GENEReviews

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Angelman Syndrome

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Summary

Disease characteristics. Angelman syndrome (AS) is characterized by severe developmental delay or mental retardation, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and a unique behavior with an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability. In addition, microcephaly and seizures are 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, and it can take several years before the correct clinical diagnosis is obvious.

Diagnosis/testing. The diagnosis of AS rests on a combination of clinical features and molecular genetic testing and/or cytogenetic analysis. Consensus clinical diagnostic criteria for AS have been developed. Analysis of parent-specific DNA methylation imprints in the 15q11.2-q13 chromosome region detects approximately 78% of individuals with AS, including those with a deletion, uniparental disomy (UPD), or an imprinting defect (ID); fewer than 1% of individuals have a cytogenetically visible chromosome rearrangement (i.e., translocation or inversion). *UBE3A* sequence analysis detects mutations in an additional approximately 11% of individuals. Accordingly, 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 a presently unidentified genetic mechanism and thus are not amenable to diagnostic testing.

Management. *Treatment of manifestations:* routine management of feeding difficulties, constipation, gastroesophageal reflux, strabismus. Antiepileptic drugs for seizures. Physical therapy, occupational therapy, and speech therapy with an emphasis on nonverbal methods of communication, including augmentative communication aids (e.g., picture cards or communication boards) and signing. Individualization and flexibility in school settings. Sedatives for nighttime wakefulness. Thoraco-lumbar jackets and/or surgical intervention for scoliosis. *Prevention of secondary complications:* Children with seizures are at risk for

medication overtreatment because movement abnormalities can be mistaken for seizures and because EEG abnormalities can persist even when seizures are controlled. Sedating agents such as phenothiazines can cause negative side effects. *Surveillance:* annual clinical examination for scoliosis. Evaluation of older children for obesity associated with an excessive appetite. *Agents/circumstances to avoid:* vigabatrin and tigabine because they increase brain GABA levels

Genetic counseling. AS is caused by the loss of the maternally imprinted contribution in the 15q11.2-q13 Angelman syndrome/Prader-Willi syndrome (AS/PWS) region that can occur by one of at least five different known genetic mechanisms. The risk to sibs of a proband depends on the genetic mechanism of the loss of the maternally contributed AS/PWS region: typically less than 1% for probands with a deletion or UPD; as high as 50% for probands with an ID or a mutation of *UBE3A*. Members of the mother's extended family are also at increased risk when an ID or a *UBE3A* mutation is present. Cytogenetically visible chromosome rearrangements may be inherited or *de novo*. Prenatal testing for pregnancies at increased risk is possible when the underlying genetic mechanism is a deletion, UPD, an ID, a *UBE3A* mutation, or a chromosome rearrangement.

Diagnosis

Clinical 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]. Newborns typically have a normal phenotype. 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, and it can take several years before the correct clinical diagnosis is obvious.

Findings typically present in affected individuals

- Normal prenatal and birth history, normal head circumference at birth, no major birth defects
- Normal metabolic, hematologic, and chemical laboratory profiles
- Structurally normal brain by MRI or CT, although mild cortical atrophy or dysmyelination may be observed
- Delayed attainment of developmental milestones without loss of skills
- Evidence of developmental delay by age six to 12 months, eventually classified as severe
- 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; hypermotoric behavior; short attention span

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

- Flat occiput
- Occipital groove
- Protruding tongue
- Tongue thrusting; suck/swallowing disorders
- Feeding problems and/or muscle hypotonia during infancy
- Prognathia
- Wide mouth, wide-spaced teeth
- Frequent drooling
- Excessive chewing/mouthing behaviors
- Strabismus
- Hypopigmented skin, light hair and eye color (compared to family); seen only in those with a deletion
- Hyperactive lower-extremity deep-tendon reflexes
- Uplifted, flexed arm position especially during ambulation
- Wide-based gait with out-going (i.e., pronated or valgus-positioned) ankles
- Increased sensitivity to heat
- Abnormal sleep-wake cycles and diminished need for sleep
- Attraction to/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 deletion)
- Scoliosis
- Constipation

See Figure 1 for clinical photographs of facial findings.

Cytogenetic testing

- Fewer than 1% of individuals with AS have a cytogenetically visible chromosome rearrangement (i.e., translocation or inversion) of one number 15 chromosome involving 15q11.2-q13.
- Typically, the 5-7 Mb common deletion is not detected by routine cytogenetic analysis.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant*

any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Gene. The cardinal features of AS are caused by deficient expression or function of the maternally inherited *UBE3A* allele in certain brain regions [Jiang et al 1999, Lossie et al 2001, Nicholls & Knepper 2001, Clayton-Smith & Laan 2003].

Clinical testing

- **DNA methylation analysis.** Unaffected individuals have a methylated and an unmethylated *SNRPN* allele in both the Southern blot analysis [Glenn et al 1996] and methylation-specific PCR assay [Kubota et al 1997, Zeschnigk et al 1997]. Individuals with AS caused by a 5-7 Mb deletion of 15q11.2-q13, uniparental disomy (UPD), or an imprinting defect (ID) have only an unmethylated (i.e., "paternal") contribution (i.e., an abnormal parent-specific DNA methylation imprint).

  Note: (1) Most commercially available DNA methylation analysis tests cannot distinguish between AS resulting from a deletion, from UPD, and from an ID. Further testing is required to identify the underlying molecular mechanism as outlined in Testing Strategy. (2) Newer methods involving pyrosequencing [White et al 2006], methylation-specific multiplex ligation-dependent probe amplification (MLPA) [Nygren et al 2005, Procter et al 2006], sequence-based quantitative methylation analysis (SeQMA) [Dikow et al 2007], and other methods [Martínez et al 2006] of copy-number analysis may soon provide sufficient quantitation to differentiate deletions from an ID or from UPD.

- **Fluorescent in situ hybridization (FISH) or array-based comparative genomic hybridization (array CGH).** In 68% of individuals, 5-7 Mb deletions are detected by FISH, array CGH, or any of various deletion testing methods (see Table 1).

  Note: FISH analysis with the *D15S10* and/or the *SNRPN* probe can identify the deletion, but typically the deletion is not detected by routine cytogenetic analysis.

- **Uniparental disomy (UPD) study.** In approximately 7% of individuals, UPD is detected using DNA polymorphism testing, which requires a DNA sample from the proband and both parents.

- **Imprinting center analysis.** IDs account for approximately 3% of affected individuals. They have an abnormal DNA methylation imprint but have a normal FISH or array CGH study and no evidence of UPD.

  Approximately 10%-20% of the IDs are caused by microdeletions (6-200 kb) that include the AS imprinting center (IC). These microdeletions are detected by any of various methods used for deletion analysis (see Table 1).

  The other 80%-90% of IDs are thought to be epigenetic mutations occurring during maternal oogenesis or in early embryogenesis [Buiting et al 2001, Buiting et al 2003].

  Characterization of the ID as either an IC deletion or epigenetic defect is available in only a few clinical laboratories.

- **Sequence analysis.** When the DNA methylation test is normal, *UBE3A* sequence analysis should be considered for individuals with clinical features of AS. Approximately 11% of individuals with AS have an identifiable *UBE3A* mutation [Malzac et al 1998, Fang et al 1999, Lossie et al 2001].

  Note: A few individuals with AS have multiexonic or whole-gene deletions of *UBE3A*. These deletions are detected by any of various methods used for deletion

analysis (see Table 1). In addition, some array-CGH platforms may be able to detect some of these deletions [Lawson-Yuen et al 2006,Sato et al 2007].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in AS after DNA Methylation Analysis

Parent-Specific DNA Methylation Imprint	Locus, Gene, or Chromosome	Test Methods	Mutations Detected	Mutation Detection Frequency by Test Method[1]	Test Availability
Abnormal	AS/PWS region	FISH or CGH [2]	5-7 Mb deletion of 15q11.2-q13	~68%	Clinical Testing
	Chromosome 15	UPD study	UPD	~7%	
	AS IC	Deletion analysis [3,4]	6-200 kb deletions	~3%	
Normal	*UBE3A*	Sequence analysis	Sequence variants	~11%	
		Deletion/ duplication analysis [3,5]	Partial or whole-gene deletions	Rare	

1. Eleven percent of individuals with the presumptive clinical diagnosis of AS have normal results for all testing methods described in this table.

2. For laboratories offering array CGH testing, see Testing.

3. Testing that detects deletions not readily detectable by sequence analysis of genomic DNA; various methods including quantitative PCR, real-time PCR, and MLPA may be used. Extent of deletion detected may vary by method and by laboratory.

4. Deletion analysis of the AS IC detects small deletions, which account for 10%-20% of IDs.

5. Although array CGH usually detects large 15q11.2-13 deletions, in rare instances array CGH has detected *UBE3A* multiexonic or whole-gene deletions [Lawson-Yuen et al 2006, Sato et al 2007].

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Possible explanations for the failure to detect AS-causing genetic abnormalities in the 11% or more of individuals with clinically diagnosed AS:

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

Testing Strategy

For diagnosis of a proband

- DNA methylation analysis identifies approximately 80% of individuals with AS and is typically the first test ordered.
- If DNA methylation analysis is normal, *UBE3A* sequence analysis is the next appropriate diagnostic test.

To establish the molecular basis of AS for genetic counseling purposes

- If the DNA methylation analysis is abnormal, the next step is FISH or array CGH analysis. If a deletion is found, a chromosome rearrangement (rarely observed) should be excluded.

  Note: Methylation analysis and UPD studies do not detect chromosomal rearrangements.
- If the FISH or array CGH analysis is normal, analysis of DNA polymorphisms on chromosome 15 can distinguish between UPD and an ID.

- If there is no UPD, further DNA studies can determine if an IC deletion is present.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mechanism in the family:

- Prenatal diagnosis using amniocytes can detect all known mechanisms that cause AS.
- PGD can detect disease-causing *UBE3A* mutations or IC deletions that have been previously identified in a family.

Note: The relative hypomethylation of the early embryo and the placental tissue makes chorionic villus sampling (CVS) for prenatal diagnosis or PGD problematic for DNA methylation testing.

Genetically Related (Allelic) Disorders

Prader-Willi syndrome (PWS) is caused by loss of the **paternally** contributed 15q11.2-q13 region. Although PWS and AS are clinically distinct in older children, some clinical overlap exists (e.g., feeding difficulties, hypotonia, developmental delay) [Cassidy et al 2000] in children younger than age two years.

Interstitial duplications of 15q11.2-q13 on the maternally derived chromosome cause a disorder clinically distinct from either AS or PWS. Individuals with dup15q11.2-1q13 do not have facial dysmorphism but have mild to moderately severe learning deficits and may have behaviors in the autism spectrum [Boyar et al 2001].

Clinical Description

Natural History

Prenatal history, fetal development, birth weight, and head circumference at birth are usually normal. Young infants with Angelman syndrome (AS) may have difficulties with breast feeding or bottle feeding (as a result of sucking difficulties) and muscular hypotonia. Gastroesophageal reflux may occur. AS may be first suspected in the toddlers because of delayed gross motor milestones, muscular hypotonia, and speech delay [Williams et al 2006]. Some infants have a happy affect with excessive chortling or paroxysms of laughter. Fifty percent of children develop microcephaly by age 12 months. Strabismus may also occur. Tremulous movements may be noted prior to age 12 months, often with increased deep-tendon reflexes.

Seizures typically occur between ages one and three years and can be 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 1997, Rubin et al 1997, Korff et al 2005].

Seizure types can be quite varied and include both major motor (e.g., grand mal) and minor motor types (e.g., petit mal, atonic) [Galvan-Manso et al 2005]. Infantile spasms are rare. Brain MRI may show mild atrophy and mild dysmyelination, but no structural lesions.

The average child with AS walks between ages two and one-half and six years [Lossie et al 2001] and at that time may have a jerky, robot-like, stiff gait, with uplifted, flexed, and pronated forearms, hypermotoric activity, excessive laughter, protruding tongue, drooling, absent speech, and social-seeking behavior. Ten percent of children are nonambulatory.

Sleep disorders are common, especially frequent night waking and early awakening [Bruni et al 2004, Didden et al 2004]. Parents report that decreased need for sleep and abnormal sleep/wake cycles are characteristic of AS.

Essentially all young children with AS have some component of hyperactivity; males and females appear equally affected. Infants and toddlers may have seemingly ceaseless activity, constantly keeping their hands or toys in their mouth, moving from object to object. Short attention span is present in most. Some behaviors may suggest an autism spectrum problem but social engagement is typically good and stereotypical behaviors such as lining up of toys or fascination with spinning objects or flashing lights rarely occur [Walz 2007].

Language impairment is severe. Appropriate use of even one or two words in a consistent manner is rare. Receptive language skills are always more advanced than expressive language skills. Most older children and adults with AS are able to communicate by pointing and using gestures and by using communication boards. Effective fluent use of sign language does not occur [Clayton-Smith 1993].

Pubertal onset and development are generally normal in AS and procreation appears possible for both males and females. Fertility appears to be normal; Lossie and Driscoll [1999] reported transmission of an AS deletion to a fetus by the affected mother.

Young adults appear to have good physical health with the exception of possible seizures. Constipation is common. Scoliosis becomes more common with advancing age.

Independent living is not possible for adults with AS, but most can live at home or in home-like placements. Life span data are not available, but life span appears to be nearly normal.

Genotype-Phenotype Correlations

All genetic mechanisms that give rise to AS lead to a somewhat uniform clinical picture of severe-to-profound mental retardation, movement disorder, characteristic behaviors, and severe limitations in speech and language. However, some clinical differences correlate with genotype [Smith et al 1997, Fridman et al 2000, Lossie et al 2001, Varela et al 2004]. These correlations are broadly summarized below (Figure 2):

- The 5-7 Mb deletion class results in the most severe phenotype with microcephaly, seizures, motor difficulties (e.g., ataxia, muscular hypotonia, feeding difficulties), and language impairment. There is some suggestion that individuals with larger deletions (e.g., BP1-BP3 [class I] break points) may have more language impairment or autistic traits [Sahoo et al 2006] than those with BP2-BP3 (class II) break points (see Figure 2).
- Individuals with UPD have better physical growth (e.g., less likelihood of microcephaly), fewer movement abnormalities, less ataxia, and a lower prevalence (but not absence) of seizures compared to those with other underlying molecular mechanisms [Lossie et al 2001, Saitoh et al 2005].
- Individuals with IDs or UPD have higher developmental and language ability than those with other underlying molecular mechanisms. Individuals who are mosaic for the nondeletion ID (approximately 20% of the ID group) have the most advanced speech abilities [Nazlican et al 2004]; they may speak up to 50-60 words and use simple sentences.
- Individuals with chromosome deletions encompassing *OCA2* frequently have hypopigmented irides, skin, and hair. The *OCA2* gene 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).

Penetrance

Inherited *UBE3A* and IC deletions follow an imprinting (or inheritance) pattern in which the paternally transmitted mutation is asymptomatic.

Prevalence

The prevalence of AS is one in 12,000-20,000 population [Clayton-Smith & Pembrey 1992, Steffenburg et al 1996].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The disorders most commonly considered in the differential diagnosis of Angelman syndrome (AS) are cerebral palsy of undetermined etiology, Rett syndrome (in infant girls), and idiopathic static encephalopathy [Williams et al 2001]:

- Hypotonia and seizures in the child with AS may raise the possibility of an inborn error of metabolism or a defect in oxidative phosphorylation, such as a mitochondrial encephalomyopathy (see Mitochondrial Disorders Overview).
- Sometimes infants with AS with feeding difficulties, hypotonia, and developmental delay have been misdiagnosed as having PWS because of the presence of a 15q11.2-q13 deletion detected by FISH analysis. FISH analysis typically does not determine the origin of the deletion (i.e., maternal in AS and paternal in PWS); however, parent-specific DNA methylation analysis can distinguish between AS and PWS. Children younger than age two years who have a 15q11.2-q13 deletion should have *SNRNP* DNA methylation analysis to distinguish between AS and PWS because of the significant clinical overlap in these two disorders.
- Infants with AS commonly present with nonspecific psychomotor delay and/or seizures; thus, the differential diagnosis is often broad and nonspecific, encompassing such entities as cerebral palsy, static encephalopathy, and idiopathic epilepsy.
- Other rare chromosome anomalies can also mimic some of the features of AS, especially the 22q13.3 deletion syndrome [Precht et al 1998]. This condition may present with nondysmorphic facial features, absent or minimal speech, and moderate to severe developmental delay, sometimes with behavioral features in the autism spectrum.
- Hypotonia and diminished muscle mass may raise the possibility of a myopathic disorder, but muscle biopsy and EMG are normal in individuals with AS. The tremulousness, jerkiness, and ballistic-like limb movements seen in individuals with AS distinguish AS from cerebral palsy with ataxia and abnormal speech.
- Infant girls with AS having seizures and severe speech impairment can resemble girls with Rett syndrome, but children with AS do not have a neuroregressive course and do not lose purposeful use of their hands, as do girls with Rett syndrome. Furthermore, girls with Rett syndrome do not have the distinctive happy affect characteristic of AS. However, older girls with undiagnosed Rett syndrome may have features that resemble AS, leading to the erroneous diagnosis of AS [Watson et al 2001]. Testing for mutations of *MECP2*, which cause Rett syndrome, is available.

- Mowat-Wilson syndrome can present with findings that suggest AS [Zweier et al 2005], including happy affect, prominent mandible, diminished speech, microcephaly, and constipation. Mowat-Wilson syndrome typically results from a *de novo* dominant mutation in *ZEB2*.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Angelman syndrome (AS), the following evaluations focused on neurologic assessment and good preventive practice are recommended:

- Baseline brain MRI and EEG

  Note: Typically, management of seizures (or assessment of risk for seizures) is not significantly helped by repetitive EEG or MRI testing.
- Musculoskeletal examination for scoliosis and gait impairment (e.g., extent of foot pronation or ankle subluxation; tight Achilles tendons) and the extent of muscular hypotonia. Orthopedic referral as needed.
- Ophthalmology examination for strabismus, evidence of ocular albinism (in deletion-positive AS), and visual acuity
- Developmental evaluation focused on: (1) nonverbal language ability and related educational and teaching strategies and (2) physical therapy to enable optimal ambulation
- Evaluation for gastroesophageal reflux in infants and young children. Diet should be evaluated to assure optimal nutritional status.

Treatment of Manifestations

Feeding problems in newborns may require special nipples and other strategies to manage weak or uncoordinated sucking.

Gastroesophageal reflux can be associated with poor weight gain and emesis; the customary medical treatment (i.e., upright positioning, motility drugs) is usually effective; sometimes fundoplication as required.

Many antiepileptic drugs (AEDs) have been used to treat seizures in individuals with AS; no one drug has proven superior. Medications used for minor motor seizures (e.g., valproic acid, clonazepam, topiramate, lamotrigine, ethosuximide) are more commonly prescribed than medications for major motor seizures (e.g., diphenylhydantoin, phenobarbital) [Nolt et al 2003]. Carbamezapine, although not contraindicated, is infrequently used compared to other common anticonvulsants. Single medication use is preferred, but seizure breakthrough is common. A few individuals with AS have infrequent seizures and are not on AEDs. Some with uncontrollable seizures have benefited from a ketogenic diet.

Hypermotoric behaviors are typically resistant to behavioral therapies; accommodation by the family and provision of a safe environment are important.

Most children with AS do not receive drug therapy for hyperactivity, although some may benefit from the use of stimulant medications such as methylphenidate (Ritalin®).

Behavioral modification is effective in treating undesirable behaviors that are socially disruptive or self injurious.

A full range of educational training and enrichment programs should be available. Unstable or nonambulatory children may benefit from physical therapy. Occupational therapy may help improve fine motor and oral-motor control. Special adaptive chairs or positioners may be required, especially for extremely ataxic children. Speech therapy is essential and should focus on nonverbal methods of communication. Augmentative communication aids such as picture cards or communication boards should be used at the earliest appropriate time. Attempts to teach signing should begin as soon as the child is sufficiently attentive. Special physical provisions in the classroom, along with teacher aides or assistants, may be needed for effective class integration. Children with AS with excessive hypermotoric behaviors need an accommodating classroom space. Individualization and flexibility in the school are important educational strategies.

Many families construct safe but confining bedrooms to accommodate disruptive nighttime wakefulness. Use of sedatives such as chloral hydrate or diphenylhydramines (Benadryl®) may be helpful. Administration of 0.3 mg melatonin one hour before sleep may be helpful in some, but should not be given in the middle of the night if the child awakens.

Strabismus may require surgical correction.

Constipation often requires regular use of laxatives such as high fiber or lubricating agents.

Orthopedic problems, particularly subluxed or pronated ankles or tight Achilles tendons, can be corrected by orthotic bracing or surgery.

Thoraco-lumbar jackets may be needed for scoliosis, and individuals with severe curvature may benefit from surgical rod stabilization.

Prevention of Secondary Complications

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.

Use of sedating agents such as phenothiazines is not advised because they cause negative side effects.

Older adults tend to become less mobile and less active; attention to activity schedules may be helpful and may help reduce the extent of scoliosis and obesity.

Surveillance

The following are appropriate:

- Annual clinical examination for scoliosis
- For older children, evaluation for the development of obesity associated with excessive appetite

Agents/Circumstances to Avoid

Vigabatrin and tigabine (AEDs that increase brain GABA levels) are contraindicated in AS and should not be used to treat the associated seizures.

Carbamezapine, although not contraindicated, is infrequently used compared to other common anticonvulsants.

Testing 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 B12, creatine, and betaine are ongoing. The therapeutic rationale is to augment DNA methylation pathways and possibly increase expression of the paternal *UBE3A* allele in the central nervous system. No final results are available yet. Click here for more information.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Excessive tongue protrusion causes drooling; available surgical or medication treatments (e.g., surgical reimplantation of the salivary ducts or use of local scopolamine patches) are generally not effective.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Angelman syndrome (AS) is caused by one of the following:

- Deletion of the AS/PWS region on the maternally inherited chromosome 15
- Paternal UPD in which the father contributes both copies of chromosome 15
- An ID
- A mutation in *UBE3A*
- Unidentified mechanism(s)

Risk to Family Members

Parents of a proband

- The parents of a proband are unaffected.

- Recommendations for genetic testing of the parents depend on the cause of AS in the proband.

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 is summarized in Table 2.

Table 2. Risks to Sibs of a Proband with AS by Genetic Mechanism

Molecular Class [1]	Families	Genetic Mechanism	Risk to Sibs
Ia	65%-75%	5-7 Mb deletion	<1%
Ib	<1%	Unbalanced chromosome translocation or inherited small interstitial deletion	Possibly as high as 50%
IIa	3%-7%	Paternal UPD	<1%
IIb	<1%	Paternal UPD with predisposing parental translocation	Approaching 100% if father has a 15;15 Robertsonian translocation
IIIa	0.5%	ID with deletion in the IC	As high as 50% if mother also has IC deletion
IIIb	2.5%	ID without deletion in the IC	<1%
IV	11%	*UBE3A* mutation	As high as 50% if mother also has a mutation
V	10%-15%	"Other" - no identifiable molecular abnormality	Undetermined risk

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

Ia. Mothers of individuals with deletions should have chromosomal and FISH analyses to determine if they have a chromosomal rearrangement. For probands with a *de novo* large deletion, the risk to sibs is less than 1%. Germline mosaicism for these large deletions has been reported on one occasion [Kokkonen & Leisti 2000].

Ib. If a chromosome rearrangement or small gene region deletion has been identified in a proband, the risks to sibs and other family members depends on whether the rearrangement is inherited or *de novo* [Horsthemke et al 1996, Stalker & Williams 1998].

IIa. In families in which AS is the result of paternal UPD and in which no Robertsonian chromosomal translocation is identified in the proband, the risk to sibs of having AS is less than 1%. This 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, and theoretical consideration regarding the mechanism of UPD. The recurrence risk is not zero, however, as recurrent meiotic nondisjunction of maternal chromosome 15 has been observed [Harpey et al 1998]. In addition, if an individual has AS resulting from paternal UPD and has a normal karyotype, a chromosomal analysis of the mother should be offered in order to exclude the rare possibility that a Robertsonian translocation or marker chromosome was a predisposing factor (e.g., via generation of maternal gamete that was nullisomic for chromosome 15, with subsequent postzygotic “correction” to paternal disomy).

IIb. Individuals with UPD should have chromosomal analysis to ensure that they do not have a paternally inherited Robertsonian translocation that would increase the family's recurrence risk.

IIIa. Individuals with an IC deletion can have a phenotypically normal mother who also has an IC deletion. In these situations, the mother has either acquired her IC deletion by a spontaneous mutation on her paternally derived chromosome 15 or inherited the IC deletion from her father, consistent with the imprinting mechanisms governing the 15q11.2-q13 region [Buiting et al 2001]. Additionally, some of these mothers may have germline mosaicism for the IC deletion; this complicates genetic counseling when the mother of a proband with an IC

deletion has normal peripheral blood IC genetic studies. If a proband's mother has a known IC deletion, the risk to the sibs is 50%.

IIIb. All IDs without an IC deletion (except for one case of an IC rearrangement, see Buiting et al [2001]) have been in individuals with no known family history of AS and thus probably represent a *de novo* defect in the imprinting process in 15q11.2-q13 during the mother's oogenesis [Buiting et al 1998]. Therefore, the risk to the sibs of a proband in such families is less than 1%.

IV. *UBE3A* mutations can be inherited or *de novo* [Kishino et al 1997, Matsuura et al 1997, Lossie et al 2001, Burger et al 2002]. In addition, several cases of mosaicism for a *UBE3A* mutation have been noted [Malzac et al 1998]. If a proband's mother has a *UBE3A* mutation, the risk to the sibs is 50%.

V. In this molecular class, clinical features of AS are present but an AS-causing genetic mechanism has not yet been identified.

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 of a proband. If a *UBE3A* mutation, IC deletion, or structural chromosomal rearrangement has been identified in the mother (or father in the case of UPD and Robertsonian translocations) of a proband, the sibs of the carrier parent should be offered genetic counseling and the option of genetic testing:

- **IC deletions or *UBE3A* mutations.** If a proband's mother carries a known IC deletion or *UBE3A* mutation, the mother's sisters are also at risk of carrying the IC deletion or the mutation. Each child of the unaffected sisters who are carriers is at a 50% risk of having AS. Unaffected maternal uncles of the proband who are carriers are not at risk of having affected children, but are at risk of having affected grandchildren through their unaffected daughters who have inherited the IC deletion or *UBE3A* mutation from them.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA particularly for probands in whom the underlying mechanism is unidentified. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

High risk. Prenatal detection of all the known molecular genetic alterations (i.e., molecular classes Ia, Ib, IIa, IIb, IIIa, IIIb, IV; see Table 2) in the 15q11.2-q13 region that give rise to AS is possible through DNA and/or chromosomal/FISH analysis of fetal cells obtained by CVS at approximately ten to 12 weeks' gestation or amniocentesis usually performed at

approximately 15-18 weeks' gestation [Kubota et al 1996,Glenn et al 2000]. DNA methylation analysis (for 5-7 Mb deletions, UPD, and IC defects) on cells obtained by CVS is theoretically possible [Kubota et al 1996,Glenn et al 2000], but the few clinical laboratories doing prenatal testing using DNA methylation analysis prefer using amniocytes as a result of the relative hypomethylation of cells derived from the placenta. FISH analysis, IC deletion analysis, and sequence analysis of *UBE3A* should be technically possible for CVS. Prenatal testing should be undertaken only after the genetic mechanism in the index case has been established and the couple has been counseled regarding the risk to their unborn child, as the risks and the type of molecular genetic testing used vary according to the type of molecular defect in the proband (see Molecular Genetic Testing).

- Parents with normal chromosomes who have had one child with AS caused by either 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* mutation should be offered prenatal testing even if the mother has tested negative for the *UBE3A* mutation because she may still be mosaic for a *UBE3A* mutation.
- Prenatal testing for an inherited translocation involving chromosome 15 is relevant because of the increased recurrence risk. FISH and parent-of-origin (DNA methylation and/or polymorphism) studies should be considered if an inherited translocation involving chromosome 15 is present.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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 or array-CGH studies are indicated to confirm the deletion. If the deletion is confirmed, parent-of-origin studies [Kubota et al 1996, Glenn et al 2000] can be performed to determine if the deletion is maternally derived (fetus has AS) or paternally derived (fetus has 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 or array CGH studies and parent-of-origin studies should be considered to evaluate for a possible deletion (of variable size) or UPD.

Preimplantation genetic diagnosis (PGD) may be available for families in which the underlying mechanism has been identified in the proband to be *UBE3A* mutations or IC deletions. (The relative hypomethylation of the early embryo makes PGD problematic for DNA methylation testing.) For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Angelman Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
UBE3A	15q11-q13	Ubiquitin-protein ligase E3A

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Angelman Syndrome

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

Table C. Genomic Databases for Angelman Syndrome

Gene Symbol	Entrez Gene	HGMD
UBE3A	7337 (MIM No. 601623)	UBE3A

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Genomic imprinting is a phenomenon in mammals in which particular genes, depending on the sex of the parent of origin, are not equally expressed. The cardinal features of AS result from deficient expression or function of the maternally inherited *UBE3A* allele [Jiang et al 1999, Lossie et al 2001, Nicholls & Knepper 2001]. Ubiquitin-protein ligase E3A is 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]. In mouse, maternal allele-specific expression is detected in specific brain subregions including hippocampus, Purkinje cells of the cerebellum, and mitral cells of the olfactory bulb [Albrecht et al 1997, Jiang et al 1998]. Primary cell cultures from fetal mouse brain have demonstrated that *UBE3A* imprinting is limited to neurons, but glial cells show biallelic expression [Yamasaki et al 2003]. Studies with RNA-FISH suggest that preferential maternal expression of *UBE3A* occurs in lymphoblasts and fibroblasts, but the differential expression between the parental alleles is not as striking as it is in brain [Herzing et al 2002].

UBE3A has a large 5' CpG island, but in contrast to genes in the "PWS critical region," DNA methylation does not differ between the maternal and paternal alleles [Lossie et al 2001].

Because no differentially methylated region is present in *UBE3A*, it has been proposed that the imprinted expression of UBE3A may be regulated indirectly through a paternally expressed antisense transcript [Rougeulle et al 1998]. 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* IC and extending more than 460 kb to at least the 5' end of *UBE3A*. It has been proposed that this *UBE3A* antisense transcript blocks paternal *UBE3A* gene expression.

Normal allelic variants. *UBE3A* spans approximately 120 kb of genomic DNA and contains 16 exons. The 5' untranslated region (UTR) extends several kilobases upstream from the initiation site and spans an additional six to nine exons [Kishino et al 1997, Vu & Hoffman 1997, Yamamoto et al 1997, Kishino & Wagstaff 1998], whereas the 3' UTR extends an additional 2.0 kb [Kishino & Wagstaff 1998]. To date, alternative splicing of the 5' UTR accounts for the production of nine adult and two fetal transcripts [Kishino et al 1997, Vu &

Hoffman 1997, Yamamoto et al 1997, Kishino & Wagstaff 1998], which are translated into three different protein isoforms.

Pathologic allelic variants

- **Deletions of 15q11.2-q13 (65%-75%).** Three chromosomal break points (proximal BP1, BP2, and a distal BP3) are involved in most AS-causing deletion events involving 15q11.1-q13, and these deletions span approximately 5-7 Mb [Knoll et al 1990, Amos-Landgraf et al 1999, Christian et al 1999] (see Figure 2). Fewer than 10% of individuals with AS may have deletions extending from the BP1/BP2 region to regions more distal, at BP4 or BP5 locations (see Figure 2) [Sahoo et al 2007]. The BP1, BP2, and BP3 regions are characterized by low-copy repeat regions (LCRs) that contain repeats mainly derived from the ancestral HECT domain and RCc1 domain protein 2 genes (HERC2) [Pujana et al 2002]. The BP sites distal to BP3 contain other LCRs (e.g., without HERC2 duplications) that share chromosome 15-derived repeated DNA elements.
- A proportion of mothers who have a child with an AS deletion have been found to have inversions in the 15q11.2-q13 region (the region deleted in the offspring with AS) [Gimelli et al 2003]. Also, 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 paracentric inversion of 15q11.2-q13 [Clayton-Smith et al 1993]. It is thus possible that in otherwise normal individuals, such preexisting genomic abnormalities may predispose to deletion of 15q11.1-q13 in the germline resulting in offspring with AS.
- **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 [Robinson et al 2000].
- **Imprinting defects (3%).** This subset of individuals with AS have a defect in the mechanism(s) involved in resetting the imprint during gametogenesis. Small deletions in a bipartite IC within 15q11.2-q13 change the DNA methylation and expression imprints along 15q11.2-q13. 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 [Glenn et al 1993, Buiting et al 2001, Buiting et al 2003]. Microdeletions in the IC, varying in size from 6 to 200 kb, have been found between the PW71 locus and the *SNRPN* gene in individuals with both AS and PWS [Buiting et al 2001, Buiting et al 2003]. The smallest deletion of the IC region common among this subset of AS cases has been narrowed to 880 base pairs [Buiting et al 1999], which is approximately 30 kb proximal to the smallest IC region deletion common among PWS cases (see Figure 2). Most individuals with AS caused by IC defects do not have a deletion of the AS IC region, but rather have epigenetic defects that disrupt IC function.
- ***UBE3A* (5%-11%).** Sequence analysis of individuals with AS reveals that the vast majority of *UBE3A* mutations result in (or predict) protein truncation [Kishino et al 1997, Matsuura et al 1997, Kishino & Wagstaff 1998, Malzac et al 1998, Lossie et al 2001] without evidence of any hot spot location. It is possible that individuals with milder mutations (e.g., missense and mild promoter mutations) may show some, but not all, of the clinical features associated with AS. A few individuals with AS have been found to have complete or partial deletions of *UBE3A*, or to have intragenic deletions. Some types of deletion testing methods may be able to detect some of these deletions (see Table 1) [Lawson-Yuen et al 2006, Sato et al 2007]. Deletions detected

vary by test method and laboratory; detection of large intragenic deletions may require molecular methods available only in a research laboratory [Boyes et al 2006].

For more information, see Genomic Databases table.

Normal gene product. *UBE3A* produces the 865-amino acid protein E6-associated protein (E6AP), which acts as a cellular ubiquitin ligase enzyme. It is termed "E6-associated" because it was first discovered as the protein able to associate with p53 in the presence of the E6 oncoprotein of the human papilloma virus, type 16. The function of the E6AP enzyme is to create a covalent linkage (e.g., the "ligase" function) between the small, approximately 76-amino acid, ubiquitin molecule and its target protein. After initial ubiquitin attachment, E6AP can then add ubiquitins onto the first ubiquitin to create a polyubiquitylated substrate. Proteins modified in this way can be targeted for degradation through the 26S proteasome complex. The E6AP is the prototype of what is termed the E3 component of the ubiquitin cycle; E1 and E2 proteins respectively activate and transfer the ubiquitin molecule to E3. Then E3 is able to bind to a target protein and transfer and ligate ubiquitin to the target. This ligation reaction occurs mainly in a catalytic region of the E3 enzyme called the homologous to E6AP C terminus (HECT) domain [Verdecia et al 2003].

Abnormal gene product. Disruption of *UBE3A* could disrupt crucial neuronal processes of protein degradation and replacement that would otherwise be balanced or maintained by a functional ubiquitin-proteosome system. Several proteins have been identified as potential targets of E6AP degradation in non-neuronal cell lines, including HHR23A (encoded by *RAD23* gene) [Kumar et al 1999], the Src family tyrosine kinase Blk [Oda et al 1999], the multicopy maintenance protein Mcm7 [Kuhne & Banks 1998], and the estrogen receptor [Li et al 2006]. In brain, epithelial cell transforming sequence 2 (Ect2) protein [Reiter et al 2006] and the androgen receptor [Khan et al 2006] have been shown to be UBE3A targets. However, it is not yet evident how any of these targets are involved in the neuropathogenesis of AS.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Angelman Syndrome Foundation
4255 Westbrook Drive Suite 216
Aurora IL 60504
Phone: 800-IF-ANGEL (800-432-6435); 630-978-4245 (for international callers)
Fax: 630-978-7408
Email: info@angelman.org
www.angelman.org

National Library of Medicine Genetics Home Reference
Angelman syndrome

NCBI Genes and Disease
Angelman syndrome

American Epilepsy Society
342 North Main Street
West Hartford CT 06117-2507

Phone: 860-586-7505
Fax: 860-586-7550
Email: info@aesnet.org
www.aesnet.org

Epilepsy Foundation
8301 Professional Place
East Landover, MD 20785-2238
Phone: 800-EFA-1000 (800-332-1000); 301-459-3700
Fax: 301-577-4941
www.efa.org

Angelman, Rett & Prader-Willi Syndromes Consortium Registry
Department of Molecular and Human Genetics
Baylor College of Medicine
One Baylor Plaza Rm. T619
Houston TX 77030
Phone: 713-798-4795
Fax: 713-798-7773
Email: sweaver@bcm.tmc.edu
Angelman, Rett & Prader-Willi Syndromes Consortium Registry

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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American College of Medical Genetics (2001) Statement on diagnostic testing for uniparental disomy (pdf)

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Chapter Notes

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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 syndromic diagnosis, but usually there is no significant facial dysmorphism.

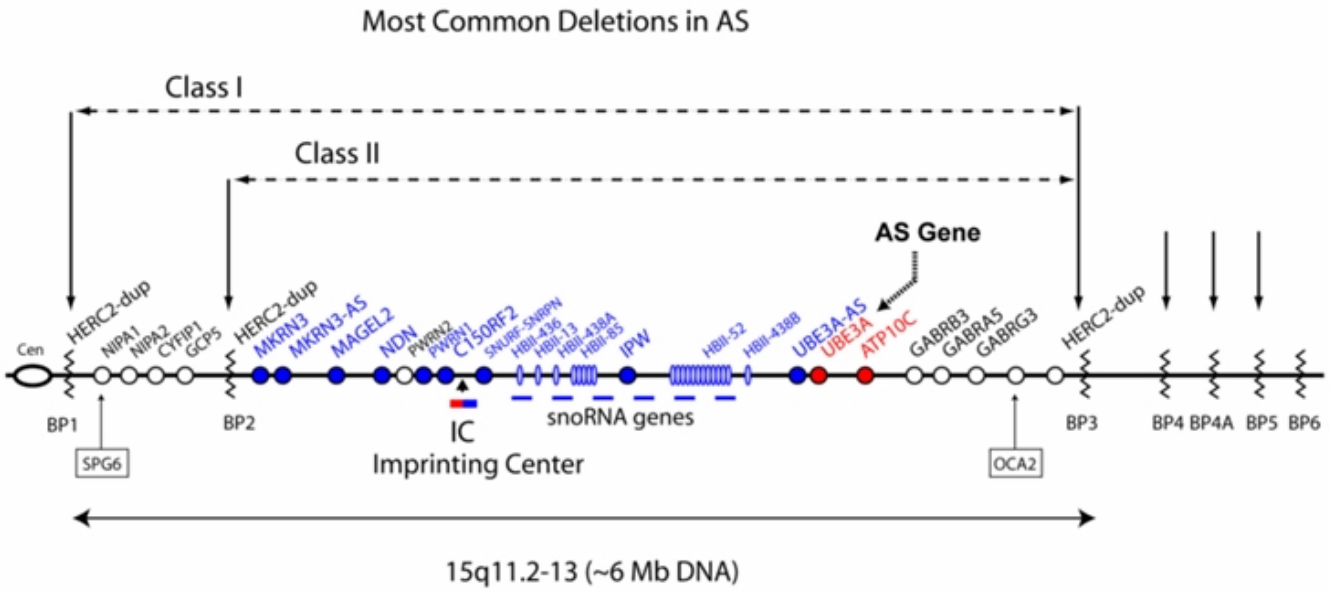

Figure 2. Schematic organization of the 15q11.2-q13 genomic region. Location of the Angelman Syndrome (AS) gene, *UBE3A*, is indicated by the arrow; its red color represents maternal chromosome expression. Genes colored in blue have paternal expression; those in black font have biparental expression. The bipartite structure of the imprinting center (IC) is indicated by combination red and blue colors. Break points (BPs), where low copy repeats are located, are indicated by the vertical arrows and jagged lines; the most common Class I and Class II deleted regions that cause AS are noted by the horizontally dashed lines.