUPD (38%) than typically reported in the literature (25%) because the longitudinal study deliberately oversampled persons with this genetic subtype.

Consistent with previous literature, the IQ scores of participants with PWS ranged from 40 to 88, with a mean IQ of 65.03 (*SD* = 12.62). IQ scores were derived in 42% of the sample from direct testing with the Kaufman Brief Intelligence Test-2 (K-BIT-2; Kaufman & Kaufman, 2004), and in remaining participants, from records of previous cognitive testing obtained from parents. IQ scores across these two sources were highly correlated (r = .86, p < .001) and remarkably similar (K-BIT *M* = 65.30; previous IQ tests *M* = 64.75). Approximately 32% of participants, primarily children, were on growth hormone treatment, and the majority (71%) were taking psychotropic medications; of these 48% were on SSRIs.

Mothers served as informants, and their average age was 52 years. Mothers were generally well educated: 36% had high school degrees, 35% completed 2 or 4 years of college, and 29% had graduate or professional school training.

TPH2 genotyping

Participants with PWS provided a saliva sample by chewing on a cotton swab, and DNA was extracted from saliva using Vanderbilt Institute for Clinical and Translational Research core facilities. TPH2 genotyping was conducted by PCR amplification of an 1154 bp fragment of the *TPH2* gene that included the -703 G/T SNP (rs4570625) using the following primers:

forward 5′ ACTCTGCATAGAGGCATCACAGGA 3′;
reverse 5′ GGAGAAATTTGAGGTGTGCGTGCT 3′.

Sequencing of the fragment was performed using an ABI Genetic Analyzer 3100 (Applied Biosystems, Foster City, CA) and standard protocols.

Procedures

Mothers completed behavioral measures either during their research visits to the lab, or at their convenience at home. The packet included the following measures.

Demographics. These responses identified family composition and parental educational and employment status, as well as specific information about offspring with PWS, including: previous diagnostic and genetic evaluations, current and previous medications, growth hormone treatment, sleep and health habits, the onset of hyperphagia, and dietary and other interventions.

Child Behavior Checklist (CBCL; Achenbach, 2001). The widely used CBCL asks parents to rate 112 problem behaviors on a three-point scale (not true to very true or often true.) The CBCL contains an Internalizing Domain (Anxiety/depression; Withdrawal, Somatic Complaints), Externalizing Domain (Aggression, Rule-Breaking) and other clinical domains (Social, Thought, and Attentional problems). The CBCL has been successfully used to identify problems in children or adults with developmental disabilities. Data analyses used CBCL Raw Scores.

Hyperphagia Questionnaire. This 13-item questionnaire (Dykens, Maxwell, Pantino, Kossler, & Roof, 2007) probes symptoms of hyperphagia in PWS. Previous factor analyses identified three robust factors: Hyperphagic Drive (e.g., how persistent in asking for food; how easy to direct away from food); Hyperphagic Behaviors (e.g., how fast or clever in obtaining food; how often steal food), and Hyperphagic Severity (time spent talking about food; 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). Raw scores for each factor were used in data analyses, and the three domains were also summed for an overall summary index of hyperphagia.

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 studies in PWS, and analyses used the sum of lifetime obsessions, compulsions, and current symptom severity (Clarke et al., 2002; Dykens et al., 1996).

Results

Genotyping

Of the 92 PWS cases examined, 36 had the G/T (*n* = 32) or T/T (*n* = 4) polymorphism. The homozygous genotype, G/G, was seen in 57 participants. As expected, the rate of the G/T or T/T polymorphisms in our PWS sample (39%) is similar to that reported for the general population (38%; Brown et al., 2005).

TPH2 and participant characteristics

We used t-test or chi-square analyses to assess if TPH2 allele status differed across such participant characteristics as medication status, age, gender, or genetic subtype of PWS. No significant differences were found. The G/G group (64% males) averaged 23.82 years (*SD* = 12.53) and the mean age in the T allele group (45% males) was 20.82 years (*SD* = 10.04). Of the PWS deletion cases, 64% had a G/G genotype, and 36% a T allele, a rate that was similar to mUPD cases, with 65% in the G/G group, and 35% with a T allele. Thus, the frequencies of TPH2 polymorphisms were distributed across those with PWS regardless of their medication status, age, gender, or genetic subtype.

TPH2 and PWS phenotype

We used 2 × 2 ANOVAS (TPH2 normal G/G versus loss G/T or T/T by gender) to determine if TPH2 genotype had a significant effect on salient phenotypic features of PWS. These features included IQ, compulsivity, maladaptive behaviors, BMI, food-related behaviors, and hyperphagia. In order to conduct meaningful statistical analyses, the 4 participants with the T/T allele were grouped with those with a G/T allele, and the T polymorphism group was compared to those with the G/G genotype. Although this practice is consistent with existent TPH2 literature, we followed up significant group differences with Neuman–Keuls post-hoc tests to ensure that group differences were not solely driven by the T/T group.

As shown in Table 2, no significant main effects or interactions for TPH2 status or gender were found for Y-BOCS compulsivity, BMI, or CBCL externalizing behavior problems. Significant main effects for TPH2 group status emerged for IQ and for all three domains of the Hyperphagia Questionnaire, such that the T allele group had higher IQ and hyperphagia scores. The T group also had a significantly younger age of onset of hyperphagia; on average, their heightened interests in food began a full year before their counterparts in the G/G group. Regarding dietary interventions, virtually all participants were on reduced calorie diets, were supervised around food, and exercised an average of 4.28 days a week, for 38 minutes. No group or gender differences were seen in their diets or exercise patterns. Those with a T polymorphism, however, slept significantly longer each night (see Table 2). Locking food sources was also more common in those with the T polymorphism (83%) than the G/G group (63%; X^2 (1) = 7.81, $p < .01$).

Post-hoc analyses of significant Hyperphagia Questionnaire and IQ findings revealed significant differences between the G/G and G/T groups, even when the 4 participants with T/T alleles were removed from analyses. Although the small size of the T/T allele group prohibited formal statistical analyses, these 4 individuals had substantially higher mean IQ and hyperphagia scores than the G/T group. Figure 1 demonstrates this relationship for IQ, and Figure 2, for the total score of the Hyperphagia Questionnaire.

A significant interaction was found between TPH2 status and gender for CBCL internalizing problems. Table 2 shows that females with the T polymorphism had significantly higher internalizing scores than all remaining participants. Figure 3 also depicts this interaction. Follow-up analyses of the subdomains that comprise the internalizing domain revealed that females with the T polymorphism specifically had significantly higher depression/anxiety subdomain scores that their counterparts.

Discussion

Aberrant serotonergic functioning has long been implicated in the phenotypic expression of PWS. This study examined the rate and phenotypic effects of an important serotonin-altering gene, TPH2, in a relatively large cohort of 92 well-characterized individuals with PWS. As expected, the frequency of the T polymorphism in our sample of 92 individuals (39%) was remarkably similar to the rate found in the general population (38%, Brown et al., 2005). Within the PWS sample, however, the presence of

Table 2 Means and SDs for behavioral measures by TPH2 group and gender, and *F* and *p* values

	G/G		G/T or T/T		
	Male	Female	Male	Female	
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*F* and *p*
IQ	62.63 (11.42)	61.42 (12.32)	71.92 (13.38)	67.70 (11.69)	Group $F = 6.18^{**}$
BMI	32.15 (8.66)	29.60 (9.54)	29.89 (7.94	34.04 (11.83)	NS
Hours sleep	9.05 (1.31)	8.90 (.97)	10.00 (1.22)	10.41 (1.31)	Group $F = 19.55$**
CBCL problems					
Externalize	14.44 (10.58)	15.20 (8.98)	17.37 (8.93)	18.42 (8.19)	NS
Internalize	12.65 (9.14)	12.36 (7.50)	11.6 (4.32)	17.74 (7.79)	Interaction $F = 4.09^{*}$
Anx/depress	4.87 (3.98)	3.72 (3.60)	3.81 (2.19)	6.58 (4.28)	Interaction $F = 6.02^{**}$
Withdrawn	3.97 (3.12)	4.76 (2.97)	3.18 (1.87)	5.58 (2.09)	Gender $F = 7.39$**
Y-BOCS					
Compulsions	3.97 (2.54)	3.69 (2.65)	4.20 (1.92)	3.75 (2.40)	NS
Obsessions	1.78 ((1.32)	1.83 (1.75)	2.00 (1.92)	2.10 (1.94)	NS
Severity	3.21 (2.05)	6.07 (4.51)	5.39 (3.82)	5.70 (3.11)	NS
Hyperphagia					
Drive	10.42 (3.31)	10.63 (3.71)	12.14 (2.28)	13.18 (3.58)	Group $F = 9.16^{**}$
Behavior	12.18 (5.21)	12.28 (4.39)	13.00 (2.34)	15.58 (4.70)	Group $F = 3.78^{*}$
Severity	4.50 (1.54)	4.13 (1.57)	4.80 (1.74)	5.58 (1.75)	Group $F = 6.23^{**}$
Age onset	4.60 (2.76)	4.07 (1.88	3.41 (1.32)	3.22 (1.34)	Group $F = 4.69^{*}$
Overweight rating	1.09 (.89)	1.16 (.80)	1.62 (.72)	1.63 (.68)	Group $F = 8.44^{**}$

Note: $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

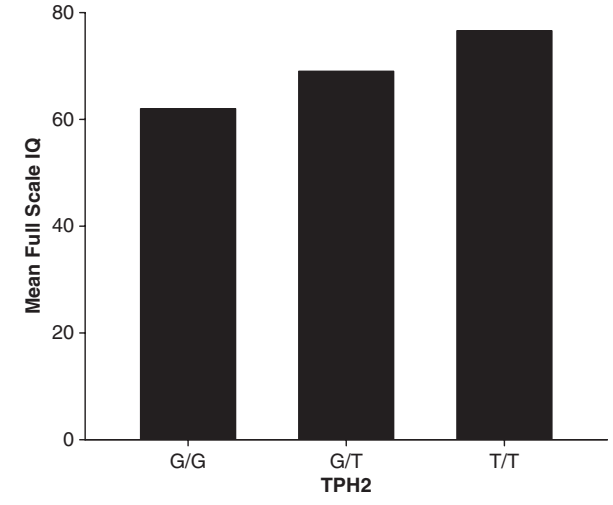

Figure 1 Mean IQ across TPH2 allele status

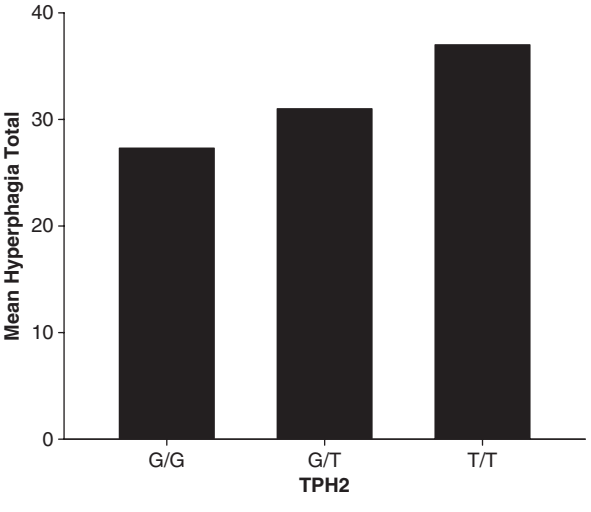

Figure 2 Mean total Hyperphagia Questionnaire scores across TPH2 allele status

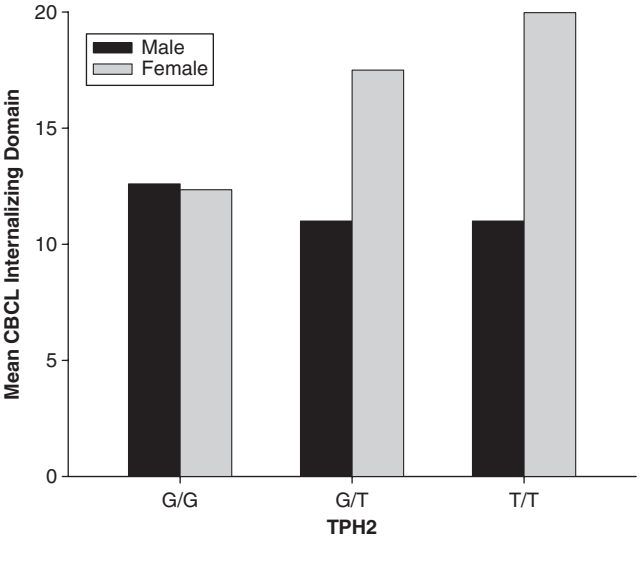

Figure 3 Gender interaction with CBCL internalizing domain and TPH2 allele status

the T polymorphism had significant, circumscribed effects on specific aspects of the PWS phenotype.

Relative to those with a G/G allele status, participants with the T polymorphism had significantly higher scores on the Hyperphagia Questionnaire, including the hyperphagic behavior, drive, and severity domains. The T allele group also had, on average, a significantly earlier age of onset of hyperphagia in childhood, and higher parental ratings of being overweight. Participants with the homozygous G/G genotype showed the lowest hyperphagia scores. Significantly higher hyperphagia scores were manifest by those with the G/T allele, and although less frequent, the highest hyperphagia scores were manifest by those with the homozygous T/T genotype. On the surface these findings seem logical, as reduced expression related to the T allele of TPH2 is associated with reduced neural synthesis of serotonin, and lower peripheral levels of serotonin are associated with increased appetite in the general population (e.g., Halford, Harrold, Boyland, Lawton, & Blundell, 2007). Conversely, treatment with SSRIs increases synaptic availability of serotonin, and is associated with decreased appetite and weight loss.

On the other hand, findings are striking in relation to PWS. Phenotypic effects of TPH2 were targeted and circumscribed, and converged on a salient, life-threatening feature of PWS. Further, while other biomarkers of appetite regulation are aberrant in PWS, it is unclear how they relate to the drive for food and eating behaviors in affected individuals (Butler & Bittel, 2007; Goldstone, 2006). Plasma levels of ghrelin, for example, are markedly higher in PWS, but do not relate to food-seeking behaviors, nor do ghrelin blockers lead to reduced appetite or food intake (De Waela et al., 2008). Although additional work with other serotonin-altering genes is necessary, TPH2 findings implicate altered serotonergic functioning as a key player in the regulation of hyperphagia in PWS.

Relations between serotonin and appetite are well established (Halford et al., 2007), yet few studies have specifically examined the impact of TPH2 polymorphisms on food intake or appetite. Schotta et al. (2010) reported a rare case of a child with hypothalamic syndrome and altered serotoninergic functioning related to TPH2 impairment. The child had early onset hyperphagia, obesity, sleep difficulties, precocious puberty, hypoventilation, and behavioral problems. To our knowledge, however, studies have yet to examine associations between TPH2 polymorphisms, obesity, and the drive for food among people in general.

While TPH2 allele status was associated with hyperphagia, it did not predict the degree of obesity (BMI) in affected individuals. The lack of association between TPH2 status and BMI likely reflects the strict environmental dietary and food controls that are universally applied to those with PWS. Regardless of their age, gender, or PWS genetic subtype, virtually

all participants in this study were closely supervised around food, on reduced calorie diets, and they also engaged in regular exercise. Beyond these standards of care in PWS, locking food sources is also often recommended, a practice that can reduce anticipatory worry about meals or food sneaking. Locking food sources was more likely to occur in the homes of PWS participants with a T allele, which likely reflects their heightened hyperphagia.

Compared to those in the G/G group, participants with TPH2 T polymorphisms also had significantly higher IQ scores. These IQ findings are puzzling, as several studies suggest impaired cognitive and executive control performance in people with G/T or T/T alleles. Although IQ has not been examined in this work, healthy adults with the T allele committed more errors on a continuous performance task (Strobel et al., 2007), and showed diminished inhibitory control on Stroop tasks (Osinsky et al., 2009). Further, individuals who undergo tryptophan depletion, which involves a transient reduction in serotonin transmission, have impaired memory consolidation (Mendelsohn, Riedel, & Sambeth, 2009). These same tryptophan-depleted individuals, however, have improved focused attention, especially on tasks requiring effortful control (Evers, van der Veen, Julles, Deutz, & Schmitt, 2006). Similarly, Reuter et al. (2008) found no differences in working memory task performance between G/G versus T carrier adults. Using fMRI, however, they report increased activation in adults with T alleles in brain regions associated with working memory, suggesting that this group uses compensatory processes to complete complex cognitive tasks. Such compensatory processes and focused attention may also be called into play during cognitive testing, leading to improved IQ test performance in PWS participants with T polymorphisms.

Higher IQs in the T group may also be associated with their longer duration of sleep each night. Compelling evidence from both clinical and typical populations links sleep duration and quality to specific aspects of memory and cognition (see Durmer & Dinges, 2005 for a review). Disrupted sleep is associated with behavior problems in people with intellectual disabilities (e.g., Malow et al., 2006; Wiggs & Stores, 1996), but few studies have examined relations between sleep and cognition in PWS or other disability groups. Persons with PWS are prone to obstructive sleep apnea, a known risk-factor for cognitive deficits, which further highlights the need for research on cognition, sleep, and the tryptophan–serotonin–melatonin pathway in this syndrome.

Despite the fact that aberrant serotonergic functioning is implicated in a variety of psychiatric disorders, we did not find uniformly elevated emotional or problem behaviors in PWS participants with the T allele. Instead, a significant interaction emerged with gender, such that females with a T allele had significantly higher internalizing problems than remaining participants. Females with T alleles had particularly elevated scores on the CBCL's depression/anxiety domain, which may reflect the increased risk of mood disorders among females versus males in general (Kessler et al., 2003). Maron et al. (2007) found that women with (versus without) panic disorders were more apt to have a TPH2 A/G polymorphism. Utge and colleagues (2010) recently completed a Finnish population-based association study of 14 candidate genes related to depression, with or without co-occurring fatigue or sleep disturbance. TPH2 was strongly and uniquely associated with depression and co-occurring fatigue, but only in women. Consistent with these population-based findings, females with PWS and TPH2 polymorphisms may be similarly vulnerable to depression and fatigue.

No associations were found in the present study between TPH2 polymorphisms and repetitive, compulsive behaviors. These behaviors are salient in PWS and are also a central feature of people with autism spectrum disorders. Previous work examining TPH2 and autism risk, as well as the effects of TPH2 on the autism phenotype, have failed to find relations between TPH2 status and repetitive, compulsive behaviors (Ramoz et al., 2006; Sacco et al., 2007). Our PWS findings are consistent with these autism studies, which collectively do not implicate TPH2 G/T polymorphisms in compulsivity in these two developmental disorders.

This study had several limitations. First, we used a screener of behavioral and emotional problems instead of psychiatric diagnoses. Although the CBCL is widely used in people with and without developmental disabilities, it is not a substitute for careful psychiatric phenotyping, and such data would have been helpful in shedding light on gender effects in this study. Second, we obtained IQ scores using different methods – direct testing with the KBIT-2 and reports of previous testing. Although scores were similar across these sources, participants did not receive the same IQ test, which adds a note of caution in interpreting IQ findings. Third, while we identified TPH2 genetic polymorphisms that are associated with altered expression of TPH2 and thus the synthesis of serotonin, we did not measure expression of TPH2 or peripheral plasma levels of serotonin. Future studies need to do so in order to better describe how alterations in serotonergic pathways relate to the PWS phenotype. Finally, this study examined just one of many genes that are known to alter serotonergic functioning. Future studies are needed on how the PWS phenotype is also impacted by genes and proteins that regulate serotonin receptors, uptake, storage, transport, and metabolism.

Despite these weaknesses, this study highlights the promise of using phenotypically relevant genes or SNPs to shed new light on behavioral phenotypes in genetic syndromes. This study is the first to demonstrate how serotonin-altering genes outside of the

PWS 15q11-q13 critical region impact salient aspects of the PWS behavioral phenotype. Persons with PWS and TPH2 -703 T polymorphism had significantly higher IQs, increased hyperphagic behavior, drive, and severity, an earlier age at onset of hyperphagia, and on average, they also slept more each night. Relative to all others in the sample, females with TPH2 T polymorphisms had increased internalizing problems, including symptoms of depression and anxiety. These findings hold promise for future studies that examine other genes involved in the production of serotonin in people with PWS. Such work can help identify important biomarkers associated with high or low levels of hyperphagia or mood problems in PWS, and eventually to more personalized interventions that reflect these relative risks.

Acknowledgements

The authors are grateful to the families and individuals with Prader–Willi syndrome who participated in the study. This work was supported by NICHD Rare Disease Consortium Grant U54 HD061222 (Dykens and Butler), the Prader–Willi Syndrome Associations (USA) (Dykens and Butler), the Vanderbilt CTSA (Vanderbilt Institute for Clinical and Translational Research), and NICHD Grants R01HD035684 (Dykens) and P30HD015052 (Dykens).

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Key points

- This study examined relations between the PWS phenotype and TPH2 -703 G/T polymorphisms in 92 individuals with PWS. THP2 is the rate-limiting enzyme in the biosynthesis of serotonin in the brain.
- Relative to those with no loss of TPH2 function (G/G), persons with G/T or T/T alleles manifested heightened hyperphagia, younger ages of onset of hyperphagia, higher IQs, increased sleep, and in females only, increased anxiety and depression.
- Findings implicate aberrant serotonergic functioning in PWS, and a need to study other genes involved with the tryptophan-serotonin-melatonin pathway in people with this syndrome.
- Variability in treatment responses to SSRI's in PWS may be associated with polymorphisms in TPH2 and other genes involved in the production of serotonin.
- Future studies need to identify biomarkers that help predict treatment response to serotonin-altering medications in PWS, with outcomes that include reduced hyperphagia and improved mood in persons with this life-threatening disorder.

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Accepted for publication: 24 November 2010
Published online: 18 March 2011