

Prader-Willi and Angelman Syndromes: Sister Imprinted Disorders

SUZANNE B. CASSIDY,* ELISABETH DYKENS, AND CHARLES A. WILLIAMS

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are clinically distinct complex disorders mapped to chromosome 15q11-q13. They both have characteristic neurologic, developmental, and behavioral phenotypes plus other structural and functional abnormalities. However, the cognitive and neurologic impairment is more severe in AS, including seizures and ataxia. The behavioral and endocrine disorders are more severe in PWS, including obsessive-compulsive symptoms and hypothalamic insufficiency. Both disorders can result from microdeletion, uniparental disomy, or an imprinting center defect in 15q11-q13, although the abnormality is on the paternally derived chromosome 15 for PWS and the maternally derived 15 for AS because of genomic imprinting. Although the same gene may control imprinting for both disorders, the gene(s) causing their phenotypes differ. AS results from underexpression of a single gene, UBE3A, which codes for E6-AP, a protein that functions to transfer small ubiquitin molecules to certain target proteins, to enable their degradation. The genes responsible for PWS are not determined, although several maternally imprinted genes in 15q11-q13 are known. The most likely candidate is SNRPN, which codes for a small nuclear ribonucleoprotein, a ribosome-associated protein that controls gene splicing and thus synthesis of critical proteins in the brain. Animal models exist for both disorders. The genetic relationship between PWS and AS makes them unique and potentially highly instructive disorders that contribute substantially to the population burden of cognitive impairment. *Am. J. Med. Genet. (Semin. Med. Genet.)* 97:136–146, 2000 © 2000 Wiley-Liss, Inc.

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INTRODUCTION

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are two clinically distinct disorders each with a characteristic cognitive, behavioral, and

neurologic phenotype. These disorders occupy an important place in the contemporary history of human genetic disorders because of their unusual and partially shared genetic basis. They are sometimes called sister disorders because they are both the result of the absence or lack of expression of one parent's contribution to the same region of the proximal long arm of chromosome 15q (15q11–q13, the PWS/AS region). The absent contribution to this region is invariably paternal in the case of PWS and maternal in the case of AS. This phenomenon of parent-of-origin difference in the expression of genes is the consequence of genomic imprinting in this region. Thus, the gene for AS and the gene(s) for PWS exhibit differential expression depending on the sex of the parent from whom they were inherited. Because PWS and AS each occurs in approximately 1/10,000–1/15,000 individuals, together they represent a substantial contribution to cognitive disability, and the nontraditional form of inheritance that causes

them thus represents an important pathogenetic mechanism of cognitive impairment.

PWS and AS are different in many ways. Patients with PWS generally have mild mental retardation, and individuals with AS have severe impairment with absent speech. Multiple endocrine abnormalities occur in PWS, whereas significant neurologic deficits, including seizures and ataxia, are characteristic of AS. The affect of people with AS is happy, with unprovoked laughter and preference for water play, whereas those with PWS tend to be relatively discontent and have temper tantrums and obsessive-compulsive behavior. However, they also share some clinical findings, including the presence of infantile hypotonia and sometimes hypopigmentation, and they have in common the presence in each of a distinctive (although different) behavioral phenotype. In addition, they both demonstrate similar genotype-phenotype correlations. Thus, it is appropriate that they be discussed together.

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The Common Genetic Basis of PWS and AS

AS and PWS map to the same genetic region at 15q11-q13. They each can be the result of three shared genetic defects: microdeletion, uniparental disomy (UPD), and imprinting defects. Also, they share similar diagnostic methodologies, including analysis of the degree of methylation of the gene SNRPN within the PWS/AS region.

PWS is known to be caused by lack of expressed paternally inherited genes in chromosome 15q11-q13, whereas AS is caused by lack of a single expressed gene, UBE3A, from the maternally inherited chromosome 15. In this region, the maternally inherited genes related to PWS are normally not expressed, having been rendered inactive because of genetic imprinting; likewise, the paternally inherited UBE3A is normally not expressed because of imprinting. Table I reviews the genetic mechanisms that are known to cause these two disorders, and the frequencies with which they occur. In approximately 70% of patients with PWS and a comparable number in AS, there is a cytogenetically small deletion in chromosome 15 between bands 15q11-q13, which is paternal in PWS and maternal in AS. In most cases, the same breakpoints on the chromosome have resulted in the same 4-Mb deletion [Christian et al., 1995; Amos-Landgraf

et al., 1999], although a few patients have smaller or larger deletions. The difference in frequency of UPD between PWS and AS is, in large part, presumably because paternal nondisjunction is much less common than maternal. Approximately 2–5% of patients with either disorder have their deletion or their UPD as a consequence of a translocation or other structural abnormality involving chromosome 15.

. . . [P]atients with UPD or imprinting defects [in PWS or AS] have milder manifestations than those with deletions.

Among those with a defect in the imprinting process, a proportion have been shown to have a very small deletion, mutation, or other abnormality in the center that controls imprinting within 15q11-q13, the imprinting center (IC) [Ohta et al., 1999]. Others have not had a detectable mutation or deletion in the IC but nonetheless have biparental-inheritance and a maternal-only (PWS) or paternal-only (AS) expression pattern [Buiting et al., 1998]. These individuals are said to have an imprinting defect, and the

mechanism is unknown but could be sporadic. All families with recurrence of PWS studied to date have had an imprinting mutation, but this is not true of AS. In AS, approximately 10–15% of cases are the result of a single gene mutation in one gene within 15q11-q13, UBE3A, which codes for a ubiquitin protein ligase [Kishino et al., 1997; Matsuura et al., 1997]. In the remaining 10%, the cause has not yet been identified.

A number of imprinted and non-imprinted genes have been found to exist within the PWS/AS critical region (Table II; Figs. 1 and 2) [Nicholls, 1993; Buiting et al., 1994; Glenn et al., 1997]. However, for none of these genes is it clear how underexpression is involved in causing the disease phenotypes. The major exception is the non-imprinted P gene [Lee et al., 1994], which codes for a tyrosine transporter gene whose deficiency results in the skin and ocular hypopigmentation that occur in 50–70% of those with PWS and AS with deletions. P protein deficiency also causes strabismus, attributable to aberrant chiasmal crossing of optic nerve fibers that depend on normal retinal pigment for proper growth and routing [Wiesner et al., 1987; King et al., 1993]. Although AS is known to result from a single gene defect, PWS is caused by at least two genes. The best candidate gene is SNRPN, discussed below.

Upstream of the SNRPN gene, in a region called SNURF (SNRPN upstream reading frame), is a putative imprinting control element (IC) for the region [Gray et al., 1999] (Fig. 2). Very small deletions within it have been identified in a few patients with AS or PWS despite biparental inheritance [Saitoh et al., 1996]. GABRB3, GABRA5, and GABRG3, are all non-imprinted receptor subunit genes for the neurotransmitter GABA (γ -amino butyric acid). There are also several identified maternally imprinted genes and transcripts whose function is unknown. ZNF127 is an imprinted zinc-finger gene of unknown function. Necdin (NDN) is an imprinted gene that encodes a DNA-binding protein. IPW

TABLE I. Genetic Abnormalities in Prader-Willi (PWS) and Angelman Syndromes (AS)

	Frequency of genetic cause		Recurrence risk (%)
	PWS (%)	AS (%)	
Deletion 15q11-q13	70	70	<1 ^a
Uniparental disomy	25–28 (maternal)	3–5 (paternal)	<1 ^a
Imprinting center defect	2–5	2–5	50 ^b
Translocation within PWS/AS critical region	<1	<1	5–50 ^b
Single gene mutation	0?	10–15 (UBE3A)	50 ^b
Unknown	0?	~10	?

^aNot yet reported.

^bMagnitude and disorder of risk dependent on the parent of origin.

TABLE II. Maternally Imprinted Genes/Transcripts in the Prader-Willi Syndrome (PWS) Deletion Region

Gene	Protein	Function
SNRPN	SmN (small nuclear ribonuclear protein)	Involved in translational control and alternative splicing
SNURF	?	Possibly the PWS imprinting center
PW71	?	?
IPW	None	?
Necdin	A DNA-binding protein	?
ZNF127	?	Zinc finger gene of unknown function
Par 1	None	Read-through transcript
Par 5	None	Read-through transcript

is an imprinted gene that does not encode a protein. Two imprinted anonymous transcripts, PAR1 and PAR5, have been identified. PW71 is another imprinted gene of unknown function; it has been used as a methylation probe for some clinical and research studies. A number of other genes and transcripts in this region have been identified, with no known pathogenetic relationship to AS or PWS.

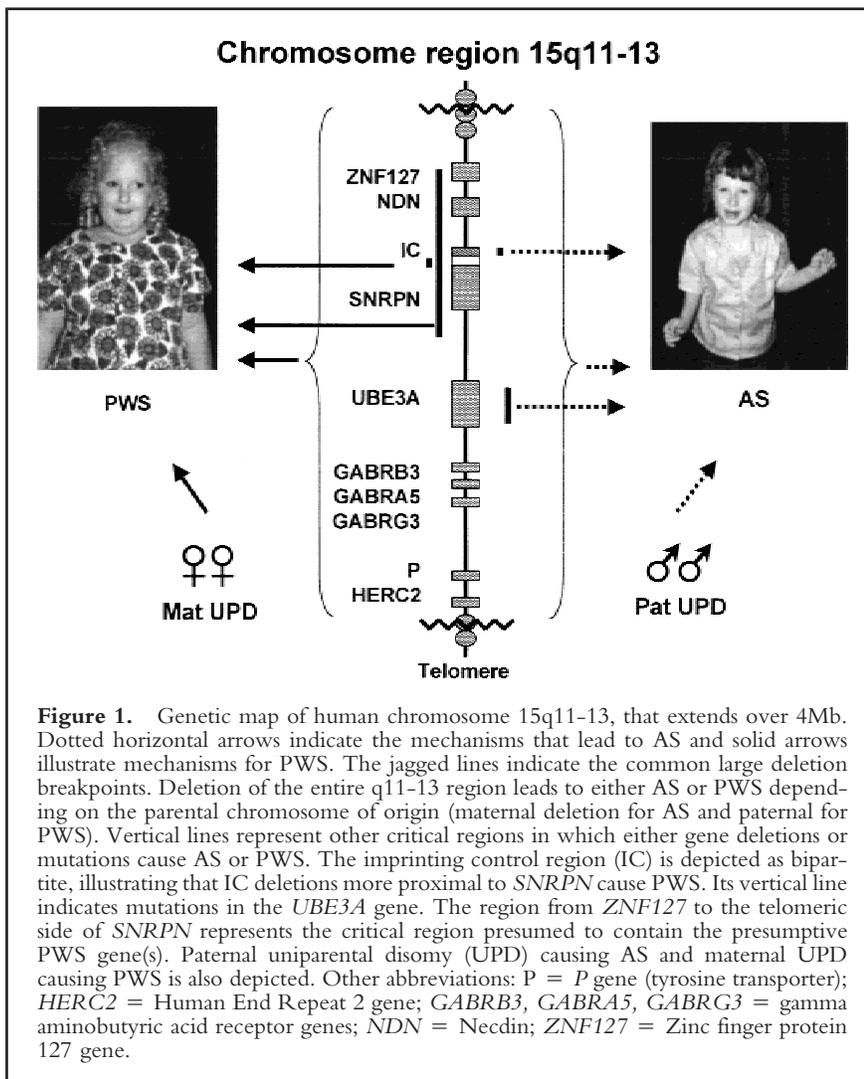
Genotype–phenotype correlations have been found for both disorders. In general, patients with UPD or imprinting defects have milder manifestations than those with deletions. Although the reason is not identified, potential explanations include incompleteness (“leakiness”) of the imprinting process, haploinsufficiency of nonimprinted gene(s) in those with deletion, and overexpression of some gene(s) in patients with UPD.

Animal models exist for both disorders, although they have as yet provided only pathogenetic insight for AS. The discussion that follows will detail these findings.

ANGELMAN SYNDROME

Physical, Neurologic, and Developmental Phenotype

The hallmarks of Angelman syndrome are mental retardation with jerky, ataxic gait, seizures, and absent speech. In addition, the presence of microcephaly, a flat occiput (microbrachycephaly), excessive laughter with protruding tongue, prognathism, and skin hypopigmentation usually present a distinctive clinical picture [Williams et al., 1995a, 1995b] (Fig. 1). Developmental delay is evident by age 6–12 months, but forward progression occurs. There is a structurally grossly normal brain, although mild cortical atrophy or dysmyelination may be seen on magnetic resonance scans. The prenatal history and birth parameters are normal. Some manifestations may be absent or late to emerge (e.g., seizures and protruding tongue), so that the syndrome may not be considered or diagnosed until later in childhood. Diagnostic consensus crite-



Imprinted Genes in 15q11-q13

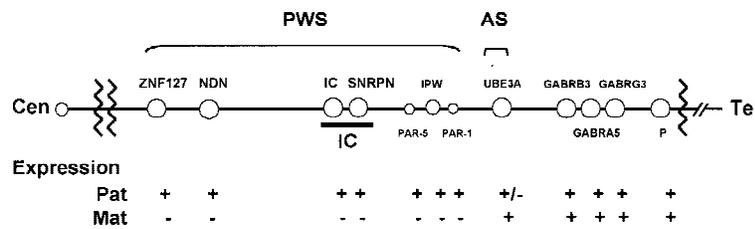


Figure 2. Genetic map of 15q11-13 to illustrate imprinted genes. The PWS bracket indicates those genes that may play a role in pathogenesis of PWS. The imprinting control (IC) region is indicated by the horizontal bar, indicating its close proximity and/or contiguity with the *SNRPN* gene. Genes are indicated by open arrows and maternal and paternal expression patterns are noted under each. The +/- notation for *UBE3A* indicates selective tissue imprinting (e.g., restricted to brain). Adapted from Ohta et al. [1999].

ria are helpful in understanding the spectrum of abnormalities and in deciding which individuals are candidates for definitive genetic testing (Table III) [Williams et al., 1995a].

Seizures occur in most children with AS, in most before 3 years, but occurrence in older children or in teenagers is not exceptional. The seizures can be severe, often major motor type, and may require multiple anticonvulsant medications [Zori et al., 1992]. Seizures may be difficult to recognize or distinguish from the child's usual tremulousness, hyperkinetic limb movements, or attention deficits. The typical electroencephalogram (EEG) is often more abnormal than expected. It usually has symmetrical high-voltage slow-wave activity (four to six cycles/sec) persisting for most of the record and unrelated to drowsiness; and very large amplitude slow activity at two to three cycles/sec occurring in runs and more prominent anteriorly. In addition, spikes or sharp waves, mixed with large amplitude three to four cycles/sec components, are seen posteriorly and are usually provoked by passive eye closure [Boyd et al., 1988; Clayton-Smith and Pembrey, 1992; Sugimoto et al., 1992]. Other EEG anomalies, including cortical myoclonus, have been described [Guerrini et al., 1996].

Many individuals show improve-

ment in their seizure disorders over time, and a subsiding of abnormal EEG patterns [Buntinx et al., 1995; Glayton-Smith, 1993]. However Laan et al. [1996], found that 82% of their sample of 28 adults with AS still manifested regular seizure activity. Others have identified patients who have a more variable course, showing periods of inactivity or "silence," followed by a sudden reemergence of hard-to-control seizures [Buckley et al., 1998; Buntinx et al., 1995].

Cognitive and Behavioral Aspects

Although most people with AS show severe levels of delay, few studies have been conducted that actually document these delays using standardized tests. Recently, Penner et al. [1993] administered a series of Piagetian tasks to seven institutionalized adults with AS. Use of objects was better developed in all patients than their vocal and gestural imitation skills. None engaged in imitative vocalizations or spontaneous speechlike babbling, instead producing single-sound, open-mouth vowel-like sounds. None was able to imitate mouth motor acts; thus, the researchers proposed that AS may involve an oral-motor or developmental verbal dyspraxia. Furthermore, most did not have prerequisite skills for successful social

interaction. Although many individuals seem to show unfocused, non-goal-related actions, and a lack of sustained attention to others, others show some babbling, use of gestures, turn-taking, and relatively well-developed receptive language skills [Williams et al., 1995b]. Clayton-Smith [1993] found that 90% of 82 people with AS used some type of signing or gesturing, but only 20% could be taught standardized sign language, and 70% had from one to three words.

Beginning with Angelman's [1965] first observations, descriptions of behavior in AS have been remarkably consistent. These include bouts of laughter unrelated to context, mouthing objects, problems falling or staying asleep, feeding problems during infancy, motoric hyperactivity and inattention, and stereotypies such as hand-flapping or twirling [e.g., Summers et al., 1995; Summers and Feldman, 1999]. Table IV summarizes rates of these and other behaviors across various studies. Hyperactivity may diminish with age, and patients may also calm down and show less sleep disturbance as they get older [Clayton-Smith, 1993; Buntinx et al., 1995], and have fewer bouts of laughter [e.g., Laan et al., 1996; Buckley et al., 1998].

Although temper tantrums were noted in 5 of 11 (45%) children with AS [Summers et al., 1995], tantrums, irritability, and social withdrawal were significantly lower among 27 children with AS compared to age- and IQ-matched controls [Summers and Feldman, 1999]. This is consistent with long-noted "happy disposition," marked by frequent smiling. Clinical observations suggest that many people with AS love water, shiny objects such as mirrors or plastic, and musical toys or objects that make loud sounds [Clayton-Smith, 1993].

Genetics of Angelman Syndrome

AS is caused by deficiency of protein E6-AP

AS is now known to be caused by mutations or dysfunction in the ubiquitin ligase gene, *UBE3A* [Kishino et al.,

TABLE III. Manifestations in Angelman Syndrome***Consistent**

Developmental delay, functionally severe
 Speech impairment, none or minimal use of words; receptive and nonverbal communication skills higher than verbal ones
 Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs
 Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with hand-flapping movements; hypermotoric behavior; short attention span

Frequent (more than 80%)

Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (absolute or relative) by age 2 years
 Seizures, onset usually <3 years of age
 Abnormal EEG, characteristic pattern with large-amplitude slow-spike waves

Associated (20–80%)

Stabismus	Hypopigmented skin and eyes
Tongue thrusting; suck/swallowing disorders	Hyperactive tendon reflexes
Feeding problems during infancy	Uplifted, flexed arms during walking
Prominent mandible	Increased sensitivity to heat
Wide mouth, wide-spaced teeth	Sleep disturbance
Frequent drooling, protruding tongue	Attraction to/fascination with water
Excessive chewing/mouthing behaviors	Brachycephaly

*Adapted from Williams et al., 1995.

TABLE IV. Behavioral Traits of Persons With Angelman Syndrome*

Behavior	%
Grabs people or things	100
Ataxic movements	100
Absent or sparse language	95–100
Frequent smiling	95–100
Characteristic EEG	92–100
Hand flapping	84
Bouts of inappropriate laughter	77–91
Excessive mouthing	75–100
Overactive, restless	64–100
Sleeping difficulty	57–100
Eating problem	45–64

*Figures derived from Clayton-Smith, 1993; Laan et al., 1996; Smith et al., 1996; Summers et al., 1995; Zori et al., 1992.

1997; Matsuura et al., 1997]. The UBE3A protein product, E6-AP, functions to transfer small ubiquitin molecules to certain target proteins, to enable their degradation through the cytoplasmic proteasome complex [Scheffner et al., 1995]. Almost all known UBE3A mutations cause truncation of E6-AP, leading to haploinsufficiency of the protein [Fang et al., 1999]. Reduced cellular amounts of the E6-AP appear to have no effect in somatic cells because the other normal allele on the paternal chromosome 15 is active and produces an apparently sufficient amount of protein. However, there is little or no expression of E6-AP from the paternal chromosome 15 in certain brain regions, reflecting the imprinted status of UBE3A (see below). Thus, these regions depend solely on maternally transcribed UBE3A.

AS is caused by several genetic mechanisms that perturb UBE3A expression on the normal, maternally derived chromosome 15 [Jiang et al., 1999; Mann and Bartolomei, 1999]

(Table II). The conceptually simplest mechanisms involve chromosomal microdeletions (70% of cases), intragenic UBE3A mutations, and paternal UPD. A more provocative mechanism involves disruption of the IC located approximately 1 Mb centromeric to UBE3A [Dittrich et al., 1996; Saitoh et al., 1996; Farber et al., 1999; Buiting et al., 1999]. The precise DNA structure and function of the IC is currently unknown, but it appears that the IC controls a turn-on/turn-off regulator of UBE3A in the brain. The IC also appears to control other genes in this region that may cause PWS (Fig. 2). Theoretical mechanisms for this regulation include the action of a second protein mediator or long-range changes in chromatin configuration [Barlow, 1997]. Such distant regulation by the IC could affect DNA sequences located near or within the UBE3A gene. One such element could be a recently discovered antisense gene that overlaps UBE3A. It has been speculated that transcription of the antisense gene in

the central nervous system could compete with and/or shut off transcription of UBE3A [Rougeulle et al., 1998].

Those with maternal deletion show most of the "classic" features of AS.

Genotype-phenotype correlations

Certain phenotypic differences between people with AS due to different genetic causes were recently identified. Those with maternal deletion show most of the "classic" signs of AS. Examining 27 individuals with confirmed deletions, Smith et al. [1996] found that all had severe mental retardation, ataxic movements, absent speech, abnormal EEG, a happy disposition, normal birth weight and head circumference at birth, and a large, wide mouth. In contrast, a milder phenotypic picture is found among the relatively few cases with AS due to paternal UPD [Bottani et al., 1994; Gillessen-Kaesbach et al., 1995a; Smith et al., 1997, 1998]. Those with paternal UPD have better growth, less hypopigmentation, more subtle facial changes, walk at earlier ages, have less severe or frequent seizure disorders, less ataxia, and a greater facility with rudimentary communication such as signing or gesturing. Those with imprinting center mutations are less apt to show microcephaly or hypopigmentation, and they also appear to have a less severe seizure disorder [Saitoh et al., 1997; Burger et al., 1996; Minassian et al., 1998]. Milder epilepsy is also noted among those AS cases with UBE3A abnormalities [Minassian et al., 1998]. Ultimately, data from different genotypes have the potential to refine gene-behavior understandings as well as treatment and prognosis.

Animal models provide clues about central nervous system E6-AP actions

Mouse models have been made that allow study of the common 4-Mb deletion region [Gabriel et al., 1999], or

genes within the region of 15q11-q13, such as UBE3A [Jiang et al., 1998] or GABRB3 [DeLorey et al., 1998]. UBE3A knockout mice with maternally derived null mutations exhibit easily inducible seizures (e.g., by rattling a cage) and have mild abnormalities in gait and motor coordination but are not obviously hypermotoric or tremulous [Jiang et al., 1998]. Wild type (m+/p+) and paternal-derived mutant mice (m+/p-) are normal. The AS mice (m-/p+) appear to have normal brain size, morphology, and histology, and these findings are consistent with limited human pathology studies in AS [Jiang et al., 1998]. Decreased expression of mouse UBE3A occurred only in Purkinje cells, in the CA3 region of the hippocampus, and in the olfactory nerve, indicating that only a limited area of the mouse brain demonstrates silencing of the paternal UBE3A allele [Albrecht et al., 1997; Jiang et al., 1998]. Precise localization of regional brain imprinting is not yet known in the human [Rougeulle et al., 1997; Vu and Hoffman, 1997].

Two types of synaptic phenomena have been evaluated by Jiang et al., in hippocampal neurons from Angelman syndrome mouse brain slices [1998]. Short-term synaptic potentiation results in modification of existing proteins without a requirement of RNA synthesis. Long-term potentiation (LTP) was markedly diminished in the AS mouse hippocampal neurons, and LTP is known to be dependent on nuclear transcription and RNA synthesis. LTP has been implicated as an important element in learning and memory, especially in the limbic system [Nayak and Browning, 1999]. Furthermore, behavioral conditioning experiments in AS mice did show learning deficits that required "memory" of the prior days' aversive environment [Jiang et al., 1998]. It is possible that the deficits in LTP in the hippocampus could be the reason for this learning problem and may have direct relevance to the mental retardation seen in AS. Interestingly, activation of the ubiquitin proteolytic pathway is essential for the maintenance of LTP in *Aplysia* [Kupfermann and

Kandel, 1969; Hegde et al., 1997]. In the human, UBE3A might function to degrade proteins that would normally inhibit or repress nuclear transcriptional events associated with phenomena such as LTP. In addition to mental retardation, UBE3A disruption could alter synaptic function in a manner that increases paroxysmal bursting and neuronal synchronization, accounting for abnormal EEG patterns and seizures in AS.

PRADER-WILLI SYNDROME

Physical, Neurologic, and Developmental Phenotype

The major findings in PWS are infantile central hypotonia with poor suck and early failure to thrive, global developmental delay with ultimate mild cognitive impairment, early childhood onset obesity, hypogonadotrophic hypogonadism with genital hypoplasia and pubertal insufficiency, mild short stature, and a characteristic behavior disorder [Prader et al., 1956]. There is a characteristic facial appearance, with narrow bifrontal diameter, almond-shaped palpebral tissues, and down-turned mouth with a thin upper lip [Fig. 1], often evolving over time. These and the more minor but often more distinctive anomalies are well described in a number of reviews [Butler, 1990; Holm et al., 1993; Cassidy, 1997]. Diagnostic criteria have been published [Holm et al., 1993].

There is marked neonatal lethargy with weak cry, decreased arousal, poor reflexes, and the need to awaken the infant to feed. Hypotonia can be severe, although it gradually improves somewhat with age. Special feeding techniques (e.g., gavage tube feeding, need for special nipples) are generally required in early infancy to avoid severely impaired weight gain. Sucking slowly improves during weeks to months, and a period of relatively normal eating ensues. Motor milestones are delayed, and average age of sitting is 12 months and walking is 24 months. Adults remain mildly hypotonic with decreased muscle bulk and tone.

Hyperphagia generally occurs between ages 1 and 6 years, most often between 2 and 4 years, and obesity soon follows if uncontrolled. Food-seeking behavior, with hoarding or foraging for food, eating of unappealing substances such as garbage, pet food, and frozen food, and stealing of food or money to buy food, is common. The hyperphagia is likely of hypothalamic origin and manifests as lack of sense of satiety [Zipf and Bernston, 1987; Holland et al., 1993]. Obesity is the major cause of morbidity in PWS.

Hypothalamic hypogonadism is prenatal in onset, and is evident at birth as genital hypoplasia. It is manifested by cryptorchidism, scrotal hypoplasia (small, hypopigmented, and poorly rugated) and sometimes a small penis in males, and by hypoplasia of the labia minora and/or clitoris in females. Hypogonadism also results in incomplete pubertal development [Cassidy, 1984, 1997]. Adult males only occasionally have voice change, male body habitus, or substantial facial or body hair, and females have amenorrhea or oligomenorrhea. Menarche may occur as late as the 30s. In both males and females, sexual activity is rare, and infertility is the rule, although one exception has recently been reported [Akefeldt et al., 1999]. This end-organ understimulation is treatable with pituitary or gonadal hormones.

Short stature is almost always present by the second half of the second decade if untreated. Growth hormone deficiency, caused by insufficiency of hypothalamic pulsatile growth hormone production, has been demonstrated in most tested patients with PWS, and treatment with growth hormone increases height and lean body mass [Lindgren et al., 1997, 1998; Carrel et al., 1999].

***There is no evidence that
IQ declines over time
[among people with PWS].***

Thick, viscous saliva related to understimulation of the salivary glands,

high pain threshold, skin picking, and a high threshold for vomiting may represent autonomic nervous system dysfunction [DiMario et al., 1994]. Sleep disturbances, especially excessive daytime sleepiness and oxygen desaturation in rapid eye movement sleep, are common even in the absence of obesity [Hertz et al., 1995]. Strabismus is often present. Scoliosis may develop at any age, and kyphosis is common in early adulthood. Osteoporosis is frequent but as yet poorly studied.

Cognitive and Behavioral Phenotype

Most people with PWS function in the mild to moderate range of mental retardation, with most IQs ranging from 60 to 70 [e.g., Curfs, 1992; Dykens et al., 1992a]. A few show severe to profound delays, and as many as 30% have IQs in the borderline (IQ 70–84) to average (IQ 85 and above) ranges. There is no evidence that IQ declines over time. Adaptively, even high-functioning individuals rarely function at a level commensurate with their IQ. Although early clinical observations suggest relative strengths in reading and weaknesses in arithmetic, formal studies do not support this profile [Taylor, 1988; Dykens et al., 1992a]. Many do show relative strengths in certain visual processing tasks, especially those requiring perceptual closure and attention to visual detail, such as jigsaw puzzles [e.g., Gabel et al., 1986; Dykens et al., 1992a]. In contrast, many show relative weaknesses in auditory or visual sequential processing tasks that tap their short-term memory, or that require them to place stimuli in serial or temporal order, including poor arithmetic skills in some [Gabel et al., 1986; Dykens et al., 1992a]. There is no correlation between IQ and body mass indices [Dykens et al., 1992a].

Behavior problems are variable but frequent (Table V), and include: temper tantrums, impulsivity, disobedience, arguing with others, stealing food or money to buy food, skin-picking, compulsivity, mood lability, worry, withdrawal, and anxiety. Such problems may reach clinically significant levels in

TABLE V. Percentage of 100 Subjects With Prader-Willi Syndrome Aged 4 to 46 Years Showing Selected Maladaptive Behaviors*

Behavior	%
Overeats	98
Skin-picking	97
Stubborn	95
Obsessions	94
Tantrums	88
Disobedient	78
Impulsive	76
Labile	76
Excessive sleep	75
Talks too much	74
Compulsions	71
Anxious, worried	70
Gets teased a lot	65
Hoards (nonfood)	55
Steals (food, money for food)	54
Withdrawn	53
Unhappy, sad	51

*Adapted from Dykens and Cassidy, 1999

as many as 70–85% of the population [Stein et al., 1994; Dykens and Cassidy, 1995; Dykens and Kasari, 1997]. Although people with PWS are variably preoccupied with food, many show a variety of obsessive and compulsive symptoms unrelated to food. Examining 91 subjects with PWS, Dykens et al. [1996] found high rates of compulsive symptoms and symptom-related adaptive impairment, suggesting high rates of obsessive-compulsive disorder (OCD) in this condition. Some adults with PWS are similar to nonretarded adult patients with OCD in the number and degree of severity of their symptoms [e.g., Dykens and Kasari, 1997; State et al., 1999]. Such symptoms begin early in childhood [Dimitropoulos et al., 1999]. Aberrant levels of oxytocin have been implicated, and may also be associated with the impaired satiety response characteristic of the syndrome [Swaab et al., 1995; Dykens, 1998; Martin et al., 1998].

Case reports suggest that 6–17% of patients with PWS have atypical psy-

chosis, especially with a depressive component [Clarke, 1993; Beardsmore et al., 1998; Clarke et al., 1998]. Sadness, depression, withdrawal, disorganized thinking, and atypical psychosis become more prominent with increasing age [Dykens et al., 1992b]. Adults with good weight control and lower body mass indices may experience more sadness, withdrawal, and disorganized thinking [Dykens and Cassidy, 1995], and more psychopathology in general [Whitman and Accardo, 1987].

Genetics of Prader-Willi Syndrome

PWS is caused by lack of paternally contributed 15q11-q13

Many of the manifestations of PWS represent hypothalamic insufficiency, although no structural defect of the hypothalamus has been documented on postmortem examination. However, recent studies have demonstrated decreased number and size of cells in the anterolateral hypothalamic nucleus, whose normal function is secretion of oxytocin [Swaab et al., 1995].

The actual genetic haploinsufficiencies that cause the phenotypic effects in PWS have not been identified as yet.

The genetic basis for PWS has been intensely investigated, although the correlation between part or all of the phenotype and specific genes in the region, and the involved pathogenetic mechanisms, are still obscure. However, PWS is known to be caused by the absence of normally active paternally inherited genes at chromosome 15q11-q13 (Table II, Fig. 1). The actual genetic haploinsufficiencies that cause the phenotypic effects in PWS have not been identified as yet. Given the absence of single gene causes of PWS, it is presumed to result from absence of at least two genes, and probably more. SNRPN, which is im-

printed in the brain, is the best described gene that is likely to cause some of the manifestations of PWS. This gene codes for a small nuclear ribonucleoprotein, which is a ribosome-associated protein that functions in controlling gene splicing and therefore may be pivotally involved in the control of synthesis of some proteins, particularly those related to hypothalamic function. It is the most frequently used gene for clinical testing purposes, because it demonstrates deletion or maternal-only expression in virtually all affected individuals. There is another gene in the upstream reading frame of SNRPN, SNURF (SNRPN upstream reading frame), which consists of exons 1-3. SNURF is thought to play a key role in the control of imprinting throughout 15q11-q13, and disruption of this gene, e.g., through chromosomal translocation, results in failure to imprint the SNRPN gene.

When all the genes in this region have been identified, and when better identification of which genes contribute to the PWS phenotype has occurred, it is hoped that the pathogenesis of PWS will be better understood, and treatment can be direct accordingly.

Genotype-phenotype correlations

Patients with deletions and those with UPD display subtle differences [Gillesen-Kaesbach et al., 1995b; Mitchell et al., 1996; Cassidy et al., 1997; Gunay et al., 1997; Dykens and Cassidy, 1999]. In general, manifestations are somewhat milder in those with UPD. In addition to statistically significant physical differences, such as more subtle facial phenotype, larger hands and feet, and fewer speech problems, preliminary findings suggest significant though subtle differences in IQ across persons with paternal deletion versus maternal UPD. Comparing 23 age- and gender-matched subjects with deletions versus UPD, Dykens et al. [1999] found that the UPD group had an average IQ of 71, whereas those with deletions showed average IQ scores of 63. Similarly, Thompson et al. [1999] found lower verbal (but not performance) IQs in subjects with paternal

deletions. Dykens et al. [1999] found more frequent and severe skin-picking [as did Symons et al., 1999], withdrawal, hoarding, aggression, and overeating in those with deletions. These differences must be considered in the context of within-group variability in findings. A few patients with UPD have also been diagnosed as having autism, as well as very low IQs, and more severe behavioral problems [Dykens and Cassidy, 1999]. Associations between autism and chromosome 15 duplications involving the PWS/AS region [Cook et al., 1998] are intriguing in this context.

Animal models of PWS do not survive long

Attempts to create mouse models of PWS have used a number of approaches. The SNRPN knock-out mouse appears normal [Yang et al., 1998]. Mice with an intragenic deletion that included the mouse homologs of SNRPN and the putative PWS-imprinting center lacked expression of the homologs of ZNF127, NECDIN and IPW [Yang et al., 1998]. They had hypotonia and poor suck, and died at a few days of age with failure to thrive. Similar findings occur with mice heterozygous for the paternally inherited IC-deletion. Mice with a large deletion of 15q11-q13, spanning the SNRPN and UBE3A homologs, manifest growth retardation, hypotonia, and lethality before weaning [Tsai et al., 1999]. Necdin knock-out mice have failure to thrive and respiratory problems in the neonatal period [Gerard et al., 1999]. Thus, attempted mouse models have not survived sufficiently long to learn whether they are, indeed, appropriate models, nor whether information on pathogenesis can be gleaned from them.

SUMMARY

Prader-Willi and Angelman syndromes are two complex disorders due to abnormalities in the imprinted region of chromosome 15q11-q13. Although they are distinct, they both have characteristic neurologic, developmental,

and behavioral phenotypes as well as other structural and functional abnormalities. They are related primarily through genetic causes, in that both can result from microdeletion, uniparental disomy, and imprinting center defect in 15q11-q13, although the abnormality is on the paternally derived chromosome 15 for PWS and the maternally derived 15 for AS. This genetic relationship makes them unique and potentially highly instructive disorders that contribute significantly to the burden of cognitive impairment.

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