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Prader-Willi Syndrome: Clinical and Genetic Findings

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Abstract

Since the initial medical description by Prader, Labhart and Willi in 1956 of individuals with overlapping features, the Prader-Willi syndrome has become recognized as a classical but sporadic genetic syndrome. Prader-Willi syndrome is the most common genetic cause of life-threatening obesity in humans. It is estimated that there are 350,000–400,000 people with this syndrome worldwide. Prader-Willi Syndrome Association USA knows of more than 3,400 persons with Prader-Willi syndrome in the USA out of an approximate 17,000–22,000. Prader-Willi syndrome with an incidence of 1 in 10,000 to 25,000 individuals and Angelman syndrome, an entirely different clinical condition, were the first examples in humans of genetic imprinting. Genetic imprinting or the differential expression of genetic information depending on the parent of origin plays a significant role in other conditions including malignancies.

The cardinal features of Prader-Willi syndrome include infantile hypotonia, mental deficiency, hypogonadism, behavior problems, early onset of childhood obesity, small hands and feet and a characteristic facial appearance. Approximately 70% of individuals have a paternally derived chromosome 15q11-q13 deletion, and about 25% of subjects have maternal disomy of chromosome 15 (both 15s from the mother). The remaining subjects having bi-parental inheritance of normal-appearing chromosomes due to imprinting mutations or other genetic anomalies involving the 15q11-q13 region.

Although Prader-Willi and Angelman syndromes are unique clinical disorders that most often arise from a 3 to 4 million base pair deletion of chromosome 15q11-q13 during paternal or maternal gametogenesis, respectively, novel DNA sequences have been identified at the common proximal and distal breakpoints that occur with a low copy number. These DNA repeats may be involved with inter- and intrachromosomal misalignment and homologous recombination leading to the common deletion in both syndromes. Environmental factors may influence this recombination leading to the deletion event but additional studies are needed.

Although several imprinted genes are present in the chromosome 15q11-q13 region and Prader-Willi syndrome due to loss of function of paternally expressed genes through multiple genetic causes, the best characterized gene is *SNRPN*. This gene (exons 4–10)

encodes a ribonucleoprotein for mRNA processing. In addition, a second highly conserved coding sequence of *SNRPN* is termed *SNVRF* (exons 1–3) encompassing the imprinting center. This polycistronic (*SNURF-SNRPN*) gene encodes two independent proteins. Mutations within the imprinting center and balanced translocation breakpoint studies in subjects with Prader-Willi syndrome indicate that this locus is key in the development of this condition.

Prader-Willi syndrome can be divided into two distinct clinical stages, with the first stage characterized by neonatal hypotonia, hypogenitalism, and feeding difficulties, and the second stage, which usually occurs between 1 and 2 years of age, characterized by psychomotor retardation and early onset of childhood obesity. Food forging and physical inactivity are found during this stage.

Obesity is the most significant health problem in Prader-Willi syndrome due to hyperphagia, physical inactivity, a decreased metabolic rate, and an inability to vomit. Marked weight gain and life threatening obesity may occur and has been the focus of several research investigations. In addition, characteristic behavior problems reported in Prader-Willi syndrome include obsessive-compulsive disorder, intense preoccupation with food, and depression. In addition, the correct diagnosis and genetic subtype assignment may be helpful for management and prognosis of individuals with this syndrome. The natural history, diagnostic criteria, phenotype/genotype correlations and molecular genetic findings and genetic testing available for the health-care provider will be discussed.

The phenotypic spectrum of Prader-Willi syndrome may be explained by the varied molecular genetic causes such as paternal deletion, maternal uniparental disomy (of which there are two types: isodisomy [identical genes from the same maternal chromosome 15] or heterodisomy [different genes from different maternal chromosome 15s]) or other chromosome 15 anomalies such as imprinting mutations or translocations. Although not common, subjects with maternal isodisomy 15 may express deleterious recessive genes leading to a second genetic diagnosis (e.g., Bloom syndrome). Maternal disomy 15 subjects are thought to arise from a trisomy 15 embryo followed by trisomy rescue or loss of the paternal chromosome 15 allowing for a normal chromosome number of 46 in the fetus at the time of delivery but with two maternal chromosome 15s. In some cases, there may be incomplete trisomy rescue with residual mosaic trisomy 15 in the fetus at the time of delivery, which may lead to a severe form of Prader-Willi syndrome. These subjects may have a higher incidence of congenital heart disease and more severe growth and developmental delays than Prader-Willi syndrome subjects with typical genetic findings (e.g., deletion or maternal heterodisomy 15). In addition, unexpected expression of 15q11-q13 genes that are imprinted and paternally expressed through relaxation of imprinting also may produce a milder phenotype than the typical Prader-Willi syndrome subject.

Phenotype/genotype correlations in Prader-Willi syndrome have been undertaken and specific characteristics identified for each genetic subtype. Individuals with the paternal 15q11-q13 deletion present with features typically seen in Prader-Willi syndrome and are more homogeneous than the other genetic subtypes. These individuals present with mild to moderate mental retardation and significant behavior problems including skin-picking.

Subjects with maternal disomy 15 have a milder physical phenotype, better cognitive function with higher verbal skills and fewer behavior problems. However, they have decreased visual acuity and impaired stereoscopic vision compared with deletion subjects. They are also more variable in their clinical presentation and may be diagnosed at a later age than deletion subjects. As mentioned, on rare occasions patients with maternal disomy 15 have atypical clinical findings (possibly due to inheritance of recessive genes on the maternal chromosome 15—as seen in isodisomic patients or due to incomplete trisomy 15 rescue). The phenotype of Prader-Willi syndrome subjects with imprinting mutations or other atypical genetic lesions of the 15q11-q13 region has not been well characterized because of their rarity. Thus, phenotype/genotype differences may be helpful in providing prognostic counseling for Prader-Willi syndrome families who present with affected individuals having different etiologies.

Although the recurrence risk is generally low, the molecular genetic etiology may affect recurrence risks significantly. For example, in a rare family the unaffected father may carry an imprinting mutation on his chromosome 15 received from his mother. The Prader-Willi syndrome genes on chromosome 15 from his mother are silent or imprinted. He then could pass the chromosome 15 from his mother with the mutation to his child and Prader-Willi syndrome would result. This would occur at a 50% risk. These family members will require more detailed laboratory genetic testing than available in the routine cytogenetic or molecular genetic laboratories. Specific molecular genetic findings and mechanisms will be further addressed in our review of Prader-Willi syndrome.

Introduction and Background

Prader-Willi syndrome (PWS) was first described by Prader, Willi, and others in 1956, and more than 1500 subjects have now been reported in the medical literature. The incidence of PWS is estimated to be about one in 10,000 to 25,000 live births and is considered the most common syndromal cause of marked human obesity [1]. PWS is generally sporadic in occurrence and characterized by infantile hypotonia (94% of subjects), early onset of childhood obesity (94%), mental deficiency (average IQ of 65, range from 20–90; 97%), short stature (76%), small hands and feet (83%), hypogenitalism/hypogonadism (95%), and a characteristic face (e.g., narrow bifrontal diameter, almond-shaped eyes, and a triangular mouth) (see Table 1) [1–9]. The recurrence risk is generally low (<1%). The syndrome has been identified in all races and ethnic groups although disproportionately more Caucasians are reported [1, 10, 11]. In 70% of subjects, a paternally derived *de novo* interstitial DNA deletion of about 3–4 million bases from the chromosome 15q11-q13 region is reported [4, 12, 13] (see Fig. 1). About 25% of subjects have maternal disomy of chromosome 15 (both 15s from the mother) and the remaining subjects have biparental inheritance of normal-appearing chromosomes with sub-microscopic deletions or genetic imprinting mutations of the chromosome 15q11-q13 region [13, 14].

PWS and Angelman syndrome (AS; an entirely different clinical syndrome generally due to a maternally derived deletion of the 15q11-q13 region) were the first examples in humans of genetic imprinting or the differential expression of genetic information depending on the

parent of origin [12, 15]. Specific diagnostic criteria and molecular genetic information regarding PWS will be reviewed in this supplement.

The course and natural history of PWS can be divided into two distinct clinical stages. The first stage is characterized by varying degrees of hypotonia during the neonatal period and early infancy, a weak cry, thermo-instability, hypogenitalism, a poor suck reflex, and feeding difficulties. The hypotonia is central in origin, nonprogressive, and on the average begins to improve between 8 and 11 months of age [4].

The second stage, which usually occurs between 1 and 2 years of age, is characterized by psychomotor retardation, with an average onset for crawling, walking and talking (>10 words) at 16, 28, and 39 months, respectively [4]. Although 60% of PWS individuals have IQs in the normal or borderline range, cognitive dysfunction is nearly always present. Early onset of childhood obesity is also seen during this stage. Other recognized findings seen in PWS individuals during the second stage include speech articulation problems, foraging for food, rumination, unmotivated sleepiness, physical inactivity, decreased pain sensitivity, picking at sores and insect bites, prolonged periods of hypothermia, hypopigmentation, scoliosis and dental problems.

Early in the second stage, infants and toddlers are usually easy going and affectionate, but in about 50 percent of PWS individuals, personality problems develop between ages 3 and 5 years. These problems include temper tantrums, depression, stubbornness, obsessive compulsivity and sudden acts of violence. These behavioral changes may be initiated by withholding of food, but may also occur with little provocation, particularly in adolescents and young adults. Poor peer interactions, immaturity and inappropriate social behavior may also occur during this time [1, 7, 16–18].

Obesity is the most significant health problem in PWS and is an increasingly common trait that now affects nearly one-half of the U.S. adult population. It is on the rise in children [19]. Obesity is a risk factor in five of the top 10 causes of death (heart disease, stroke, diabetes, atherosclerosis, and malignancies) in this country. There are several genetic syndromes besides PWS with obesity as a cardinal component (e.g., Cohen, Bardet-Biedl, Albright hereditary osteodystrophy, Borjeson-Forssman-Lehmann, Carpenter, fragile X, and Down syndromes) but PWS is an excellent syndrome to study to better understand genetic causation of obesity, behavioral dysfunction and genotype/phenotype correlations.

Weight control and diet restriction are constant key management issues in PWS. Caloric restrictions of 6–8 calories/cm of height will usually allow for weight loss and 10–12 calories/cm of height may be required to maintain weight in PWS subjects. This caloric requirement to maintain weight is about 60% of normal [1].

The onset of obesity usually occurs during the second stage but may occur as early as 6 months of age [20]. About one-third of PWS patients weigh more than 200% of ideal body weight and without intervention, significant morbidity and mortality may occur from complications of obesity (e.g., cardiopulmonary compromise, hypertension, diabetes mellitus). PWS individuals may have 40–50% body fat, which is two to three times more than normal [21]. In addition, the fatness pattern appears to be sex reversed with males

having more fat than females [22, 23]. The heaviest deposition of subcutaneous fat in PWS individuals is in the trunk and limb regions [23]. In addition, a different peripheral-visceral fat storage pattern in PWS subjects is seen compared with obese controls and may account for abnormal pathways of fat storage and lipolysis in PWS.

Obesity is thought to result from hyperphagia, persistent hunger, decreased perception of satiety and an uncontrollable appetite with impaired emesis [1]. The role of energy expenditure in the causation of obesity is not clear, although a combination of excessive caloric intake, decreased energy expenditure, and/or decreased physical activity leads to the morbid obesity [1, 24, 25]. Medications to suppress appetite have met with little success in PWS individuals, but studies with lipase inhibitors and newer appetite suppression medications may be helpful. In addition, growth hormone therapy has helped in increasing stature and muscle mass while decreasing obesity in PWS subjects. Growth hormone therapy and related issues will be discussed elsewhere in this PWS supplement.

Natural History

Pregnancy and Delivery

Reduced fetal movement or activity is noted in nearly all PWS pregnancies. About one-fourth of babies with PWS are delivered in breech presentation. Approximately one-half of babies with PWS are born 2 weeks earlier or later than the anticipated delivery date [1, 3].

Birth and Early Infancy

Because of generalized hypotonia, infants with PWS are floppy and can be mistaken for other disorders such as Werdnig-Hoffman, trisomy 18 or metabolic conditions [1, 26]. Extensive medical evaluations, including muscle biopsies and brain imaging studies (CT and MRI scans) have frequently been performed on infants and are reported normal or not diagnostic for a specific syndrome [1].

Most infants with PWS have a weak cry, little spontaneous movement, excessive sleep, and a poor suck reflex, which may necessitate tube feedings. Failure to thrive and poor weight gain are common features of infants with PWS. They may have temperature instability during early infancy with high or low body temperatures for no known reason. This change in body temperature and abnormal appetite may be due to a hypothalamic abnormality, although gross neuropathologic studies have not identified a brain lesion in this area [1]. However, recent studies have shown abnormal oxytocin levels in brains of PWS subjects [27] and limited specialized brain imaging studies with positron emission tomography for evaluating brain metabolism has shown decreased glucose metabolism in the parietal lobes and hypothalamus region [28].

Mild dysmorphic features are seen during infancy, including a narrow forehead; small upturned nose; thin upper lip and down-turned corners of the mouth; a long, narrow-appearing head (dolichocephaly); mild upward slanting of the palpebral fissures and sticky saliva. They may have fair skin and hair color and small hands and feet at birth [1, 4, 29].

Early Childhood

Although infants with PWS may be tube fed during infancy, by 18 months to 2 years of age their feeding behavior changes radically with an insatiable appetite. In addition, typical developmental milestones are delayed in children with PWS. On average, toddlers with PWS learn to walk at about 28 months of age. By the time they enter kindergarten, they are nearly always overweight and short for age. PWS children should be evaluated for endocrine abnormalities such as hypothyroidism and growth hormone deficiency and treated accordingly. About one-half of children with PWS have lighter skin, eye and hair color than other family members and associated with the chromosome 15q11-q13 deletion (see Fig. 2) [29]. During early childhood PWS children may develop nystagmus, but the most common recognized eye finding is myopia, followed by decreased visual acuity and impaired stereoscopic vision (the latter finding is more common in PWS subjects with maternal disomy 15 and will be discussed in more depth later) [30, 31].

About one-half of children with PWS function in the low normal intellectual range (70–100 IQ), and the remaining PWS children (and adults) function in the mild to moderate range of mental retardation (50–70 IQ) [1, 4, 6, 16,32,33]. Many children with PWS begin school in mainstream settings. By elementary school age, children with PWS may steal or hide food at home or at school to be eaten later. Because of behavior problems and learning deficiency, children with PWS are often referred for special education services. Many children with PWS have difficulties learning to read and in developing math skills. Additional psychobehavioral information regarding PWS will be discussed in more depth in other sections of this supplement.

Adolescence and Adulthood

Adolescents with PWS do not mature sexually as rapidly as their peers. Puberty is absent or delayed in both males and females with PWS. Gonadotropin hormone production is low and other endocrine disturbances may also be present [34]. As a result, adolescents and young adults with PWS look young for their chronologic age. About one-third of appropriately aged females have menstrual periods although not regular [1]. Adolescent girls are unlikely to become pregnant, and males with PWS do not produce sperm; however, a 33-year-old woman with PWS confirmed by molecular genetic analysis recently gave birth to a normal infant [35].

Typical adolescent rebelliousness is often exaggerated by the constant struggle with parents and teachers over access to food. Psychotropic agents can be helpful in controlling abnormal behavior of some PWS adolescents and adults. Adolescents with PWS may weigh 250 to 300 pounds by their late teens. Adults with PWS are short if not treated with growth hormone. The average adult male with PWS without growth hormone therapy is 155 cm and the adult female is 147 cm. Classical findings of this syndrome including small hands and feet are particularly evident during adolescence and adulthood [36–38].

By late adolescence, some with PWS begin stealing food from stores and rummaging through discarded lunch bags or trash cans to find partially eaten left-over food. Some parents find it necessary to lock the refrigerator and cabinets containing food to prevent

excessive eating. Despite these precautions youth with PWS often pry open locked cabinets to gain access to food. Stomach rupturing as a cause of death has been reported to occur in PWS individuals. Thus, this eating disorder and complications of obesity can reduce the life expectancy of a PWS person. However, if weight is adequately controlled, life expectancy should be normal. The oldest reported person to date with PWS is 68 years old [39]. Hence, caloric diet restriction is important to control the obesity and continued consultation with a dietitian is required.

Genetic Findings

The chromosome 15q11-q13 region contains imprinted genes or genes expressed differentially depending on the parent of origin. Since PWS and AS were reported due to genetic imprinting, other imprinted genomic regions have been identified [12, 15, 40, 41]. Imprinting appears to play a significant role in other conditions such as Beckwith-Weidemann syndrome, certain malignancies (e.g., Wilms) [40, 41] and possibly in *in vivo* aging.

PWS and AS are distinct neurobehavior disorders that most often arise from a 4 million base pair (Mb) deletion of the chromosome 15q11-q13 region during paternal or maternal gametogenesis, respectively. The deletions represent a common structural chromosome change, including a large cluster of imprinted genes (2–3 Mb) and a non-imprinted domain (1–2 Mb). Novel DNA sequences have been identified with low copy repeats (the END repeats) which cluster at or near the proximal and distal 15q11-q13 chromosome breakpoints. Two breakpoint clusters have been reported centromeric to ZNF127 with the most proximal breakpoint accounting for 37% of cytogenetic deletions while 60% of deletions occur at the second proximal breakpoint [42]. One breakpoint region lies between loci D15S541/S542 and D15S543 with an additional breakpoint being proximal to D15S541/S542 [43]. The distal 15q11-q13 breakpoint cluster is mapped telomeric to the P locus (involved in hypopigmentation) in nearly all deletion subjects studied. This apparent genetic instability found in the 15q11-q13 region may be attributed to an expressed low copy repeat DNA sequence located in the vicinity of the common breakpoints occurring in patients with PWS or AS. The END repeats are derived from large genomic duplications of a novel gene (HERC2) [42, 44]. The END repeats flanking the 15q11-q13 region may be involved with inter- and intra- chromosomal misalignment and homologous recombination resulting in the common PWS and AS deletion and facilitated by active transcription of the END repeats in male and female gametogenesis [42, 45]. In addition, environmental factors that may influence recombination between END repeats could impact on this process. However, no difference in the number of chromosome and chromatid aberrations were reported previously in cells grown in conditions to induce damage and no clustering of chromosome/chromatid breaks or sister chromatid exchanges were seen in PWS subjects or their parents [46].

There are at least one dozen genes identified in the 4Mb chromosome region commonly deleted in PWS and AS subjects. However, this chromosome region may contain about 100 genes based on gene density estimates [47]. To date five imprinted, paternally expressed genes (ZNF127, *NDN*, *MAGEL2*, *SNURF/SNRPN* and *IPW*) have been localized within the

15q11-q13 region and toward the centromere end and five paternally expressed transcription units (ZNFJ27AS, PAR5, PARSN, IPW, and PARI) mapped to this region. In addition, three genes with an unclear imprinting status, the gamma butyric acid receptor genes (GABRB3, GABRA5 and GABRG3), are located toward the telomere end of the 15q11-q13 region (see Fig. 3). Since the PWS critical region is large, it is likely to contain more than one paternally expressed gene involved in the pathogenesis of this condition and thus termed a contiguous gene syndrome. Studies with animal models (e.g., transgenic knockout mice) have shown that loss of a single specific candidate gene does not necessarily correlate with the PWS phenotype but additional genetic animal models are under investigation.

The best characterized paternally expressed gene to date is *SNRPN* (Small Nuclear Ribonucleoprotein N) with exons 4–10 encoding the SmN spliceosomal protein which is important for mRNA production. A second highly conserved coding sequence of *SNRPN* is termed *SNURF* (*SNRPN* upstream reading frame) consisting of exons 1–3 encompassing the imprinting center. *SNURF* encodes a highly basic 71-amino acid protein which is localized in the nucleus and implicated as a principal component in PWS [48, 49]. Both *SNURF* and *SNRPN* are translated in vivo in normal but not in PWS individuals. *SNURF* is a novel protein along with SmN from a bicistronic *SNURF/SNRPN* transcript (a single *SNURF-SNRPN* mRNA transcript codes for two proteins, *SNURF* and SmN). This genetic locus appears to have a key role in the regulation of imprinting throughout the chromosome 15q11-q13 region as disruption of this locus will cause the loss of function of paternally expressed genes in this region. Furthermore, evidence from *de novo* paternally inherited balanced chromosome translocation patients with a disrupted *SNURF* gene have typical findings of PWS while those individuals with breakpoints distal to *SNURF-SNRPN* possess an atypical appearance [50–52]. Selection for imprinting in this region may have arisen as a result of a postnatal growth advantage to a paternally-derived gene given the failure to thrive phenotype seen in PWS neonates and some PWS mouse model pups [53].

In a small percentage of patients with PWS, microdeletions upstream to *SNRPN* have been reported [13]. These subjects have deletions disrupting the putative cis-acting imprinting control center and are termed to have imprinting mutations. They have a normal biparental inheritance of chromosome 15 and methylation DNA studies show a maternal chromosome 15 pattern (hypermethylation with silent paternal genes) as a result of the imprinting center mutation. The imprinting center covers about 100 kb of genomic DNA sequence [54], but family studies show that the PWS critical DNA region is less than 4.3 kb in size and spans the *SNRPN* gene CpG island and exon 1 [13]. There are sporadic PWS patients reported with an imprinting mutation by methylation DNA studies but no detectable abnormalities of the imprinting center. Additional studies are needed to determine the cause of their PWS mutation.

There appear to be five main molecular genetic classes of PWS. Approximately 70% of subjects have a *de novo* paternally derived deletion from the proximal 15q11-q13 region (see Fig. 4); 25% have maternal uniparental disomy 15 (both intact chromosome 15s from the mother) (see Fig. 5), and a third class of subjects, less than 5%, have very small deletions in the imprinted controlling element of the 15q11-q13 region or are sporadic in nature with no deletion of biparentally inherited chromosome 15s termed imprinting mutations [13, 41, 55,

56]. A subset of these unusual subjects with a submicroscopic or atypical deletion can be detected with fluorescence *in situ* hybridization (FISH) analysis using classical 15q11-q13 DNA probes (e.g., *SNRPN*), but other subjects require additional specialized testing with chromosome breakpoint analysis and DNA sequencing studies. Specific genetic testing will be discussed below. The deletion size may vary from a few thousand base pairs (in imprinting mutation subjects) to a few million base pairs (in subjects with the typical 15q11-q13 deletion) [13, 40, 41, 56, 57]. The smallest region of DNA deletion overlap is 4 kb in size reported in seven individuals with microdeletions [13, 40, 41, 58]. A fourth class of subjects with features of PWS are those with a balanced reciprocal chromosome translocation involving the 15q11-q13 region and distinguished from the unbalanced translocations that may cause maternal disomy 15 or produce 15q11-q13 (or larger) deletions. This rare class probably accounts for < 0.3% of PWS subjects [40, 59]. A potential candidate gene for PWS is *SNURF-SNRPN* (*SNURF* consists of exons 1–3, and *SNRPN* consists of exons 4–10). *SNURF* exon 1 is within the imprinting center where mutations have been identified [13, 41, 48, 49, 50]. *SNURF* gene is the only PWS gene specifically broken by balanced translocations and deleted in all PWS imprinting mutation subjects with an identified deletion [41, 44, 49, 59]. In a review of literature in 1990, 38 subjects with reciprocal translocations of chromosome 15q11-q13 were identified [1]. Since 1990, at least 16 relevant additional subjects have been identified with a reciprocal translocation involving the chromosome 15q11-q13 region (see Table 2). The fifth class of PWS subjects may be those with structural gene mutations of the chromosome 15q11-q13 region. This class is theoretical and has yet to be identified in subjects. Targeting these unusual PWS subjects (those with imprinting mutations, reciprocal translocations, or possibly structural gene mutations of chromosome 15) and studying expressed genes or transcripts from the 15q11-q13 region may allow for a better understanding of the effect of genetic anomalies on the clinical phenotype and the location of candidate genes for specific clinical features.

Testing for PWS

There are currently five cytogenetic and molecular genetic testing protocols utilized for the diagnosis and identification of the genetic subtype in PWS subjects (and AS). These include: 1) high-resolution chromosome studies and/or FISH of DNA probes such as the *SNURF-SNRPN* gene. 2) DNA methylation testing of *SNURF-SNRPN* gene (methylation analysis measures the *SNURF* promoter or the *SNURF-SNRPN* promoter because exon 1 encodes *SNURF*) of patient's DNA with Southern hybridization or with polymerase chain reaction (PCR) (will give laboratory confirmation of either PWS or AS). PWS subjects will show only a maternal DNA signal, whereas AS subjects show only a paternal signal, but neither condition will show both signs [60]. This test will not determine whether a subject has a 15q11-q13 deletion, maternal disomy 15, or an imprinting mutation but will identify all PWS (and AS) subjects with these genetic causes. No other method will identify all three causes. 3) DNA microsatellite analysis using PCR and polymorphic genomic markers from chromosome 15q11-q13 will confirm a paternal 15q11-q13 deletion in PWS or identify maternal disomy 15 (2–3% of AS subjects will show paternal disomy 15). A DNA sample from the patient and each parent will be required for PCR analysis. 4) gene expression

studies of imprinted genes (e.g., paternally expressed *SNRPN* gene) from the 15q11-q13 region using Northern hybridization or reverse transcription PCR of messenger RNA isolated from the patient's cells will determine gene activity [61]. The lack of paternally expressed genes will confirm the diagnosis of PWS but will not determine the genetic subtype (e.g., deletion or maternal disomy). Similarly, methods for detecting protein from the specific gene expression (e.g., *SNURF-SNRPN*) can be helpful but are of limited use in the diagnostic genetics laboratory [59]. 5) DNA replication studies are available on a limited basis using gene markers from the 15q11-q13 region with molecular cytogenetic techniques. The DNA replica-birth length in PWS males with maternal disomy than males with the 15q deletion and a shorter course of gavage feeding with a later onset of hyperphagia in PWS females with maternal disomy. Cassidy et al. [8] observed that people with PWS and maternal disomy were less likely to have the typical facial appearance and were less likely to show certain behavioral features of PWS, including skin-picking, skill with jigsaw puzzles, a high pain threshold and articulation problems. Gunay-Aygun et al. [72] reported that the diagnosis of PWS among individuals with maternal disomy was typically reported later than those with a deletion. Thus, there is increasing evidence for phenotype differences in PWS subjects having the chromosome 15q deletion compared with those with maternal disomy.

Cognition and Behavior

In a recent comprehensive study at Vanderbilt University on genetics, behavior, metabolism and cognition of PWS subjects with 15q deletions or maternal disomy, additional psychobehavioral differences were found. Intellectual and achievement tests were administered by a licensed psychological examiner experienced with the PWS subject population. Spelling skills were assessed using the WRAT-3 test [73]. The subjects received a chronologic age-appropriate version of the Wechsler scales [74, 75], and the Mathematics and Reading portions of the Woodcock-Johnson Revised scales [76]. Parents and guardians or primary caregivers served as informants for the adaptive and maladaptive behavior findings.

In this study measures of intelligence and academic achievement were administered to 38 (16 males and 22 females) individuals with PWS (24 with deletion and 14 with maternal disomy). PWS subjects with maternal disomy 15 had significantly higher verbal IQ scores than those with the deletion ($p < 0.01$). The magnitude of the difference in verbal IQ was 9.1 points (69.9 vs. 60.8 for maternal disomy and deletion PWS subjects, respectively). Only 17% of subjects with the 15q11-q13 deletion had a verbal IQ ≥ 70 , whereas 50% of those with maternal disomy had a verbal IQ ≥ 70 . Performance IQ scores did not differ between the two PWS genetic subtype groups (62.2 vs. 64.7 for maternal disomy and deletion PWS subjects, respectively). The full scale IQ did not differ between the two groups (64.1 vs. 61.0 for maternal disomy and deletion, respectively) [33].

Specific subtest differences were noted in numeric calculation skill, attention, word meanings, factual knowledge and social reasoning, with the maternal disomy PWS subgroup scoring higher than the deletion subgroup. Deletion PWS subgroup subjects scored higher than the maternal disomy subgroup on the object assembly subtest further supporting specific visual perceptual skills being a relative strength for the deletion subgroup. This 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 maternal disomy subgroup have yet to be identified. Whether this phenomenon is caused by the genetic imprinting vs. the nonimprinting status of genes in the 15q11-q13 region is not known. The presence of more functional (expressed) genes in maternal disomy individuals may be due to possible dosage mechanisms where by only one allele is normally functional or expressed. If a gene is paternally imprinted (inactive) and if two functional (active) maternal alleles are now present in maternal disomy PWS individuals in contrast to those with a deletion and no expression (a normal individual would have only one gene allele expressed) then there may be a relative strength for the PWS individual with maternal disomy and over expression of a gene and its product. This report further documents the difference between verbal and performance IQ score patterns among subjects with PWS and the deletion vs. the maternal disomy subtype.

Visual Capacity

During our comprehensive study of PWS and obese control subjects at Vanderbilt University, we identified differences in visual findings between deletion and maternal disomy subjects [30]. Previous studies have examined the ophthalmic status of persons with PWS, and a number of eye findings have been noted to occur at a greater frequency than in the general population [77, 78]. The eye disorders have included strabismus, decreased visual acuity, moderate to high refractive error, and iris hypopigmentation [29]. Individuals with this disorder have been reported with cataracts, congenital ocular fibrosis, diabetic retinopathy, congenital ectopia uvea and misrouting of the optic chiasmata [1, 77].

We performed a comprehensive investigation of 27 PWS subjects and 16 obese controls comparable in age and IQ. The participants received a complete ophthalmologic examination consisting of visual acuity tests of each eye, an external examination, ocular motility evaluation, determination of stereoacuity, a biomicroscopic examination of the anterior segment, a cycloplegic refraction, and an examination of the ocular fundus. In addition, three assessments for stereoscopic vision were made that focused on visual perception. The results of a standard ophthalmic examination were comparable on all measures except myopia and stereopsis between PWS and obese controls. PWS subjects were noted to have more myopia and lower stereoscopic vision scores compared with the obese controls [30, 31]. Significant differences between the 15q11-q13 deletion and maternal disomy PWS subjects were not found for the general clinical eye measures. However, an effect of genetic subgroup was observed for random element stereopsis testing with the maternal disomy group having a greater degree of impairment. In addition, an analysis of the patterns of errors revealed a striking difference in performance between the PWS genetic subtypes (maternal disomy and deletion). The performance of the maternal disomy group (24.4% correct) was substantially inferior to the deletion PWS group (61.5% correct), a difference that is statistically significant (control subjects averaged 75%). Moreover, there appeared to be only a modest relationship of scores on the general clinical eye examinations and performance on the specialized random element stereogram test for

stereoscopic vision. This observation of differences in random element form discrimination between deletion and maternal disomy PWS subjects warrants further investigation [31].

Self-Injurious Behavior

PWS subjects are noted to have behavioral problems including obsessive-compulsivity and self-injurious behavior [8, 16]. Self-injurious behavior in persons with intellectual impairment, autism and related developmental disabilities ranges from 5% to 60%, depending on the methods used and populations studied [79]. Serious health problems can occur from persistent self-injury, including blindness associated with eye-poking, subdural hemorrhage from forceful head-banging, infections from self-inflicted skin-picking, and anorectal disease resulting from rectal picking and digging [80]. Self-injurious behaviors are among the most clinically problematic behavioral consequences associated with PWS. In previous studies, investigators have reported that self-injurious behavior (most notably skin-picking) is a prevalent behavioral problem for 69% of adolescents with PWS studied [81] and in 81% of adults with this disorder [82].

In collaboration with the Prader-Willi Syndrome Association, a self-injury survey was conducted by mailing and distributing questionnaires to parents and guardians of children with PWS at regional, national and international meetings [66]. Self-injury body grid charts were included where the self-injury location could be noted. This study was undertaken to determine the prevalence, topography and specific body locations for self-injurious behavior in PWS subjects. In total, 62 families (38 females with PWS and 24 males with PWS) returned questionnaires and 50 of the 62 individuals were self-injurious at more than one site. Sixty-one percent of the individuals with PWS were reported with a 15q11-q13 deletion, 18% had maternal disomy 15 and 21 % were unknown. The mean age was 18 years (range = 3 to 44). The degree of mental retardation was reported by the parent or care provider to range from mild to moderate. Overall, 869 self-injury body sites were reported from the 50 PWS persons. The most prevalent form of self-injury was skin-picking (82%) followed by nose-picking (28%). The front of the legs and head were disproportionately targeted as preferred self-injury body sites. As suggested by others, PWS individuals with the 15q11-q13 deletion injured at significantly more body sites than did individuals with maternal disomy 15 with skin-picking being the most common form of self-injury. Thus, the phenotypic spectrum of PWS is quite variable and may be dependent on the genetic subtype. In addition, phenotype/genotype differences may be helpful in guiding the clinician in the evaluation of patients with suspected PWS and in providing prognostic counseling for families once the diagnosis (and specific genetic subtype) of PWS is established.

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Figure 1.

A prometaphase chromosome 15 ideogram and a representative pair of high-resolution chromosome 15s from a subject with Prader-Willi syndrome and an interstitial deletion of chromosome 15q11-q13. The arrows on the ideogram indicate the deletion breakpoints at bands 15q11 and 15q13. The 15q12 band is indicated by the arrow on the normal chromosome 15 on the right. The deleted chromosome 15 is on the left. Modified from Clinical and cytogenetic survey of 39 individuals with Prader-Labhart-Willi syndrome. Butler MG, Meaney FJ, Palmer CG. Am J Med Genet 23: 793–809. Copyright 1986 by Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Figure 2.

Frontal views of two children with Prader-Willi syndrome showing the typical appearance. The 8.5-year-old boy on the left with the 15q11-q13 deletion has hypopigmentation, and the 10.5-year-old boy on the right has normal pigment and maternal disomy 15 with normal-appearing chromosomes. Modified from Prader-Willi syndrome: current understanding of cause and diagnosis. Butler MG. Am J Med Genet 35:319–332. Copyright 1990 by Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Figure 4.

Representative fluorescence in situ hybridization (FISH) using a SNRPN probe from the proximal chromosome 15q11-q13 region (red color), a centromeric probe from chromosome 15 (green color), and a distal control probe from chromosome 15q (red color) showing the absence of the SNRPN signal close to the centromere on the deleted chromosome 15 from a Prader-Willi syndrome subject.

Figure 5.

Polymerase chain reaction amplification of genomic DNA using GABRB3 gene from the 15q11-q13 region from a Prader-Willi syndrome family with normal chromosome studies in the Prader-Willi syndrome individual. The mother (on the left), the Prader-Willi syndrome individual (in the middle) and the father (on the right) each show two DNA bands representing the presence of the GABRB3 gene in each chromosome 15 (non-deleted status). The DNA pattern from the mother and Prader-Willi syndrome individual are identical but no DNA signal from chromosome 15 was inherited from the father. The Prader-Willi syndrome individual has two chromosome 15s from the mother and no chromosome 15 from the father, thus demonstrating uniparental maternal disomy 15 (both 15s from the mother).

Table 1

Findings seen in the majority of individuals with Prader-Willi syndrome

Reduced fetal activity
Hypotonia
Feeding problems
Developmental delay/mental deficiency
Cryptorchidism
Hypogenitalism/hypogonadism
Narrow forehead
Almond-shaped eyes
Strabismus
Sticky saliva
Early childhood obesity
Behavior problems
Skin-picking
Small hands and feet
Short stature

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Unbalanced

Kuslich et al. 1999 [52]**	Personal Communication 1999	Rivera et al. 1990 [87]	Qumsiyeh et al. 1992 [88]	Reeve et al. 1993 [89]	Vickers et al. 1994 [90]	Susuki et al. 1996 [91]	Eliez et al. 1997 [92]	Park et al. 1998 [93]
Severe MR	Seizures	15q11.2 deletion	Strabismus, autism	15q11.2 deletion	Contractures, mat disomy, familial t(3;15)	Del by FISH and DNA studies familial t(Y;15)		

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... failure to express most or all imprinted genes ... subjects reported by Sun et al., 1996 and Comroy ... of affected subjects. This preliminary ... presentations.