LETTER TO JMG

Relationship between clinical and genetic diagnosis of Prader-Willi syndrome

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As part of a population based study of Prader-Willi syndrome (PWS), we have examined more closely the relationship between clinical and genetic diagnoses in a large number of people with established or suspected PWS. We report here on agreements and disagreements between clinical and genetic diagnoses. We consider whether a genetic diagnosis implies the presence of any one (or more) of the major, minor, or supportive diagnostic criteria, and also whether the presence of any one (or more) particular diagnostic criteria[1] implies a positive genetic finding, and what minimal genetic findings correspond to a positive finding on the basis of the clinical diagnostic criteria. In this paper, we also report on four specific cases that illustrate diagnostic difficulties. An early diagnosis of PWS is of particular importance as the propensity to overeat can start as early as 2 years of age, and parental control of access to food can prevent the development of life threatening obesity. As part of this study, we have found high rates of physical morbidity and mortality that are likely to be preventable if weight is adequately controlled.[2 3]

Initially, as reported by Prader *et al*,[4] PWS was conceptualised as a syndrome of obesity, short stature, cryptorchidism, and mental retardation following severe hypotonia in the neonatal period (decreased activity in utero, "floppy" at birth, marked feeding difficulties). With increasing clinical experience and research studies, behavioural characteristics such as hyperphagia, outbursts of temper, obsessional traits, and stubbornness, and clinical features such as central adiposity, sleep disorders, abnormalities of temperature and pain perception were added, culminating in the Consensus Diagnostic Criteria.[1] A weighted score of 8 or more for ages >3 (5 or more for ages <4), based on the presence of eight major (score 1) and 11 minor (score 0.5) symptoms, is considered sufficient for a clinical diagnosis of PWS (see Appendix for these criteria). According to the Consensus Diagnostic Criteria, there is no requirement that any particular one (or more) of the criteria are present, rather that the total number present exceeds a given limit.

Questionnaire based studies have shown that people with PWS have a characteristic behavioural profile in which outbursts of temper (including aggressive behaviour and screaming), self-harm (especially skin picking), mood swings, and repetitive speech are common.[5] In addition, repetitive questioning, compulsive behaviours, and hoarding are more common and it has been proposed that people with PWS are at increased risk for obsessive/compulsive disorder.[6] Adaptive behaviours (Vineland Adaptive Behaviour Scales)[7] show strengths in the Daily Living Skills domain and weaknesses in the Socialisation domain.[8] The most striking behaviour is that of severe and persistent overeating which, if unrestricted, leads to life threatening obesity. It has been proposed that this is the result of a failure of the normal feedback mechanisms that lead to a state of satiation following food intake.[9]

Over 50% of those suspected of having PWS have been shown to have a deletion of part of the long arm of chromosome 15 of paternal origin. This has led to the characterisation of the PWS critical region (15q11-13) of about 4 Mb and to the recognition that other types of genetic abnormality (uniparental maternal disomy, unbalanced translocations, mutations of the imprinting centre) of this region of chromosome 15 are also associated with PWS. The observation of deletions within the same region of chromosome 15 resulting in different clinical and behavioural manifestations (Angelman's syndrome) led to the identification of the importance of gender specific genomic imprinting as the differentiating factor.[10] Thus, it is now thought that the absence of expression of genes in the PWS critical region (that are normally maternally imprinted, and only expressed when on the chromosome 15 of paternal origin) is the fundamental genetic defect in PWS. One of the mechanisms governing the establishment of

Key points

- The objective was to investigate which of the clinical diagnostic criteria for Prader-Willi syndrome (PWS) best predict a positive genetic diagnosis, thereby providing guidance to clinicians as to what clinical features should increase or decrease their index of suspicion.
- The clinical and genetic data were obtained as part of a population based genotype-phenotype study of PWS being undertaken in one health region. The population based cohort was augmented by people with PWS living in other regions, and a contrast group of people with learning disabilities of other aetiologies.
- Using a structured informant interview and direct assessments, the presence or absence of the established major, minor, and supportive diagnostic criteria and a range of maladaptive behaviours were obtained for each person with possible PWS, together with direct assessments of IQ and attainments.
- The genetic diagnosis was established using the standard investigation of DNA methylation at *SNRPN*, supplemented with cytogenetic studies. The five clinical features floppy at birth, weak cry or inactivity, poor suck, feeding difficulties, and hypogonadism were present in 100% of people with positive genetic findings, the absence of any one predicting a negative genetic finding.
- The combination of poor suck at birth, weak cry/inactivity of the infant, decreased vomiting, and thick saliva correctly classified 92% of all cases. It was hypothesised that those criteria ("core criteria") invariably present when genetic findings were positive are necessary accompaniments of the genetics of PWS. No subset of clinical and behavioural criteria is sufficient to predict with certainty a positive genetic diagnosis, but the absence of any of the core criteria predicts a negative genetic finding.

this parent of origin epigenetic modification is methylation of specific DNA sequences. This has been exploited in the molecular diagnosis of both PWS and AS.

A key clinical issue is whether there are certain clinical diagnostic features, which, if present or absent, predict with a high degree of certainty a positive or negative genetic diagnosis. Previous reports describing the prevalence of clinical diagnostic criteria in groups with genetic diagnoses of PWS have suggested that no such necessary criteria exist.[11–14] Unlike these studies, this study has the advantage of direct interviews rather than relying on questionnaire based information. Also, we have been deliberately over-inclusive in the initial selection of possible cases, and have recruited a significant number of people with obesity syndromes who have been found to be genetically negative for PWS. Thus, the specificity of particular diagnostic symptoms to PWS, compared to those with other causes for their obesity, can be considered. In addition, a control group of people with learning disabilities not resulting from PWS has been included, and therefore symptoms that might be considered potentially diagnostic of PWS, but are in fact associated with having a learning disability in general, and not specific to PWS, can be identified.

METHODS

The sample

We attempted to identify all people with PWS in the former Anglia and Oxford Health Region in the UK, comprising a total population of approximately 5 million people (about one tenth of the population of England and Wales). The ascertainment methods and the over-inclusive screening criteria are reported elsewhere.[2] From 124 nominations of possible cases, a total of 93 people responded and agreed to take part. Sixty-one of this group met genetic criteria for PWS (see Genetic diagnosis section below), and 19 had negative genetic findings; the other 13 did not give blood samples and had no previous positive genetic records (fig 1). Six of the negative genetic participants also failed to meet clinical criteria, as did four of the 13 who did not give blood samples (criteria score <5). Thirteen of the people who gave blood samples with negative genetic findings and nine* who did not give blood samples either met clinical criteria or some clinical data were missing (for example, parents were dead or could not remember or the person was adopted) but they had previously been given a "PWS" label. Additional people said to have PWS were recruited from outside the region in an effort to increase the numbers in the study with the rarer genetic subtypes of PWS. Of these, 42 had positive genetic tests and six had negative genetics but clinical criteria were positive (criteria score >5) or missing. In addition, a comparison group of 22 people with learning disabilities of other (mixed) aetiologies (no blood samples requested) was recruited to augment the 10 people from the original 93 who clearly met neither clinical nor genetic criteria. The derivation of the various samples is shown in fig 1. This report is based on the full sample of people seen, omitting the nine* noted above. (Family circumstances, social class, and ethnicity were not recorded; however, we believe that three of the total PWS sample were from ethnic minorities or mixed races.)

Measures used

All those participating in the study were assessed for cognitive function (ages >3 years) and attainment in literacy and numeracy (ages >7 years) by a Chartered Psychologist (JEW), while a research assistant (JB) interviewed a family member and/or paid carer. The semi-structured interview included questions about the presence or absence of most of the diagnostic criteria (see Appendix), and supplementary questions were used to clarify answers or to seek examples (for example, shoe size, example of high pain threshold). Some diagnostic criteria, which we felt were too subjective, were omitted from our questionnaire (compare the two lists in the Appendix). As these data were largely gathered retrospectively from parents (and in many cases they were making judgments with respect to sibs), we divided positive endorsements into "very positive" and "positive". This may have created a false division, depending on parental style and memory; for example, "floppy and how!" *v* "floppy more than normal" or "went to work on a broken ankle...didn't complain" *v* "never seems to notice injuries, burns, and so on". Similarly, the definitions of the different severity of reported behaviours were operationalised and divided into those considered "very bad" (frequency and/or severity), "bad" (worse than normal), or "absent" (no worse than normal).

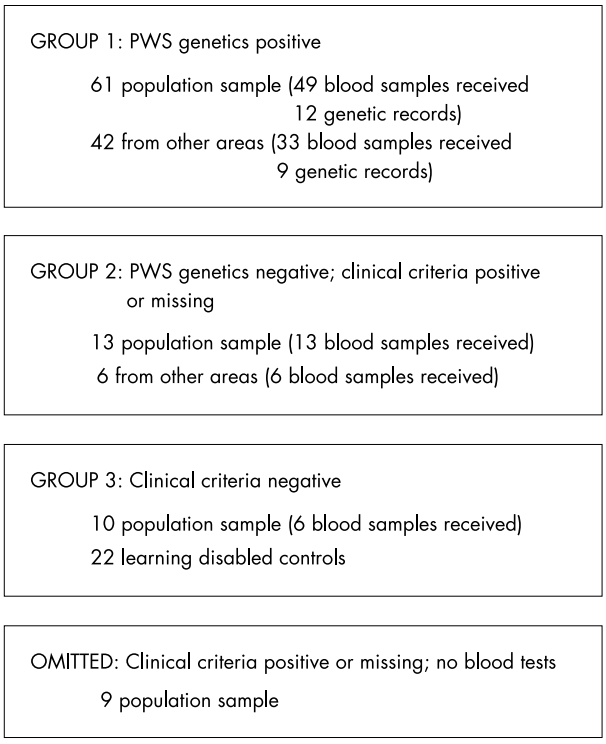

Figure 1 Definition and derivation of groups used in analyses.

The same assessments and interviews, by the same two researchers, were used for all groups, thus removing some possible sources of variation in the data.

Genetic diagnosis

Blood samples were later obtained, or genetic records accessed, from all people suspected of having PWS who gave their consent (that is, interviews were conducted blind to genetic findings). The blood samples were sent to the same geneticist (TW). Methylation analysis was undertaken at the *SNURF/SNRPN* locus and a genetic diagnosis of PWS confirmed if only a maternal band was detected.[15] Cytogenetic analysis was then used to establish whether a deletion was present and parental samples were requested to confirm disomies. Microsatellite analysis at 10 or more loci spanning the entire deletion region from D15S11 to D15S219 was also undertaken for all samples. In contrast, the genetics records accessed often contained only a positive genetic diagnosis.

Analyses

Frequencies of clinical diagnostic symptoms and characteristic PWS behaviours were obtained for three groups: (1) those with a genetic diagnosis; (2) those with negative genetics (that is, PWS region of chromosome 15 appears normal on all the genetic tests described), but clinical criteria positive (score >5) or missing (see description of the sample above); and (3)

Table 1 Endorsement of clinical criteria in genetic subgroups

	Genetics positive (n=103) all clinically positive			Genetics negative, (n=19) clinical criteria positive/missing			Genetics negative, (n=32) clinical criteria negative		
Criterion	Yes	Mild	No	Yes	Mild	No	Yes	Mild	No
Severe floppiness	96	5	0	10	1	2	4	4	22
Poor suck	94	5	0	7	1	5	4	1	25
Difficulty feeding	98	2	0	11	1	3	11	1	19
Decreased movement	65	7	23	6	1	4	2	3	20
Weak cry/inactive	94	6	0	7	4	2	2	4	22
Childhood obesity	77	4	18	13	2	2	17	2	12
Overeat/food obsess	78	12	11	15	3	0	18	3	10
Hypogonadism	54	0	0	5	0	1	4	1	9
Periods per year	22	8	0	1	0	6	1	0	7
Disturbed/noisy sleep	56	10	34	14	2	3	13	2	16
Short height	73	1	23	14	0	3	10	0	21
Fair for family	7	49	43	1	7	7	2	11	18
Small hands or feet	85	11	3	8	3	5	6	7	16
Eye problems	74	1	24	14	0	3	17	0	14
Thick saliva	55	23	21	3	2	14	1	3	27
Articulation problems	65	16	16	9	4	2	17	4	10
High pain threshold	50	29	10	6	7	2	3	13	11
Temperature insensit	44	11	30	8	1	7	3	1	22
Skill with jigsaws	28	14	48	0	3	15	0	3	28
Stubborn	80	14	3	16	3	0	18	5	9
Scoliosis	30	8	62	2	1	16	0	4	28
Reduced vomiting	46	39	10	0	7	10	4	7	19
Severity eating	45	24	27	4	8	5	3	10	18
Possessive	47	31	24	7	5	7	11	8	12
Skin picking	56	19	25	8	5	5	3	9	20
Temper tantrums	63	26	4	11	2	2	15	9	8
Repeated questions	63	12	20	12	3	2	7	5	18
Obsessional behaviour	66	26	6	10	7	0	8	14	10
Violent behaviour	34	33	28	9	2	6	11	6	15
Mood swings	34	18	48	8	5	5	6	7	19
Argumentative	37	28	27	8	0	6	12	5	13
Lying	34	25	32	3	6	5	9	7	12
Stealing	40	23	30	8	7	3	6	4	21

full comparison group (negative clinically and genetically, including some from the population sample in whom a possibility of PWS had at some time been raised). Fig 1 gives the derivation of the three groups. Nine cases are missing because no blood samples were obtained and no genetic records were available.

Discriminant analyses were performed for the following contrast groups: group 1 *v* group 3, group 1 *v* combined groups 2 and 3.

Phenotypic and behavioural differences between deletion and disomy forms of PWS are reported elsewhere.[16 17]

Case studies

Four unusual cases are described; one 32 year old man with negative genetics but a very positive clinical diagnosis; one 22 year old man with normal *SNRPN* methylation but with a small deletion in the PWS region (del(15q12)); one 36 year old man with normal chromosome 15 findings but with a deletion

Table 2 Variables which best discriminate between positive and negative genetic diagnoses of PWS

				Classification results			
						Predicted group	
Action step entered removed	Vars in	Wilks' Lambda	Sig	Actual group	No of cases	1	2
(A) PWS +ve genet *v* control 50 PWS and 15 control had full data							
1 Floppy at birth	1	0.14863	0.0000	Group 1	95	95	0
2 Weak cry/inactive	2	0.09996	0.0000			100%	0%
3 Poor suck at birth	3	0.08388	0.0000	Group 2	26	1	25
4 Childhood obesity	4	0.07439	0.0000			3.8%	96.2%
				Ungrouped	19	14	5
						73.7%	26.3%
				Percent of "grouped" cases correctly classified: 99.2%			
(B) PWS +ve genet v PWS -ve genet combined with control 50 PWS +ve, 4 PWS -ve and 15 control had full data							
1 Poor suck at birth	1	0.28916	0.0000	Group 1	89	87	2
2 Weak cry/inactive	2	0.17886	0.0000			97.8%	2.2%
3 Vomiting	3	0.16721	0.0000	Group 2	38	8	30
4 Thick saliva	4	0.15756	0.0000			21.1%	78.90%
				Ungrouped	7	6	1
						85.7%	14.3%
				Percent of "grouped" cases correctly classified: 92.1%			

Table 3 Variables excluding infancy data which best discriminate between positive and negative genetic diagnoses of PWS

Action step entered removed	Vars in	Wilks' Lambda	Sig	Classification results: Actual group	No of cases	Predicted group 1	Predicted group 2
(A) PWS +ve genet *v* control hypogonadism excluded 53 PWS and 16 control had full data							
1 Small hands or feet	1	0.47241	0.0000	Group 1	78	73	5
2 Thick saliva	2	0.34721	0.0000			93.6%	6.4%
3 Not feel hot/cold	3	0.29825	0.0000	Group 2	22	1	21
4 Stubborn > usual	4	0.27820	0.0000			4.5%	95.5%
				Ungrouped	18	12	6
						66.7%	33.3%
				Percent of "grouped" cases correctly classified: 94.0%			
(B) PWS +ve genet *v* control hypogonadism included 42 PWS +ve and 12 control had full data							
1 Hypogonadism	1	0.22736	0.0000	Group 1	80	79	1
2 Small hands or feet	2	0.15904	0.0000			98.8%	1.3%
				Group 2	22	5	17
						22.7%	77.3%
				Ungrouped	20	13	7
						65%	35%
				Percent of "grouped" cases correctly classified: 94.1%			
(C) PWS +ve genet *v* PWS -ve genet combined with control hypogonadism excluded 53 PWS +ve, 4 PWS -ve, and 16 control had full data							
1 Small hands or feet	1	0.48512	0.0000	Group 1	88	82	6
2 Thick saliva	2	0.35625	0.0000			93.2%	6.8%
3 Vomiting	3	0.31691	0.0000	Group 2	41	12	29
4 Stubborn > usual	4	0.29990	0.0000			29.3%	70.7%
				Ungrouped	8	5	3
						62.5%	37.5%
				Percent of "grouped" cases correctly classified: 86.1%			
(D) PWS +ve genet *v* PWS -ve genet combined with control hypogonadism included 42 PWS +ve, 3 PWS -ve, and 12 control had full data							
1 Hypogonadism	1	0.44567	0.0000	Group 1	77	76	1
2 Small hands or feet	2	0.29624	0.0000			98.7%	1.3%
3 Thick saliva	3	0.27508	0.0000	Group 2	33	8	25
						24.2%	75.8%
				Percent of "grouped" cases correctly classified: 91.8%			

on chromosome 6 (del(6)); and one 18 year old woman with positive PWS genetics and with our "core" clinical features but with very few behavioural symptoms and an IQ of 103.

RESULTS

In the genetically positive group, and in the PWS-like group identified above, we found two pervasive characteristics. Firstly, the eating disturbance associated with the syndrome; although some mothers denied having problems with their son's or daughter's eating behaviour, when challenged all admitted that their offspring could not cope totally independently. In cases where apparently self-controlled people with PWS had tried to live independently, weight had always become a problem. Secondly, even when IQ was above 70 (19.6% of our population sample), there were impairments in social cognition, flexibility, abstract ideas, and concepts of time and number, that is, learning disabilities.

In table 1, the prevalences of the clinical diagnostic criteria (including behaviours) are given for the positive and negative genetic groups and the LD controls. We note that the population sample of people with PWS is included and that the full PWS sample did not differ from the population sample in the prevalence of any criterion (data not shown). Learning disabilities are not included, since these were common to all groups. We also note that some clinical features and behaviours are almost as common in the LD group, and especially in the PWS-like group, as in the PWS group, and should probably not be considered as characteristic of PWS so much as of learning disability.

Some clinical features appeared always to be present (floppy at birth, weak cry or inactivity, poor suck, feeding difficulties, hypogonadism; see Appendix) whenever genetic testing indicated abnormal methylation at *SNRPN*. A definite "no" to the question of whether any of these features were present was sufficient to ensure the finding of a normal methylation pattern. On the other hand, seven out of 51 (six of 19 in group 2 and one of 32 in group 3) of people with normal methylation fulfilled the first four of these criteria and three males and one adult female also had hypogonadism. This is quite a high rate of "false positives" if we use these criteria alone and we investigated whether a different subset of criteria might discriminate better than this.

Table 2 shows the result of the discriminant analyses between (A) the group with positive genetic diagnoses *v* controls and (B) the group with positive genetic diagnoses *v* combined group with negative genetics and controls. There was too much missing data in the group with negative genetics to do a three way discriminant analysis. The first of these analyses, between genetically confirmed PWS and people with learning disabilities of other aetiology and without clinical suspicion of PWS, shows that 99% of cases were correctly classified using four criteria, floppy at birth, weak cry/inactivity of infant, poor suck at birth, and childhood obesity. The second analysis shows that four variables, poor suck at birth, weak cry/inactivity of infant, decreased vomiting, and thick saliva, best discriminated between genetically confirmed PWS and all other learning disabled, but correct classification fell to 92% of cases.

We have considered the issue of clinical diagnosis in later life when clinical information from birth may not be available (that is, the first five items of the Appendix). Table 3 shows the results of four discriminant analyses: (A), (B) between the group with positive genetic diagnoses and controls, and (C), (D) between the group with positive genetic diagnoses and

Table 4 Four cases

	Case 1	Case 2	Case 3	Case 4
Major criteria				
Severe floppiness at birth with later improvement	Yes, some	Yes	Yes	Yes
Poor suck at birth with later improvement	Yes, some	Yes	Yes	Yes
Difficulty feeding at birth	Yes	Yes	Yes	Yes
Obesity during childhood (age when noticed)	Yes (2)	Yes (3)	Yes (1.25)	Yes (8)
Hypogonadism with any of the following, depending on age:	Yes	Yes	No	Yes
Males				
Undescended testes, surgery on testes, decreased	No	Yes	No	
facial and body hair, lack of voice change/age at voice change, early pubertal signs	Yes	Yes	No	
Females				
Does/did she have periods (no if only when on pill), age of first period, how many periods per year				No
early pubertal signs				
Learning difficulties	Yes	Yes	Yes	No MR
Tendency to overeat/obsession with food (from age)	Yes (2.5)	Yes (2)	Yes (2)	No
Deletion 15q11-13 on high resolution (>650 bands) or other	Yes	No	No	Yes
cytogenetic/molecular abnormality of the PWS chromosome	del 15q12		del on 6	Small del
region, including maternal disomy	Meth normal	Meth normal	Meth normal	Meth PWS
Minor criteria				
Decreased movement of baby during pregnancy	Yes	Yes	Yes	Yes
Weak cry or inactivity as a baby	Yes	Yes	Some	Yes
Frequency and severity of any: temper tantrums, repetitive questioning, obsessional behaviour, violent/aggressive behaviour, fluctuations in mood, argumentative, lying, stealing, stubborn, any other behaviour problems	6	9	8	2
Disturbed or noisy sleep	Yes	Yes	Yes	No
Short height	No?	Yes	No	Yes
Growth hormone ever	No	Yes	No	Yes
Hypopigmentation, fair skin and hair compared to family	Sandy hair	Fair skin	No	No
Small hands or feet	Yes	Yes	Hands	Hands
Eye problems (short sight, long sight, squint)	Yes	Yes	Yes	No
Thick saliva with crusting at corners of mouth	No	No	No	No
Difficulty with articulating words	Yes	Yes	Yes	Yes
Skin picking	Yes	Yes	Yes	Some
Supportive findings				
High pain threshold	Yes	Yes	Yes	Some
Decreased vomiting. Ever vomited: frequency	Little	Little	Little	Never
Not feeling hot or cold: abnormal temperature response	Yes	Yes	?	?
Scoliosis or spinal curvature	No	No	No	No
Unusual skill with jigsaw puzzles	Yes	No	No	Yes

combined group with negative genetics and controls. Infancy data are omitted from all four discriminants and also hypogonadism from (A) and (C). The first two of these analyses, between genetically confirmed PWS and learning disabilities of other aetiology and without clinical suspicion of PWS, shows that 94% of cases were correctly classified using two criteria, small hands or feet and hypogonadism in (A) and four criteria, small hands or feet, thick saliva, not feeling hot/cold, stubborn > usual in (B). The other analyses show that the latter four variables best discriminated in (C) and hypogonadism, small hands or feet, and thick saliva best discriminated in (D) between genetically confirmed PWS and all other learning disabled, but correct classification fell to 86-92% of cases.

As an indication of the possible relationships between clinical criteria and genetics, four unusual cases are presented, all of which come from our population sample. Case 2 is certainly more positive on the diagnostic criteria than cases 1 and 4; case 3 is positive on the diagnostic criteria , but lacks one of the "core" characteristics. Table 4 shows the prevalences of clinical diagnostic criteria (including behaviours) in the four cases: (1) normal methylation and expression at *SNRPN* but deleted at 15q12 (probe p1R39) in the PWS region (included as PWS since there is a deletion in the PWS region, as noted in a previous genetic record and confirmed by TW); (2) genetically normal PWS region (see Genetic diagnosis) but clinically very positive; (3) genetically normal chromosome 15 but deletion on chromosome 6; (4) abnormal methylation and expression at *SNRPN*, but has no behavioural problems and an IQ of 103.

DISCUSSION

The initial suspicion that an infant or child might have PWS is raised because of the presence or not of particular clinical characteristics. Confirmation of the diagnosis has then been on the basis of the presence or not of specific clinical criteria now combined with increasingly sophisticated genetic testing showing an abnormality in the PWS region of the paternal chromosome 15. Over time, PWS has come to be regarded as primarily a genetic syndrome. We agree with Gunay-Aygun *et al*[18] that the purpose of clinical diagnostic criteria has shifted from making the diagnosis to raising the suspicion of PWS. Our aim here is to try to refine the use of the criteria in this respect. Our results show that, in both our population sample and in our augmented sample of people with PWS, there appear to be core symptoms that are always present in the case of a positive genetic diagnosis. In our findings, a definite "no" to any one of these criteria implies a normal methylation pattern. However, the data in table 1, the discriminant analysis, and case 2 all show that they are not sufficient, in that their presence does not predict with certainty the genetic diagnosis of PWS. Moreover, we were unable to find a set of clinical criteria that were sufficient to ensure a positive genetic finding, although the predictive power of the above four "core" criteria was greater than 90%.

The methodology used in our study may account for the differences between our results and those in previously published studies (in which our "core" criteria, although most strongly endorsed, were not always present in 100% of cases). Not only did we use semi-structured interviews, conducted in

an informal manner in the clients' own homes, but the same two people carried out all the interviews. If we had not used our interview method, but had used Yes/No questionnaires, we believe that our results would have been less clear. For example, three mothers said that their babies were "stiff" at birth but became "very floppy" within hours and had to be tube fed. Ideally, we would have liked hospital records of babies' condition at birth, but this was not possible in the present study. We were impressed by the number of first time mothers who said they had known that "something was wrong" during pregnancy (less surprisingly, most of those mothers with experience of previous pregnancies reported similar feelings).

A second advantage of this study is that it was based on a population sample and the prevalences of the various clinical criteria in the full sample could be compared with those of the population. (All of the "core" criteria were present in 100% in both. Prevalences of other criteria were very similar in the population and the full sample of PWS.) This report is therefore more likely than most published reports to be representative of PWS.

Genetic tests for PWS have not always been made, especially in the past, when symptoms have been suggestive. This may have been because of a number of factors: ignorance of the syndrome, the cost of genetic analyses, and the cost of unnecessary emotional upset to the parents if the suspicion were not confirmed. Clearly, we need to include all positive cases and as few negative cases as possible in the set of people tested for PWS. All positive cases are included in the set of people with all of the "core" symptoms. Our investigations indicate two circumstances, for infants and for older people respectively, in which genetic tests for PWS should be made. All of the "core criteria" identified above can be recognised in the first few weeks of life in the case of males and all but one in the case of females. Therefore, if none of these criteria is definitely absent, a genetic test for PWS is clearly indicated. We estimated the cost of such a policy in terms of the number of negative genetic tests (and upset parents) that might be involved. It would have resulted in one out of those 32 (3%) of our learning disabled control group, with scores on all of these criteria, being tested and four out of 19 (21%) of those with PWS features but negative genetics. One fewer of these core criteria (four for males, three for females) would have added four more negative cases (6% and 11%, respectively); two fewer would have added eight more cases (16% and 16%, respectively). We also investigated indications for genetic testing later in life if data from the first weeks of life are missing. In these cases, indicators of PWS would be an eating disturbance and learning disabilities, as discussed above, with the following additional criterion. In the case of females, absent or infrequent (less than five per year) and sparse menses would appear to be a necessary symptom and undescended testes (in the absence of surgery) or tiny penis in the case of males. Using this criterion, no positive genetic cases would have been missed, but two out of 15 females with negative genetics would have been included and 12 out of 25 males. Such cases should be increasingly rare, given the increasingly early age of diagnosis. Discriminant analysis (table 3) showed that again no subset of criteria was sufficient to discriminate genetic cases. The results of the discriminant analyses indicate that certain criteria should be given more weight in diagnosis, either as core characteristics of PWS or as discriminators between PWS and other learning disabled groups.

Our findings also raise questions about more theoretical issues. Why do the "core" criteria have such high prevalences in all studies that look at genetically diagnosed PWS and why is there such a variation in the prevalences within PWS of other criteria which distinguish PWS from other groups? The genetic test for PWS assumes that the genetic mechanisms identified to date are the only such mechanisms and operate through their effect on several specific imprinted genes. It is possible that the "core" clinical features of PWS are the result of the failure of expression of a single gene and that a mutation in that gene would lead to the core clinical features of the syndrome. Thus, we cannot exclude the possibility that those with the core clinical features of PWS but apparently normal genetics for the PWS critical region in fact have a mutation in the putative "core" gene. This could also in principle be true for case 3, in which case the findings on chromosome 6 are an additional genetic abnormality. We believe this to be unlikely and, rather, that abnormalities at different genetic loci (as in case 3) can give a similar clinical picture to that of PWS, as is clear from published reports.

The variable strengths of various PWS characteristics and behaviours have been explained elsewhere by our research group[19] in terms of natural genetic variation (usually resulting in a normal distribution of values in the population as a whole) combined with mechanisms we have described as "all or none" (found in all people with PWS), "threshold shift" (that is, a distribution shifted in one direction relative to the general population so that only one tail conforms to acceptable values), and "arrested development" (that is, behaviour common to a certain developmental age that persists into adulthood in people with PWS). The five core symptoms, together with an eating disturbance and learning disabilities, would then constitute the "all or none" characteristics of PWS. Prevalence of characteristics such as a high pain threshold and daytime sleepiness would be explained by the threshold shift model, and typical PWS obsessive-compulsive behaviour (which is similar to that of normal children) would be explained by arrested development. The prevalence of a symptom explained by the "threshold shift" model would then depend on the strength of that symptom relative to the normal population, and would be expected to vary between families as well as between people. It would be appropriate in scoring such a symptom to take account of family background.

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Appendix

Consensus diagnostic criteria	Our questionnaire
Major criteria	
Neonatal and infantile central hypotonia with poor suck, gradually improving with age	Severe floppiness at birth with later improvement Poor suck at birth with later improvement
Feeding problems in infancy with need for special feeding techniques and poor weight gain/failure to thrive	Difficulty feeding at birth (need for special feeding techniques)
Excessive or rapid weight gain on weight for length chart (excessive defined as crossing two centile channels) after 12 months but before 6 years of age; central obesity in the absence of intervention	Obesity during childhood, age when noticed, maximum weight ever and age when reached
Characteristic facial features with dolichocephaly in infancy, narrow face or bifrontal diameter, almond shaped eyes, small appearing mouth with thin upper lip, downturned corners of the mouth (3 or more required)	
Hypogonadism with any of the following, depending on age:	Males: undescended testes, surgery on testes, decreased facial and body hair, lack of voice change/age at voice change, early pubertal signs, small penis
(A) Genital hypoplasia, male: scrotal hypoplasia, cryptorchidism, small penis and/or testes for age (<5th centile); female: absence or severe hypoplasia of labia minora and/or clitoris	Females: does/did she have periods (no if only when on pill), age of first period, how many periods per year, early pubertal signs
(B) Delayed or incomlete gonadal maturation with delayed pubertal signs in the absence of intervention after 16 years of age (male: small gonads, decreased facial and body, hair lack of voice change; female: amenorrhoea/oligomenorrhoea after age 16)	
Global developmental delay in a child younger than 6 years of age; mild to moderate mental retardation or learning problems in older children	Learning difficulties
Hyperphagia/food foraging/obsession with food	Tendency to overeat/obsession with food.
Deletion 15q11-13 on high resolution (>650 bands) or other cytogenetic/molecular abnormality of the PWS chromosome region, including maternal disomy	Genetic testing done, result of testing, where testing was done
Minor criteria	
Decreased fetal movement or infantile lethergy or weak cry in infancy, improving with age	Decreased movement of baby during pregnancy Weak cry or inactivity as a baby
Characteristic behaviour problems: temper tantrums violent outbursts and obsessive-compulsive behaviour, tendency to be argumentative, oppositional, rigid, manipulative, possessive, and stubborn; perseverating, stealing, and lying (5 or more of these symptoms required)	Frequency and severity of any: temper tantrums, skin picking, repetitive questioning, obsessional behaviour, violent/aggressive behaviour, fluctuations in mood, argumentative, lying, stealing, stubborn, any other behaviour problems
Sleep disturbance or sleep apnoea	Disturbed or noisy sleep
Short stature for genetic background by age 15 (in the absence of growth hormone intervention)	Short height: heights of proband, mother, father, height centile. Growth hormone ever (dates)
Hypopigmentation: fair skin and hair compared to family	Fair skin and hair compared with family
Small hands (<25th centile) and/or feet (<10th centile) for height age	Small hands or feet (parents & researchers agree)
Narrow hands with straight ulnar border	
Eye abnormalities (esotropia, myopia)	Eye problems (short sight, long sight, squint)
Thick viscous saliva with crusting at corners of the mouth	Thick saliva with crusting at corners of mouth
Speech articulation defects	Difficulty with articulating words
Skin picking	
Supportive findings	
High pain threshold	High pain threshold (examples)
Decreased vomiting	Ever vomited: circumstances, frequency (0, <normal, normal)
Temperature instability in infancy or altered temperature sensitivity in older children and adults	Not feeling hot or cold when others are: abnormal temperature response
Scoliosis and/or kyphosis	Scoliosis or spinal curvature
Early adrenarche	
Osteoporosis, thin bones, eg, easily broken	
Unusual skill with jigsaw puzzles	Unusual skill with jigsaw puzzles
Normal neuromuscular studies	