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Prader-Willi, Angelman, and 15q11-q13 duplication syndromes

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Abstract

Three distinct neurodevelopmental disorders arise primarily from deletions or duplications that occur at the 15q11-q13 locus: Prader-Willi syndrome (PWS), Angelman syndrome (AS), and 15q11-q13 duplication syndrome (Dup15q syndrome). Each of these disorders results from the loss of function or over-expression of at least one imprinted gene. Here we discuss the clinical background, genetic etiology, diagnostic strategy, and management for each of these three disorders.

Keywords

Prader-Willi syndrome; Angelman syndrome; chromosome 15q11-q13 duplication; genomic imprinting; copy number variation; DNA methylation; *UBE3A*; *SNRPN*

Introduction

Chromosome 15q11-q13 is a region that harbors several genes regulated by genomic imprinting, a phenomenon in which genes are expressed preferentially from one parental allele. As a result, genes subject to regulation by genomic imprinting are functionally haploid, having only a single functional copy. Three distinct neurodevelopmental disorders arise primarily from deletions or duplications that occur at the 15q11-q13 locus: Prader-Willi syndrome (PWS), Angelman syndrome (AS), and 15q11-q13 duplication syndrome (Dup15q syndrome). Each of these disorders results from the loss of function or over-

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expression of at least one imprinted gene. They each occur with a frequency of approximately 1/15,000 to 1/30,000 live births.

The deletions and duplications of chromosome 15q11-q13 that cause PWS, AS or Dup15q syndrome are mediated by local DNA repeats that occur at the common breakpoints. There are five such elements, which comprise breakpoints 1 through 5 (BP1-BP5). Deletions involving either BP1 or BP2 and BP3 are most common, while the duplications are more complicated, but can frequently involve BPs 4 and 5 and are discussed below. A map of the 15q11-q13 genetic region is shown in Figure 1. Here we discuss the clinical background, genetic etiology, diagnostic strategy, and management for each of these three disorders.

Prader-Willi syndrome

1. Clinical background of the disease

Prader-Willi syndrome (PWS) is characterized by hypotonia; failure to thrive with poor suck; hypogonadism; short stature with small hands and feet; hyperphagia leading to morbid obesity, beginning during early childhood; developmental delay/intellectual disability; and behavioral issues, including obsessive compulsive disorder (Table 1). Characteristic facial features are also evident.

Hypotonia—Hypotonia becomes evident during pregnancy as decreased fetal movement and atypical presentation at delivery. Assisted delivery and caesarean section are increased with PWS births¹. Hypotonia is nearly universal in infants with PWS, thus, a molecular test for PWS should be performed whenever neonatal hypotonia is observed. Infants with PWS are lethargic with reduced movement, often having a weak cry, poor suck, and failure-to-thrive². The infantile hypotonia improves, but mild to moderate hypotonia persists throughout life in PWS children and adults.

Hypogonadism—Hypogonadism is often evident at birth as gonadal hypoplasia in both males and females. Males typically have a small scrotum and may have a small penis. Unilateral or bilateral cryptorchidism is frequent. Females often have a small labia minoris and clitoris. Puberty can be delayed or disorganized in adolescents with PWS, and most adults are infertile. Hypogonadism is thought to result from both hypothalamic dysfunction resulting in low levels of gonadotropins (and therefore gonadal hormones), as well as primary gonadal deficiency³.

Growth deficits—Growth deficits associated with PWS likely begin *in utero*. Infants with PWS are typically 15–20% smaller than their siblings^{1,4}. Short stature is often apparent in childhood and persists through adulthood. The lack of a pubertal growth spurt may exacerbate the growth deficit⁵. Hands and feet are often particularly small, usually averaging below the 5th percentile. Growth deficits are caused, at least in part, by growth hormone deficiency⁶, which appears to result from hypothalamic-pituitary dysfunction. Indeed, growth hormone replacement therapy improves body mass index and muscle mass in children with PWS, and may even improve body habitus in adults with PWS^{7–9}.

Hyperphagia and obesity—Individuals with PWS pass through a series of seven nutritional phases relating to appetite and weight gain¹⁰. The first phase, phase 0, occurs from prenatal to birth with reduced fetal movement and lower birth weight than siblings. The second phase, phase 1a, occurs from birth to approximately 9 months and is characterized by failure-to-thrive with difficulty feeding and decreased appetite. The third phase, phase 1b, occurs from approximately 9 months to 2 years and is marked by improved feeding and appetite and appropriate growth. The fourth phase, phase 2a, occurs between approximately 2 and 4.5 years. This phase involves weight gain without increased appetite or excess calories. The fifth phase, phase 2b, occurs between approximately 4.5 and 8 years. This phase involves continued weight gain with increased appetite and calories, however, individuals in this phase can still feel full. The sixth phase, phase 3, lasts from approximately age 8 to adulthood. This phase is characterized by extreme hyperphagia, and individuals rarely feel full. If food consumption is not limited, obesity is inevitable. The seventh and final phase, phase 4, occurs throughout adulthood. During this phase, appetite is no longer insatiable.

The etiology of hyperphagia in PWS is poorly understood, although it is likely to result from hypothalamic dysfunction⁵. It has been suggested that increased ghrelin levels may underlie hyperphagia in individuals with PWS¹¹, however, there are no consistently identified hormonal abnormalities that explain the hyperphagic behavior in PWS. Nonetheless, it is not unusual for individuals in phase 3 to exhibit extreme food seeking behaviors, including consumption of non-food items, hoarding of food, or stealing money to buy food⁵.

The etiology of obesity in PWS manifold. The onset of weight gain in phase 2a, before increased appetite occurs suggests that individuals with PWS have lower caloric requirement¹⁰. This is due, at least in part, to decreased resting energy expenditure caused by decreased activity and decreased lean muscle mass compared with neurotypical individuals¹². Increased appetite and hyperphagia also contributes to obesity. The obesity in PWS primarily occurs in the abdomen, buttocks, and thighs; there is less visceral fat than would be expected¹³. Obesity is the major cause of morbidity and mortality in PWS.

Developmental delay/intellectual disability—Motor development and language skills are delayed in most PWS individuals, although nearly all individuals with PWS walk and can effectively communicate verbally. Individuals with PWS have mild to moderate intellectual disability^{14,15} and poor academic achievement is typical and may be exacerbated by behavioral difficulties in addition to developmental and intellectual disability¹⁴.

Behavioral difficulties—Up to 90% of individuals with PWS have characteristic behaviors including stubbornness, temper tantrums, manipulative behaviors, compulsivity, and difficulty with change in routine¹⁶. Features similar to obsessive compulsive disorder and skin picking are common. Some of the behaviors are consistent with autism, and indeed some individuals with PWS meet diagnostic criteria for autism. This may be more common in individuals with maternal uniparental disomy¹⁴. Psychosis is also prevalent in approximately 10–20% of adults with PWS^{17,18}.

Other features—Facial features associated with PWS include almond shaped eyes; narrow, but prominent nasal bridge; high, narrow forehead; thin upper lip; and downturned mouth. Other features associated with PWS include sleep disorders including sleep apnea¹⁹, strabismus (60–70%)⁵, scoliosis (40–80%)⁵, light colored hair and skin, striae, and tapering of fingers.

2. Recent advances in genetics and pathomechanism of diseases

Prader-Willi syndrome is caused by the loss of paternally-inherited chromosome 15q11.2-q13. The loss of expression from this chromosomal region typically occurs by one of three mechanisms: 1.) approximately 70% of individuals with PWS have a large deletion of the entire 15q11-q13 imprinted region; 2.) approximately 25% of individuals with PWS have maternal uniparental disomy (matUPD) in which both copies of chromosome 15 have been inherited from the mother; and 3.) less than 5% of individuals with PWS have an imprinting defect that causes paternal 15q11-q13 to behave as though it were inherited from the mother⁵. Notably, there are no instances of a point mutation in any gene causing PWS, suggesting that PWS is a true contiguous gene syndrome, resulting from the loss of more than one gene.

In the vast majority of PWS individuals, approximately 20 paternally-expressed genes are missing, including *Necdin* (*NDN*), *Makorin ring 3* (*MKRN3*), *Mage-like 2* (*MAGEL2*), *PWRN2*, *PWRN1*, *Nuclear pore associated protein 2* (*NPAP2*), *SNURF*, *SNRPN*, *SNORD109A*, *SNORD116*, *SNORD115*, *SNORD109B*, and *SNHG14* (formerly known as *UBE3A-ATS*). Typical individuals with deletions of paternal *NDN*, *MKRN3*, and *MAGEL2* and with deletions of paternal *SNORD115* and distal portions of *SNHG14* have been identified, suggesting that these genes are not causative for PWS. Conversely, individuals with PWS have been identified with smaller, atypical deletions that have narrowed down the PWS critical region to a 91 kb region that includes *SNORD109A*, *SNORD116*, and *IPW*^{20–23}. Mouse models further suggest that deletions of *Snord116* are sufficient to cause PWS, however, no human patient with PWS caused by deletion of *SNORD116* alone has been reported to date.

The *SNORD* genes that are located in 15q11.2-q13 are orphan CD box snoRNA genes that have been reported to modify mRNAs^{24,25,26} and rRNAs²⁷, as well as act as small interfering RNAs (siRNAs)²⁸. *SNORD116* is actually a cluster of 29 similar, but not identical snoRNA genes that although evolutionarily related may affect different mRNAs and rRNAs. It is not known how loss of *SNORD116* results in the phenotypic manifestations of PWS.

3. Diagnostic Strategy

Methylation analysis—DNA methylation analysis using southern blot or methylation-specific PCR will diagnose PWS in 99 % of cases, including all three classes; paternal deletion, maternal UPD, and imprinting defect⁵ (Figure 2). The most widely used assays target the 5' CpG island of the *SNURF-SNRPN* (*SNRPN*) locus, a region known as the imprinting center. The promoter, exon 1 and intron 1 of *SNRPN* are unmethylated on the paternal allele and thus expressed, and methylated on the maternal, non-expressed allele. A

normal individual will have both a methylated and unmethylated *SNRPN* allele, whereas individuals with PWS will have only the maternally methylated allele⁵.

Methylation analysis allows for identification of patients with PWS, but provides no information about the molecular class of the disease. As discussed, 65–75 % of cases results from a deletion at 15q11.2–q 13, 20–30 % result from uniparental disomy in which both copies of chromosome 15 are maternally inherited and less than 5% are caused by some form of imprinting defect⁵. Differentiation of the molecular class of PWS allows the physician to provide more accurate prognostic information and is crucial for accurate recurrence risk counseling. Testing should proceed in the order outlined below, from most to least common cause.

1. *Search for a deletion.* FISH with a *SNRPN* probe is the most cost efficient means of identifying a deletion. If done with simultaneous chromosomal analysis, rare cases caused by translocation or inversion will be identified. Increasingly, CMA (chromosomal microarray analysis) is sent instead of FISH, and allows for accurate measurement of deletion size in addition to providing information about other genomic changes, if present. The extent of the deletion is expected to become increasingly important as our understanding of genotype-phenotype correlations in PWS grows. CMA is more expensive than FISH, but is increasingly available, and typically is the first test done when a patient with a suspected genetic condition is evaluated, particularly if PWS was not initially considered. In this case, methylation testing is important as a confirmatory test, as identification of a deletion does not distinguish between Prader-Willi and Angelman Syndromes, which may have considerable clinical overlap in the young child. Additionally, CMA may identify rare patients that have deletions that do not include the imprinting center.
2. *UPD testing.* DNA polymorphism analysis of chromosome 15 loci on the proband and parents' DNA will identify cases of maternal uniparental disomy in which both copies of chromosome 15 are maternally inherited²⁹.
3. *Imprinting Defect.* Sequencing of the imprinting center can be done in specialized laboratories. Mutations are found in 15 % of those with imprinting defects, with the remainder caused by epimutations. Epimutations carry a low recurrence risk whereas an IC mutation on the paternal allele may be associated with a 50% recurrence risk, thus searching for a mutation provides important information to families about future risk.

Additional Options—MPLA testing is another increasingly popular option as a first line test for diagnosis of PWS, particularly in Europe. MPLA testing has the ability to assess methylation at 5 sites in the PWS region, as opposed to one site in the standard methylation assay. It also will detect a deletion, if present, but cannot distinguish between UPD and imprinting defects.

4. Current Management

Diet and Nutrition—Failure to thrive in infancy results from poor suck in the setting of hypotonia. Special nipples or gavage feeding are often required. Close monitoring of growth parameters is required in the first year of life². If failure to thrive is noted, despite adequate caloric intake, testing for hypothyroidism is indicated, as this is not uncommon in infancy³⁰.

As weight gain begins to increase from the age of 2 onwards, careful supervision of caloric intake is necessary. Weight gain often begins after the age of 2, though appetite increase is not typical until after age 4. It is important to monitor food intake, before the onset of obesity. Nutritional supervision to assess appropriate intake and supplementation of vitamin D, calcium and other nutrients is recommended. Locking of cupboards and refrigerator is often necessary as appetite increases. Evidence suggests that early dietary intervention with a controlled prescribed diet as early as 14 months of age may result in a normal BMI³¹. Continued monitoring of diet and weight is central to long-term health including avoidance of diabetes mellitus and other obesity related complications.

Hormonal / Endocrine—Treatment with Growth Hormone (GH) is now recommended as standard of care for children with PWS. Early treatment appears beneficial with normalization of height, increase in muscle mass and decrease in fat mass. Treatment should begin between 4 months and two years of age as benefits in head circumference, gross motor and language development and cognition have been demonstrated with early treatment^{32,33}. Due to concern about the possibility of an increase in the rate of sudden death from upper airway obstruction in the first months of treatment, a sleep study is recommended prior to initiating treatment, 6 to 12 weeks after initiation of treatment and on an annual basis thereafter³⁴. Children with PWS are at increased risk of obstructive and central apnea and this risk may rise with GH treatment, possibly due to lymphoid hyperplasia. While receiving GH treatment, close monitoring for scoliosis, hypothyroidism, diabetes and elevation of IGF-1 is suggested³². Treatment with GH may need to continue into adulthood, as recent studies suggest that BMI may increase significantly following cessation of GH therapy³⁵.

Cryptorchidism should be identified with referral to urology and treatment if noted in infancy. Treatment of hypogonadism should be considered, with human chorionic gonadotrophin (hCG) or testosterone, to assist with testicular descent, as well as scrotal and phallic development and growth². In early adolescence, replacement of sex hormones may be appropriate; low dose estrogen or combined estrogen/progestin for girls beginning at age 11 to 12, particularly if there is amenorrhea/oligomenorrhea or low bone mineral density in the setting of low estradiol levels. Testosterone or hCG (increases endogenous testosterone production) in the setting of hypogonadism in boys beginning at 12 to 13 years³⁶.

Monitoring of free thyroxine in addition to TSH should be done annually in childhood³⁶. Awareness of elevated risk for adrenal insufficiency is important as it may be present in up to 60% of children. Central adrenal insufficiency has been observed in PWS, though frequency is unclear. Consideration of measuring ACTH and Cortisol levels with illness is appropriate and some have advocated stress dose steroids with illness or before surgery³⁶. Monitoring for Type 2 Diabetes Mellitus is essential in adults.

Behavioral and Educational—Physical therapy beginning in infancy assists with motor skills development with speech therapy often warranted by 2 years of age. Requirement for educational support should be anticipated including personal classroom aides and behavior management given the frequency of challenging behaviors such as tantrums, compulsive and stubborn behaviors. Serotonin reuptake inhibitors can be helpful for severe behavioral issues, including psychosis, which may emerge in adolescence³⁷. Adolescents and adults often are successful residing in a group home where attention to daily exercise and diet can be emphasized.

Other—Annual assessment for scoliosis should begin in early childhood. Ophthalmological evaluation for strabismus and impaired acuity should be done in the first year of life and continue thereafter. Given the increased risk for osteoporosis, bone density studies (DEXA studies) are recommended beginning in adolescence and continuing to adulthood³⁸.

Future Potential Therapies—Several medication trials are ongoing, aimed at addressing the hyperphagia and associated symptoms of PWS. Oxytocin nasal spray is being studied, as there is a reduction in oxytocin producing neurons in the hypothalamic periventricular nucleus in individuals with PWS. A recent publication, however, did not demonstrate benefit in 30 individuals in an 18-week double-blind, placebo-controlled crossover trial³⁹. Other trials are ongoing. A trial of a candidate obesity drug called Beloranib is also underway. Beloranib is an inhibitor of methionine aminopeptidase-2 and works to reduce fatty acid synthesis, insulin levels, and food consumption. It also increases mobilization of fats and energy expenditure⁴⁰.

Recommendation for family counseling—Family counseling is recommended. Most deletions, UPD, and epimutations are associated with a low recurrence risk. However, IC mutations and some translocations may be associated with a 50% recurrence risk.

Angelman syndrome

1. Clinical background of the disease

Angelman syndrome (AS) is characterized by developmental delay, intellectual disability, absent speech, seizures, ataxic gait, easily excitable happy demeanor, and characteristic facies (Table 2). This disorder has been referred to as “happy puppet syndrome” due to the ataxic gait and disposition of children with AS.

Developmental delay/intellectual disability—Most infants with AS do not show any signs of the disorder at birth. However, delayed attainment of gross and fine motor skills, language, and social skills are usually evident within the first year of life⁴¹. Motor skill delays can be severe, and many individuals with AS are not able to walk. Tremors can further complicate fine motor skill development. Toilet training is typically severely delayed, but is achieved in many with adults with AS. Functionally, individuals with AS only reach a developmental level of approximately 24 to 30 months⁴². Cognitive ability is severely impaired, however, cognition is difficult to ascertain due to the profound lack of speech, hyperactivity, and inability to pay attention in individuals with AS. Adults with AS

are not capable of independent living, although many can perform tasks with supervision, can dress themselves, and can use feeding utensils^{43,44}.

Speech—Language development in individuals with AS is severely impaired. Most individuals with AS are entirely non-verbal, some will speak a few words, and a rare few have some phrase speech. Augmentative communication devices and sign language can be successfully used to communicate with individuals with AS. Their receptive communication exceeds expressive communication⁴⁵.

Epilepsy—Epilepsy occurs in 80 to 95% of those with Angelman Syndrome, typically with onset before 3 years of age^{44,46}. Angelman Syndrome is typically associated with generalized epilepsy, though focal seizures occur in up to one third, often in combination with other seizure types^{44,46,47}. Myoclonic, atypical absence, generalized tonic clonic and atonic seizures are most common, and status epilepticus, frequently myoclonic or non-convulsive, has been reported to occur in up to 90%⁴⁸. Epilepsy tends to be more severe in early childhood, often easing as children reach puberty, though epilepsy risk appears to persist in to adulthood⁴⁴. Epilepsy tends to be more severe in those with a maternal deletion, as does disease severity in general^{47,49}. EEG often shows a characteristic pattern, most classically with posterior predominant spike and sharp waves mixed with high amplitude sharply contoured 3 to 4 Hz activity.

Movement disorder—Ataxic gait and/or tremulous movement of the limbs is a consistent finding in AS⁵⁰. Individuals with AS have a slow, stiff legged gait. Typical posture includes raised arms, flexed at the elbows and wrists. Hand flapping is common when walking or excited. Movements are generally jerky and abrupt. The specific brain region responsible for the movement disorder is not known.

Happy demeanor—Individuals with AS have a characteristic happy demeanor and are easily excitable. They have frequent, sometimes inappropriate laughter. Hyperactivity and hypermotoric activity often accompany the happy disposition. Individuals with AS are typically highly social, with social interest beginning in infancy. Most children with AS are eager to communicate, despite difficulty in doing so⁴¹. Social disinhibition is common and there is little fear of strangers.

Other features—Other behavioral features associated with AS include stereotypic movements (such as hand flapping), difficulty sleeping, and anxiety. Individuals with AS are frequently fascinated with water. Facial features associated with AS include lightly pigmented skin, hair, and eyes; strabismus; tongue protrusion; prognathia; and widely spaced teeth.

2. Recent advances in genetics and pathomechanism of diseases

AS is caused by the lack of function of maternal *UBE3A*^{51,52}. This arises due to one of four mechanisms: 1.) deletion of maternal 15q11.2-q13 is found in approximately 74% of individuals with AS, 2.) loss of function mutation of maternal *UBE3A* is found in approximately 11% of individuals with AS, 3.) paternal uniparental disomy (UPD) is found

in approximately 8% of individuals with AS, and 4.) imprinting defect is found in approximately 7% of individuals with AS⁵³. In contrast to PWS, the presence of individuals with AS due to point mutations in the maternal copy of the *UBE3A* gene demonstrate that AS is a single gene disorder, although other genes in the deletion region can contribute to the severity of AS.

The mechanism by which loss of *UBE3A* causes AS is still not completely understood. The *UBE3A* protein, also known as E6AP, is an E3 ubiquitin ligase, which transfers an activated ubiquitin from an E2 ubiquitin ligase to its target protein⁵⁴. *UBE3A/E6AP* typically adds lysine 48 (K48)-linked polyubiquitin chains to its substrates, thus targeting them for degradation by the proteasome⁵⁵. Some substrates of *UBE3A/E6AP*, such as *HHR23A*⁵⁶, *RPN10*⁵⁷, and *EPHEXIN5*⁵⁸ have been identified. *HHR23A* (also known as *RAD23A*) stimulates nucleotide excision repair, *RPN10* is a subunit of the proteasome and *EPHEXIN5* is a rho-GEF involved in regulating dendritic spine density.

Mouse models of AS have suggested some underlying neuronal pathologies associated with the disorder. Deficits in long-term potentiation^{59,60}, inhibitory CAMKII phosphorylation⁶⁰, presynaptic release probability in inhibitory neurons⁶¹, and golgi acidification and protein surface sialylation⁶² have been reported. Full connections between *UBE3A/E6AP* substrates and the neuronal pathologies have not yet been made.

3. Diagnosis

Methylation analysis—Methylation analysis using southern blot or methylation-specific PCR of the promoter region of the *SNRPN* gene/imprinting center will identify roughly 75 to 80 % of cases of AS (Figure 3). Absence of a maternal methylation pattern is indicative of AS, but typically will not distinguish between deletion, UPD or imprinting defect as the cause. If methylation testing is consistent with AS, testing should proceed as follows:

1. *Deletion testing*. The majority of AS cases (65%) are caused by de novo microdeletion of the 15q11.2-13.1 region, which can be identified by FISH or microarray, and are associated with very low recurrence risk.
2. *UPD testing*. If a deletion is not found, UPD testing will identify the presence of two paternal copies of chromosome 15 in 8% of cases, though parental samples are required. Paternal UPD is also generally associated with a low recurrence risk.
3. *Imprinting center sequencing*. If methylation testing is positive, but microdeletion and UPD testing are negative, an imprinting center defect is suspected. Imprinting defects account for roughly 3 % of AS cases. Molecular testing to look for deletion in the imprinting center will be successful in roughly 10 to 20 % of these cases and carry up to a 50% recurrence risk. If an imprinting center deletion is not found, an epimutation is presumed and recurrence risk again appears low.

***UBE3A* sequencing**—For those patients with clinically suspected AS, but a negative methylation test, *UBE3A* sequencing should be sought. Mutations in *UBE3A* are the second most common molecular cause of AS, found in 12% of cases, and can carry a 50% recurrence risk.

If methylation testing and *UBE3A* sequencing are negative, AS is unlikely to be the diagnosis, and diagnosis of “Angelman-like” syndromes should be considered including Pitt Hopkins syndrome, *CDKL5* mutation, and Kleefstra syndrome, among others.

4. Management of Angelman Syndrome

Epilepsy—Seizures are often difficult to control. Patients may require polypharmacy and status epilepticus is not uncommon^{47,63}. Seizures typically respond best to medications traditionally effective for generalized epilepsy including valproic acid, levetiracetam, lamotrigine, clonazepam and clobazam. Seizures also may respond well to the ketogenic diet. Medications most likely to exacerbate seizures include vigabatrin, tiagabine, oxcarbazepine and carbamazepine⁶⁴.

Sleep Disturbance—Children with AS frequently have disrupted sleep with difficulty both in falling asleep and maintaining sleep and possibly a reduced requirement for sleep^{65,66}. Sleep disturbance can be a tremendous strain on caregivers and families. Treatment with melatonin one hour before bedtime has been shown to decrease sleep latency and nighttime awakening⁶⁷. Doses as low as 0.3 mg can be effective, with typical doses ranging from 0.3 mg to 5 mg nightly⁶⁸. Additional medical management may be needed as well as providing a safe and restricted environment for children when they do wake at night.

Diet and Nutrition—In infancy and early childhood feeding issues may require special nipples and gastroesophageal reflux can lead to poor weight gain and vomiting, typically managed with positioning and/or medication.

Muscle tone and gait—Hypotonia is frequent in young children though spasticity of limbs often develops over time. Gait is typically ataxic⁵⁰. Children should receive physical and occupational therapy services. Orthotics and other adaptive devices are often helpful and orthopedic consultation may be warranted for issues including scoliosis.

Speech—Early intervention with speech therapy is important to maximize communication, with emphasis on non-verbal methods of communication such as picture boards and devices recommended.

Other—Children with AS should have regular ophthalmologic assessment for management of strabismus, and hyperopia⁶⁹.

Future potential therapies—Strategies to augment DNA methylation through administration of supplements such as betaine, folate, or other supplements are being investigated with the goal of increasing expression of the dormant allele, though the results of trials have been disappointing. Recent studies are focusing on methods of unsilencing the paternal *UBE3A* allele. Studies by Huang et al and others, using topoisomerase inhibitors or other approaches to “unsilence” the paternal *UBE3A* allele are ongoing in animal models⁷⁰. A recent report of restoration of paternal *Ube3a* expression in the AS mouse model by genetically terminating transcription of the antisense RNA also provides hope for improving disease treatment in the future⁷¹.

Recommendation for family counseling—Family counseling is recommended. Most deletions, UPD, and epimutations are associated with a low recurrence risk. However, IC mutations, *UBE3A* mutations, and some translocations may be associated with a 50% recurrence risk.

Dup15q syndrome

1. Clinical background of the disease

Individuals with 15q11.2-q13 duplication (Dup15q) syndrome have features of both PWS and AS, as well as some features unique to the disorder. Dup15q syndrome is characterized by central hypotonia, developmental delay, intellectual disability, seizures, and autism (Table 3). There is remarkable diversity in the severity of these symptoms, even in individuals with exactly the same genotype. Duplications involving 15q11.2 or 15q13.3 alone are distinct from 15q11.2-q13 duplications and are not discussed here.

Hypotonia—Muscle hypotonia is observed in almost all individuals with Dup15q syndrome, and can be severe, prompting testing for PWS⁷². Feeding difficulties are common. Joint hyperextensibility and drooling accompanies the hypotonia in most individuals. Major motor milestones such as rolling over, sitting and walking are delayed. Weak cry is often reported. While hypotonia can persist in some adults, it also can subside or progress to hypertonia in the limbs⁷².

Developmental delay/intellectual disability—Gross and fine motor skill delays are common in individuals with Dup15q syndrome. Hypotonia contributes to these delays. Sitting is reportedly achieved between 10 and 20 months, with walking typical between 2 and 3 years. Although some children with Dup15q syndrome do not walk, the vast majority do walk independently. Fine motor delays include non-functional use of objects and immature exploration of objects. Cognitive and social/emotional delays are apparent in all children with Dup15q. Comprehension is very limited. Cognitive impairment/intellectual disability is frequently in the severe to profound range.

Epilepsy—Seizures are a major medical issue for Dup15q syndrome. Seizures affect approximately 60% of children with Dup15q syndrome, with the typical onset occurring before age 5⁷³. Seizures often first present as infantile spasms and later progress to a Lennox-Gastaut type syndrome. Seizures are more common in children with isodicentric chromosome 15 (idic(15)) than in those with interstitial duplications. Most affected children reportedly have multiple seizure types, including infantile spasms, tonic, atonic, tonic-clonic, myoclonic, complex partial, and atypical absence⁷³. Seizures can be intractable. There is an increased risk of sudden unexpected death in epilepsy (SUDEP) in individuals with Dup15q syndrome. Many individuals without overt seizures, have abnormal electroencephalogram (EEG) activity⁷⁴.

Autism—A majority of individuals with Dup15q syndrome meet the diagnostic criteria for autism⁷⁴. Speech and language delays occur in most individuals. While some individuals are completely non-verbal, a few are highly verbal. Expressive language is typically severely impacted, and may even be absent. Language is often echolalic with pronoun reversal⁷².

Intent to communicate is also absent or very poor in many individuals. Inappropriate social interactions are typical in individuals with Dup15q. Gaze and bodily contact avoidance is common. Symbolic play is almost never acquired, and individuals with Dup15q syndrome usually do not show interest in their peers. Difficult behaviors such as tantrums, shouting, and aggressiveness often occur, as do stereotypies. Hand flapping, clapping, or wringing are frequently seen, as well as finger biting, head turning, and repeated spinning. Despite a frequent diagnosis of Autism, many individuals with Dup15q syndrome score well on the Autism Diagnostic Observation Scale-general (ADOS-G) test.

Other—Subtle facial features that are characteristic for Dup15q syndrome can be seen in most affected individuals. These include a small button nose, down-slanting palpebral fissures, and low-set and/or posteriorly rotated ears. Increased pigmentation can be observed. Growth retardation occurs in approximately 20–30% of individuals⁷². Hypogonadism occurs in approximately 20% of affected individuals, although precocious puberty sometimes occurs⁷².

2. Recent advances in genetics and pathomechanism of diseases

Dup15q syndrome usually occurs in one of two forms. Isodicentric chromosome 15q (idic(15)) and maternal interstitial duplication⁷⁴. Idic(15) is the most common presentation. In addition to the two normal chromosomes 15, individuals with idic(15) have a small supernumerary chromosome harboring two extra copies of the maternal 15q11.2-q13 region in a tail-to-tail orientation. As the name implies, the idic(15) chromosome also contains two centromeres, but is apparently stable despite this, possibly owing to the inactivation of one of the centromeres. Individuals with idic(15) are tetrasomic for the 15q11.2-q13 region, having three maternal copies and one paternal copy of the locus. Maternal interstitial duplications consist of one extra copy of the maternal 15q11.2-q13 region inserted inverted and in tandem with another copy of the region. Thus, these individuals are triploid for the 15q11.2-13 region; two maternal copies and one paternal copy of the locus are present. Individuals with paternal interstitial duplications do exist in the population, but appear to have a distinct, milder phenotype compared to individuals with maternal interstitial duplications.

Due to the dependence of the phenotypes of individuals on the parent-of-origin of the duplicated allele(s), it is assumed that UBE3A, the gene whose loss of function causes AS, contributes significantly to the Dup15q syndrome. A mouse model carrying two extra copies of murine Ube3a has autistic features and supports this hypothesis⁷⁵, although mice with only a single extra copy of maternal Ube3a do not have an autistic phenotype^{75,76}. Other, biallelically expressed genes could also play important roles. A cluster of GABA receptor subunit genes (*GABRB3*, *GABRA5*, and *GABRG3*), and a gene encoding another ubiquitin ligase, *HERC2*, are duplicated in individuals with both maternal interstitial duplication and idic(15). These genes may also contribute to the disorder.

3. Diagnosis

Duplications in the 15q11q13 region, which is prone to genomic rearrangement due to the presence of repeated DNA elements, are most often detected through array CGH⁷⁷, which

has become a standard screening tool when evaluating children with hypotonia, autism or developmental delay. Prior to the widespread use of this technology, standard high resolution karyotype along with FISH analysis identified cases of inverted duplication 15 (idic 15) syndrome, visible as a marker chromosome⁷². Cases of idic (15) may still be identified in this manner, though interstitial duplications, would typically not be detectable by chromosomal analysis. Array CGH also allows for the precise delineation of break points and size of the duplicated material.

Identification of an interstitial duplication or idic (15) should be followed by a test to clarify parent of origin, which impacts phenotype⁷⁴. This could be done either by methylation analysis of the proband sample, or targeted array of parental samples.

4. Treatment/Management

Several studies have confirmed that phenotype is more severe for those children with idic (15) than interstitial duplications^{78,79}. In addition, maternally inherited interstitial duplications appear to be more consistently expressed than paternally inherited ones, and are associated with significantly higher risk of autism spectrum disorder⁷⁴. The impact of paternally inherited duplications remains unclear, though some pathogenicity is clear.

Muscle tone/growth and nutrition—Hypotonia, particularly impacting oro-facial musculature can lead to feeding difficulties in infancy, more often in idic (15) children, and may require special attention to feeding and growth. Delay in acquisition of motor milestones is also most pronounced in those with idic (15) than interstitial duplications, and early intervention with physical therapy may be beneficial.

Autism—Given the high risk of autism with idic (15) and maternally inherited duplication, evaluation by a Developmental Pediatrician is recommended. This should be considered for paternally inherited duplications as well, particularly if concerns about behavior and social relatedness exist. Children with Dup15q syndrome will also benefit from early intervention with speech and educational therapies.

Epilepsy—Seizures are significantly more common and severe in children with idic (15), affecting roughly two thirds, as opposed to 25 % of those with interstitial duplications⁷³. Risk for infantile spasms is high in idic (15) and parents should be advised to watch for early signs of this seizure type, as early treatment is beneficial. Screening EEG may be warranted. Treatment with ACTH/steroids for infantile spasms appears to be more effective in this group than vigabatrin (75 % versus 29 %)⁷³, thus should be considered as initial therapy. Seizures often evolve into Lennox Gastaut and appear to respond to medications typically beneficial for those with generalized epilepsy including valproic acid, rufinamide, lamotrigine and zonisamide, though formal studies remain limited. Carbamazepine was also reported to be effective in many, suggesting epilepsy may be multifocal as opposed to primary generalized. Children with idic(15) do not respond well to benzodiazepines and seizure exacerbation was also reported in almost half of those treated with Leviteracetam⁷³. There is little information available regarding the efficacy of the ketogenic diet or vagal nerve stimulator in this population. Unfortunately, epilepsy risk appears persistent in idic

(15) with seizures continuing into adulthood in two thirds⁷³. Refractory epilepsy does appear to be associated with risk of early death secondary to status epilepticus or SUDEP (sudden unexplained death in epilepsy), reported in 8 % of idic (15) patients with seizures⁷³.

Behavior and sleep—Behavioral difficulties with defiant and aggressive behaviors, particularly in idic (15) patients, can be challenging and may require medical management⁸⁰. In addition, sleep difficulties may be noted, possibly secondary to epileptic discharges, thus overnight EEG and sleep study may be helpful in directing management.

Future potential therapies—Current work toward future therapies may focus on reducing *UBE3A* expression levels or activity in Dup15q patients⁸¹, although no specific therapies have been reported.

Recommendation for family counseling—Family counseling is recommended. Idic (15) is associated with a low recurrence risk. However, interstitial duplication may be associated with a 50% recurrence risk.

Conclusion

The chromosome 15q11-13 region contains several genes that are regulated by genomic imprinting and impact neurodevelopment. Despite being caused by variation of the same genetic region, Prader-Willi, Angelman, and Dup15q syndromes are distinct disorders with different phenotypic manifestations and diagnostic strategies. Since imprinted genes are involved in these disorders, potential therapies may involve modulating expression of the implicated genes and provide optimism for improved outcomes in the future.

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Key Points

1. Three distinct neurodevelopmental disorders are caused by copy number variation at human chromosome 15q11-q13: Prader-Willi syndrome, Angelman syndrome, and 15q11-q13 duplication syndrome.
2. Prader-Willi and Angelman syndromes can also be caused by uniparental disomy, microdeletions and/or single gene mutations, and imprinting defects. An organized diagnostic strategy is required in order to confirm or full exclude the diagnosis.
3. Prader-Willi syndrome is characterized by infantile hypotonia and failure to thrive followed by obesity, hyperphagia, small stature, and behavioral issues. Early growth hormone treatment improves body habitus and stature.
4. Angelman syndrome is characterized by severe intellectual disability, absent speech, epilepsy, and characteristic happy affect. It is caused by the loss of function from the maternal UBE3A gene.
5. 15q11-q13 duplication syndrome is characterized by developmental delay, epilepsy, and autism. Duplications that lead to this syndrome are almost always of maternal origin.

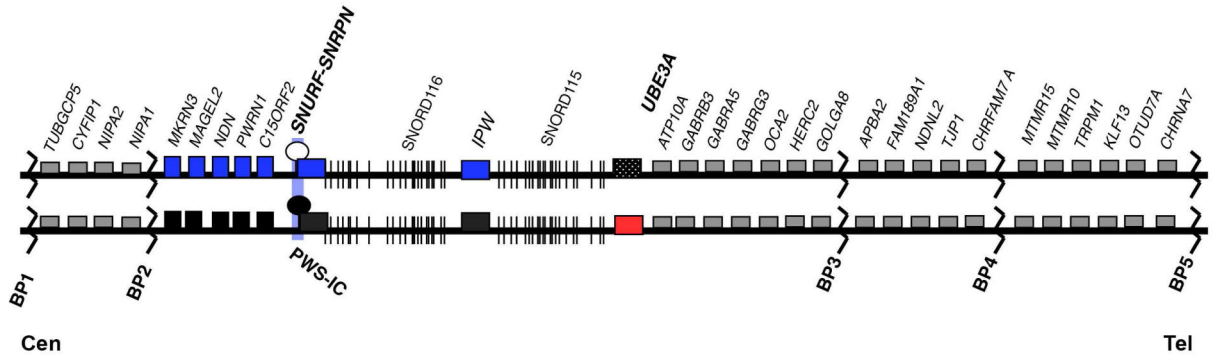


Figure 1. Map of 15q11-q13 region

Individual genes are depicted as boxes with their respective names above them. Genes shown in blue and red are imprinted and expressed from the paternal and maternal alleles, respectively. Black boxes mark the silenced allele. Gray boxes indicate genes expressed from both parental alleles. BP1-4 indicate the common breakpoints 1–4. PWS-IC indicates the Prader-Willi imprinting center. Cen and Tel mark the centromere and telomere, respectively to indicate orientation relative to the rest of the chromosome.

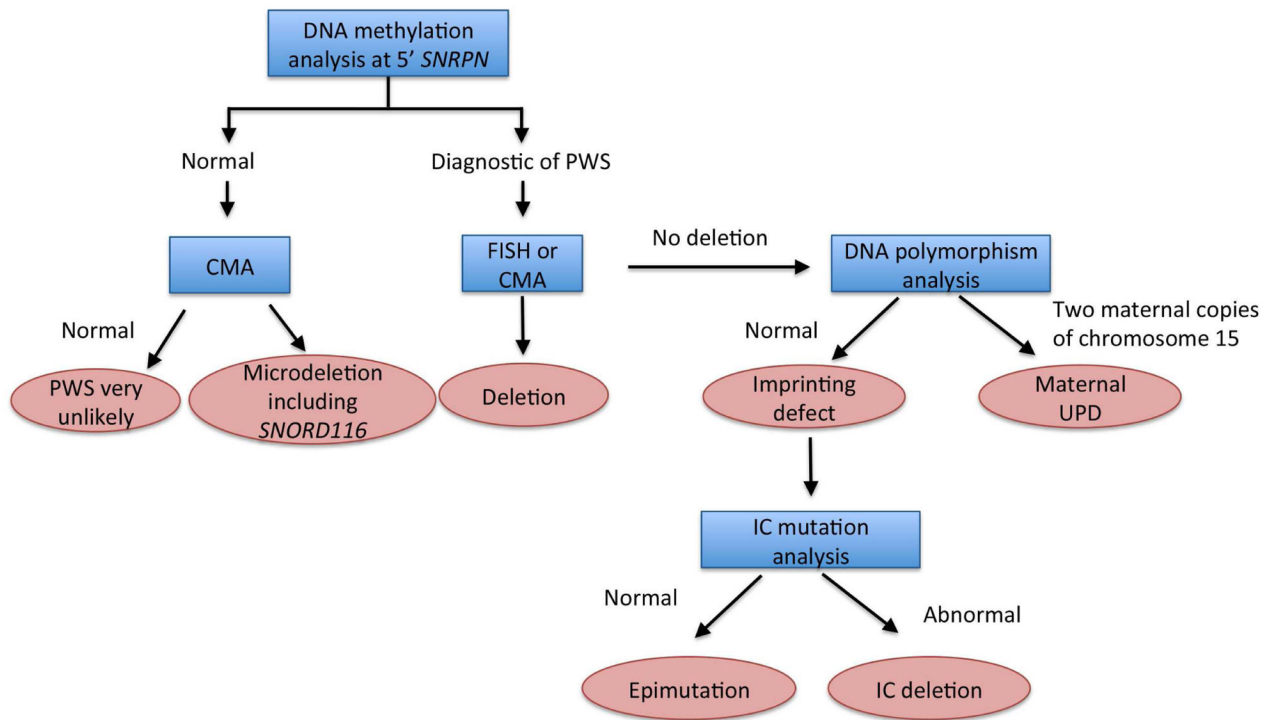


Figure 2. Diagnostic strategy for Prader-Willi syndrome
 Blue boxes indicate the diagnostic test, pink boxes indicate the diagnostic decision.

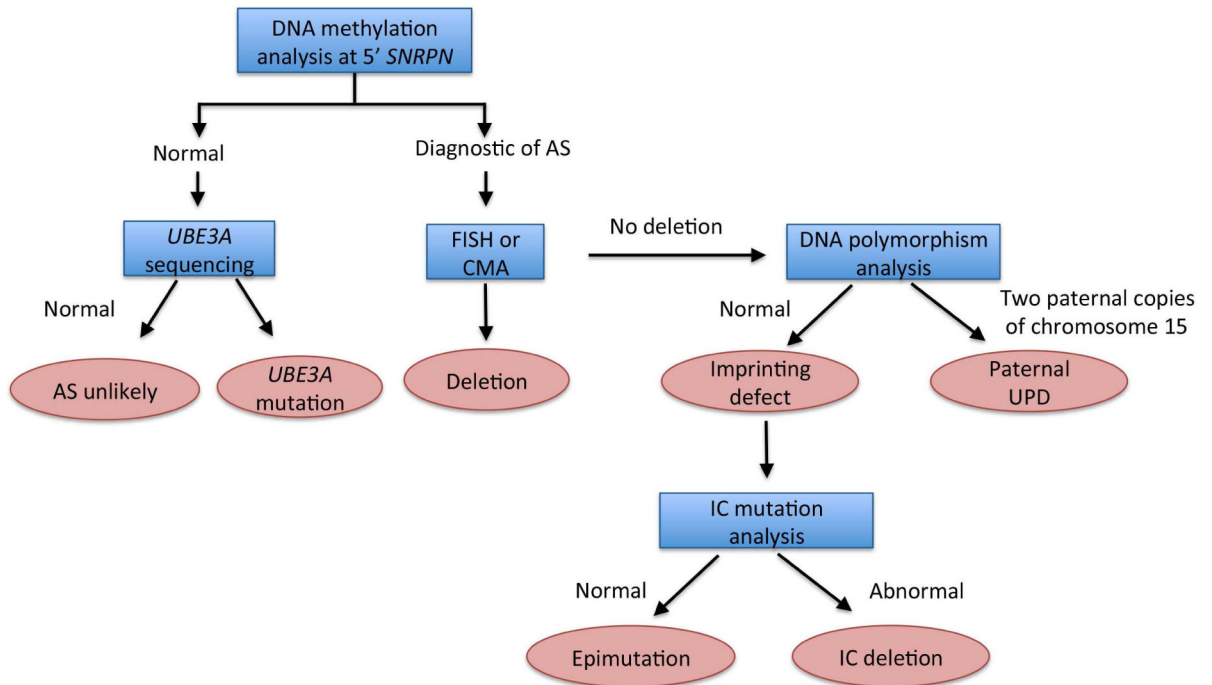


Figure 3. Diagnostic strategy for Angelman syndrome
 Blue boxes indicate the diagnostic test, pink boxes indicate the diagnostic decision.

Table 1

Features of Prader-Willi syndrome

Consistent (100%)	Frequent (80%)	Associated (20–80%)
Hypotonia	Hypopigmentation	Speech articulation defects
Failure to thrive	Behavioral problems	Autism
Feeding difficulty	Developmental delay	
Hypogonadism	Short stature, if untreated with growth hormone	
Obesity, in absence of intervention	Distinctive facial features	
Hyperphagia	Sleep disturbances	
	Small hands/feet	

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Table 2

Features of Angelman syndrome

Consistent (100%)	Frequent (80%)	Associated (20–80%)
Developmental delay	Seizures	Hypotonia
Ataxia and/or tremors	Microcephaly	Strabismus
Absent speech		Frequent drooling, mouthing behaviors
Happy demeanor: including hand flapping, frequent laughter/ smiling		Protruding tongue, tongue thrusting
		Wide mouth, wide spaced teeth Sleep disturbances
		Sleep disturbances
		Fascination with water
		Anxiety

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Table 3

Features of Dup15q syndrome

Consistent (100%)	Frequent (80%)	Associated (20–80%)
	Hypotonia	Characteristic facial features
	Speech/language disorder	Reduced growth
	Developmental delay	Autism
	Behavior challenges	Sensory processing disorders
	Abnormal EEG	Seizures
		Hyperpigmentation
		Autism

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