

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 six months of age; however, the unique clinical features of AS do not become manifest until after one year of age, and it can take several years before the correct clinical diagnosis is obvious.

Diagnosis/testing. The diagnosis of Angelman syndrome rests upon 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](#), or an [imprinting](#) defect; fewer than 1% of individuals have a cytogenetically visible [chromosome rearrangement](#) (i.e., [translocation](#) or inversion). [UBE3A sequence analysis](#) detects [mutations](#) in an additional ~11% of individuals. Accordingly, [molecular genetic testing](#) (methylation analysis and [UBE3A](#) sequence analysis) identifies alterations in about 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. Feeding difficulties in newborns with AS may require special nipples; gastroesophageal reflux associated with poor weight gain and emesis is treated with upright positioning and motility drugs; fundoplication is sometimes required. Anticonvulsant medications such as valproic acid, clonazepam, topiramate, lamotrigine, and ethosuximide, are used to treat seizures; vigabatrin and tigabine should be avoided. Unstable or non-ambulatory children may benefit from physical therapy. Occupational therapy may help improve fine motor and oral-motor control. Adaptive chairs or positioners may be required for extremely ataxic children. Speech therapy should focus on nonverbal methods of communication; augmentative communication aids such as picture cards or communication boards are used at the earliest appropriate time and signing should be taught as soon as the child is sufficiently attentive. Children with AS with excessive hypermotoric behaviors need an accommodating classroom space; some children may benefit from the use of stimulant medications such as methylphenidate. Individualization and flexibility in the school are important educational strategies. Sedatives such as chloral hydrate or diphenylhydramines may accommodate nighttime wakefulness. Strabismus may require surgical correction. Laxatives such as high fiber or lubricating agents are used to treat constipation. Orthopedic problems can be corrected by orthotic bracing or surgery. Thoraco-lumbar jackets may be needed for scoliosis; individuals with severe spinal curvature may benefit from surgical rod stabilization.

Genetic counseling. AS is caused by the loss of the maternally **imprinted** contribution in the 15q11.2-q13 (AS/PWS) region that can occur by one of at least five different known genetic mechanisms. The risk to sibs of an **affected** child of having AS depends upon the genetic mechanism of the loss of the maternally contributed AS/PWS region. The risk to sibs of an **affected** child who has a **deletion** or **uniparental disomy** is typically less than 1%. The risk is as high as 50% to the sibs of a child with an **imprinting** defect or a **mutation** of the **UBE3A gene**. Members of the mother's extended family are also at increased risk when an **imprinting** defect or a **UBE3A mutation** is present. Cytogenetically visible **chromosome rearrangements** may be inherited or *de novo*. **Prenatal testing** is possible when the underlying genetic mechanism is a **deletion**, **uniparental disomy**, an **imprinting** defect, 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, Angelman et al 1995]. Newborns typically have a normal **phenotype**. Developmental delays are first noted at around six months of age. However, the unique clinical features of AS do not become manifest until after one year of age, and it can take several years before the correct clinical diagnosis is obvious.

All **affected** individuals typically have:

- 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 six to 12 months of age, eventually classified as severe
- Speech impairment, with minimal to no use of words; receptive language skills and nonverbal communication skills are 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

More than 80% of **affected** individuals have:

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

Fewer than 80% of **affected** individuals have:

- Flat back of the head (brachycephaly)
- Strabismus
- Hypopigmentation of the skin and eyes
- Tongue thrusting, sucking and swallowing disorders, frequent drooling, excessive chewing and mouthing behaviors
- Feeding problems during infancy
- Wide mouth, wide-spaced teeth, prominent mandible
- Hyperactive tendon reflexes
- Uplifted, flexed arms during walking
- Increased **sensitivity** to heat
- Sleep disturbance
- Attraction to/fascination with water

Testing

Fluorescent in situ hybridization (FISH). Approximately 70% of individuals with AS have a 4-6 Mb

deletion of 15q11.2-q13.

Note: [Fluorescent in situ hybridization \(FISH\)](#) analysis with the D15S10 and/or the SNRPN [probe](#) is the preferred method of identifying the [deletion](#) since it is typically not detected by routine [chromosome](#) study. Alternatively, [comparative genomic hybridization \(CGH\)](#) can be used to detect the [deletion](#).

Cytogenetic analysis. 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 that can usually be detected using [chromosome](#) and [FISH](#) studies.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by at least one US CLIA-certified laboratory or a clinical laboratory outside the US. GeneTests does not independently verify information provided by laboratories and does not warrant any aspect of a laboratory's work. Listing in GeneTests does not imply that laboratories are in compliance with accreditation, licensure, or patent laws. 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 uses

- [Diagnostic testing](#)
- [Prenatal diagnosis](#)

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 \(MSP\)](#) assay [[Kubota et al 1997](#) , [Zeschnighk et al 1997](#)].
 - Individuals with AS caused by a 4-6 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: Because an abnormal parent-specific [DNA methylation](#) imprint cannot distinguish between AS resulting from a [deletion](#), from [UPD](#), or from ID, further testing of individuals with an abnormal parent-specific [DNA methylation](#) imprint using the following methods is required to identify the underlying molecular mechanism:

- **Fluorescent in situ hybridization (FISH).** In 68% of individuals, 4-6 MB [deletions](#) are detected by [cytogenetic](#) analysis using [FISH](#).
- **Uniparental disomy (UPD) study.** In approximately 7% of individuals, [uniparental disomy \(UPD\)](#) is detected using [DNA polymorphism](#) testing.
- **Targeted mutation analysis.** Individuals with an [imprinting](#) defect (ID) account for about 3% of [affected](#) individuals. They have abnormal (paternal-only pattern) [DNA methylation](#) imprint, but inheritance of 15q11.2-q13 [DNA polymorphisms](#) from both parents. Data suggest that about 10-20% of the [imprinting](#) defects are micro-deletions (6-200 kb) that include the AS [imprinting](#) center (IC). The nature of the other 80-90% is thought to be an epigenetic [mutation](#) occurring during maternal [oogenesis](#) or in early embryogenesis [[Buiting et al 2001](#) , [Buiting et al 2003](#)]. Characterization of the [imprinting](#) defect as either an [imprinting](#) center [deletion](#) or epigenetic defect is available in only a few clinical laboratories.
- **Sequence analysis.** [UBE3A sequence analysis](#) is available for individuals with a normal parent-specific [DNA methylation](#) imprint who are suspected of having AS. It is estimated that approximately 11% of [probands](#) with AS have identifiable [UBE3A mutations](#) [[Malzac et al 1998](#) , [Fang et al 1999](#) , [Lossie et al 2001](#)].

Table 1 summarizes [molecular genetic testing](#) for this disorder.

Table 1. Molecular Genetic Testing Used in AS

Parent-Specific DNA Methylation Imprint	Test Method	Abnormality Detected	Prevalence of Abnormality 1	Test Availability
Abnormal	FISH	4-6 Mb deletion 15q11.2-q13	~68%	Clinical Testing
	Uniparental disomy (UPD) study	UPD	~7%	
	Targeted mutation analysis 2	Imprinting defect (ID)	~3%	
Normal	Sequence analysis	<i>UBE3A</i> sequence alteration	~11%	

1. In 11% of individuals with Angelman syndrome, all testing for Angelman syndrome described in this table is normal.

2. Targeted **mutation** analysis is available for the detection of small **deletions**, which account for 10-20% of **imprinting** defects.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click [here](#).

Possible explanations for the failure to detect **mutations** in the 11% or more of individuals with clinically diagnosed AS who do not have laboratory proof of AS include: (1) incorrect clinical diagnosis, (2) undetected **mutations** in the regulatory region(s) of *UBE3A*, and (3) other unidentified mechanisms or gene(s) involved in *UBE3A* function that can result in AS when a **mutation** occurs.

Testing Strategy

For diagnosis

- **DNA methylation analysis** identifies approximately 80% of individuals with AS and thus is the single most sensitive diagnostic test for AS.
- If **DNA methylation analysis** is normal, ***UBE3A* sequence analysis** is the next appropriate diagnostic test.
- Note: For an older child (>5 years old) with classic AS features and hypopigmentation (see [Genotype-Phenotype Correlations](#)) some clinicians may opt to start with **FISH** analysis rather than **DNA methylation**.

For genetic counseling

- If the **DNA methylation analysis** is positive, the next step is **FISH** analysis.
- If the **FISH** analysis is normal, studies using **DNA polymorphism** analysis can be used to distinguish between **UPD** and **ID**.
- If an **ID** is present, further **DNA** studies can determine if an **ID deletion** is present.
- For all **affected** individuals, it is appropriate to have standard or high-resolution **chromosome** analysis in addition to the specific diagnostic test because it is possible (though rare; see [Table 1](#)) to have a chromosomal **rearrangement** that alters the **recurrence risks**. Note: **DNA** analyses (methylation and **uniparental disomy** studies) do not detect chromosomal **rearrangements**.

Genetically Related (Allelic) Disorders

[Prader-Willi syndrome](#) (PWS) is caused by loss of the **paternally** contributed 15q11.2-q13 region. While PWS and Angelman syndrome 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.

Maternally inherited interstitial **duplications** of 15q11.2-q13 can 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 AS may have breast or bottle feeding difficulties (as a result of sucking difficulties) and muscular hypotonia. Angelman syndrome may be first suspected in the toddlers because of delayed gross motor milestones, muscular hypotonia, and speech delay [Williams, Angelman et al 1995 ; Williams, Zori et al 1995]. Some infants have a happy affect with excessive chortling or paroxysms of laughter. Fifty percent of children develop microcephaly by 12 months of age. Strabismus may also occur. Tremulous movements may be noted prior to 12 months of age, often with increased deep tendon reflexes.

Seizures typically occur between one and three years of age and can be associated with generalized, somewhat specific EEG changes: runs of high-amplitude delta activity with intermittent spike and slow wave discharges; 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]. 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 two and one-half and six years of age [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 [Zori et al 1992]. Ten percent of children are non-ambulatory. Sleep disorders are common, especially frequent night waking and early awakening [Didden et al 2004 , Bruni et al 2004]. 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. Parents report that decreased need for sleep and abnormal sleep/wake cycles are characteristic of AS. Sleep disturbances have been reported in infants with AS and abnormal sleep/wake cycles have been studied in one affected child who benefited from a behavioral treatment program [Summers et al 1992].

Short attention span is present in most. 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].

Puberty is generally normal in adolescents with AS and procreation appears possible for both males and females [Williams, Zori et al 1995]. Until recently no cases of reproduction in either a male or female with AS had been documented. Lossie and Driscoll (1999) reported transmission of AS by an affected mother who has a 15q11.2-q13 deletion. Therefore, the absence of reproduction previously seen in individuals with AS was most likely social or cognitive rather than physiologic in origin.

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

In general, all of the AS genetic mechanisms lead to a somewhat uniform clinical picture of severe-to-profound mental retardation, movement disorder, characteristic behaviors, and severe limitations in speech and language. Despite great variability within each group, some clinical differences correlate with genotype [Bottani et al 1994 , Fridman et al 2000 , Lossie et al 2001 , Smith et al 1997 , Varela et al 2004]. These correlations are broadly summarized below:

- The 4-6 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 breakpoints compared to those with BP2-BP3 deletions) may have more impaired ability to speak single words.
- 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 [Lossie et al 2001].
- Individuals with ID and UPD have relatively higher developmental and language ability. Individuals

who are [mosaic](#) for the non-deletion [imprinting](#) defect (about 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 the *P* [gene](#) frequently have hypopigmented irides, skin, and hair. The *P* [gene](#) encodes a [protein](#) important in tyrosine metabolism that is associated with the development of pigment in the skin, hair, and irides.

Penetrance

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

Nomenclature

Prior to the 1980s, AS was called the "happy puppet syndrome," based in large part on the original paper published by Dr. Harry Angelman who made note of a puppet-like gait and laughter present in his three patients.

Prevalence

The prevalence of Angelman syndrome 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 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 [Prader-Willi syndrome](#) (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.
- Infants with AS commonly present with either 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 neuro-regressive course nor do they lose purposeful use of their hands, as do individuals with Rett syndrome. Furthermore, individuals with Rett syndrome do not have the distinctive happy affect characteristic of AS. However, Rett syndrome in older girls can escape earlier diagnosis and may resemble features of the AS, and occasionally a girl with Rett syndrome is mislabeled as having AS [[Watson et al 2001](#)]. Testing for [mutations](#) of the *MCP2* [gene](#), which causes Rett syndrome, is available.
- Some individuals with Mowat syndrome can present with features suggestive of AS [[Zweier et al 2005](#)]. These include happy affect, diminished speech, microcephaly, and history of constipation.

Management

Evaluations Following Initial Diagnosis

Evaluations at the time of diagnosis are focused on neurologic assessment and good preventive practice.

- Baseline brain MRI and EEG are advised. Typically, management of seizures (or assessment of risk for seizures) is not significantly helped by repetitive EEG or MRI testing.
- Musculoskeletal examination should assess the possibility of scoliosis and gait impairment (e.g., extent of foot pronation or ankle subluxation; tight Achilles tendons) and the extent of muscular hypotonia. Orthopedic referral should be made if needed.
- Ophthalmology examination should evaluate for strabismus, determine the extent of ocular albinism (in deletion-positive AS), and assess visual acuity.
- Developmental evaluation should focus on: (1) nonverbal language ability and related educational and teaching strategies and (2) physical therapy needs to enable optimal ambulation.
- Infants and young children should be assessed for gastroesophageal reflux; diet should be evaluated to assure optimal nutritional status.

Treatment of Manifestations

- Feeding problems in newborns may require special nipples and other strategies to deal with 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 surgical tightening of the esophageal sphincter is required.
- Many anticonvulsant medications 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 are ones for major motor seizures (e.g., diphenylhydantoin, phenobarbital) [Nolt et al 2003]. Single medication use is preferred, but seizure breakthrough is common. A few individuals with AS have infrequent seizures and are not on anticonvulsant drugs. Some with uncontrollable seizures have benefited from a ketogenic diet. Children with AS are at risk for medication over-treatment because their movement abnormalities can be mistaken for seizures and because EEG abnormalities can persist even when seizures are controlled.
- 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). Use of sedating agents such as phenothiazines is not advised because they cause negative side effects.
- 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 non-ambulatory 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.
- Most individuals with AS significantly benefit from speech, physical and occupational therapy, in combination with educational and behavioral interventions.

Prevention of Secondary Complications

Older adults tend to become less mobile and less active; attention to activity schedules may be helpful

and may help reduce extent of scoliosis and obesity.

Surveillance

- Vigilant observation for the onset of scoliosis is advised.
- Older children should be evaluated for the development of obesity associated with an excessive appetite.

Agents/Circumstances to Avoid

Vigabatrin and tigabine (anticonvulsants that increase brain GABA levels) should not be used to treat seizures.

Therapies Under Investigation

Clinical trials involving the use of high-dose, orally administered folate and betaine are ongoing. The therapeutic rationale is to augment [DNA methylation](#) pathways and possibly increase *UBE3A* expression of the paternal [allele](#) in the CNS. No published 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 reimplants of the salivary ducts or use of local scopolamine patches) are generally not effective.

Genetics clinics, staffed by genetics professionals, provide 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](#) 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](#). —Ed.

Mode of Inheritance

AS can be caused by: (1) [deletion](#) of the AS/PWS region on the copy of [chromosome](#) 15 inherited from the mother; (2) paternal [uniparental disomy \(UPD\)](#) in which the father contributes two copies of [chromosome](#) 15; (3) an [imprinting](#) defect (ID); (4) a [mutation](#) in the *UBE3A* gene; or (5) 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 depends upon 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	Families	Genetic Mechanism	Risk to Sibs
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Class ¹			
Ia	65-75%	4-6 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 Robertsonian translocation	Approaching 100% if father has a 15;15 Robertsonian translocation
IIIa	0.5%	Imprinting defect with deletion of imprinting center	As high as 50% if mother also has imprinting center deletion
IIIb	2.5%	Imprinting defect without deletion of imprinting center	Probably <1%
IV	11%	UBE3A mutation	As high as 50% if mother also has a mutation
V	10-15%	"Other" — no identifiable molecular abnormality	Most cases are not familial , but risk could be as high as 50%

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

Ia. Mothers of individuals with [deletions](#) should have chromosomal and [FISH](#) analyses to determine if the mother has a balanced subtle chromosomal [rearrangement](#) [[Burke et al 1996](#)]. In addition, in spite of the reduced fertility in the Prader-Willi syndrome, a woman with PWS (caused by a paternally derived 15q11.2-q13 deletion) gave birth to an infant with classic AS. This occurrence illustrates the [imprinted](#) aspect of the [chromosome](#) 15q11.2-q13 region [[Schulze et al 2001](#)].

- For [probands](#) with a *de novo* large [deletion](#), the risk to sibs is less than 1% [[Connerton-Moyer et al 1997](#)]. [Germline mosaicism](#) for these large [deletions](#) has been reported on one occasion [[Kokkonen & Leisti 2000](#)].

Ib. If a [chromosome rearrangement](#) 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](#)]. Smaller interstitial [deletions](#) that cause AS when inherited maternally and result in a normal [phenotype](#) when inherited paternally are rare, but significantly change the [recurrence risk](#) for sibs [[Saitoh et al 1992](#)].

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 upon 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 as a result of 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 post-zygotic "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 defect 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](#) [[Saitoh et al 1996](#)]; 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 [imprinting](#) defects without an IC [deletion](#) 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. The majority of cases in this molecular class have not been [familial](#), but some families with more than one [affected](#) sibling have been reported.

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 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 [UBE3 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.

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 [DNA Banking](#) for a list of laboratories offering this service.

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 chorionic villus sampling (CVS) at about 10-12 weeks' gestation or amniocentesis usually performed at about 15-18 weeks' gestation [[Kubota et al 1996](#) , [Glenn et al 2000](#)]. [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](#)).

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

- Parents with normal [chromosomes](#) who have had one child with AS caused by either [deletion](#) or [uniparental disomy](#) 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.

Low risk. For low-risk pregnancies in which no [family history](#) of AS exists, 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** is 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 **dicentric chromosome 15 marker** is detected, **FISH** and **parent-of-origin studies** should be considered to evaluate for a possible **deletion** or **UPD**.

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the underlying mechanism has been identified in the **proband**. For laboratories offering PGD, see **Testing** .

Molecular Genetics

Information in the Molecular Genetics tables may differ from that in the text; tables may contain more recent information. —Ed.

Molecular Genetics of Angelman Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
<i>UBE3A</i>	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](#).

OMIM Entries for Angelman Syndrome

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

Genomic Databases for Angelman Syndrome

Gene Symbol	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
<i>UBE3A</i>	601623	UBE3A	UBE3A	228487	UBE3A

For a description of the genomic databases listed, click [here](#).

Molecular Genetic Pathogenesis

Genomic imprinting is a phenomenon in mammals in which particular **genes**, depending upon the sex of the parent of origin, are not equally expressed. The phenomenon is in distinct contrast to Mendelian inheritance, in which both parental contributions (alleles) are equally expressed. AS represents one of the best examples of **genomic imprinting** in humans [Nicholls & Knepper 2001].

AS is caused by the loss of a key maternally **imprinted** contribution in the 15q11.2-q13 region by one of at least five different genetic mechanisms (four of which are known; one has yet to be elucidated). At the present time it is presumed that 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* has been found to be **imprinted** only in certain areas of the mouse brain [Jiang et al 1998], but the sublocalization of the tissue-specific **imprinting** has not yet been characterized in humans.

While initial evidence did not detect [imprinted](#) expression of *UBE3A*, subsequent studies by three groups demonstrated evidence for allele-specific regional expression of *UBE3A* in the mouse and human [[Albrecht et al 1997](#) , [Rougeulle et al 1997](#) , [Vu & Hoffman 1997](#)]. In situ hybridization analysis of mice with paternal *UPD* for the AS region of mouse [chromosome 7](#) by [Albrecht et al \(1997\)](#) showed lack of *UBE3A* mRNA in the hippocampus, Purkinje neurons, and the mitral cells of the olfactory bulb compared to normal litter mates. In addition, the murine *UBE3A* mRNA levels were markedly reduced compared to controls in the cerebellum and several cell types of the olfactory bulb, including the periglomerular cells, the tufted cells surrounding the glomeruli, the external plexiform layer, and the granule-cell layer [[Albrecht et al 1997](#)].

While extensive murine analysis has illustrated the specific cells in which *UBE3A* shows [imprinted](#) expression, work in the human has relied on the use of whole brain mRNA from individuals with AS and PWS, [unaffected](#) individuals, and fetal tissues. However, it is clear that *UBE3A* shows [imprinted](#) expression in both adult and fetal brain samples. RT-PCR analysis of adult AS brain mRNA showed an almost complete absence of all *UBE3A* [isoforms](#) compared to [unaffected](#) individuals and individuals with PWS, and identified two brain-specific transcripts [[Rougeulle et al 1997](#)]. In addition, [Vu and Hoffman \(1997\)](#) demonstrated that [imprinted](#) expression of *UBE3A* during fetal development is limited to the brain. They used RT-PCR analysis of an expressed [polymorphism](#) in position 84 of [exon U4](#) of *UBE3A* to differentiate between the two [alleles](#) in four [heterozygous](#) fetuses with equal molar ratios of both [alleles](#). Their findings showed that, in tissues from all four fetuses, both [alleles](#) were transcribed in relatively equal amounts in the kidney, heart, adrenal gland, limb, lung, intestine, and placenta, while one [allele](#) was preferentially amplified in the brain. However, they were unable to determine whether it was the maternal or paternal [allele](#) that was predominantly expressed, but inferred that it was the maternal [allele](#) because of the relationship of this [gene](#) with AS [[Vu & Hoffman 1997](#)]. [Herzing et al \(2002\)](#) have suggested by RNA-FISH 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.

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](#)].

The *ATP10C* [gene](#) maps to the AS "critical region" and is also preferentially maternally expressed in brain and lymphoblasts [[Herzing et al 2001](#) , [Meguro et al 2001](#)]. *ATP10C* is located 200 kb distal to the *UBE3A* [gene](#) and is transcribed in the same direction as *UBE3A*. It spans more than 160 kb of [genomic DNA](#), contains 21 [exons](#), and encodes a 1499 amino acid-long aminophospholipid-transporting ATPase that is believed to be involved in transferring phospholipids across the cell membrane [[Herzing et al 2001](#) , [Meguro et al 2001](#)]. It also contains a large CpG island at its 5' end, but as in the case of *UBE3A*, [DNA methylation](#) does not differ between the parental [alleles](#) [[Dong et al 2002](#)].

Since no differentially methylated region (DMR) is present in the AS region, it has been proposed that the [imprinted](#) expression of the [genes](#) (*UBE3A* and *ATP10C*) in the AS region 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* [imprinting](#) center 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. To date, 148 [exons](#) are included in the transcript; the 3' end has not yet been described [[Runte et al 2001](#)].

Mouse studies support the above hypothesis. [Chamberlain and Brannan \(2001\)](#) found that deleting the PWS [imprinting](#) center results in the loss of *Ube3a* antisense expression and increased *Ube3a* expression on the paternal [allele](#). [Yamasaki et al \(2003\)](#) found in mouse neuronal cells that *Ube3a* was expressed from the maternal [allele](#) and the *Ube3a* antisense was expressed from the paternal [allele](#).

Normal allelic variants: *UBE3A* spans approximately 120 kb (E6-AP ubiquitin [protein](#) ligase) was identified in 1993 by its ability to associate with the E6 oncoprotein of the human papillomavirus and selectively degrade *p53*. [Huibregtse et al \(1995\)](#) determined that the 2.7 kb *UBE3A* cDNA included the entire [open reading frame](#) (ORF) and encoded an 865-amino acid [protein](#). Analyses by several groups have shown that *UBE3A* spans approximately 120 kb of [genomic DNA](#) and contains 16 [exons](#). Examination of the *UBE3A* [genomic](#) structure indicated that the 5' untranslated region (UTR) extended several kb upstream from the initiation site and spanned an additional six to nine [exons](#) [[Kishino et al 1997](#) , [Vu & Hoffman 1997](#) , [Yamamoto et al 1997](#) , [Kishino & Wagstaff 1998](#)], while the 3' UTR extended 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%).** The majority of individuals with AS and [Prader-Willi syndrome](#) (PWS) have a large 3-5 Mb **interstitial deletion** of 15q11.2-q13. The **deletion** is maternal in origin for AS and paternal in origin for PWS [[Knoll et al 1989](#) , [Williams et al 1990](#)]. The **deletions** in AS and PWS typically extend from *MKRN3* proximally to the *P* locus distally. However, some individuals show alternative breakpoints at one or both boundaries of 15q11.2-q13. These alternative breakpoints extend the **deletion** region to IR39 (D15S18) proximally and CMW1 (D15S24) distally [[Christian et al 1995](#)]. While **deletions** that include CMW1 are rare, [Christian et al \(1995\)](#) found two main classes of proximal **deletion** breakpoints. BP1 and BP2 are other terms used to describe these breakpoint clusters [[Amos-Landgraf et al 1999](#) , [Christian et al 1999](#)]. **Deletions** that included IR39 were classified as class I **deletions** (47% of the 32 individuals examined) and those that were intact for IR39 but deleted for *MKRN3* were classified as class II (53% of the 32 individuals examined). To date, no one has reported clinical differences between individuals with class I and II AS **deletions**. Individuals with PWS had a similar **deletion** class frequency.

Molecular analysis has revealed that low-copy repeats of the *HERC2* gene map to both the proximal and distal ends of the common breakpoint regions of 15q11.2-q13 [[Christian et al 1999](#) , [Ji et al 1999](#) , [Ji et al 2000](#)]. It has been postulated that the homology of the repeats and **transcription** of the *HERC2* repeats can result in unequal **recombination**, causing the 3-4 Mb **deletions** observed in the majority of individuals with AS and PWS, as well as **duplications** of this region [[Christian et al 1999](#) , [Ji et al 1999](#) , [Ji et al 2000](#)]. 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, pre-existing **genomic** abnormalities may predispose to **deletion**.

- **Paternal unipaternal disomy of chromosome 15 (3-7%).** [Nicholls et al \(1989\)](#) initially showed that **UPD** (maternal) of **chromosome 15** was a mechanism in PWS. Subsequently, it was demonstrated that **UPD 15 (paternal)** was an etiology in AS [[Malcolm et al 1991](#) , [Nicholls et al 1992](#)]. The identification of individuals with AS with paternal **UPD** conclusively demonstrated that it was the lack of the maternally derived 15q11.2-q13 chromosomal region that resulted in the AS **phenotype** and that the rest of **chromosome 15** is not **imprinted**.
- **Imprinting defects (3%).** The third subset of individuals with AS have a defect in the mechanism(s) involved in resetting the imprint during **gametogenesis**. These have been termed **imprinting defects** (ID). Small **deletions** in a bipartite **imprinting** center (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](#) , [Reis et al 1994](#) , [Saitoh et al 1996](#) , [Buiting et al 2001](#) , [Buiting et al 2003](#)]. Microdeletions in the IC, varying in size from six to 200 kb, have been found between the PW71 locus and the *SNRPN* gene in individuals with both AS and PWS [[Saitoh et al 1996](#) , [Buiting et al 2001](#) , [Buiting et al 2003](#)]. The AS smallest region of overlap (SRO) for the IC region has been narrowed to 880 kb [[Buiting et al 1999](#)], which is about 30 kb proximal to the PWS SRO for the IC region.
- **UBE3A (5-11%).** Several individuals with AS with biparental inheritance and normal **DNA methylation analysis** (non-deletion, non-UPD, and non-ID) were found to have **mutations** in *UBE3A*, the gene encoding ubiquitin-protein ligase E3A [[Kishino et al 1997](#) , [Matsuura et al 1997](#)]. Approximately 40-50% of the individuals with normal **DNA methylation** have been found to have a **mutation** in *UBE3A* [[Lossie et al 2001](#)].

[Kishino et al \(1997\)](#) and [Matsuura et al \(1997\)](#) identified the involvement of *UBE3A* in AS by the finding of **protein** truncating **mutations** in this gene in several individuals with AS. **Protein** truncating **mutations** of *UBE3A* are sufficient to cause classic AS [[Lossie et al 2001](#)]. Preliminary studies in human lymphoblast and skin fibroblast cell lines, as well as whole mouse brain and testis, failed to show evidence of **imprinted** expression [[Nakao et al 1994](#) , [Sutcliffe et al 1997](#)]. However, the finding of **imprinted gene** expression in human brain and specific areas of the mouse brain provided conclusive evidence for the role of *UBE3A* in the pathogenesis of AS [[Albrecht et al 1997](#) , [Rougeulle et al 1997](#) , [Vu & Hoffman 1997](#)].

Sequence analysis of individuals with AS has revealed that the vast majority of *UBE3A* **mutations** are protein-truncating **mutations** [[Kishino et al 1997](#) , [Matsuura et al 1997](#) , [Kishino & Wagstaff](#)

1998 , Malzac et al 1998 , Lossie et al 2001], which suggests that individuals with milder mutations (e.g., missense and mild promoter mutations) may show some, but not all the clinical features associated with AS. Therefore, molecular and clinical examination of individuals with "AS-like" disease may yield clues to the function of specific domains of UBE3A.

- **Other mechanisms (11-20%).** The last group of individuals have biparental inheritance of chromosome 15q11.2-q13, normal DNA methylation, no evidence of an interstitial deletion, and no disruption of the imprinting process, but do show the full AS phenotype [Lossie et al 2001]. UBE3A mutations have been detected in only 20-50% of the individuals with normal DNA methylation (AS in one family member only and familial AS), although this frequency rises to 80% (8/10) if only the familial cases are analyzed [Malzac et al 1998]. It is conceivable that a mutation in another gene (located elsewhere in the genome) involved in the ubiquitin pathway could result in AS. Therefore, whether loss of expression or function of UBE3A in the brain accounts for all the individuals with normal DNA methylation and no mutation in the coding region of UBE3A remains to be determined.

For more information, see [Genomic Databases table](#) above.

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 [Scheffner et al 1993]. 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 [Huibregtse et al 1995]. After initial ubiquitin attachment, for example onto p53, E6AP can then add ubiquitins onto the first ubiquitin to create a polyubiquitylated substrate. Proteins modified in this way can then be targeted for degradation through the 26S proteasome complex [Ciechanover 1994]. 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. The E3 is then 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 HECT (homologous to E6AP C terminus) domain [Verdecia et al 2003].

Abnormal gene product: Most Angelman UBE3A mutations disrupt function of this region of the protein [Malzac et al 1998]. Disruption of E6AP ultimately causes an abnormality in the ubiquitin protein degradation pathway, but no clear AS-causing target protein has been identified as yet. The cell cycle control protein p53, a target in the presence of the E6 protein, was first to be identified as an E6AP target, but its role in AS is unclear [Miura et al 2002]. The activated form of Src family tyrosine kinase Blk, and HHR23A and HHR23B (homologues of RAD23, an excision repair protein in yeast) appear to be targets [Kumar et al 1999 , Oda et al 1999]. However, these targets do not yet give insight into the neuronal pathophysiology 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. -Ed.

- **Angelman Syndrome Foundation**
3015 E. New York Street Suite A2265
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
Email: webmaster@efa.org
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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