

Phenotypic Heterogeneity of Growth and Psychometric Intelligence in Prader-Willi Syndrome: Variable Expression of a Contiguous Gene Syndrome or Parent–Child Resemblance?

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Phenotypic variability in children with Prader-Willi syndrome (PWS) was investigated with respect to variable expression of the contiguous gene syndrome and trait variance. In a prospective study, parent/child resemblance of anthropometric and psychometric measures was analyzed in 22 children with PWS (11 females and 11 males; 18 deletions, 4 uniparental disomy (UPD)) and in a control group (88 females and 88 males). The average child-midparent Z-score difference for height in females was -1.9 and in males -0.9 , head circumference -1.7 and -1.0 , and body mass index (BMI) 2.3 and 2.7 , respectively. Intellectual performance of females and males was, on average, -2.7 and -2.6 below maternal performance. Range and standard deviation were moderately increased for height and head circumference, doubled for BMI, and unchanged for IQ. Parent/child correlations for anthropometric and psychometric measurements in the study group did not significantly differ from those of the control group. Exceptions were higher correlations between mothers and daughters for height ($P < 0.05$) and BMI ($P < 0.01$), and lower correlations for head circumference between midparent values and daughters ($P < 0.05$) than in the control group. In conclusion, parent-child resemblance in growth and intellectual development among children with PWS was found to be comparable to that noted in the normal population, indi-

cating a strong determination by trait variance. Children with PWS differed significantly with respect to a lower trait level and—with the exception of IQ—a larger variability. The latter may indicate a variable expression of the contiguous gene syndrome. *Am. J. Med. Genet.* 91:298–304, 2000.

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INTRODUCTION

Most chromosomal disorders are variable in their clinical phenotypes. For phenotypic variability, essentially two explanations are conceivable: variable expression of the deleterious genes and/or the trait variance of the normal population. Since the genetic defect produces one commonly identifiable phenotype, its phenotypic variability is frequently attributed to the effects of the syndrome. So the fact that one-fifth of males with the fragile X marker are phenotypically normal may be ascribed to the highly variable expression of the fragile X gene [Barnes, 1989]. Based on the results of quantitative genetics, it can be assumed that in the normal population about 90% of the phenotypic trait variance for height is accounted for by effects of parental genes [Preece, 1996]; corresponding values for general cognitive abilities (IQ) vary between 30–70% [Plomin, 1990; Devlin et al., 1997; Furlow et al., 1997]. There is thus a strong to moderate genetic determination of these traits in the normal population.

To what extent does a chromosomal disorder disrupt the parent-offspring resemblance? In Ullrich-Turner syndrome (UTS), the parental determination for stature remains unchanged. In a multicenter study involving 216 UTS females, Rochiccioli et al. [1994] found a

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correlative dependency on fathers' and mothers' heights of $r = 0.50$ and $r = 0.42$, respectively. Similar results for the midparent/child height relationship were obtained by Massa and Vanderschueren-Lodeweyckx [1991] ($r = 0.49$), Holl et al. [1994] ($r = 0.69$) and Brook et al. [1977] ($r = 0.61$). Klinefelters syndrome also does not interfere with the correlations between midparent and child height ($r = 0.62$) [Brook et al., 1977]. However, in children with Down syndrome, Brook et al. [1977] reported markedly lower midparent/child height correlations for 27 females and 48 males ($r = 0.29$ and $r = 0.21$), which might be caused by the diverse occurrence and severity of congenital heart disease [Cronk et al., 1988]. In contrast, parent/child correlations of IQ were comparable to those found in the normal population. In children with Down syndrome over 5 years of age and reared at home, Fraser and Sadovnick [1976] noticed correlative dependencies on mothers' and fathers' IQ scores of $r = 0.42$ and $r = 0.50$, respectively. To our knowledge, there are no such data on disorders caused by gene defects.

It was, therefore, the aim of this study to investigate the parent/child resemblance in children with Prader-Willi syndrome (PWS). Due to the absence of a paternal contribution to chromosome 15q11-q13, growth and intellectual abilities in these children differ considerably from those noted in the normal population. Short stature, microcephaly, obesity, and developmental delay are accepted valid criteria for diagnosis, although their manifestations are highly variable and overlap widely with the normal population [Butler et al., 1991; Curfs and Fryns, 1992].

Our investigation focused on the following four complex quantitative traits: standing height, head circumference, body mass index (BMI), and intelligence quotient (IQ). In order to estimate the extent to which the contiguous gene syndrome and the general parental gene pool contribute to the phenotype in children with PWS, we linked the anthropometric and psychometric measurements of parents and their offspring by computing Z-score values and correlations, and compared the results with those obtained in a control group of healthy children.

SUBJECTS AND METHODS

Subjects

Children were only eligible for inclusion in this study if they were older than 3 years. Longitudinal investigations have shown that parent-child correlations in normal growth [Largo, 1993] and in normal psychomotor development [Honzik, 1971a,b] are low and not stable during the first years of life. In addition, early growth in children with PWS differs considerably from growth later on [Butler et al., 1991].

We obtained data on the growth and development of 22 children (11 females, 11 males) with PWS who were being reared at home. The median age of the affected children was 7.1 years (range 3.0–19.6 years). The diagnosis of PWS had been confirmed clinically, as well as by using cytogenetic and molecular techniques. In-

formed consent was obtained from children and parents before examination. Informed consent was obtained from the participants and their parents after the procedures and goals of the study had been fully explained.

The group consisted of 18 children with a 15q chromosome deletion (all 11 females, 7 out of 11 males) and four males with a maternal UPD 15—two of them heterodisomic and two isodisomic for the PWS-region. The difference of the proportion of deletions by sex (11 out of 11 females and 7 out of 11 males) did not achieve significance ($P = 0.09$). Twelve of these 22 children had been treated with growth hormone [Eiholzer et al., 1998]; the body parameters used for these children were those obtained before treatment commenced.

As a control cohort, 176 healthy, nonrelated, term Swiss children (88 females, 88 males) and their parents were recruited from the Zurich Longitudinal Studies on Growth and Development. They formed a representative sample of a Swiss urban population according to the socioeconomic status of their families.

Anthropometric and Psychometric Measurements and Socioeconomic Status

Weight, standing height, and head circumference of the children and parents were measured according to Prader et al. [1989]. BMI (weight in kg / height in m²) was then calculated.

In the children with PWS, intellectual performance was assessed by the Swiss version of Wechsler Intelligence Scales for Children (HAWIK-R 10) [Tewes, 1988] in three subjects. For 19 children, the Kaufman-Assessment Battery for Children (K-ABC 11) [Kaufman and Kaufman, 1994] was used for testing. In the control group, HAWIK-R was applied at the age of 9 years. A short version of HAWIK-R consisting of four subtests (similarities, picture arrangement, block design, and object assembly) was presented to all mothers.

Socioeconomic status (SES) was estimated by means of a six-point scale for both paternal occupation and maternal education; the lowest combined SES score was 2, the highest 12 [Largo et al., 1989].

Statistical Procedures

In order to control for age and sex differences, Z-scores were calculated using the formula: $Z \text{ score} = (X - M) / SD$, where X is one particular measurement of an individual child, M is the mean value, and SD the standard deviation of the reference for the corresponding age and sex.

The reference values for the anthropometric measurements were obtained from the First Zurich Longitudinal Study, as given by Prader et al. [1989]. The standardization of psychomotor and intellectual performance (mean: 100; SD: 15) was made on the basis of test norms [Tewes, 1988; Kaufman and Kaufman, 1994].

In a preliminary analysis, we considered the possibility that the Z-score deficit in children with PWS

might depend on age. No such dependence was found for stature and head circumference, while a highly significant increase of the BMI Z-score of 0.6/year ($P = 0.003$) for males, and a decrease of IQ Z-score of 0.1/year ($P = 0.007$) for both sexes was noted. Therefore, for these parameters the mean Z-score given in Table I was corrected for sex and age. Also, for the calculation of parent/child correlations, residuals from regressions for age and sex were used for BMI and for age only for IQ.

For the conversion of parental anthropometric and psychometric measures into Z-scores, reference data of 200 parents forming a representative sample of a Swiss urban population were used. Nonparametric tests (Wilcoxon and Mann-Whitney test) were used to compare one subgroup with the reference or two independent subgroups. The equality of correlation coefficients (Spearman) was tested by considering them as normally distributed after transformation via the Fisher z-transformation (not to be confused with the Z-score transformation). For testing the equality of two variances, the F-test was applied.

RESULTS

The individual data on growth and intellectual development for children with PWS and their parents are given in Table I.

Z-Scores

Means, SDs, and ranges of Z-scores for the anthropometric and psychometric measurements for children and parents of the PWS group and the control group are presented in Table II.

Anthropometric Measurements

In the PWS group, a mean Z-score for height of -2.1 was noted in females and -1.1 in males. Five females and three males had a stature below -2. The mean head circumference Z-score for females and males was -1.3 and -0.6, respectively. Microcephaly, a Z-score of less than -2, was observed in three females and two males. For both sexes, a mean BMI of about 3 was noted. For six females and nine males, the BMI was more than 2 SD above the mean.

The sex difference favoring the males in height and head circumference, although notable, was not significant ($P > 0.05$). Children with a deletion and those with UPD did not significantly differ from each other with respect to height, head circumference, and BMI.

For all three anthropometric measurements, but in particular for BMI, standard deviations and ranges were increased in comparison with the control group. Height and head circumference were significantly more variable among the males (F-test; $P < 0.001$), and BMI for both sexes in the PWS group (females: $P = 0.005$; males: $P < 0.001$). Age-corrected BMI varied between +6.3 and -0.3.

Parents of the children with PWS were slightly different from the reference population. The mothers showed larger head circumferences ($P = 0.01$) and higher BMI values ($P = 0.03$).

Children and parents of the control group did not differ significantly from the reference population for all three anthropometric measurements.

Psychometric Measurements

In the PWS children, the mean Z-score for IQ was -2.9 in females and -2.8 in males. With the exception of

TABLE I. Individual Data for Children With PWS and Their Parents: Age, Type of Gene Defect, Sex, Z-Scores for Height, Head Circumference, BMI, IQ, and SES

Child No.	Child							Mother				Father			Parent
	Age (years)	Sex	Gene defect	Height	Head circ.	BMI	IQ	Height	Head circ.	BMI	IQ	Height	Head circ.	BMI	SES
1	14.6	f	Del	-4.23	-0.46	-0.22	-3.87	-1.30	1.48	-0.47	-2.64	-1.34	-0.01	1.60	8
2	3.0	m	Del	-1.93	-0.70	0.10	-0.80	-0.51	1.54	-0.35	0.29	1.24	1.22	-1.39	10
3	13.3	f	Del	-3.87	-2.64	1.50	-3.00	-1.42	-0.35	-0.17	-0.20	-0.82	-0.01	-0.10	8
4	5.0	f	Del	-0.73	-0.20	2.93	-2.80	0.50	-0.03	1.57	-0.53	-1.27	0.61	1.67	6
5	7.0	m	Del	-1.58	-0.82	3.97	-2.13	-0.11	0.95	-0.99	-0.28	-0.53	-1.29	-1.76	7
6	7.1	f	Del	-2.38	-2.87	0.54	-1.93	-0.53	-0.09	-0.70	0.46	0.21	-0.31	-0.90	11
7	6.8	f	Del	-2.06	-1.35	5.47	-3.27	-0.97	0.10	-0.12	0.36	-1.27	-0.01	-0.70	7
8	6.8	m	UPD	-1.41	-1.36	3.85	-2.80	0.44	0.95	1.28	-0.05	0.94	0.61	-0.45	8
9	4.1	m	UPD	-3.38	-2.49	-2.08	-3.40	0.81	1.74	-1.13	0.46	-1.47	-0.80	-0.29	5
10	3.8	f	Del	-1.84	-1.74	4.16	-2.67	0.24	1.74	1.39	1.25	1.09	1.22	1.54	10
12	9.5	m	UPD	-2.35	-0.37	2.83	-3.67	-1.28	-0.16	-0.58	0.27	-0.38	-0.44	-0.40	10
13	13.5	m	Del	-0.75	-1.38	9.76	-3.07	-0.29	-1.01	-0.65	0.75	-0.38	-0.99	0.46	7
14	6.5	m	Del	-0.70	-2.49	2.88	-3.40	1.10	-0.09	3.26	-0.21	-0.31	0.55	-1.23	5
15	10.7	f	Del	-0.38	0.43	5.60	-2.13	0.13	1.02	0.74	0.68	0.94	0.30	-1.22	8
16	4.8	f	Del	-1.97	-2.40	0.51	-2.93	1.38	1.08	-0.12	0.54	0.21	0.61	-0.66	3
17	19.6	f	Del	-1.63	-1.40	4.02	-3.53	0.00	0.17	1.75	0.11	0.59	-0.01	-0.14	5
18	11.5	m	Del	1.79	1.15	6.75	-2.47	2.33	1.48	6.66	1.02	1.78	-0.25	0.97	9
19	6.6	m	UPD	0.12	-0.36	5.99	-2.60	0.26	-0.22	2.65	-3.27	-1.71	-1.85	0.15	2
20	19.5	m	Del	-3.42	0.13	8.25	-4.80	-1.57	2.65	7.39	-3.18	-2.47	1.22	2.03	2
21	11.5	m	Del	1.79	2.09	7.89	-2.73	0.08	1.87	1.44	0.35	0.15	-0.50	1.96	6
22	6.8	f	Del	-1.48	0.45	6.32	-3.33	-0.88	-0.35	1.00	-0.18	-1.75	1.47	1.89	4
23	11.3	f	Del	-2.56	-1.59	1.47	-4.67	-0.77	1.48	1.38	0.05	-0.53	0.61	-0.92	6

TABLE II. Means, Standard Deviations and Ranges of Z-Scores of Height, Head Circumference, BMI, IQ, and SES for Children and Parents of the PWS Group and the Control Group*

	N	Height			Head circumference			BMI			IQ			SES		
		M	SD	Range	M	SD	Range	M	SD	Range	M	SD	Range	M	SD	Range
PWS																
Females	11	-2.1	1.2	-4.2/0.4	-1.3	1.2	-2.9/0.5	2.9	2.3	-2.2/6.3	-2.9	0.7	-4.2/-1.9			
Males	11	-1.1	1.8	-3.4/1.8	-0.6	1.4	-2.5/2.1	3.3	2.1	-0.3/6.2	-2.8	0.8	-3.7/-1.3			
Deletion	18	-1.6	1.6	-4.2/1.8	-0.9	1.4	-2.9/2.1	3.2	2.1	-0.2/6.3	-2.8	0.8	-4.2/-1.3			
UPD	4	-1.8	1.5	-3.4/0.1	-1.1	1.0	-2.5/0.4	2.8	2.9	-0.3/6.2	-3.2	0.5	-3.7/-2.8			
Parents																
Mother	22	-0.1	1.0	-1.6/2.3	0.7	1.0	-1.0/2.7	1.1	2.2	-1.1/7.4	-0.2	1.2	-3.3/1.2	3.3	1.3	1/5
Father	22	-0.3	1.1	-2.5/1.8	0.1	0.9	-1.8/1.5	0.1	1.2	-1.8/2.0				3.5	1.4	1/6
Midparent	22	-0.2	0.9	-2.0/2.1	0.4	0.7	-1.0/1.9	0.6	1.5	-1.4/4.7				6.9	2.4	2/11
Controls																
Females	88	0.2	0.9	-2.7/2.3	0.1	1.0	-1.9/2.9	0.1	1.3	-2.1/3.6	0.1	0.8	-2.0/2.0			
Males	88	0.0	0.9	-2.4/2.3	-0.1	0.7	-1.9/1.5	-0.1	1.1	-1.8/3.1	0.2	0.7	-1.4/2.2			
Parents																
Mother	176	0.2	1.0	-2.7/3.4	0.2	0.9	-2.8/2.5	0.0	1.0	-1.8/3.4	0.2	0.8	-3.1/1.4	3.8	1.0	2/6
Father	176	0.2	1.0	-2.3/2.7	0.2	0.9	-2.3/2.8	-0.1	0.9	-1.8/3.3				4.5	1.1	1/6
Midparent	176	0.2	0.8	-2.2/2.5	0.2	0.7	-1.7/1.8	-0.1	0.7	-1.7/2.0				8.3	1.9	3/12

*Z-scores for BMI are corrected for age and sex, Z-scores for IQ are corrected for age.

one female and one male, all children achieved an IQ that was lower than -2 SD. Only one boy performed in the low normal range (-0.8 SD). In contrast to the anthropometric measurements, SDs of the IQ Z-score were not increased; the ranges were comparable to the control group but shifted toward lower values.

Children and mothers of the control group did not differ significantly from the reference population in their intellectual performance.

Socioeconomic Status

The children with PWS came from families having a lower, but not significantly different SES than those of the control children ($P = 0.06$). This difference was due to the low SES of four families originating from southern European countries. In the PWS group, no significant differences with respect to sex and type of gene defect were noted. Among mothers of both the study and the control group, their educational SES-score correlated significantly with their HAWIK-performance (PWS group: $r = 0.54$ ($P = 0.009$); control group: $r = 0.44$ ($P < 0.001$)).

CORRELATIONS

Parent/child correlations between anthropometric and psychometric measurements for the children with PWS and the control group are presented in Table III. Scatter plots of child vs. midparent value for the four measurements are shown in Figure 1.

Anthropometric Measurements

Height in children with PWS seemed to be more strongly correlated to maternal than to paternal height. However, this difference was not significant ($P > 0.05$). No significant parent/child relationship was noted for head circumference in the PWS group. With respect to BMI, correlations for the PWS children tended to be higher, and there was even a significantly higher correlation between mother/daughter values ($P < 0.01$) than in the control group.

The correlation matrix in the PWS group was comparable to that of the control group. Although the correlations measured in the study group were less frequently significantly different from 0 because of the small sample size, most were not significantly different from the corresponding values for the control group. Exceptions were higher correlations for height ($P < 0.05$) and BMI between mothers and daughters ($P < 0.01$), and lower correlations of head circumference between midparent values and daughters ($P < 0.05$).

Psychometric Measurements

Intellectual performance of the child and parental SES was consistently moderately correlated for both

TABLE III. Child/Parent Correlations for Height, Head Circumference, BMI, and IQ/SES*

	Children with PWS			Control children		
	All	Females	Males	All	Females	Males
Height						
Mother	0.64 ^c	0.65 ^a	0.58 ^a	0.34 ^c	0.25	0.40 ^c
Father	0.37	0.27	0.49	0.35 ^c	0.49 ^c	0.23
Midparent	0.53 ^a	0.46	0.54	0.40 ^c	0.42 ^c	0.39 ^c
Head circumf.						
Mother	0.18	-0.05	0.37	0.27 ^c	0.36 ^c	0.15
Father	0.04	0.40	0.09	0.20	0.04	0.34 ^c
Midparent	0.16	0.18	0.26	0.34 ^c	0.28	0.44 ^c
BMI						
Mother	0.50 ^a	0.71 ^b	0.29	0.30 ^c	0.24	0.37 ^c
Father	0.29	0.27	0.36	0.24	0.16	0.33 ^c
Midparent	0.53 ^b	0.66 ^a	0.41	0.31 ^c	0.24	0.38 ^c
SES						
Mother	0.40 ^a	0.47	0.48	0.36 ^c	0.38 ^c	0.35 ^c
Father	0.54 ^b	0.56 ^a	0.63 ^a	0.38 ^c	0.39 ^c	0.35 ^c
Midparent	0.53 ^b	0.54 ^c	0.63 ^a	0.40 ^c	0.42 ^c	0.36 ^c
IQ						
Mother	0.33	0.58 ^a	0.12	0.46 ^c	0.63 ^c	0.29 ^c

*Correlations of BMI and IQ are calculated from corrected Z-scores.

^a $P < 0.05$.

^b $P < 0.01$.

^c $P < 0.001$.

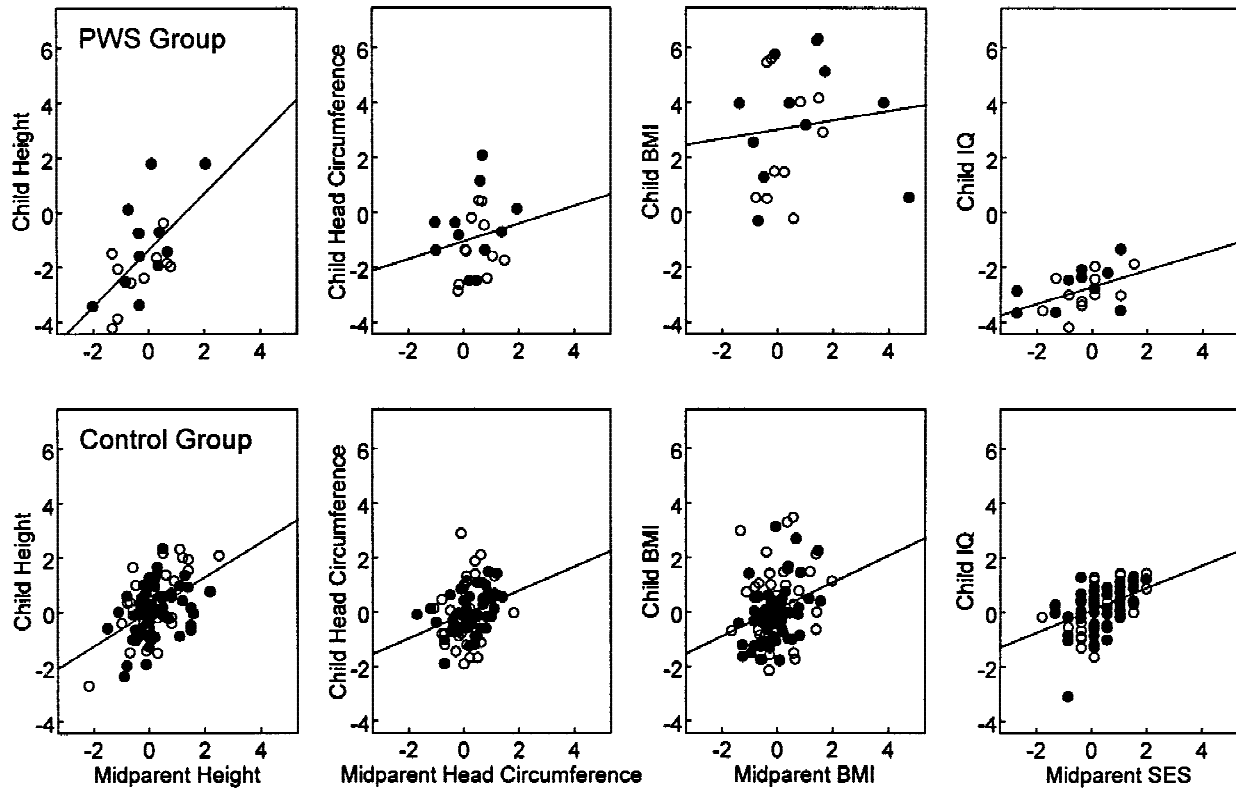


Fig. 1. Relationship between child and midparent Z-scores of height, head circumference, BMI, and IQ for the PWS and the control group. Child Z-scores of BMI are corrected for age and sex; those of IQ for age. Open circles = females; filled circles = males.

parents and both sexes. This was also true for IQ between mothers and daughters, to a lesser extent between mothers and sons.

Because of the small sample size, possible differences between children with deletion and those with UPD were not analyzed. The regression equation in Table IV summarizes the parent/child relations for the anthropometric and psychometric measurements. Residual standard deviations in the PWS group are considerably larger than in the control group.

DISCUSSION

A significant lower trait level in growth and intellectual development was the most significant characteristic observed among the children with PWS. The extent to which the children differed from normal children was in agreement with the findings of previous studies. In 43 PWS-patients of the same age group, Butler et al. [1991] reported a mean deficit in height

and head circumference of -1.71 and -0.91 SD, respectively. They observed a weight gain of $+1.55$ SD with an approximately doubled SD. In 25 PWS children between the age of 3 and 19 years, Dykens et al. [1992] noted a mean score of 57 ($= -2.9$ SD) for the IQ. Curfs et al. [1991, 1995] observed a mean value of 62 ($= -2.5$ SD) for the IQ in 28 children having PWS.

Not all children with PWS showed markedly reduced growth. Two males displayed no growth deficit in relation to midparent height, one male even gained about 1.7 SD. Three boys displayed a larger head circumference than the midparent value. Robinson et al. [1991] reported in one of 12 females and in six of 15 males, a stature over the 50th centile. Gillissen-Kaesbach et al. [1995] observed a height and a head circumference over the 50th centile in 14 of 84 females and in 19 of 63 males, respectively. In one girl and one boy, we noted lower BMI than midparent values.

In our study group, mean Z-scores in height and head circumference were lower in females than in males. In

TABLE IV. Regression Equation of Child (Z-Score) on Midparent Value (Z-Score) and Age

Parameter	Difference PWS/control	Midparent coefficient	Age	Residual standard deviation PWS	Residual standard deviation control
Height	-0.72	0.73	0.00	1.30	0.88
Head circumference	-0.57	0.41	0.07	1.20	0.90
BMI females	3.10	0.90	0.16	2.16	1.20
BMI males	1.00	0.70	0.60	2.11	1.20
IQ/parental SES	-1.40	0.19	-0.09	0.64	0.68

an age-combined PWS sample of 57 subjects, Butler et al. [1991] obtained a similar sex drift with a mean height for females of $-2.14 (\pm 1.15 \text{ SD})$ and for males of $-1.84 (\pm 1.50 \text{ SD})$, and with a mean head circumference of $-1.54 (\pm 0.94 \text{ SD})$ and $-1.03 (\pm 1.25 \text{ SD})$, respectively. Robinson et al. [1991] observed a stature below the 3rd centile in 8 of 11 girls, but in only 4 of 15 boys. In a group of 56 PWS patients, Hudgins and Cassidy [1991] noted higher deficits for females, not only in height but also in hand and foot length. One might speculate that the growth deficit in children with PWS is in part an X-linked process due to the absence of the paternally derived critical region for PWS.

The variability of the four complex traits investigated in this study may be best described through a polygenic model which is based on the assumption that various genes make small additive contributions toward phenotypic trait outcome [Preece, 1996]. In this case, the parent-child resemblance of a trait in the normal population is as follows: First, Z-scores in children and parents follow a standardized normal distribution with mean = 0 and SD = 1. Second, a parent/child correlation of 0.5 and a midparent/child correlation of about 0.7 ($\sqrt{2}/2$; depending on the mother/father correlation) are expected.

In our control group, the first expectation was confirmed, while in the children with PWS, SDs and ranges were moderately larger in height and head circumference, greatly increased in BMI, and about equal for IQ. The larger variability of the anthropometric parameters may reflect a variable expression of the contiguous gene syndrome. BMI is regarded as an environmentally unstable trait, even in the normal population. In PWS, its variability is likely to be increased by variable expression of hyperphagia, of familial eating habits and of parental ability to assert dietary management. Although psychometric measurements are judged as less reliable than anthropometric ones, IQs in the children with PWS were less variable than height and head circumference, and its variability was comparable to that of the control group.

The parent/child correlations in the control group were somewhat lower than theoretically expected. There are several reasons for this discrepancy: During childhood, different growth rates, environmental factors, and measurement errors hamper the correlational relationships. Thus, a parent/child correlation of 0.5 is not reached before adult age, if ever. In the PWS group, midparent/child correlations for anthropometric measurements were comparable to those reported by Butler et al. [1990]. The tendency of a maternal effect on some physical characteristics was confirmed. Children with maternal UPD did not differ significantly from those with deletion PWS. Most importantly, the correlation matrix was not significantly different from that of the control children with respect to anthropometric and psychometric parameters. Thus, the parent/child resemblance in the children with PWS was comparable to that in the normal population, indicating a strong determination by the trait variance.

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