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## Prader-Willi Syndrome: Consensus Diagnostic Criteria

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### Abstract

The diagnosis of Prader-Willi syndrome (PWS) is based on clinical findings that change with age. Hypotonia is prominent in infancy. Obesity, mild mental retardation or learning disability, and behavior problems, especially in association with food and eating, result in a debilitating physical and developmental disability in adolescence and adulthood. No consistent biological marker is yet available for PWS in spite of recent research activity in cytogenetics and molecular genetics. Diagnostic criteria for PWS were developed by consensus of seven clinicians experienced with the syndrome in consultation with national and international experts. Two scoring systems are provided: one for children aged 0 to 36 months and another one for children aged 3 years to adults. These criteria will aid in recognition of the syndrome in hypotonic infants and in obese, mildly retarded, behaviorally disturbed adolescents and adults. They will also ensure uniform diagnosis for future clinical and laboratory research in PWS.

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Prader-Willi syndrome (PWS) was first described in the medical literature in 1956.<sup>1</sup> Subsequently, several case reports appeared in the English-language literature,<sup>2-4</sup> but it was not until 1968 that major review articles emerged.<sup>5,6</sup> An evaluation of prevalence of symptoms was published in 1972.<sup>7</sup> Diagnostic criteria were first proposed 10 years ago based on parental report of symptom prevalence in approximately 100 patients.<sup>8</sup> Prader-

Willi syndrome remains difficult to diagnose because many features are subtle or nonspecific and others change with age. Misdiagnoses still occur. Underdiagnosis in younger children and overdiagnosis in obese retarded adolescents and adults are both common.

Approximately 70% of clinically typical patients with PWS have a characteristic deletion of the proximal part of the long arm of chromosome 15 [del15(q11q13)].<sup>9,10</sup> The remaining 30% cannot be diagnosed using this criterion alone. Recently a majority of nondeletion patients have been shown to have PWS on the basis of maternal disomy (two maternal copies of 15q and no paternal copy) for chromosome 15.<sup>11,12</sup> However, the molecular genetic testing required to recognize this disomy is currently not widely available and requires DNA from both parents, which is not always possible. Further complicating the laboratory diagnosis of PWS is the presence of the same chromosomal deletion in patients with Angelman syndrome, a disorder with entirely different symptomatology. Angelman syndrome results from a deletion in the maternally derived chromosome 15, whereas PWS occurs from a deletion in the paternally derived chromosome 15.<sup>13–15</sup> Variability in the technical skill of performing the high-resolution chromosome analysis required to identify the interstitial microdeletion of chromosome 15 in PWS adds a final point of confusion. Sometimes a deletion is recognized cytogenetically but not confirmed with molecular genetic analysis. At other times a deletion is detected molecularly but not visible cytogenetically.

Criteria for clinical diagnosis of PWS will serve several purposes. Practicing clinicians, awaiting definite and accessible laboratory testing, can use the criteria to confirm or rule out the diagnosis. Diagnostic criteria can serve as a tool to alert clinicians unfamiliar with the syndrome. They can also serve to identify patients with PWS for whom molecular genetic studies should be undertaken. Finally, they could ensure greater purity of patient populations for research studies.

In recent years, diagnostic criteria have been developed by consensus of clinical experts for several genetic disorders in which diagnosis is largely clinical.<sup>16–18</sup> Five physicians, a nurse, and a social worker, each of whom had many years of clinical experience with PWS, held a dedicated workshop in January 1991 to develop such consensus diagnostic criteria for PWS. The criteria were tested by five of the participating clinicians (V.A.H., S.B.C., M.G.B., J.M.H., L.R.G.) on 113 patients. This study compared the accuracy of the proposed criteria with experienced clinical judgment and determined the prevalence of symptoms obtained in these 113 patients.<sup>19</sup> Minor alterations in the criteria were made following input from national and international experts at several scientific meetings. The final criteria are presented in this communication. Criteria clarification is provided with pertinent references to aid in the interpretation of the new PWS criteria.

## DIAGNOSTIC CRITERIA

Three categories of diagnostic criteria for Prader-Willi syndrome have evolved: major, minor, and supportive (Table). These are scored on a weighted point system. Major criteria are valued at one point and minor at one half point. Supportive criteria are not included in

the point system. They serve to increase the confidence of the results determined by the other criteria and to educate the user about nonspecific and less frequent characteristics of the syndrome.

The symptoms of PWS change dramatically with age.<sup>20</sup> Infants and young children demonstrate fewer symptoms than older children and adults. Therefore, the scoring system varies, depending on age. In children 3 years of age and younger, only five points are required for diagnosis; four of those must come from the major group (Table). A total score of eight is necessary for the diagnosis in the 3 year to adulthood group. In this age group major criteria items must comprise five or more points of the total score (Table).

## CRITERIA CLARIFICATION

Most of the major diagnostic criteria for Prader-Willi syndrome apply to all age groups. Most of the minor criteria are present only in older children and adults.

### **Hypotonia in Infancy With Normal Neuromuscular Studies.**

Prader-Willi Syndrome should be in the differential diagnosis of neonatal hypotonia and strongly suspected if nonspecific laboratory neuromuscular studies (a supportive finding) result in a diagnosis of “benign, congenital hypotonia.”<sup>21,22</sup> It might be difficult to confirm the presence of neonatal hypotonia in an older person in whom PWS is suggested. If known, delayed motor landmarks (eg, the average age of independent sitting is 13 months, walking 28 months) might support the presence of this symptom.<sup>8</sup>

### **Feeding Problems in Infancy.**

Most infants with PWS require special feeding techniques, eg, gavage feeding or bottles with preemie nipples. The infant does not appear hungry and weight gain is slow. A history of feeding problems in infancy might be difficult to elicit in older persons.

### **Obesity.**

Excessive weight gain follows the period of failure-to-thrive in early infancy in PWS. Early-onset obesity, ie, the infant who was chubby from birth, does *not* qualify as a diagnostic criterion. In very young children, crossing of two centile channels, eg, from the 5th to the 25th percentile, on weight-for-length charts<sup>23</sup> in a short period of time after 12 months of age is a reliable criterion. Onset of obesity must occur before 6 years of age to count as a criterion in this diagnosis. Late childhood and preadolescent onset of obesity does *not* satisfy this requirement.

Life-threatening obesity was once thought inevitable and incurable in PWS. Lower caloric need in persons with this syndrome has been documented and successful weight loss has been well and repeatedly demonstrated.<sup>24</sup> A major goal in early diagnosis of PWS is obesity prevention.<sup>20</sup> This goal is now frequently reached, hence the provision of obesity *in the absence of intervention* in this diagnostic criteria.

### **Characteristic Facial Features.**

The facies typical of PWS are illustrated in the Figure. The head shape is often dolichocephalic and the mouth appears small in infancy.

### **Hypogonadism.**

The manifestations of hypogonadism vary in the two sexes.

Males. In the male, penile length and testicular size should be evaluated and compared to age norms.<sup>25,26</sup> Penile length—measured stretched with a ruler resting on the pubic bone—less than the fifth percentile for age satisfies this criterion. So does truly undescended testes, often accompanied by a flat, underdeveloped scrotum, which has thin skin and is poorly rugated and pigmented. If one or both testes are palpable in the inguinal canal or in the scrotal sac, their size is best evaluated by estimating volume using an orchimeter. Norms for testicular volume and length are available.<sup>25,26</sup>

In the postadolescent male with PWS, virilization is incomplete unless hormonal replacement has been provided. Successful sexual development with testosterone treatment has been described<sup>27</sup>; therefore, “in the absence of intervention” is stipulated in the wording of this criterion.

Females. In females, the size of labia minora and clitoris is admittedly difficult to assess but norms for clitoral size are available.<sup>28</sup> In postadolescent females, estrogen treatment is sometimes deemed appropriate.<sup>27</sup> Breast development might be difficult to assess in obese older preadolescent and adolescent females because fat accumulation may simulate true breast tissue. Therefore, the extent of breast development is not included as a criterion for diagnosis in PWS.

### **Developmental Delay and Mental Retardation.**

Children younger than 6 years of age show delayed motor, cognitive, and language development. The average intelligence quotient of older individuals is in the upper range of mild mental retardation, in the high 60s.<sup>29,30</sup> Many have borderline or low-normal cognition but demonstrate learning disabilities.

### **Food-Related Behavior Problems.**

Excessive appetite and overeating (hyperphagia), seemingly absent sense of satiation, food seeking (from raiding of garbage cans to shoplifting in food stores to pilfering money at home and in school to buy food), and obsession with food and eating are examples of food-related behavior problems found in children and adults with PWS. Such behaviors are seldom found in young children.

### **Abnormalities of the Prader-Willi Chromosome Region on the Proximal Part of the Long Arm of Chromosome 15.**

Besides the 15q11–13 deletion, other cytogenetic abnormalities involving chromosome 15 have also been encountered. Any documented cytogenetic or molecular abnormality in the

Prader-Willi chromosome region satisfies this criterion. Such findings may eventually provide a biological marker for this condition.<sup>12</sup>

### **History of Decreased Fetal Movements, Weak Cry, and Lethargy.**

Fetal inactivity is probably directly related to the degree of hypotonia and is quite subjective. Typically, parents describe the cry in their infant with PWS as squeaky, kitten-like, or sometimes absent. Hypoarousal (inactivity and listlessness) are often noted in infants. The abnormal cry is the most reliable of these symptoms.

### **Behavioral Characteristics.**

In addition to the food-seeking behaviors described above, older children and adults with PWS have other behavioral traits peculiar to the syndrome. Initially, the parents frequently complain of “stubbornness” in their young child with other symptoms listed in the Table emerging with age. Verbal perseverance on favorite topics is one of the most common and annoying behavioral characteristics in PWS.

### **Sleep Disturbances.**

Excessive daytime sleeping frequently occurs in older children and adults with PWS.<sup>31</sup> The sleep apnea may be obstructive or central or both. In some individuals, these symptoms abate with weight loss, although in most they persist.

### **Short Stature.**

A typical pattern of growth has been demonstrated in PWS: normal length at birth, deceleration of linear growth during the first few months of life, relatively steady length growth during childhood, and a fall-off in growth in adolescence.<sup>32,33</sup> Mean adult height is approximately 147 cm for females and 155 cm for males.<sup>30,32,33</sup> Stature for genetic background can be assessed using parent-specific adjustment for height available on US population.<sup>34</sup> Another method utilizes target height. In females: mother’s height plus father’s height minus 13 cm divided by 2 is plotted for age 19 on the female growth chart; in males: father’s height plus mother’s height plus 13 cm divided by 2 is plotted at age 19 on the male growth chart; two standard deviations is  $\pm 8.5$  cm.<sup>35</sup> Charts are also available to directly plot the heights for midparental height of children aged 2 to 9 years.<sup>35</sup>

Growth hormone deficiency has been documented in PWS.<sup>36</sup> Synthetic growth hormone is now available and is beginning to be used successfully.<sup>37</sup> Thus the fourth minor criterion is worded “in the absence of growth hormone.” It is assumed that if intervention has been deemed necessary, this criterion is fulfilled.

### **Hypopigmentation.**

Fairer skin and lighter hair compared to other family members is a relatively recent observation in about 50% of patients.<sup>38</sup> This phenomenon is difficult to appreciate in younger children, who normally tend to have lighter coloring than their parents. Most hypopigmented children have a cytogenetic deletion.<sup>38</sup>

**Small Hands and Feet.**

Published standards are available and should be consulted before determining that small hands and feet are present.<sup>25,26</sup> Their size should be compared to height age, not chronological age, standards. Hands and feet may be of normal size in younger children.<sup>33,39,40</sup>

**Narrow Hands With Straight Ulnar Border.**

Decrease in hand breadth has been demonstrated in PWS.<sup>33</sup> The presence of straight ulnar border is admittedly a subjective finding, but the combination of the two findings is distinctive.

**Eye Abnormalities.**

Esotropia may be present at any age. Refractive errors, hyperopia, and nonfamilial myopia are often encountered in older children.

**Thick, Viscous Saliva.**

A peculiar feature of PWS, which has not been well studied, is the common presence of thick viscous saliva which tends to crust at the corners of the mouth and often covers the teeth.<sup>20</sup> Recently, it has been pointed out that this symptom might be a diagnostic clue in infancy.<sup>41</sup>

**Speech Articulation Defect.**

Clinically the most prominent speech articulation defect in PWS is hypernasal speech.<sup>42</sup>

**Skin Picking.**

Self-mutilating habits, especially picking at minor skin lesions, are common behaviors in older children and adults with PWS. The cause of these behaviors, which often are annoying to parents and other caretakers, is poorly understood.

**High Pain Threshold.**

Parents and caretakers frequently notice that people with PWS seem to have a surprisingly high tolerance for pain. Scrapes, burns, and bruises are often not brought to their attention and only noted incidentally.

**Decreased Vomiting.**

A high threshold for vomiting is another peculiar and unexplained observation in many individuals with PWS. When the whole family has gastroenteritis, the person with PWS may get the diarrhea but may not vomit.

The combination of the last two symptoms (high tolerance for pain and high threshold for vomiting) in the same person literally can be deadly. One of the authors had a patient with PWS who died of a perforated ulcer and knows of another one who died of a perforated appendix because the lack of normal physiological responses prevented the detection of these conditions.

### **Temperature Instability and Altered Temperature Sensitivity.**

Temperature instability has been noted in infants with this syndrome. Occasionally a history of hospitalization for “fever of unknown origin” is obtained.<sup>43,44</sup> Some older individuals with PWS do not appear to react to cold with shivering and discomfort and tolerate heat without being uncomfortable. Again, the basis for these peculiar physiological phenomena remains unexplained.

### **Scoliosis and Kyphosis.**

Scoliosis occurs to some degree in more than 85% of individuals with PWS, occasionally in its infantile form.<sup>45</sup> Kyphosis is also common in older persons but the prevalence has not been documented.

### **Early Adrenarche.**

Isolated precocious adrenarche is sometimes found in children with a variety of neurological impairments and is often encountered in PWS.<sup>46</sup> True precocious puberty has also been described but is unusual.<sup>47</sup>

### **Osteoporosis.**

Fractures following minor trauma in people with PWS have been described.<sup>8</sup> It has recently been demonstrated that osteoporosis frequently is present at all ages in this condition,<sup>27</sup> explaining this earlier observation.

### **Unusual Skills With Jigsaw Puzzles.**

Children and adults with PWS also have some strengths. In many, strong visual-perceptual-motor skills have been documented which may explain the common observation of exceptional proficiency with jigsaw puzzles.

## **CONCLUSION**

In spite of recent increase in research activity in cytogenetic and molecular genetics, a consistent biological marker is not yet available for PWS. Until now, clinicians have used their personal experience to determine whether an individual patient has PWS.

The proposed and tested diagnostic criteria presented here are purposefully stringent. It is acknowledged that PWS may eventually be diagnosed by molecular testing in some patients excluded by these criteria. However, for the present, these criteria will identify those in need of additional laboratory studies and ensure uniform clinical diagnosis for laboratory and clinical research. In addition, these criteria will continue to alert clinicians to a suspicion of PWS in hypotonic infants and obese, mildly retarded, and behaviorally disturbed older children and adults.

Diagnostic criteria have been developed by consensus of informed clinicians for several disorders such as neurofibromatosis, Rett syndrome, and tuberous sclerosis, all of which currently lack undisputable diagnostic biological markers.<sup>17-19</sup> Prader-Willi Syndrome now

joins this list. Other conditions will likely undergo similar attempts at organizing symptomatology in fields of medicine that still are more art than science.

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## ABBREVIATION.

PWS Prader-Willi syndrome

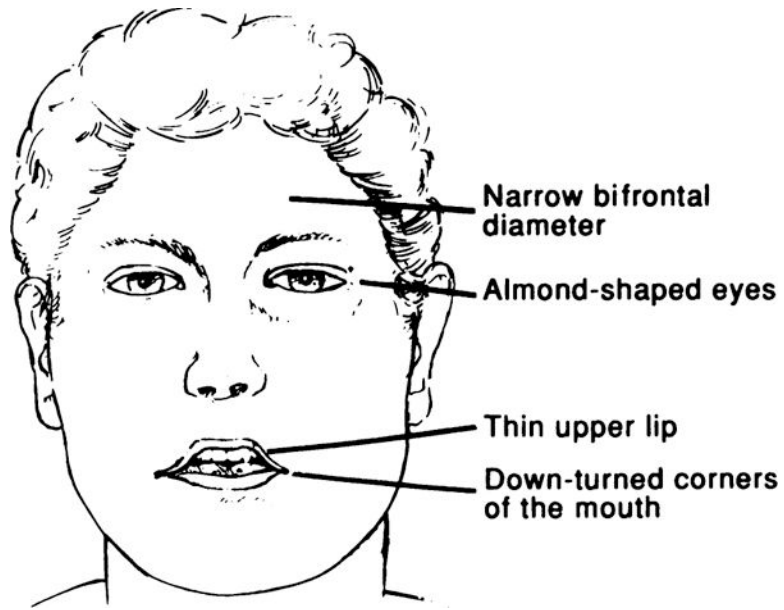
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**Figure.**  
Composite drawing of facial features in Prader-Willi syndrome.

**TABLE.****Diagnostic Criteria for Prader-Willi Syndrome\***

## Major criteria

1. Neonatal and infantile central hypotonia with poor suck, gradually improving with age
2. Feeding problems in infancy with need for special feeding techniques and poor weight gain/failure to thrive
3. Excessive or rapid weight gain on weight-for-length chart (ex-cessive is defined as crossing two centile channels) after 12 months but before 6 years of age; central obesity in the absence of intervention
4. Characteristic facial features with dolichocephaly in infancy, narrow face or bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip, down-turned corners of the mouth (3 or more required)
5. Hypogonadism—with any of the following, depending on age:
  - a. Genital hypoplasia (male: scrotal hypoplasia, cryptorchidism, small penis and/or testes for age [ $<5$ th percentile]; female: absence or severe hypoplasia of labia minora and/or clitoris)
  - b. Delayed or incomplete 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: amenorrhea/oligomenorrhea after age 16)
6. Global developmental delay in a child younger than 6 years of age; mild to moderate mental retardation or learning problems in older children
7. Hyperphagia/food foraging/obsession with food
8. Deletion 5q11–13 on high resolution ( $>650$  bands) or other cytogenetic/molecular abnormality of the Prader-Willi chromosome region, including maternal disomy

## Minor criteria

1. Decreased fetal movement or infantile lethargy or weak cry in infancy, improving with age
2. Characteristic behavior problems—temper tantrums, violent outbursts and obsessive/compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative, possessive, and stubborn; perseverating, stealing, and lying (5 or more of these symptoms required)
3. Sleep disturbance or sleep apnea
4. Short stature for genetic background by age 15 (in the absence of growth hormone intervention)
5. Hypopigmentation—fair skin and hair compared to family
6. Small hands ( $<25$ th percentile) and/or feet ( $<10$ th percentile) for height age
7. Narrow hands with straight ulnar border
8. Eye abnormalities (esotropia, myopia)
9. Thick viscous saliva with crusting at corners of the mouth
10. Speech articulation defects
11. Skin picking

## Supportive findings (increase the certainty of diagnosis but are not scored)

1. High pain threshold
2. Decreased vomiting
3. Temperature instability in infancy or altered temperature sensitivity in older children and adults
4. Scoliosis and/or kyphosis
5. Early adrenarche
6. Osteoporosis
7. Unusual skill with jigsaw puzzles
8. Normal neuromuscular studies

\* Scoring: Major criteria are weighted at one point each. Minor criteria are weighed at one half point. Children 3 years of age or younger: Five points are required for diagnosis, four of which should come from the major group. Children 3 years of age to adulthood: Total score of eight is necessary for the diagnosis. Major criteria must comprise five or more points of the total score.