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Angelman Syndrome

Aditi I Dagli, MD,[1] Jennifer Mathews, MS, CGC,[2] and Charles A Williams, MD[3]

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Summary

Clinical characteristics

Angelman syndrome (AS) is characterized by severe developmental delay or intellectual disability, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and unique behavior with an apparent happy demeanor that includes frequent laughing, smiling, and excitability. Microcephaly and seizures are also common. Developmental delays are first noted at around age six months; however, the unique clinical features of AS do not become manifest until after age one year.

Diagnosis/testing

The diagnosis of AS is established in a proband who meets the consensus clinical diagnostic criteria and/or who has findings on molecular genetic testing that suggest deficient expression or function of the maternally inherited *UBE3A* allele. Analysis of parent-specific DNA methylation imprints in the 15q11.2-q13 chromosome region detects approximately 80% of individuals with AS, including those with a deletion, uniparental disomy, or an imprinting defect; fewer than 1% of individuals have a cytogenetically visible chromosome rearrangement (e.g., translocation or inversion). *UBE3A* sequence analysis detects pathogenic variants in an additional approximately 11% of individuals. Therefore, molecular genetic testing (methylation analysis and *UBE3A* sequence analysis) identifies alterations in approximately 90% of individuals. The remaining 10% of individuals with classic phenotypic features of AS have the disorder as a result of an as-yet unidentified genetic mechanism.

Management

Treatment of manifestations: Anti-seizure medication for seizures. Accommodation for hypermotoric behaviors and disruptive nighttime wakefulness. Behavior modification can be effective for disruptive or self-injurious behaviors. Physical therapy, occupational therapy, and speech therapy with an emphasis on nonverbal methods of communication, including augmentative communication aids (e.g., picture cards, communication boards) and signing. Individualization and flexibility in school settings. Routine management of gastroesophageal reflux,

Author Affiliations: 1 Medical Genetics Orlando Health Arnold Palmer Hospital Orlando, Florida; Email: aditidagli@gmail.com. 2 Division of Genetics and Metabolism University of North Carolina at Chapel Hill Chapel Hill, North Carolina; Email: muelljm@email.unc.edu. 3 Division of Genetics and Metabolism Department of Pediatrics University of Florida College of Medicine Gainesville, Florida; Email: willicx@peds.ufl.edu.

feeding difficulties, constipation, and strabismus. Thoraco-lumbar jackets and/or surgical intervention for scoliosis. Bracing or surgery as needed for subluxed or pronated ankles or tight Achilles tendons.

Surveillance: Monitor for new seizures and/or changes in seizures, developmental progress, behavior issues, mobility, motor skills, gastroesophageal reflux, constipation, and feeding issues at each visit. Evaluation of older children for obesity associated with an excessive appetite. Annual clinical examination for scoliosis; ophthalmology examination in the first year if strabismus is present; ophthalmology exam at age two years with follow up per ophthalmologist; clinical examination for scoliosis annually.

Agents/circumstances to avoid: Overtreatment with sedating medications in order to reduce hyperexcitable and hypermotoric behavior. Overtreatment with anti-seizure medication when movement abnormalities are mistaken for seizures and/or when EEG abnormalities persist even as seizures are controlled.

Genetic counseling

Individuals with AS typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration associated with a very low recurrence risk. Less commonly, an individual with AS has the disorder as the result of a genetic alteration associated with an imprinting pattern of autosomal dominant inheritance or variable recurrence risk. Reliable recurrence risk assessment therefore requires identification of the underlying genetic mechanism in the proband and confirmation of the genetic status of the parents. Prenatal detection of all the known molecular genetic alterations in the 15q11.2-q13 region that give rise to AS is possible and is an option for families once the underlying genetic mechanism in the proband has been identified.

Diagnosis

Consensus criteria for the clinical diagnosis of Angelman syndrome (AS) have been developed in conjunction with the Scientific Advisory Committee of the US Angelman Syndrome Foundation [Williams et al 2006]. Several reviews are available [Bird 2014, Buiting et al 2016, Prasad et al 2018].

Suggestive Findings

AS **should be suspected** in individuals with the following clinical, laboratory, and radiographic findings.

Clinical

- Normal prenatal and birth history, normal head circumference at birth, no major birth defects
- Delayed attainment of developmental milestones by age six to 12 months, eventually classified as severe, without loss of skills
- Speech impairment, with minimal to no use of words; receptive language skills and nonverbal communication skills higher than expressive language skills
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of the limbs
- Behavioral uniqueness including any combination of frequent laughter/smiling, apparent happy demeanor, excitability (often with hand-flapping movements), and hypermotoric behavior

Clinical criteria that help establish the diagnosis [Williams et al 2006]

Findings in more than 80% of affected individuals

- Delayed or disproportionately slow growth in head circumference, usually resulting in absolute or relative microcephaly by age two years
- Seizures, usually starting before age three years
- Abnormal EEG, with a characteristic pattern of large-amplitude slow-spike waves

Findings in fewer than 80% of affected individuals

- Craniofacial features including flat occiput, occipital groove, wide mouth, widely spaced teeth, protruding tongue, prognathia (See Figure 1.)
- Feeding problems and/or hypotonia during infancy, tongue thrusting, suck/swallowing disorders, frequent drooling, excessive chewing/mouthing behaviors
- Strabismus
- Hypopigmented skin, light hair and eye color compared to family members; seen only in those with a 15q11.2-q13 deletion
- Hyperactive lower-extremity deep-tendon reflexes
- Uplifted, flexed arm position especially during ambulation
- Wide-based gait with pronated or valgus-positioned ankles
- Increased sensitivity to heat
- Abnormal sleep-wake cycles and diminished need for sleep
- Attraction to and fascination with water; fascination with crinkly items such as certain papers and plastics
- Abnormal food-related behaviors
- Obesity (in the older child; more common in those who do not have a 15q11.2-q13 deletion)
- Scoliosis
- Constipation

Laboratory

Deletion of the 15q11.2-q13 genomic region (detected by chromosomal microarray or other methods) is suggestive of AS but not, in and of itself, diagnostic.

Metabolic, hematologic, and chemical laboratory profiles are normal.

Radiographic

Brain imaging shows structurally normal brain by MRI or CT, although mild cortical atrophy or dysmyelination may be observed.

Establishing the Diagnosis

The clinical diagnosis of AS can be **established** in a proband based on clinical diagnostic criteria (see Suggestive Findings, Clinical criteria that help establish the diagnosis) [Williams et al 2006] or the molecular diagnosis can be established in a proband with suggestive findings and findings on molecular genetic testing that suggest deficient expression or function of the maternally inherited *UBE3A* allele (see Table 1).

Molecular diagnosis. The diagnosis of AS **is established** in a proband with suggestive findings who has **one of the following** on molecular genetic testing (see Table 1):

- Abnormal methylation at 15q11.2-q13 due to one of the following:
  - Deletion of the maternally inherited 15q11.2-q13 region (which includes *UBE3A*)
  - Uniparental disomy (UPD) of the paternal chromosome region 15q11.2-q13
  - An imprinting defect of the maternal chromosome 15q11.2-q13 region
- A pathogenic variant in the maternally derived *UBE3A*

Molecular genetic testing approaches to establish the diagnosis can be based on either the clinical findings or the laboratory findings that suggested the diagnosis of AS.

Based on clinical findings in a symptomatic individual who has not had any prior molecular genetic testing:

Figure 1. Individuals depicted have a genetically confirmed diagnosis of Angelman syndrome. Happy expression and an unstable gait accompanied by uplifted arms are commonly observed. At times, the facial appearance can suggest the diagnosis, but usually facial features are not distinctive.

- **DNA methylation analysis** is typically the first test ordered. Individuals with AS caused by a 5- to 7-Mb deletion of 15q11.2-q13, UPD, or an imprinting defect have only an unmethylated (i.e., "paternal") contribution (i.e., an abnormal parent-specific DNA methylation imprint). DNA methylation analysis identifies approximately 80% of individuals with AS.

  Note: Most commercially available DNA methylation analysis tests cannot distinguish between AS resulting from a 15q11.2-q13 deletion, UPD, or an imprinting defect. Further testing is required to identify the underlying molecular mechanism (see Genetic Counseling).

If DNA methylation analysis is normal:

- **Single-gene testing.** Sequence analysis of *UBE3A* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **A multigene panel** that includes *UBE3A* (e.g., most epilepsy, autism, and intellectual deficiency multigene panels) and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **More comprehensive genomic testing** (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if DNA methylation and *UBE3A* analysis (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of AS.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Based on laboratory findings in an individual who has been found to have a 15q11.2-q13 deletion on chromosomal microarray (CMA), fluorescent in situ hybridization (FISH), or karyotype,* perform **DNA methylation analysis** to determine if the deletion is on the maternally derived chromosome 15.

* Fewer than 1% of individuals with AS have a cytogenetically visible chromosome 15 rearrangement (i.e., translocation or inversion) involving 15q11.2-q13.

Table 1. Molecular Genetic Testing Used in Angelman Syndrome

Method	Genetic Mechanism Detected [1]					Total Proportion of Probands Detectable by Method [2]
	15q11.2-q13del	UPD	Imprinting defect	*UBE3A* sequence variant	*UBE3A* deletion/ duplication	
DNA methylation analysis [3, 4]	X	X	X [5]			~80%
MS-MLPA [6]	X	X	X			~80%
FISH [7]	X					~68%
CMA [8]	X	X [9]				~70%-75%
UPD analysis [10]		X				~3%-7%
AS imprinting center deletion analysis [11, 12]			X			<0.3%
UBE3A sequence analysis [13]				X		~11%

Table 1. continued from previous page.

Method	Genetic Mechanism Detected [1]					Total Proportion of Probands Detectable by Method [2]
	15q11.2-q13del	UPD	Imprinting defect	*UBE3A* sequence variant	*UBE3A* deletion/ duplication	
UBE3A gene-targeted del/dup analysis [11, 14]					X	Rare

CMA = chromosomal microarray analysis; del/dup = deletion/duplication; IC = imprinting center; MS-MLPA = methylation-specific multiplex ligation-dependent probe amplification; UPD = uniparental disomy

1. See Molecular Genetics for more details.

2. About 10% of individuals with the presumptive clinical diagnosis of AS have normal results for all testing methods described in this table [Williams et al 2010].

3. Individuals with AS caused by a 5- to 7-Mb deletion of 15q11.2-q13, uniparental disomy (UPD), or an imprinting defect have only an unmethylated (i.e., "paternal") contribution (i.e., an abnormal parent-specific DNA methylation imprint).

4. DNA methylation analysis will not distinguish the genetic mechanism.

5. More than 90% of imprinting defects are thought to be epigenetic pathogenic variants occurring during maternal oogenesis or in early embryogenesis [Buiting et al 2016, Beygo et al 2019]. Characterization of the imprinting defect as either an imprinting center deletion or epigenetic defect is available primarily through research laboratories.

6. Beygo et al [2019]

7. FISH analysis with the *D15S10* and/or the *SNRPN* probe can identify the common 15q11.2-q13 deletion, but typically this deletion is not detected by routine cytogenetic analysis.

8. CMA has a slightly higher sensitivity for 15q11.2-q13 deletions than FISH and will provide detailed information regarding size of the deletion. CMA also can identify deletions and duplications in other regions of the genome.

9. SNP-based chromosomal microarray can identify UPD, but not UPD due to heterodisomy.

10. UPD is detected using polymorphic DNA markers, which requires a DNA sample from the affected individual and both parents.

11. Gene-targeted deletion/duplication analysis detects deletions or duplications in intragenic or other targeted regions. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, MLPA, and a gene-targeted microarray designed to detect single-exon deletions or duplications.

12. Although 3% of all individuals with AS have imprinting center defects, <10% will have detectable small deletions in the imprinting center.

13. Sequence analysis detects variants that are benign, likely benign, of uncertain significance (VUS), likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Since *UBE3A* is imprinted, demonstration of paternal inheritance of a VUS will downgrade classification to benign. For issues to consider in interpretation of sequence analysis results, click here.

14. CMA usually detects large 15q11.2-q13 deletions, but in rare instances has detected *UBE3A* multiexon or whole-gene deletions.

Possible explanations for the failure to detect AS-causing genetic abnormalities in approximately 10% of individuals with clinically diagnosed AS:

- Incorrect clinical diagnosis
- Undetected pathogenic variants in the regulatory region(s) of *UBE3A*
- Other unidentified mechanisms or gene(s) involved in *UBE3A* function

Clinical Characteristics

Clinical Description

Angelman syndrome (AS) is characterized by severe developmental delay and intellectual disability, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and a unique behavior with an apparent happy demeanor that includes frequent laughing, smiling, and excitability. Microcephaly and seizures are also common. Developmental delays are first noted at around age six months; however, the unique clinical features of AS do not become manifest until after age one year.

Table 2. Angelman Syndrome: Frequency of Select Features

Feature	% of Persons with Feature	Comment
Seizures	90%	Many seizure types; nonconvulsive status epilepticus in 20%
Nonepileptic myoclonus	20%	More common in adults
Sleep problems	80%-90%	Frequent awakening, dyssomnias, irregular sleep-wake cycles
Behavioral features	100%	Hypermotoric activity, oral exploration, frequent smiling & laughter, aggression, anxiety, autism spectrum traits
Motor delay / tremor	100%	
Language delay / Cognitive impairment	100%	Persons mosaic for imprinting center defects demonstrate better language development.
Feeding/GI issues	85%	
Microcephaly [1]	25%-80%	Apparent by age 2 yrs; most common in those w/15q11.2-q13 deletion
Characteristic facial features	<80%	Flat occiput, occipital groove, wide mouth, widely spaced teeth, protruding tongue, & prognathia; ± light hair, skin, & eyes
Strabismus	40%-50%	
Scoliosis	≤50%	Children: 10%-30%; adults: 30%-50%

GI = gastrointestinal

1. Normal occipital frontal circumference should not exclude AS diagnosis.

Seizure onset typically occurs between ages one and three years but can occur at any age; most appear by age five years. Epilepsy occurs in up to 90% of individuals and is more commonly observed in those with 15q11.2-q13 deletions [Khan et al 2019, Bindels-de Heus et al 2020]. The seizures are usually associated with generalized, somewhat specific EEG changes: runs of high-amplitude delta activity with intermittent spike and slow-wave discharges (at times observed as a notched delta pattern); runs of rhythmic theta activity over a wide area; and runs of rhythmic sharp theta activity of 5-6/s over the posterior third of the head, forming complexes with small spikes. These are usually facilitated by or seen only with eye closure [Boyd et al 1988, Samanta 2021].

Seizure types can be quite varied; the most common are myoclonic, atonic, generalized tonic-clonic, and atypical absence [Thibert et al 2009, Fiumara et al 2010]. Multiple seizure types occur in up to 50% of individuals. Infantile spasms are rare. Seizures continue to be present throughout adulthood.

Brain MRI may show mild atrophy and mild dysmyelination, but no structural lesions [Harting et al 2009, Castro-Gago et al 2010].

Nonconvulsive status epilepticus (NCSE) may occur in children [Bindels-de Heus et al 2020] and adults [Prasad et al 2018]. This type of status may not be recognized clinically but can be associated with loss of developmental skills and diminished awareness and may last for hours or even days. Most common is an atypical absence or myoclonic type NCSE causing decreased alertness, atypical absence status, atonic head drop, hypotonia, and/or myoclonic movements [Elia 2009, Worden et al 2018].

Nonepileptic myoclonus (NEM), also termed cortical myoclonus, should be distinguished from true seizures that have an EEG signature. NEM can include jerking, tic-like, or twitching movements without obvious alteration in awareness and with no epileptiform EEG changes. NEM typically occurs in teenagers and young adults [Pollack et al 2018].

Sleep problems are common in individuals with AS and include frequent and early awakening, dyssomnias (difficulties initiating or maintaining sleep), fragmented and irregular sleep-wake cycles, disruptive night behaviors such as periods of laughter, and sleep-related seizures [Pelc et al 2008, Spruyt et al 2018]. Sleep

difficulties are further influenced by constipation, gastroesophageal reflux disease, and scoliosis [Bindels-de Heus et al 2020]. Sleep related issues may improve with age, though some individuals continue to require co-sleeping [Walz et al 2005, Dosier et al 2017]. Given the comorbidity of behavior issues, seizures, and sleep problems, management largely focuses on behavior modification, epileptic control, medication, and improving sleep hygiene to approach these issues.

Behavioral features include frequent laughter and smiling, apparent happy demeanor, excitability, often with hand-flapping movements, and hypermotoric behavior. Some infants have an apparent happy affect with excessive chortling or paroxysms of laughter. Infants and toddlers may have seemingly ceaseless activity, constantly keeping their hands or toys in their mouth, and/or moving from object to object. After infancy, exploratory play tends to be by oral manipulation and chewing. Essentially all young children with AS have a component of hyperactivity. Males and females appear equally affected. Laughter can be an appropriate response to a humorous situation, but more often appears in response to a nonspecific event (mental or physical stimulus) or possible expression of anxiety. Aggressive and self-injurious behaviors can occur, including pinching, grabbing, biting, slapping, and hitting. These behaviors often represent attention seeking and frustration due to difficulty with communication, rather than ill intent [Arron et al 2011, Sadhwani et al 2019]. Individuals with AS experience the full spectrum of emotions, develop meaningful relationships with family and friends, and participate in household, recreational, and other activities.

Certain behaviors may suggest a diagnosis of autism spectrum disorder (e.g., fascination with water and crinkly items such as certain papers and plastics, increased sensitivity to heat, abnormal food-related behaviors) but social engagement is typically good. Stereotypic behaviors such as lining up of toys or fascination with spinning objects or flashing lights rarely occur. Some individuals with AS have good response to ABA (applied behavior analysis) therapy [Walz & Baranek 2006, Moss & Howlin 2009, Summers 2012].

The behavior profile generally continues into the adult years. Particularly challenging in teenage and adult years include frustration in communicating wants and preferences, seeking sensory stimulation and social attention, and avoidance of undesired situations [Larson et al 2015].

Motor development and tremor. Tremulous movements can be noted prior to age 12 months and are associated with increased deep-tendon reflexes (see also Clinical Description, **Nonepileptic myoclonus**).

AS may first be suspected in a toddler because of delayed gross motor milestones and hypotonia. Mildly impaired children may walk fairly normally or have minimal toe-walking or prancing gait, at times accompanied by leaning forward. Being placed in a standing position can result in anxiety or rigidity. The average age of walking is between 2.5 and six years [Lossie et al 2001]. In a recent study of 100 children with AS, those with the 15q11.2-q13 deletion achieved walking on average by 58 months and those without the deletion by age 41 months [Bindels-de Heus et al 2020]. Children who are significantly affected have a jerky, robot-like, stiff gait, with legs kept wide based and arms uplifted and flexed with pronated forearms.

Frequently voluntary movements appear irregular. On the mild end they can present as slight jerkiness to uncoordinated coarse movements on the severe end of the spectrum. These movements can prevent reaching for objects, feeding, and walking. Failure to achieve independent walking may be a result of instability resulting from tremor, epilepsy, vision issues, abnormal muscle tone, or balance problems. Ten percent of children are nonambulatory [Clayton-Smith 1993].

Language impairment and cognitive delay are severe. Although formal psychometric testing appears to indicate developmental achievement at around the 24-30 month range, developmental testing is challenging due to language impairment and hypermotoric and attention-deficit behaviors [Peters et al 2004]. Cognitive abilities may be higher than what is captured on testing, but delays are still likely in the severe range. Individuals with the 15q11.2-q13 deletion usually demonstrate the most severe cognitive delays across all domains.

Appropriate and consistent use of one or two words is rare. Babies and young infants have decreased cooing and babbling. At age ten to 18 months, a single word such as "mama" may develop but is often used indiscriminately. In a survey of 47 individuals, 39% spoke up to four words but it was unclear if these words were used with purpose [Buntinx et al 1995]. Larson et al [2015] reported that 13% of individuals had five or more words. Receptive language skills are always more advanced than expressive language skills [Bindels-de Heus et al 2020].

Seizures and significant hyperactivity can impede early communication development including eye contact. Most older children and adults with AS are able to communicate by pointing and reaching, using gestures, pointing to body parts, and by using communication boards. Effective fluent use of sign language does not occur [Larson et al 2015, Pearson et al 2019]. However, some individuals with mosaic imprinting center defects have considerable language, speaking in short sentences and using up to 60 words [Fairbrother et al 2015, Le Fevre et al 2017].

Feeding and gastrointestinal issues. Young infants with AS may have difficulties with breast feeding or bottle feeding (as a result of sucking difficulties) and hypotonia. Almost 50% demonstrate poor feeding – particularly those with the 15q11.2-q13 deletion. Approximately 10%-15% require a gastrostomy tube or nasogastric tube [Glassman et al 2017, Khan et al 2019, Bindels-de Heus et al 2020].

Gastroesophageal reflux disease (GERD) occurs in 45%-65% of individuals with AS, resulting in poor weight gain and emesis in infants [Glassman et al 2017, Khan et al 2019]. Parents may first notice difficulty swallowing or spitting up, trouble breathing, gagging, back arching, refusal to feed, pain, and discomfort with feeding. Treatment is necessary to prevent upper gastrointestinal bleeding and esophagitis. Issues related to GERD can continue to be a problem throughout life [Larson et al 2015].

Vomiting is not uncommon and can be either cyclic or intermittent. Cyclic vomiting appears to be more common in individuals with a 15q11.2-q13 deletion or uniparental disomy (UPD). Vomiting (unrelated to illness or food allergies) can be due to a variety of factors including anxiety and behavior issues, side effects of medication, and constipation [Glassman et al 2017].

Hyperphagia and problematic food-related behaviors are seen in all genetic subtypes with a prevalence of 20%-50% [Welham et al 2015, Bindels-de Heus et al 2020].

Constipation is common and can occur at any age. Symptoms include hard or infrequent stools, poor or worsening appetite, vomiting, and stomach pain. Appropriate and timely management is important, as constipation can result in behavioral changes, weight loss, poor sleep quality, and increased seizures [Glassman et al 2017, Khan et al 2019].

Microcephaly. Delayed or disproportionately slow head growth usually results in absolute or relative microcephaly (< -2 SD) by age two years, often accompanied by a flattened occiput. The reported frequency of microcephaly varies from 25% to 80%. Microcephaly is more prevalent in individuals with the 15q11.2-q13 deletion. A normal head circumference should not exclude Angelman syndrome as a possible diagnosis [Tan et al 2011, Bindels-de Heus et al 2020].

Characteristic facial features. Flat occiput, occipital groove, wide mouth, widely spaced teeth, protruding tongue, and prognathia are reported in fewer than 80% of affected individuals (see Figure 1). Individuals with AS can have lighter hair, skin, and eyes relative to family members, particularly those with the 15q11.2-q13 deletion.

Although the tongue is normal in shape and size, about 30%-50% have persistent tongue protrusion. For some individuals, the problem persists into adulthood. Drooling can lead to skin irritation and aspiration, but is generally not associated with significant complications. Surgical or medication treatments (e.g., surgical reimplantation of the salivary ducts or use of local scopolamine patches) are generally not effective. Treatment is usually conservative including bibs and sometimes occupational therapy [Boyce & Bakheet 2005, Scully et al 2009].

Strabismus and other eye findings. The incidence of strabismus is 40%-50%, regardless of molecular cause [Tan et al 2011, Khan et al 2019, Bindels-de Heus et al 2020]. *OCA2* is located in the 15q11.2-q13 region and has a role in pigmentation of the skin, hair, and irides. Strabismus appears to be more common in genetic disorders that cause ocular hypopigmentation. Pigment in the retina is crucial for normal development of the optic nerve pathways. Although ocular hypopigmentation is reported in the iris and choroid (not the fovea) in individuals with AS, hypopigmentation can be found in individuals without the 15q11.2-q13 deletion and *OCA2* may not be the sole explanation. Standard treatments are used for strabismus including glasses, patching, and surgery when appropriate. Hypermotoric activities can make compliance challenging. Approximately 30% require strabismus surgery with overall successful outcomes [Ye et al 2019].

Astigmatism is the most common refractive error. Keratoconus can occur and may be secondary to persistent eye rubbing or gouging behaviors or other causes. Additional ocular findings include myopia, hyperopia, nystagmus, optic nerve atrophy or optic disk pallor, retinochoroidal atrophy, ptosis, and amblyopia [Michieletto et al 2011].

Orthopedics. Scoliosis can develop in adolescence and becomes more common with advancing age [Giroud et al 2015, Larson et al 2015]. Approximately 10%-20% of children develop scoliosis. At least 30%-50% of adults have scoliosis that is typically thoracic. Increased lumbar lordosis is reported in 20%-25% of adults [Sachdeva et al 2016, Prasad et al 2018]. Scoliosis can limit mobility and is treated with bracing to prevent progression. Surgical correction may be necessary for individuals with severe scoliosis. Additional orthopedic complications include hip dysplasia and low bone mineral density. Osteopenia appears to be more common in those treated with anti-seizure medication [Coppola et al 2007, Larson et al 2015].

Pubertal development is generally normal in individuals with AS. Larson et al [2015] reported early menarche in 17% and late menarche in 27%. Hormonal changes during puberty can affect both behavior and epilepsy. Fertility appears to be normal and procreation appears possible for both males and females. Discussion with a gynecologist is appropriate to explore options to regulate menses [Kaskowitz et al 2016]. Lossie & Driscoll [1999] reported transmission of a 15q11.2-q13 deletion to a fetus by a mother with AS.

Growth. Length, weight, and head circumference at birth are usually normal. Average height during childhood in individuals with AS is lower than in the general population, but most have a normal final adult height. Individuals with AS have an increased weight-to-height ratio, which is more frequently reported in individuals without the 15q11.2-q13 deletion [Mertz et al 2014, Carson et al 2019, Bindels-de Heus et al 2020].

Prognosis. Young adults appear to have generally good physical health. Seizures, abnormal movements (ataxia, decreased ambulation), and difficult behaviors may continue throughout adulthood, as well as other described gastrointestinal, sleep, and orthopedic issues. With respect to other health issues, adults with AS appear to be at the same risk as the general population. Independent living is not possible for adults with AS. Many live at home or in home-like placements. Life span data are not available, but life span appears to be nearly normal [Larson et al 2015].

Genotype-Phenotype Correlations

All molecular causes of AS lead to a similar phenotype of severe-to-profound intellectual disability, movement disorder, characteristic behaviors, and severe limitations in speech and language. However, some phenotypic differences correlate with genotype [Tan et al 2011, Valente et al 2013, Bindels-de Heus et al 2020, Keute et al 2020]. These correlations are broadly summarized here:

- The 5- to 7-Mb 15q11.2-q13 deletion results in the most severe phenotype with microcephaly, seizures, motor difficulties (e.g., ataxia, hypotonia, feeding difficulties), and language impairment. These individuals also have lower body mass index compared to individuals with UPD or an imprinting defect. It is unclear

if individuals with larger deletions (e.g., BP1-BP3 [class I; ISCA-37404] break points) can be clinically distinguished from those with BP2-BP3 (class II; ISCA-37478) break points (see Figure 2).
- Individuals with *UBE3A* pathogenic variants and those with imprinting defects may be less clinically affected that those with UPD.
- *UBE3A* truncating variants may cause more severe clinical manifestations than *UBE3A* missense variants [Keute et al 2020].
- Individuals who are mosaic for nondeletion imprinting defects (~20% of those with an imprinting defect) have the most advanced speech abilities [Nazlican et al 2004]; they may speak up to 50-60 words and use simple sentences [Fairbrother et al 2015, Le Fevre et al 2017].
- Individuals with a 15q11.2-q13 deletion including *OCA2* frequently have hypopigmented irides, skin, and hair. *OCA2* encodes a protein important in tyrosine metabolism that is associated with the development of pigment in the skin, hair, and irides (see Oculocutaneous Albinism Type 2). However, other factors in addition to *OCA2* haploinsufficiency appear to account for the relative hypopigmentation in individuals with AS, as UBE3A has been shown to modulate melanocortin 1 receptor (MC1R) activity in somatic tissues [Low & Chen 2011].

Penetrance

UBE3A pathogenic variants, imprinting center deletions, very small 15q11.2-q13 deletions that include *UBE3A* [Kuroda et al 2014], and certain chromosome translocations affecting the paternal allele may be non-penetrant (see Figure 3).

Prevalence

The population prevalence of AS is estimated at 1:12,000-1:24,000 [Mertz et al 2013].

Genetically Related (Allelic) Disorders

Prader-Willi syndrome (PWS) is caused by an absence of expression of imprinted genes in the **paternally** contributed 15q11.2-q13 region. Although PWS and Angelman syndrome (AS) are clinically distinct in older children, some clinical overlap exists (e.g., feeding difficulties, hypotonia, developmental delay) in children younger than age two years.

Interstitial duplications of 15q11.2-q13 on the maternally derived chromosome cause a disorder clinically distinct from AS and PWS. Individuals with dup15q11.2-q13 do not have facial dysmorphism but have mild to moderately severe learning deficits and may have behaviors in the autism spectrum. See 15q Duplication Syndrome and Related Disorders.

Differential Diagnosis

Infants with Angelman syndrome (AS) commonly present with nonspecific psychomotor delay and/or seizures; therefore, the differential diagnosis is broad and nonspecific, encompassing such entities as cerebral palsy, static encephalopathy, or mitochondrial encephalomyopathy. The tremulousness and jerky limb movements seen in most infants with AS may help distinguish AS from these conditions.

AS-mimicking conditions have been reviewed [Tan et al 2014] and many of these, as well as additional disorders to consider in the differential diagnosis, are listed in Table 3.

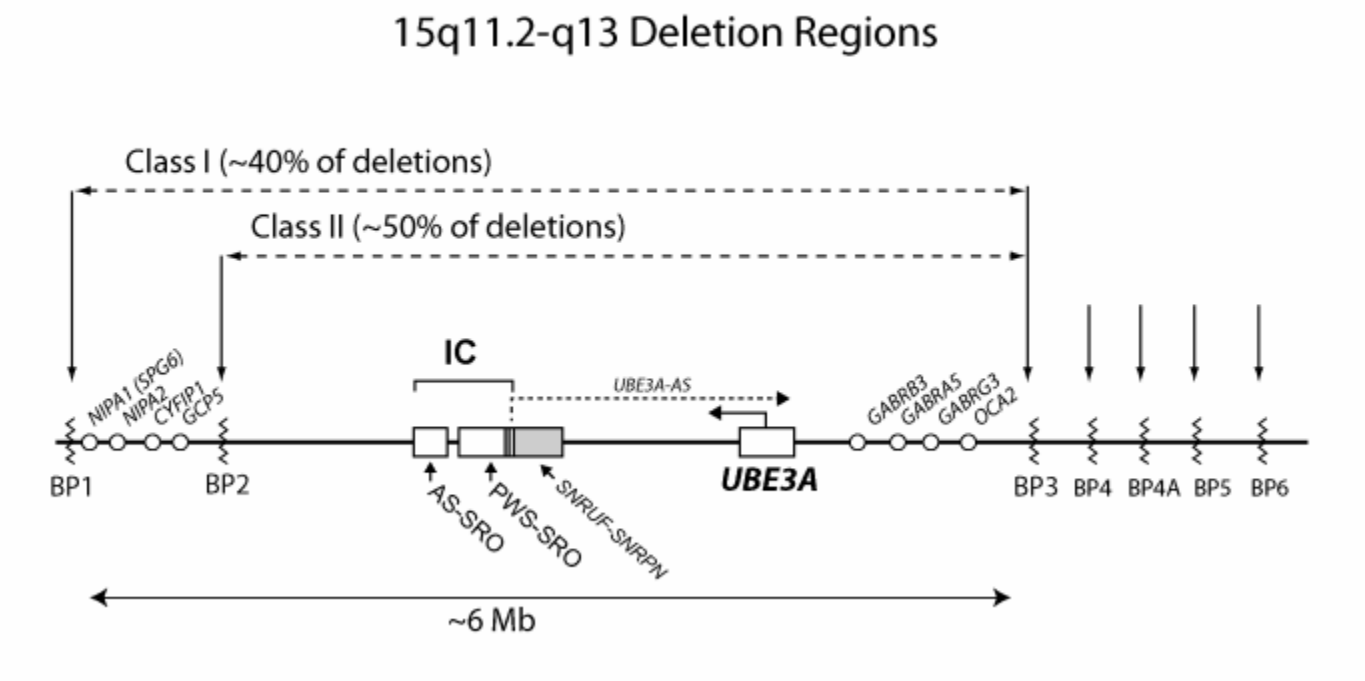

Figure 2. Schematic drawing of chromosome region 15q11.2-q13 indicating the breakpoint regions BP1-BP6. Low copy repeat elements are located within these breakpoint regions (see text for details). Approximately 90% of chromosome deletions resulting in Angelman syndrome initiate at BP1 or BP2 and terminate in region BP3 (class I and class II). Approximately 10% of deletions are larger, typically spanning from BP1 to BP5, rarely beyond BP5. Genes that are not imprinted and thus biparentally expressed are noted by the open circles. The two critical imprinting center (IC) elements, the AS-SRO and the PWS-SRO, are drawn as open boxes. The gene *SNRUF-SNRPN*, drawn as a shaded box, has some overlap with the PWS-SRO. The *SNURF-SNRPN* sense/*UBE3A* antisense transcript is labeled *UBE3A*-AS.

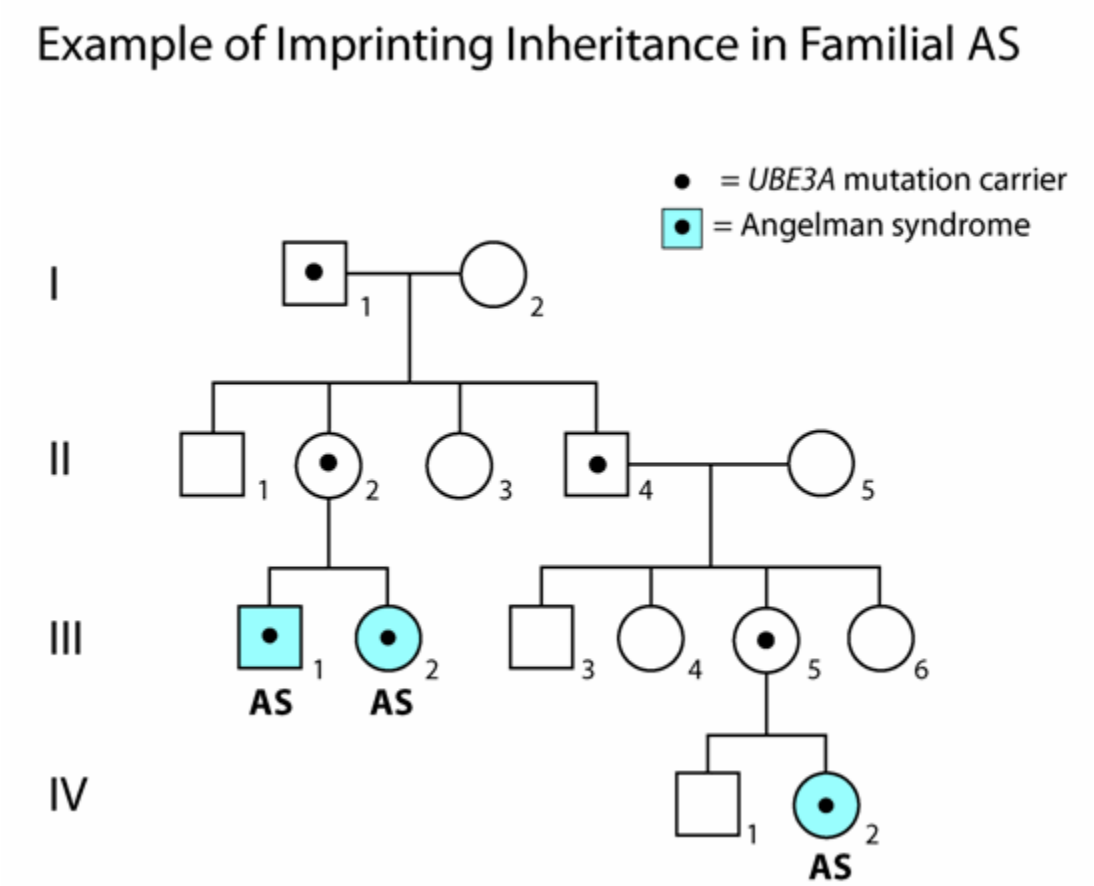

Figure 3. The pedigree illustrates imprinting inheritance in Angelman syndrome (AS). Inheritance of a deleterious *UBE3A* pathogenic variant from the male (top left, I-1) has no effect on the two children (II-2, II-4) who inherit his pathogenic variant because the mutated *UBE3A* has already been inactivated in his germ cells (i.e., by imprinting) and because each of these children also inherited a normally activated *UBE3A* from their mother (I-2). (Note: Only one active *UBE3A* allele is required for normal brain functioning.) If his carrier daughter (II-2) transmits the *UBE3A* pathogenic variant to the grandson and granddaughter (III-1, III-2), they both will have AS since each will have also inherited an inactivated *UBE3A* from their father; thus, neither child will express a *UBE3A* allele. The same explanation pertains for AS occurring in the great grand-niece (bottom right, IV-2).

Table 3. Genes of Interest in the Differential Diagnosis of Angelman Syndrome

Gene	Disorder	MOI	Characteristic Features	Distinguishing Features
ADSL	Adenylosuccinate lyase deficiency (ADSLD, OMIM 103050)	AR	Psychomotor disability, autistic features, hypotonia, seizures, motor apraxia, severe speech deficits, excessive laughter, very happy disposition, hyperactivity, short attention span, mouthing of objects, tantrums, & stereotypic movements	In ADSLD: brain MRI may show cerebral &/or cerebellar atrophy.
ATRX	Alpha-thalassemia X-linked ID syndrome (ATR-X)	XL	Microcephaly, hypotonia, drooling, GERD, affable behavior	In ATR-X: genital & skeletal abnormalities
EHMT1	Kleefstra syndrome (KS)	AD	Moderate-to-severe ID w/severe speech delay, childhood hypotonia	In KS: distinctive facial features (synophrys, everted vermilion of lower lip) & speech ability; mildly affected persons may have >100-word vocab & speak in sentences.

Table 3. continued from previous page.

Gene	Disorder	MOI	Characteristic Features	Distinguishing Features
HERC2	*HERC2*-ID (OMIM 615516)	AR	DD, ID, hypotonia, delayed independent ambulation (age 2.5-5 yrs), & a broad-based gait w/arms upheld & flexed at the elbow when running	In *HERC2*-ID: absence of easily provoked laughter & (in some persons) relatively mild ID
MBD5	*MBD5* haploinsufficiency	AD	DD, ID, severe speech impairment, seizures, sleep disturbances, & abnormal behaviors (e.g. autistic-like behaviors, self-injury, aggression)	Tremulous movements or happy, excitable behavior may not be present in *MBD5* haploinsufficiency.
MECP2	Rett syndrome	XL	In females, partial/complete loss of acquired purposeful hand skills & of acquired spoken language or language skill (e.g., babble); gait abnormalities; stereotypic hand movements (e.g., hand wringing/squeezing, clapping/tapping, mouthing, & washing/rubbing automatisms)	In Rett syndrome: a neuroregressive course, lack of purposeful use of hands, & (usually) absence of a distinctive happy demeanor
	MECP2 duplication syndrome	XL	In males [1], severe-to-profound ID w/ limited or absent speech, early-onset hypotonia w/very slow motor development, seizures	In *MECP2* duplication syndrome: progressive spasticity esp of lower limbs, predisposition to infection manifest as recurrent respiratory infections
MTHFR	Severe MTHFR deficiency (OMIM 236250)	AR	Reported in a boy w/happy demeanor, ataxic gait, absent speech, & flattened occiput [2]	Hypotonia & joint laxity may be more severe in MTHFR deficiency.
SLC9A6	Christianson syndrome (CS)	XL	In males: DD/ID (usually severe to profound); absent to minimal language development; hyperkinesis; epilepsy (onset age usually <3 yrs); truncal ataxia; postnatal-onset microcephaly	In CS: progressive cerebellar atrophy (generally after 1st decade) & lifelong problems w/poor weight gain & low BMI
TCF4	Pitt-Hopkins syndrome (PTHS)	AD	DD, ID, behavioral differences (may be described as a happy disposition); most are nonverbal w/receptive often stronger than expressive language	In PTHS, distinctive facial features [3], unusual breathing patterns
WAC	*WAC*-ID	AD	DD, ID, hypotonia in infancy ± oral hypotonia, neonatal feeding difficulties, GERD, &/or constipation, behavioral abnormalities, respiratory problems, recurrent infections, asthma &/or abnormal breathing pattern, abnormal vision	In *WAC*-ID, typically less severe ID, ability to speak words & sentences, lower prevalence of seizures, & absence of microcephaly
ZEB2	Mowat-Wilson syndrome (MWS)	AD	DD, ID, limited or absent speech w/ relative preservation of receptive language skills; most have happy demeanor & wide-based gait.	In MWS, distinctive facial features [4] & multiple congenital anomalies

Table 3. continued from previous page.

Gene	Disorder	MOI	Characteristic Features	Distinguishing Features
>40 genes	Congenital disorders of N-linked glycosylation (CDG-N-linked)	AR (XL)	Rarely, can mimic AS, esp if affected child has unstable gait, speech impairment, & seizures	CDG-N-linked typically presents in infancy & has multisystem clinical manifestations (e.g., failure to thrive, DD, hepatopathy, hypotonia/neurologic abnormalities).

AD = autosomal dominant; AR = autosomal recessive; AS = Angelman syndrome; BMI = body mass index; DD = developmental delay; GERD = gastroesophageal reflux disease; ID = intellectual disability; MOI = mode of inheritance; MTHFR = methylenetetrahydrofolate reductase; XL = X-linked

1. *MECP2* duplication syndrome occurs rarely in females because of skewing of X inactivation against the X chromosome that carries the duplicated fragment. In rare instances, however, females can be as severely affected as males and similar clinical findings can be observed.

2. Arn et al [1998]

3. Craniofacial features are an important aspect for the diagnosis of PTHS, but may be less obvious in infancy. In many cases, the prominence of the nose and lower face may be the earliest clue to PTHS in an infant with developmental concern.

4. Widely spaced eyes, broad eyebrows with a medial flare, low-hanging columella, prominent or pointed chin, open-mouth expression, and uplifted earlobes with a central depression

Some **chromosome disorders** may mimic features of AS including Phelan-McDermid syndrome (22q13.3 deletion), Koolen-de Vries syndrome (associated with either a 17q21.31 deletion or a heterozygous intragenic *KANSL1* pathogenic variant), 1q21.1 recurrent microdeletion, and others. These disorders are characterized by nondysmorphic facial features, language and intellectual impairment, and (in some individuals) happy or excitable behaviors.

Note: Infants with AS who present with feeding difficulties and hypotonia may be misdiagnosed as having Prader-Willi syndrome if a 15q11.2-q13 deletion, detected by chromosomal microarray or FISH, was not proven by DNA methylation analysis to be of maternal origin (see Genetically Related Disorders).

Management

No clinical practice guidelines for Angelman syndrome (AS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with AS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Angelman Syndrome

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	To incl brain MR, EEG
Development & behavior	Developmental & behavioral assessment	To incl: • Motor, adaptive, cognitive, & nonverbal language ability • Language ability & need for special communication devices • Eval for early intervention / special education • Screening for behavior concerns incl sleep disturbances
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	To incl eval for gastroesophageal reflux & nutritional status
Ophthalmology	Ophthalmology exam	To assess for strabismus, evidence of ocular albinism, visual acuity

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Orthopedics / physical medicine & rehabilitation / PT/OT eval	To incl assessment of: • Gross motor & fine motor skills • Scoliosis & gait impairment (e.g., extent of foot pronation or ankle subluxation; tight Achilles tendons) & extent of hypotonia • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Need for orthopedic referral
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of AS in order to facilitate medical & personal decision making
Family support/ resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Angelman Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASM by experienced neurologist: • Single medication use is preferred, but seizure breakthrough is common. • Some w/uncontrollable seizures have benefited from a ketogenic or low-glycemic diet. [1]	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. [2] • Treat NCSE. [3] • Treat NEM. [4] • Provide rescue medication. • Educate parents/caregivers. [5]
Hypermotoric behaviors	• Accommodation by the family & provision of a safe environment • Children w/AS w/excessive hypermotoric behaviors need an accommodating classroom space	• Most children do not receive drug therapy for hyperactivity, but some may benefit from use of stimulant medications (e.g., Ritalin®). • Typically resistant to behavior therapies
Sleep disturbance	Safe but confining bedrooms to accommodate disruptive nighttime wakefulness	Administration of 0.3 mg melatonin 1 hr before sleep may be helpful, but should not be given in the middle of the night if the child awakens.
Socially disruptive or self-injurious behaviors	Behavior modification can be effective.	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Motor delay	• OT may help improve fine-motor & oral-motor control. • Unstable or nonambulatory children may benefit from PT. • Special adaptive chairs or positioners may be required, esp for extremely ataxic children.	Special physical provisions in the classroom, along w/teacher aides or assistants, may be needed for effective class integration.
Speech delay	• Speech therapy is essential & should focus on nonverbal methods of communication. • Use of augmentative communication aids (e.g., picture cards, communication boards) at the earliest appropriate time • Attempts to teach signing should begin as soon as child is sufficiently attentive.	Individualization & flexibility in the school are important educational strategies.
Gastroesophageal reflux	Standard treatments per gastroenterologist: • Upright positioning • Motility drugs	Sometimes fundoplication is required.
Poor weight gain / Failure to thrive	Newborns may require feeding therapy, special nipples, & other strategies to manage weak or uncoordinated sucking.	
Constipation	Often requires use of high fiber or lubricating agents	
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	Community vision services through early intervention or school district
Scoliosis	• Thoraco-lumbar jackets as needed • Those w/severe curvature may benefit from surgical rod stabilization	Older adults tend to become less mobile & less active; attention to activity schedules may be helpful in reducing scoliosis & obesity.
Other orthopedic manifestations	Subluxed or pronated ankles or tight Achilles tendons can be corrected by orthotic bracing or surgery	

ASM = anti-seizure medication; NCSE = nonconvulsive status epilepticus; NEM = nonepileptic myoclonus; OT = occupational therapy; PT = physical therapy

1. Thibert et al [2012]

2. Anticonvulsants most commonly used in the initial approach to treatment include clobazam, levetiracetam, lamotrigine, and clonazepam, based on clinical survey use [Shaaya et al 2016, Prasad et al 2018]. Other anti-seizure medication, less frequently used, have minimal data regarding efficacy (e.g., brivaracetam, cenobamate, felbamate, gabapentin, lacosamide, pregabalin, rufinamide, tiagabine, or cannabidiol). A parent survey suggested relatively diminished benefit from phenobarbital, primidone, carbamazepine, phenytoin, valproic acid, and vigabatrin [Nolt et al 2003]. A few individuals with AS have infrequent seizures and do not require anti-seizure medication.

3. Diazepam can be useful in outpatient treatment of NCSE [Worden et al 2018].

4. NEM can be difficult to treat; levetiracetam, clobazam, and clonazepam have been used [Pollack et al 2018]. There is a recent report of success with perampanel [Kawano et al 2020].

5. Individuals with AS and seizure history should have availability of rescue medications for emergency treatment of prolonged seizures, including rectal diazepam gel or intranasal midazolam or diazepam [Fedak Romanowski et al 2021]. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Surveillance

Table 6. Recommended Surveillance for Individuals with Angelman Syndrome

System/Concern	Evaluation	Frequency
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures, changes in tone, movement disorders.	At each visit
Development	• Monitor developmental progress & educational needs. • Speech assessment	
Psychiatric/ Behavioral	Behavioral assessment for hypermotoric/self-injurious behavior, sleep disturbance	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Gastrointestinal	Monitor for gastroesophageal reflux & constipation.	
Nutrition/ Feeding	• Measurement of growth parameters • Eval of nutritional status • Eval of older children for obesity	
Eyes	Ophthalmology exam	In 1st yr if strabismus is present; general eval by age 2 yrs; follow up per ophthalmologist
Scoliosis	Clinical exam	Annually

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Overtreatment

- Children with AS are at risk for medication overtreatment because their movement abnormalities can be mistaken for seizures and because EEG abnormalities can persist even when seizures are controlled.
- The behavioral phenotype of AS includes hyperexcitability, hypermotoric behaviors, and deficits in social communication. These limitations place affected individuals at risk for social disruptions. On occasion, the use of risperidone (Risperdal®) or other atypical antipsychotic drugs provides some but often limited benefit. When such drugs are needed, care must be taken to avoid oversedation and other side effects.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Clinical trials involving oral administration of folate, vitamin B_{12}, creatine, and betaine have been undertaken in an attempt to augment DNA methylation pathways and possibly increase expression of the paternal *UBE3A* allele in the central nervous system; however, the initial trial did not demonstrate significant clinical benefit [Peters et al 2010]. An ongoing study using oral gaboxadol, a highly selective GABA receptor agonist, has not yet shown clear benefit [Bird et al 2021]. A study of oral levodopa/carbidopa did not show significant benefit in AS [Tan et al 2018]. Two clinical trials are currently evaluating antisense oligonucleotide-mediated enhancement of UBE3A expression: one trial is sponsored by Hoffmann-La Roche (molecule RO7248824; NCT04428281) and the other is sponsored by GeneTX Biotherapeutics (molecule GTX-102; NCT04259281).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Individuals with Angelman syndrome (AS) typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration associated with a very low recurrence risk (e.g., deletion of the maternally inherited 15q11.2-q13 region). Less commonly, an individual with AS has the disorder as the result of a genetic alteration associated with an imprinting pattern of autosomal dominant inheritance (e.g., a pathogenic variant in *UBE3A*) or variable recurrence risk (e.g., an unbalanced chromosome translocation). Reliable recurrence risk assessment therefore requires identification of the underlying genetic mechanism in the proband and confirmation of the genetic status of the parents.

Risk to Family Members

Parents of a proband. The parents of a proband are unaffected.

Sibs of a proband. The risk to the sibs of an individual with AS depends on the genetic mechanism of AS in the proband and the genetic status of the parents:

- If the proband does not have a *UBE3A* pathogenic variant and the DNA methylation pattern is characteristic for absence of the maternal contribution, the underlying genetic mechanism (i.e., deletion of the maternally inherited 15q11.2-q13 region, uniparental disomy [UPD] of the paternal chromosome region 15q11.2-q13, or an imprinting defect of the maternal chromosome 15q11.2-q13 region) should be determined for genetic counseling purposes; recommended testing for the proband is as follows:
  - 15q11.2-q13 deletion analysis (by chromosomal microarray or other methods) should be performed first.
  - If a 15q11.2-q13 deletion is not detected and the microarray (or other method used to detect copy number variants) does not identify segmental or whole-chromosome isodisomy, analysis of DNA polymorphisms on chromosome 15 can be used to rule out a whole-chromosome heterodisomy (to the authors' knowledge, this type of heterodisomy has not been reported in AS, although it is relatively common in Prader-Willi syndrome [Fridman & Koiffmann 2000]).
  - If UPD is not detected, the presumption is that an imprinting defect is present; additional studies can then determine if there is a deletion in the imprinting center.
- Once the underlying genetic mechanism has been established in the proband, the genetic status of the parents can be assessed.
- Recommendations for parental testing (based on the genetic mechanism in the proband) and corresponding recurrence risks to sibs are summarized in Table 7.

Table 7. Risks to Sibs of a Proband with Angelman Syndrome by Genetic Mechanism and Parental Genetic Status

Molecular Class [1]	Families	Genetic Mechanism in Proband	Recommended Parental Testing	Risk to Sibs
Ia	65%-75%	5- to 7-Mb 15q11.2-q13 deletion	Mother: chromosome & FISH analyses	<1% if maternal chromosome & FISH analyses are normal [2]
Ib	<1%	Unbalanced chromosome translocation or inherited small interstitial deletion in 15q11.2-q13 region	Mother: chromosome & FISH analyses	• <1% if maternal chromosome studies are normal • Possibly as high as 50% if the mother has a chromosome rearrangement [3]
IIa	3%-7%	Paternal UPD (w/normal karyotype)	Mother & father: chromosome analysis	• <1% if both parents have normal chromosome analyses [4] (Recurrence risk ≠ 0, as recurrent meiotic nondisjunction of maternal chromosome 15 has been observed. [5]) • Approaches 100% if father has a 15;15 Robertsonian translocation
IIb	<1%	Paternal UPD (w/ predisposing parental translocation)		
IIIa	0.3%	Imprinting defect w/ deletion in the IC	Mother: targeted testing for the IC deletion (a phenotypically normal mother may have a *de novo* IC deletion on her paternally derived chromosome 15 or a paternally inherited IC deletion [6])	• <1% if the IC deletion is not identified in maternal leukocyte DNA [6] • 50% if the mother is heterozygous for the IC deletion
IIIb	2.5%-3%	Imprinting defect w/o a deletion in the IC		<1% (to date, recurrence of AS in families of probands who have an imprinting defect w/o a deletion in the IC has not been reported) [7]
IV	11%	*UBE3A* pathogenic variant	Mother: targeted testing for the *UBE3A* pathogenic variant	• 50% if the mother is heterozygous for the *UBE3A* pathogenic variant (~30% of *UBE3A* pathogenic variants are inherited.) • <1% if the *UBE3A* pathogenic variant is not identified in maternal leukocyte DNA [8]
V	10%	"Other" - no identifiable molecular abnormality	NA	Undetermined risk

IC = imprinting center; NA = not applicable; UPD = uniparental disomy

1. Based on terminology by Jiang et al [1999]

2. Maternal germline mosaicism for large 15q11.2-q13 deletions has been reported [Sánchez et al 2014, Tang et al 2019].

3. Torisu et al [2004], Kuroda et al [2014]

4. Risk figure is based on the lack of recurrence among all known cases of UPD in AS with normal chromosomes, the experience with UPD in other disorders, & theoretic consideration regarding the mechanism of UPD.

5. Harpey et al [1998], Bramswig et al [2018]

6. Theoretically, the mother could have germline mosaicism for the imprinting center deletion; to the authors' knowledge, this has not yet been reported.

7. There is a single report of a pair of sibs with AS who had a 1-1.5-Mb inversion separating the two imprinting center elements, but no imprinting center deletion [Buiting et al 2001, Williams et al 2010]

8. Maternal somatic/germline mosaicism for a *UBE3A* pathogenic variant has been reported [Hosoki et al 2005].

Offspring of a proband. To date, only one individual with AS has been reported to have reproduced [Lossie & Driscoll 1999]. The risk to offspring should be determined in the context of formal genetic counseling.

Other family members

- If a *UBE3A* pathogenic variant, imprinting center deletion, or structural chromosome rearrangement has been identified in the mother (or father in the case of UPD and Robertsonian translocations) of a proband, the sibs of the parent with the predisposing genetic alteration should be offered genetic counseling and the option of genetic testing.
- If a proband's mother is heterozygous for a known imprinting center deletion or *UBE3A* pathogenic variant, the mother's sibs are also at risk of having the imprinting center deletion or the *UBE3A* pathogenic variant. Each child of the unaffected heterozygous sister is at a 50% risk of having AS. Unaffected maternal uncles of the proband who are heterozygous are not at risk of having affected children, but are at risk of having affected grandchildren through their unaffected daughters who inherited the imprinting center deletion or *UBE3A* pathogenic variant from them.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk of having children with AS.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Prenatal testing and preimplantation genetic testing for high-risk pregnancies require prior identification of the underlying genetic mechanism in the proband.

High risk. Prenatal detection of all the known molecular genetic alterations (i.e., molecular classes Ia, Ib, IIa, IIb, IIIa, IIIb, IV; see Table 7) in the 15q11.2-q13 region that give rise to AS is possible through DNA and/or chromosome/FISH analysis of fetal cells obtained by chorionic villus sampling (CVS) or amniocentesis.

DNA methylation analysis (for 5- to 7-Mb deletion of 15q11.2-q13, UPD, and imprinting center defects) on fetal cells obtained by CVS is theoretically possible. However, the few clinical laboratories doing prenatal testing using DNA methylation analysis prefer to use amniocytes because of the relative hypomethylation of cells derived from the placenta. FISH analysis, imprinting center deletion analysis, and sequence analysis of *UBE3A* should be technically possible using fetal cells obtained by CVS [Beygo et al 2019].

Prenatal testing should be undertaken only after the genetic mechanism in the index case has been established and the couple has been counseled regarding recurrence risk, as the risks and the type of molecular genetic testing used vary according to the type of molecular defect in the proband (see Establishing the Diagnosis).

- Parents with normal chromosomes who have had one child with AS caused by either 15q11.2-q13 deletion or UPD have a low recurrence risk but may be offered prenatal testing for reassurance.

- Parents who have had one child with AS caused by a *UBE3A* pathogenic variant should be offered prenatal testing even if the mother does not have a *UBE3A* pathogenic variant because of the possibility of maternal germline mosaicism.
- Prenatal testing for an inherited translocation involving chromosome 15 is relevant because of the increased recurrence risk. FISH analysis and parent-of-origin (DNA methylation and/or polymorphism) studies should be considered if an inherited translocation involving chromosome 15 is present.

Low risk. For low-risk pregnancies with no family history of AS, AS needs to be considered in the following instances:

- **If a 15q11.2-q13 deletion is suspected** on cytogenetic studies from CVS or amniocentesis, FISH analysis or chromosomal microarray analysis (CMA) is indicated to confirm the deletion. If the 15q11.2-q13 deletion is confirmed, parent-of-origin studies [Beygo et al 2019] can be performed to determine if the 15q11.2-q13 deletion is maternally derived (fetus has AS) or paternally derived (fetus has Prader-Willi syndrome [PWS]).
- **If trisomy 15 or mosaic trisomy 15 is detected** on CVS, and if subsequent amniocentesis reveals 46 chromosomes, the possibility of trisomy rescue leading to AS (paternal UPD) or PWS (maternal UPD) through the loss of a parental chromosome 15 must be considered. In this instance, parent-of-origin (DNA) studies on amniocytes can be performed.
- **If a *de novo* translocation involving chromosome 15 or a supernumerary chromosome 15 marker is detected,** FISH analysis or CMA and parent-of-origin studies should be considered to evaluate for a possible 15q11.2-q13 deletion (of variable size) or UPD.

Preimplantation genetic testing (PGT) may be an option for families in which the underlying mechanism has been identified in the proband to be a *UBE3A* pathogenic variant or an imprinting center deletion. (The relative hypomethylation of the early embryo makes PGT problematic for DNA methylation testing.)

Other

Assisted reproductive technology (ART). In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have been demonstrated to increase the chance of certain imprinting disorders (e.g., Beckwith-Wiedemann syndrome) in offspring. A 2018 report detected one occurrence of AS caused by an imprinting error in 949 pregnancies analyzed for AS following IVF. Although the researchers hypothesized that there may be an increased risk in IVF of imprinting errors, the study was limited by its small sample size and number of participating prenatal centers [Johnson et al 2018]. Additional studies have demonstrated no significant association between AS and IVF or ICSI [Vermeiden & Bernardus 2013, Hattori et al 2019].

Fertility. Research from the Netherlands and Germany demonstrates an association between fertility issues and the incidence of AS. The percent of couples who experienced fertility issues before having a child with AS ranged from 19% to 25%. A positive association with fertility issues and AS was not identified in families queried in the United Kingdom [Vermeiden & Bernardus 2013].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Angelman Syndrome Foundation, Inc. (ASF)**
  4255 Westbrook Drive
  Suite 219

Aurora IL 60504
Phone: 800-432-6435 (toll-free); 630-978-4245
Fax: 630-978-7408
Email: info@angelman.org
www.angelman.org

- **Foundation for Angelman Syndrome Therapeutics (FAST)**
  PO Box 608
  Downers Grove IL 60515
  Phone: 630-852-FAST; 866-783-0078
  Fax: 630-852-3270
  Email: info@CureAngelman.org
  www.cureangelman.org
- **Medical Home Portal**
  Angelman Syndrome
- **MedlinePlus**
  Angelman syndrome
- **NCBI Genes and Disease**
  Angelman syndrome
- **American Epilepsy Society**
  aesnet.org
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Angelman Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
UBE3A	15q11.2	Ubiquitin-protein ligase E3A	UBE3A database	UBE3A	UBE3A

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Angelman Syndrome (View All in OMIM)

105830	ANGELMAN SYNDROME; AS
601623	UBIQUITIN-PROTEIN LIGASE E3A; UBE3A

Molecular Pathogenesis

The cardinal features of Angelman syndrome result from deficient expression or function of the maternally inherited *UBE3A* allele [Jiang et al 1999, Lossie et al 2001, Nicholls & Knepper 2001]. *UBE3A* encodes ubiquitin-

protein ligase E3A, a protein involved in the ubiquitination pathway, which targets selected proteins for degradation. *UBE3A* displays predominant maternal expression in human fetal brain and adult frontal cortex [Rougeulle et al 1997, Vu & Hoffman 1997, Herzing et al 2001].

UBE3A has a large 5' CpG island; DNA methylation does not differ between the maternal and paternal alleles. Because no differentially methylated region is present in *UBE3A*, imprinted expression of *UBE3A* is regulated indirectly through a paternally expressed antisense transcript. Runte et al [2001] have shown that a long *SNURF-SNRPN* sense/*UBE3A* antisense RNA transcript exists in the AS/PWS region, starting from the *SNURF-SNRPN* imprinting center and extending more than 460 kb to at least the 5' end of *UBE3A*. This antisense transcript can block paternal *UBE3A* expression [Meng et al 2013].

Disruption of *UBE3A* could affect crucial neuronal processes of protein degradation, replacement, and/or regulation that would otherwise be balanced or maintained by a functional ubiquitin-proteasome system. The ubiquitin-proteasome pathway is essential for cellular functioning including signal transduction, cell-cycle progression, DNA repair, and transcriptional regulation [Ciechanover 1998, Hershko & Ciechanover 1998].

Pathogenic variants

- **Deletions of 15q11.2-q13 (65%-75%).** Three chromosome break points characterized by low copy repeat regions (proximal BP1, BP2, and a distal BP3) are involved in most AS-causing deletion events involving 15q11.1-q13. These deletions span approximately 5-7 Mb [Amos-Landgraf et al 1999, Christian et al 1999] (see Figure 2). Fewer than 10% of individuals with 15q11.2-q13 deletions have a deletion extending from the BP1/BP2 region to more distal low copy repeat regions, BP4 or BP5 (see Figure 2) [Sahoo et al 2007].

  Note: Microdeletions that flank the typical deletion region and include areas between BP1 and BP2 [Doornbos et al 2009], BP3 and BP4 [Rosenfeld et al 2011], and the more distal microdeletion syndrome involving region 15q13.3 [Masurel-Paulet et al 2010] have been described. However, individuals with these deletions do not exhibit features of AS.

- **Genomic abnormalities of 15q11.1-q13.** It is possible that in otherwise healthy individuals, preexisting genomic abnormalities may predispose to deletion of 15q11.1-q13 in the germline, resulting in offspring with AS.
  - A proportion of mothers who have a child with AS due to a 15q11.1-q13 deletion have been found to have inversions in the 15q11.2-q13 region [Gimelli et al 2003].
  - A kindred in which two individuals had deletions (one deletion causing PWS and the other causing AS) has been previously reported to be associated with an inherited inverted intrachromosomal insertion of 15q11.2-q13 [Collinson et al 2004].

- **Paternal uniparental disomy of chromosome 15 (3%-7%).** In contrast to PWS, the paternal UPD observed in AS is most likely to be postzygotic in origin [Fridman & Koiffmann 2000, Robinson et al 2000]. Paternal UPD of meiotic origin does occur but this mechanism is less common than the maternal UPD associated with PWS.

- **Imprinting defects (3%).** This subset of individuals with AS have an imprinting defect that disrupts the resetting of the normal imprint during gametogenesis. Even though these individuals have biparental inheritance of chromosome 15, the maternal 15q11.2-q13 region has a paternal epigenotype and is, therefore, transcriptionally incompetent for the maternal-only expressed gene(s) in this region [Buiting et al 2016].

  Mapping these imprinting center deletions (as well as mapping the imprinting center deletions that are associated with PWS) has delineated two small regions of deletion overlap (SRO) that define two critical elements in the imprinting center, the AS-SRO and the PWS-SRO [Buiting et al 1995] (see Figure 2). The

PWS-SRO is 4.3 kb and overlaps with the *SNURF-SNRPN* exon1/promoter region [Ohta et al 1999]. Imprinting center deletions in individuals with AS affect the more centromeric *SNURF-SNRPN* promoter/exon 1 region. The AS-SRO is 880 bp and is 35 kb proximal to *SNURF-SNRPN* exon 1 [Buiting et al 2016]. Most individuals with AS caused by imprinting defects do not have a deletion of the AS imprinting center, but rather have epigenetic defects that disrupt imprinting center function.

***UBE3A* (~11%).** More than 250 pathogenic variants have been reported including small deletions and duplications leading to frameshifts, missense and nonsense pathogenic variants, splicing defects, large deletions, and complex rearrangements.

Chapter Notes

Author History

Adati I Dagli, MD (2008-present)
Hui-Ja Dong; University of Florida College of Medicine (2003-2005)
Daniel J Driscoll, PhD, MD; University of Florida College of Medicine (1998-2011)
Amy C Lossie, PhD; University of Florida College of Medicine (1998-2003)
Jennifer Mathews, MS, CGC (2015-present)
Charles A Williams, MD (1998-present)

Revision History

- 22 April 2021 (sw) Comprehensive update posted live
- 21 December 2017 (aa) Revision: *WAC*-related intellectual disability added to Differential Diagnosis
- 14 May 2015 (me) Comprehensive update posted live
- 16 June 2011 (me) Comprehensive update posted live
- 5 September 2008 (me) Comprehensive update posted live
- 30 July 2007 (cd) Revision: targeted mutation analysis no longer available clinically
- 21 February 2007 (cd) Revision: clarification of Genetic Counseling section
- 8 November 2005 (me) Comprehensive update posted live
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- 29 July 2003 (me) Comprehensive update posted live
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