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# Intellectual characteristics of Prader–Willi syndrome: comparison of genetic subtypes

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## Abstract

Advances in genetics have led to an increased understanding of the role of the genotype on behavioural functioning. The purpose of the present study was to examine differences in intellectual functioning in individuals with Prader–Willi syndrome (PWS) with a paternal 15q11–q13 deletion versus maternal uniparental disomy (UPD) of chromosome 15. Measures of intelligence and academic achievement were administered to 38 individuals with PWS (24 with deletion and 14 with UPD). The subjects with UPD had significantly higher verbal IQ scores than those with deletion ($P < 0.01$). The magnitude of the difference in verbal IQ was 9.1 points (69.9 versus 60.8 for UPD and deletion PWS subjects, respectively). Only 17% of subjects with the 15q11–q13 deletion had a verbal IQ ⩾ 70, while 50% of those with UPD had a verbal IQ ⩾ 70. Performance IQ scores did not differ between the two PWS genetic subtype groups. This is the first report to document the difference between verbal and performance IQ score patterns among subjects with PWS of the deletion versus the UPD subtype.

### Keywords

chromosome 15q deletion; genetic subtype differences; intellectual functioning; maternal uniparental disomy; Prader–Willi syndrome

## Introduction

Advances in genetic techniques and our understanding of this subject have renewed interest in the genetic causes and classification of intellectual disability. Prader–Willi syndrome (PWS) shares behavioural features with other disorders and disabilities, such as obsessive-compulsive disorder and autism, but only PWS includes the unique combination of characteristics which distinguishes this syndrome. Prader–Willi syndrome is a classical genetic condition with two primary genetic subtypes and unusual behavioural characteristics.

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Prader–Willi syndrome is characterized by infantile hypotonia, hypogonadism, feeding difficulties, early childhood obesity, short stature, small hands and feet, intellectual disability and characteristic facial abnormalities (Cassidy 1984; Butler 1990; Thompson *et al.* 1996; Cassidy *et al.* 1997). Prader–Willi syndrome most often results from a paternal deletion of 15q11–q13 (in about 70% of cases), or sometimes, from maternal disomy of chromosome 15 (in about 30% of cases) (Ledbetter *et al.* 1981; Butler *et al.* 1986; Mascari *et al.* 1992; Nicholls 1993; Cassidy *et al.* 1997). The prevalence of this syndrome is estimated to be one in 10–20 000 live births and is the most common syndromal cause of marked human obesity (Butler 1990). Prader– Willi syndrome and Angelman syndrome, which is caused by a maternal deletion of chromosome 15q but is an entirely different clinical condition, were the first examples in humans of genetic imprinting or the differential expression of genetic information depending on the parent of origin.

Intellectual disability and related adaptive behaviour deficits are common in PWS, although some relative strengths in self-help skills have been noted (Holm 1981; Thompson *et al.* 1996). In addition, people with PWS show problem behaviours, including stubbornness, demanding attention and arguing (Taylor 1988; Dykens *et al.* 1992). Many people with PWS engage in compulsive skin picking and impulsive temper outbursts, verbal abuse and regressive behaviour which may reach ‘psychotic proportions’ (Sulzbacher *et al.* 1981; Clarke *et al.* 1989). Clarke (1998) reported a higher than non-chance association of PWS and psychotic symptoms which was not entirely accounted for by the increased prevalence of psychosis associated with intellectual disability. The presence of visual and auditory hallucinations, delusions, irrational fears and paranoia seem to suggest that people with PWS are vulnerable to psychotic symptoms in adult life (Clarke *et al.* 1998; Verhoeven *et al.* 1998). Compulsive behaviour frequently appears in PWS and is more disruptive to daily functioning than in other mixed populations with intellectual disability (Vitiello *et al.* 1989; Dykens *et al.* 1996). These behavioural problems may take a greater toll on caregivers than adherence to strict weight-management protocols (Greenswag 1987; Hodapp *et al.* 1997).

Phenotypic differences relating to the PWS genotypes are of interest to geneticists and behavioural scientists because these may reveal genes causing specific clinical manifestations or enhance understanding of the impact of imprinting on genotype and phenotype studies in PWS. In the past, hypopigmentation (i.e. lighter hair, eye and skin colours compared with similarly aged family members) was noted to occur at a higher frequency in PWS patients with chromosome 15 deletions (Butler *et al.* 1986; Butler 1989; Spritz *et al.* 1997). Cassidy *et al.* (1997) reported relatively less impairment in articulation and skin picking among PWS individuals with UPD in comparison to those with deletion. Symons *et al.* (1999) found that individuals with deletion injure significantly more body sites (via skin picking) than subjects with UPD. Dykens *et al.* (1999) noted that a group of UPD subjects had higher full-scale IQ scores than the matched deletion subgroup. The above author also saw differences in maladaptive behaviour on the Child Behavior Checklist in the deleted subgroup on domains of internalizing, externalizing and total domains. A limitation of the above study was that some subjects were tested with the Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman 1990), while the IQ of others was derived via parental report of scores from different tests (which were administered at different ages).

Previous studies have also revealed that individuals with PWS with the chromosome 15 deletion have more homogeneity in anthropometric variables, including radiographic measurements of the bones of the hand, as reflected in the metacarpophalangeal pattern profile (MCPP) and in dermatoglyphic patterns (Butler *et al.* 1982). Individuals with deletion PWS were much more homogeneous than non-deletion cases with respect to plantar patterns with a lack of plantar interdigital II–IV patterns with almost exclusive hallucal distal loops (Reed & Butler 1984). However, earlier studies were conducted before the recognition of uniparental disomy (UPD) as the most common cause of the non-deletion status among people with PWS. With the recent advent of molecular testing for all cases of PWS, other differences between individuals with deletion and UPD have been reported. Gillessen-Kaesbach *et al.* (1995) noted lower birth weights in individuals with the deletion subtype. Mitchell *et al.* (1996) reported shorter birth length in males with uniparental maternal disomy than males with the 15q deletion, and a shorter course of gavage feeding and later onset of hyperphagia in females with UPD. Cassidy *et al.* (1997) observed that people with PWS with UPD were less likely to have a typical facial appearance and were also less likely to show minor behavioural characteristics of PWS, including skin picking, skill with jigsaw puzzles, a high pain threshold and articulation problems. Gunay-Aygun *et al.* (1997) reported that the diagnosis of PWS among individuals with maternal UPD of chromosome 15 was typically reported later than those with a deletion. Thus, there is evidence of differences in people with PWS having the chromosome 15q deletion compared with those with UPD. The present paper reports the findings of a study on the intellectual characteristics of people with PWS with the 15q11–q13 deletion and those with UPD of chromosome 15.

## Materials and methods

### Subjects

Thirty-eight individuals with Prader–Willi syndrome (16 males and 22 females) served as subjects. These people represent all individuals with Prader–Willi syndrome (of the deletion and UPD subtypes) who have been studied to date as part of a Program Project which addresses a variety of cognitive, behavioural and metabolic aspects of PWS at the John F. Kennedy Center, Vanderbilt University, Nashville, Tennessee, USA. The age of the subjects ranged from 10 to 44 years (mean = 22.2, SD = 9.1). There were 24 subjects (nine males and 15 females) with a 15q11–q13 deletion and 14 subjects (seven males and seven females) with UPD of chromosome 15 identified by high-resolution chromosome analysis, *in situ* hybridization, and DNA microsatellite analysis of 15q11–q13 probes from patients and their parents using currently established techniques (Mutirangura *et al.* 1993; Christian *et al.* 1995; Butler *et al.* 1996; Spritz *et al.* 1997). There were two black people in the deletion subgroup (one male and one female) and none in the maternal UPD subgroup. The imbalance in the subgroup sample sizes is to be expected given the natural frequencies of the two aetiologies (deletion versus UPD) in the PWS population. The subject characteristics with respect to body composition and age are presented in Table 1.

### Procedure

The subjects received a chronological-age-appropriate version of the Wechsler scales (either the WAIS-R or the WISC-III; Wechsler 1981, 1991), and the Mathematics and Reading portions of the Woodcock–Johnson Revised scales (Woodcock & Johnson 1990). Spelling skills were assessed using the WRAT-3 (Wilkinson 1993). The intellectual and achievement tests were administered by a licensed psychological examiner experienced with the PWS population as part of a comprehensive evaluation spanning a 3-day period. Parents and guardians or primary caregivers served as informants for the adaptive and maladaptive behaviour measures.

## Results and discussion

Summary statistics (means and standard deviations) for the intelligence and achievement measures are displayed by genetic subgroup (deletion and UPD) in Table 2. Statistical tests for between-group differences (Bonferroni *t*-tests) revealed a statistically significant effect of genetic subtype on verbal IQ [$t(36) = -3.45$, $P < 0.01$]. In addition, the distribution of verbal IQ scores did not deviate from normal, as reflected by the Shapiro–Wilk statistic (deletion, $P = 0.31$; UPD, $P = 0.97$), and the 9.1-point difference between the deletion and UPD mean scores may be expressed in terms of an effect size of > 1.0. This large effect size provides evidence that the difference in verbal IQ is not only statistically significant, but that its magnitude is substantial (see Cohen 1988).

Interestingly, the UPD subjects' average verbal IQ of 69.9 falls at the classification point for 'mild mental retardation', while the deletion group averages 60.8, which is well within the classification range for 'mild mental retardation', as defined by the American Psychological Association (Editorial Board 1996). Only 17% (four out of 24) of the subjects in the deletion group had a verbal IQ ⩾ 70, while 50% (seven out of 14) of those with UPD had verbal IQ scores ⩾ 70, a finding which carries substantial implications for individual classification, placement and service decisions. However, the apparent relative strength in verbal IQ evidenced by the UPD group did not translate into statistically significant, concordant effects on measures of academic achievement as measured by the Woodcock–Johnson Reading and Math clusters or the WRAT-3 Spelling subtest. The UPD subgroup demonstrated significantly higher scores on four verbal subtests: Information and Arithmetic ($P < 0.05$), and Vocabulary and Comprehension ($P < 0.01$). The Arithmetic subtest is a measure of numeric calculation skill and attention, while the Vocabulary, Information and Comprehension subtests are measures of word meanings, factual knowledge and social judgement/reasoning, respectively. In contrast, the deletion group demonstrated a significant strength in Object Assembly ($P < 0.05$), a performance subtest measuring visual–perceptual skills.

The effect of PWS genetic subtype on verbal IQ was explored further by characterizing each subject on the basis of: (1) the difference between verbal and performance IQ; and (2) whether verbal IQ was greater than performance IQ. Subjects with deletion had a mean verbal-performance IQ difference of −4.0 ± 7.2, which indicates that performance IQ was, on average, 4.0 points higher than verbal IQ in this group. In contrast, the verbal IQ of subjects with UPD averaged 7.6 ± 8.0 points higher than their performance IQ. The

between-group difference on this measure (verbal-performance IQ difference) was statistically significant [$t(36) = -4.60$, $P < 0.001$]. This effect is also reflected in the odds ratio, which addressed the extent to which subjects with UPD are more likely than those with a deletion to have a verbal IQ score which exceeded their performance IQ score. Subjects with UPD were 31.6 times more likely to have a verbal IQ that was higher than their performance IQ than subjects with deletion ($P = 0.001$). Moreover, the 95% confidence interval of the odds ratio indicated that subjects with UPD were at least 5.1 times as likely to have a positive verbal-performance IQ differential.

On average, the UPD subgroup attained higher verbal IQ scores than the deletion subgroup. Specific subtest differences were noted in numeric calculation skill, attention, word meanings, factual knowledge and social reasoning, with the UPD subgroup scoring higher than the deletion subgroup. Another interesting subtest difference was noted on the object assembly subtest, with the deletion subgroup scoring higher than the UPD subgroup. Specific visual perceptual skills may be a relative strength for the deletion subgroup and may explain anecdotal accounts of subjects with PWS having an uncanny ability to assemble jigsaw puzzles.

The mechanisms whereby certain skills appear to be preserved in the UPD subgroup have yet to be identified. Whether this phenomenon is caused by genetic imprinting versus the hemizygous state of the 15q11–q13 region in the deletion PWS patients is not known. The presence of more intact genes in UPD individuals in contrast to those with a deletion may be a relative strength for the PWS individual with the UPD subtype.

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**Table 1**

Characteristics of the Prader–Willi syndrome subgroups. No differences were statistically significant. The values are presented as means SD

| | | | | | Percentage fat | |
|---|---|---|---|---|---|---|
| **Subgroup** | **Age (years)** | **Height (cm)** | **Weight (kg)** | **Body mass index (kg m$^{-2}$)** | **1*** | **2†** |
| Deletion | 21.8 ± 8.3 | 150.2 ± 7.9 | 78.1 ± 0.5 | 34.5 ± 8.2 | 42.2 ± 7.2 | 51.4 ± 7.4 |
| Uniparental disomy | 22.8 ± 10.6 | 149.6 ± 8.4 | 82.3 ± 22.9 | 36.7 ± 9.8 | 42.1 ± 5.1 | 51.4 ± 5.5 |

* Derived from bioelectrical impedance (Segal *et al.* 1985).

† Derived from dual energy X-ray absorptiometry (DEXA; Mazess *et al.* 1990).

**Table 2**

Cognitive and achievement assessments. The values are presented as the mean SD

| Test | Deletion | Uniparental disomy |
|---|---|---|
| *Intelligence* | | |
| Wechsler Verbal IQ* | 60.8 ± 8.6 | 69.9 ± 6.4 |
| Wechsler Performance IQ | 64.7 ± 9.3 | 62.2 ± 9.7 |
| Wechsler Full-Scale IQ | 61.0 ± 9.2 | 64.1 ± 7.9 |
| *Achievement* | | |
| W-J/R Read | 53.1 ± 25.5 | 69.5 ± 35.0 |
| W-J/R Math | 53.8 ± 20.6 | 65.1 ± 26.6 |
| WRAT-3 Spelling | 60.2 ± 16.5 | 62.4 ± 12.6 |

* $P < 0.01$.