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Angelman Syndrome

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Summary

Clinical characteristics

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

Diagnosis/testing

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

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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 risperidone or other atypical antipsychotic drugs 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: Carbamezapine, vigabatrin, and tigabine as they may exacerbate seizures.

Genetic counseling

AS is caused by disruption of maternally imprinted *UBE3A* located within the 15q11.2-q13 Angelman syndrome/Prader-Willi syndrome (AS/PWS) region. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of *UBE3A* function: typically less than 1% risk for probands with a deletion or UPD, and as high as 50% for probands with an ID or a pathogenic variant of *UBE3A*. Members of the mother's extended family are also at increased risk when an ID or a *UBE3A* pathogenic variant is present. Cytogenetically visible chromosome rearrangements may be inherited but are usually *de novo*. Prenatal testing for pregnancies at increased risk is possible when the underlying genetic mechanism is a deletion, UPD, an ID, a *UBE3A* pathogenic variant, or a chromosome rearrangement.

Diagnosis

Consensus criteria for the clinical diagnosis of Angelman syndrome (AS) have been developed in conjunction with the Scientific Advisory Committee of the US Angelman Syndrome Foundation [Williams et al 2006]. Several recent reviews are available [Dagli et al 2012, Thibert et al 2013, Bird 2014].

Suggestive Findings

The diagnosis of Angelman syndrome **may be suggested** by the following clinical and/or laboratory findings.

Clinical Findings

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 and hypermotoric behavior

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, widely 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 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.

Laboratory Findings

Abnormality of 15q11.2-q13 detected by chromosomal microarray (CMA) or by karyotype performed for nonspecific clinical findings is suggestive of Angelman syndrome.

Establishing the Diagnosis

The diagnosis of AS **is established** in a proband who meets the consensus clinical diagnostic criteria and/or who has findings on molecular genetic testing that suggest deficient expression or function of the maternally inherited *UBE3A* allele (see Table 1) through **one of the following** mechanisms:

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

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

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

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

- **DNA methylation analysis** is typically the first test ordered. Individuals with AS caused by a 5- to 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). DNA methylation analysis identifies approximately 80% of individuals with AS.

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

- If DNA methylation analysis is normal:
  - **Testing of *UBE3A*** may be considered. Sequence analysis is performed first. If a pathogenic variant is not identified, gene-targeted deletion/duplication analysis can be considered.

- **Use of a multigene panel** that includes *UBE3A* and other genes of interest (see Differential Diagnosis) may be considered in individuals who have features of AS and normal DNA methylation analysis. Note: The genes included and sensitivity of multigene panels vary by laboratory and over time.

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

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

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

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

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

Table 1. Testing Used in Angelman Syndrome (AS)

Method	Genetic Mechanism Detected [1]					Total Proportion of AS Detected by Method [2]
	15q11.2-q13del	UPD	ID	*UBE3A* seq	*UBE3A* del/dup	
DNA methylation analysis [3, 4]	X	X	X [5]			~80%
MS-MLPA [6]	X	X	X			~80%
FISH [7]	X					~68%
CMA [8]	X	X [9]				~68%
UPD study [10]		X				~7%
AS IC deletion analysis [11, 12]			X			~3%
UBE3A sequence analysis				X [13]		~11% [14]

Table 1. continued from previous page.

Method	Genetic Mechanism Detected [1]					Total Proportion of AS Detected by Method [2]
	15q11.2-q13del	UPD	ID	*UBE3A* seq	*UBE3A* del/dup	
UBE3A gene-targeted deletion/duplication analysis [11, 15]					X	Rare

IC = imprinting center; ID = imprinting defect; UPD = uniparental disomy
1. See Molecular Genetics for more details.
2. 11% of individuals with the presumptive clinical diagnosis of AS have normal results for all testing methods described in this table.
3. Individuals with AS caused by a 5- to 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).
4. Will not distinguish genetic mechanism
5. 80%-90% of IDs are thought to be epigenetic pathogenic variants occurring during maternal oogenesis or in early embryogenesis [Buiting 2010]. Characterization of the ID as either an IC deletion or epigenetic defect is available primarily through research laboratories.
6. Methylation-specific multiplex ligation-dependent probe amplification (MLPA) can test for deletion along with the methylation assay amplification [Nygren et al 2005, Procter et al 2006, Ramsden et al 2010].
7. FISH analysis with the *D15S10* and/or the *SNRPN* probe can identify the common 15q11.2-q13 deletion, but typically this deletion is not detected by routine cytogenetic analysis.
8. Chromosomal microarray (CMA) has a slightly higher detection frequency than FISH and will provide detailed information regarding size of the deletion. Also, it gives information regarding deletions and duplication in the remainder of the genome.
9. SNP-based chromosomal microarray may diagnose whole-chromosome and segmental uniparental isodisomies but cannot detect all instances of uniparental disomy.
10. UPD is detected using polymorphic DNA markers, which requires a DNA sample from the affected individual and both parents.
11. Gene-targeted deletion/duplication analysis detects deletions or duplications in intragenic or other targeted regions. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single exon deletions or duplications.
12. Deletion analysis of the AS imprinting center (IC) detects small deletions (6- 200-kb reported), which account for 8%-15% of all imprinting defects (IDs) [Buiting 2010]
13. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
14. Malzac et al [1998], Fang et al [1999], Lossie et al [2001]
15. Although CMA usually detects large 15q11.2-q13 deletions, in rare instances CMA has detected *UBE3A* multiexon or whole-gene deletions [Lawson-Yuen et al 2006, Sato et al 2007].

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

Clinical Characteristics

Clinical Description

Prenatal history, 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.

Some infants have an apparent happy affect with excessive chortling or paroxysms of laughter. 50% of children develop microcephaly by age 12 months. Strabismus may also occur. Tremulous movements may be noted prior to age 12 months, associated with increased deep-tendon reflexes.

AS may first be suspected in a toddler because of delayed gross motor milestones, muscular hypotonia, and/or speech delay [Williams et al 2006].

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 and minor motor types (e.g., petit mal, atonic) [Galván-Manso et al 2005, Pelc et al 2008a, Thibert et al 2009, Fiumara et al 2010]. Infantile spasms are rare. Non-convulsive status epilepticus may occur [Pelc et al 2008a]. Brain MRI may show mild atrophy and mild dysmyelination, but no structural lesions [Harting et al 2009, Castro-Gago et al 2010].

The average child with AS walks between ages 2.5 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. 10% of children are nonambulatory.

Sleep problems are well known in individuals with AS; frequent awakening at night is common [Bruni et al 2004, Didden et al 2004]. Dyssomnias (difficulties in initiating or maintaining sleep), irregular sleep-wake cycles, disruptive night behaviors such as periods of laughter, and sleep-related seizures have been reported [Pelc et al 2008b].

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, and/or moving from object to object. Some behaviors may suggest an autism spectrum problem but social engagement is typically good and stereotypic 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 [Gentile et al 2010]. 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]. Relatively higher language skills can be seen in those with mosaic imprinting defects.

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

Young adults appear to have generally good physical health, although seizures continue to be present throughout adulthood. Constipation is common. Many are treated for gastroesophageal reflux symptoms. Scoliosis becomes more common with advancing age [Giroud et al 2015, Larson et al 2015].

Independent living is not possible for adults with AS; many live at home or in home-like placements.

Life span data are not available, but life span appears to be nearly normal.

Genotype-Phenotype Correlations

All genetic mechanisms that give rise to AS lead to a somewhat uniform clinical picture of severe-to-profound intellectual disability, movement disorder, characteristic behaviors, and severe limitations in speech and language. However, some clinical differences correlate with genotype [Fridman et al 2000, Lossie et al 2001, Varela et al 2004, Tan et al 2011, Valente et al 2013]. These correlations are broadly summarized below:

- The 5- to 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. They also have lower body mass index compared to individuals with UPD or imprinting defects [Tan et al 2011]. There is some suggestion that individuals with larger deletions (e.g., BP1-BP3 [class I; ISCA-37404] break points) may have more language impairment or autistic traits than those with BP2-BP3 (class II; ISCA-37478) break points [Sahoo et al 2006] (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 than do those with other underlying molecular mechanisms [Lossie et al 2001, Saitoh et al 2005, Valente et al 2013].
- 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. *OCA2* encodes a protein important in tyrosine metabolism that is associated with the development of pigment in the skin, hair, and irides (see Oculocutaneous Albinism Type 2). However, other factors in addition to haploinsufficiency of *OCA2* appear to account for the relative hypopigmentation in individuals with AS, as UBE3A has now been shown to modulate melanocortin 1 receptor (MC1R) activity in somatic tissues [Low & Chen 2011].

Penetrance

Inherited *UBE3A* pathogenic variants, IC deletions, very small 15q11.2-q13 deletions that include *UBE3A* [Kuroda et al 2014] and certain chromosome translocations follow an imprinting (or inheritance) pattern in which an individual who inherits a paternally transmitted pathogenic variant is asymptomatic (see Figure 3).

Prevalence

The prevalence of AS is one in 12,000-24,000 population [Clayton-Smith & Pembrey 1992, Steffenburg et al 1996, Mertz et al 2013].

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-q13 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]. See 15q Duplication Syndrome and Related Disorders.

Differential Diagnosis

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

The following disorders that mimic AS need to be considered in the differential diagnosis [Tan et al 2014]:

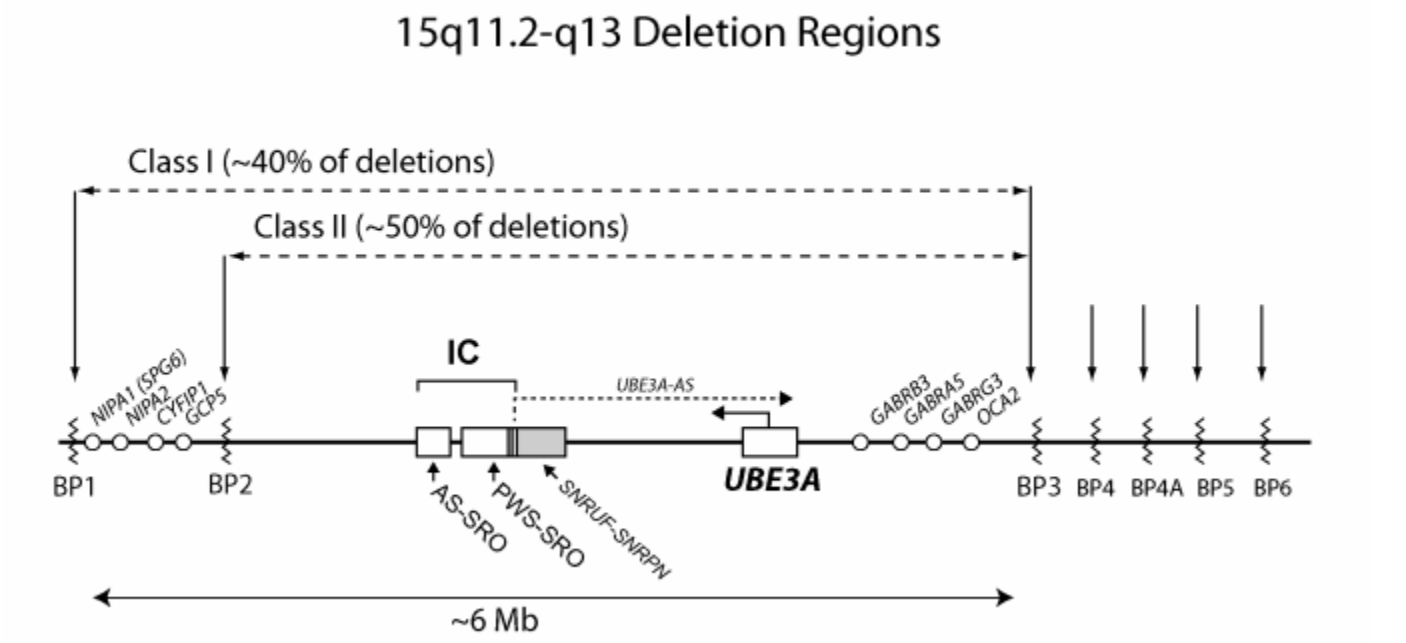

Figure 2. Schematic drawing of chromosome region 15q11.2-q13 indicating the breakpoint regions BP1-BP6. Low copy repeat elements (LCRs) are located within these breakpoint regions (see text for details). Approximately 90% of chromosome deletions resulting in Angelman syndrome initiate at BP1 or BP2 and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

- Mowat-Wilson syndrome can present with happy affect, seizures, prominent mandible, upturned prominent ear lobes, diminished speech, microcephaly, constipation, and, on occasion Hirschsprung disease [Zweier et al 2005]. Congenital heart defects or agenesis of the corpus callosum can also occur. Mowat-Wilson syndrome is typically the result of a dominant *de novo* pathogenic variant in, or deletion of, *ZEB2*.
- The characteristic features of the Pitt-Hopkins syndrome (PTHS) are intellectual disability, wide mouth and distinctive facial features, and intermittent hyperventilation followed by apnea [Zweier et al 2007]. Features that may overlap with AS include microcephaly, seizures, ataxic gait, and happy personality [Takano et al 2010]. Diurnal hyperventilation, a salient feature in some, occurs after age three years [Peippo et al 2006]. PTHS is caused by haploinsufficiency of *TCF4* resulting from either a pathogenic variant in *TCF4* or a deletion of the chromosome region in which *TCF4* is located (18q21.2). Most affected individuals reported to date represent simplex cases (i.e., a single occurrence in a family) resulting from a *de novo* pathogenic variant or deletion.
- Christianson syndrome can mimic AS. The clinical features include apparently happy disposition, severe cognitive delays, ataxia, microcephaly, and a seizure disorder [Christianson et al 1999, Gilfillan et al 2008, Schroer et al 2010]. Affected individuals may have a thin body appearance and may lose ambulation after age ten years. Some may have cerebellar and brain stem atrophy [Gilfillan et al 2008]. Although seizures are present in both conditions, the EEG pattern appears to differ: AS typically shows a generalized high amplitude, slow spike/wave (1.5-3 Hz) pattern while those with an *SLC9A6* pathogenic variant lack the AS EEG pattern and have a more rapid (10-14 Hz) background frequency [Gilfillan et al 2008]. Christianson syndrome is an X-linked disorder caused by mutation of *SLC9A6*.

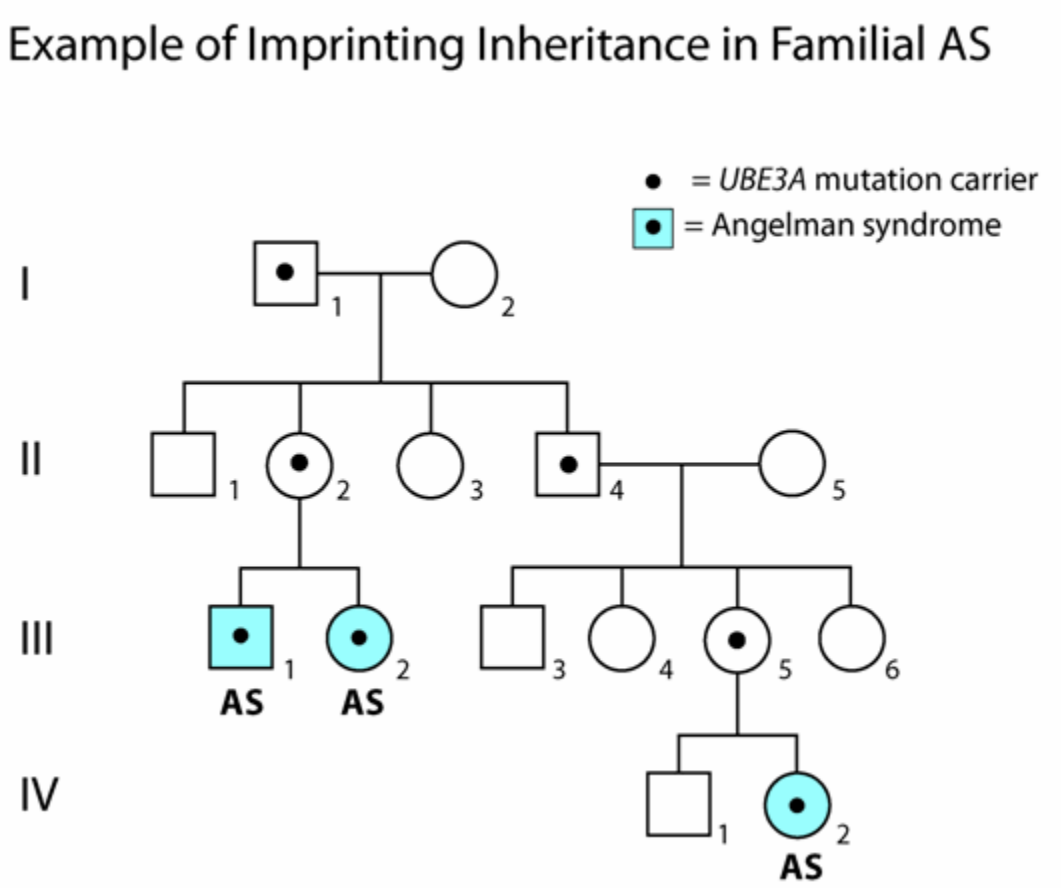

Figure 3. The pedigree illustrates imprinting inheritance in AS. Inheritance of a deleterious *UBE3A* pathogenic variant from the male (top left, I-1) has no effect on the two children (II-2, II-4) who inherit his pathogenic variant because the mutated *UBE3A* has already been inactivated in his germ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

- Female infants with seizures, acquired microcephaly, and severe speech impairment can resemble girls with Rett syndrome. Girls with Rett syndrome usually do not have a distinctive happy demeanor and girls with AS do not have a neuroregressive course or lack purposeful use of their hands. Older girls with undiagnosed Rett syndrome may have features that resemble AS [Watson et al 2001]. Rett syndrome is an X-linked disorder caused by mutation of *MECP2*.
- Sometimes infants with AS who present with feeding difficulties and muscle hypotonia are misdiagnosed as having Prader-Willi syndrome because the 15q11.2-q13 deletion, detected by chromosomal microarray or FISH, was not proven by DNA methylation analysis to be of maternal origin.
- Microdeletions of 2q23.1 involving *MBD5* may result in severe speech delay, seizures, behavioral disorders, and microcephaly. Some individuals present with an AS-like phenotype [van Bon et al 2010, Williams et al 2010]. See MBD5 Haploinsufficiency.
- Other chromosome disorders can mimic some of the features of AS, especially 22q13.3 deletion syndrome (Phelan-McDermid syndrome) [Precht et al 1998], characterized by nondysmorphic facial features, absent or minimal speech, and moderate to severe developmental delay, sometimes with behavioral features in the autism disorders spectrum. Additional microdeletion disorders, especially newer ones detected by chromosomal microarray, may be associated with some features of AS [Brunetti-Pierri et al 2008, Sharkey et al 2009].

- *MECP2* duplication (typically encompassing an approximately 500-kb region at Xq28) in males is characterized by severe developmental impairment, absent speech, seizures, and ataxic gait with spastic paraparesis. Although adult males are typically nonambulatory and are prone to infectious illnesses, children may have relatively nonspecific findings that include features of intellectual disability with autism, absent speech, and unstable gait [Van Esch et al 2005, Friez et al 2006, Lugtenberg et al 2009]. *MECP2* duplication syndrome is inherited in an X-linked manner.
- Adenylosuccinate lyase deficiency (OMIM 103050) results in accumulation of succinylpurines leading to psychomotor retardation, autistic features, hypotonia, and seizures [Spiegel et al 2006]. Motor apraxia, severe speech deficits, excessive laughter, a very happy disposition, hyperactivity, a short attention span, mouthing of objects, tantrums, and stereotyped movements have been reported in female sibs [Gitiaux et al 2009]. Diagnostic testing involves detection of succinylaminoimidazole carboxamide riboside (SAICA riboside) and succinyladenosine (S-Ado) in cerebrospinal fluid, urine, and (to a lesser extent) in plasma. Adenylosuccinate lyase deficiency is inherited in an autosomal recessive manner and is caused by pathogenic variants in *ADSL*.
- The rare metabolic disorder of severe methylene-tetrahydrofolate-reductase (MTHFR) deficiency (OMIM 236250) associated with low methionine and elevated homocysteine blood levels was reported in a boy with happy demeanor, ataxic gait, absent speech, and flattened occiput [Arn et al 1998]. MTHFR deficiency is inherited in an autosomal recessive manner and is caused by pathogenic variants in *MTHFR*.
- On rare occasions, congenital disorders of glycosylation (CDG) can mimic the features of AS especially if the affected child has unstable gait, speech impairment, and seizures.
- Kleefstra syndrome is caused by haploinsufficiency of *EHMT1* on chromosome 9q34.3 [Willemsen et al 2012]. The clinical features that have been reported in both AS and Kleefstra syndrome include: moderate-to-severe intellectual disability with minimal speech; better receptive language as compared to expressive language skills; hypotonia in childhood; sleep disturbances with multiple awakenings; and midface retrusion with prognathism. Facial features that differentiate Kleefstra syndrome from AS include synophrys and everted vermilion of the lower lip. Some mildly affected individuals with Kleefstra syndrome have a greater than 100-word vocabulary and speak in sentences, which would be very unusual in an individual with AS.
- *HERC2*-related cognitive impairment (OMIM 615516). *HERC2* is located on chromosome 15q13.1 and encodes a protein that binds to and affects the ubiquitin ligase activity of E6AP. A homozygous c.1781C>T (p.Pro594Leu) pathogenic variant in *HERC2* has been identified in 22 members of four Amish families and one mixed Amish-Mennonite family who presented with global developmental delay and intellectual disability, hypotonia, delayed independent ambulation at between age 2.5 and 5 years, and a broad-based gait with arms upheld and flexed at the elbow when running [Harlalka et al 2013]. Many of these findings are reminiscent of those observed in mildly affected individuals with AS, but the lack of easily provoked laughter and the relatively mild intellectual disability in at least some of these individuals distinguish it from AS.
- *WAC*-related intellectual disability (ID) is caused by heterozygous pathogenic variants in *WAC*, a gene involved in transcriptional regulation. Most affected infants have significant but nonspecific features at birth such as neonatal hypotonia and feeding problems. The diagnosis of *WAC*-related ID is rarely suspected clinically; the condition is typically identified through either screening gene panels or whole-exome sequencing. The clinical features reported in both AS and *WAC*-related ID include intellectual disability, speech delay, sleep disorders, seizures, and craniofacial changes (e.g., relatively large mouth and prominent chin/mandible). Individuals with *WAC*-related ID, however, typically have less severe intellectual deficiency (mild to severe) than seen in individuals with AS (severe to profound), a larger repertoire of speech ability (e.g., usually can speak words and sentences); and a lower prevalence of seizures, and do not have microcephaly [DeSanto et al 2015, Lugtenberg et al 2016]. To date, 18 individuals have been identified with *WAC*-related ID.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs 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; dietary evaluation to assure optimal nutritional status
- Consultation with a clinical geneticist and/or genetic counselor

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) [Thibert et al 2009]. Carbamezapine, although not contraindicated, is less frequently used than 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 or low glycemic diet [Thibert et al 2012].

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.

Individualization and flexibility in the school are important educational strategies.

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.

Many families construct safe but confining bedrooms to accommodate disruptive nighttime wakefulness. 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.

The behavioral phenotype of Angelman syndrome includes hyperexcitability, hypermotoric behaviors, and deficits in social communication. These limitations place them at risk for social disruptions. On occasion, the use of risperidone (Risperdal®) or other atypical antipsychotic drugs provides some but often limited benefit. When such drugs are needed, care must be taken to avoid over-sedation and other side effects.

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

Agents/Circumstances to Avoid

Carbamezapine, although not contraindicated, is less frequently used than other common anticonvulsants.

Vigabatrin and tigabine (anticonvulsants that increase brain GABA levels) are contraindicated in individuals with Angelman syndrome. For unknown reasons, carbamazapine, vigabatrine, and tigabine can cause development of other seizure types or non-convulsive status epilepticus. This paradoxic seizure development is not limited to individuals with Angelman syndrome [Pelc et al 2008a]

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Clinical trials involving oral administration of folate, vitamin B_{12}, creatine, and betaine have been undertaken in an attempt to augment DNA methylation pathways and possibly increase expression of the paternal *UBE3A* allele in the central nervous system; however, the initial trial did not demonstrate significant clinical benefit [Peters et al 2010] (see full text for more information). More recent therapeutic efforts have focused on activating the otherwise silenced paternal *UBE3A* allele by use of telomerase inhibitors [Huang et al 2011] and antisense oligonucleotides [Meng et al 2015].

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

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.

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. —ED.

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
- UPD of the paternal chromosome 15
- An imprinting defect (ID)
- A pathogenic variant 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 (summarized in Table 2).

For recurrence risk assessment. If the DNA methylation pattern is characteristic for absence of the maternal contribution, the underlying genetic mechanism (deletion, UPD, or ID) should be determined for genetic counseling purposes.

- Deletion analysis should be performed first.

- If no deletion is found, analysis of DNA polymorphisms on chromosome 15 can be used to detect UPD.
- If UPD is not detected, the presumption is that an ID is present; additional studies can then determine if there is a deletion in the IC.

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- to 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* pathogenic variant	As high as 50% if mother also has a pathogenic variant
V	10%-15%	"Other" - no identifiable molecular abnormality	Undetermined risk

IC = imprinting center; ID = imprinting defect; UPD = uniparental disomy
1. Based on terminology by Jiang et al [1999]

Ia. Mothers of individuals with deletions should have chromosome and FISH analyses to determine if they have a chromosome 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 [Kokkonen & Leisti 2000, Sánchez et al 2014].

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, Gimelli et al 2003, Collinson et al 2004, Kuroda et al 2014].

IIa. In families in which AS is the result of paternal UPD and in which no Robertsonian chromosome 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 theoretic consideration regarding the mechanism of UPD. Recurrent meiotic nondisjunction of maternal chromosome 15 has been observed and therefore the recurrence risk is not zero [Harpey et al 1998].

If an individual has AS resulting from paternal UPD and has a normal karyotype, chromosome analysis should be offered to the mother 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 chromosome 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 imprinting center (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 *de novo* pathogenic variant 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, Horsthemke & Buiting 2008]. 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. To date, recurrence of AS in families of probands who have IDs without deletion in the IC has not been reported. Thus, the proband's ID probably represents a *de novo* defect in the imprinting process in 15q11.2-q13 during the mother's oogenesis [Buiting et al 1998]. The risk to the sibs of a proband in such families is less than 1%. There is a single report of a pair of sibs with AS who had a 1-1.5 Mb inversion separating the two IC elements, but no actual IC deletion [Buiting et al 2001].

IV. *UBE3A* pathogenic variants can be inherited or *de novo* [Kishino et al 1997, Matsuura et al 1997, Lossie et al 2001, Bürger et al 2002]. Approximately 30% of pathogenic variants are inherited. Familial studies should be offered to establish maternal inheritance or lack of paternal inheritance [Sadikovic et al 2014]. In addition, several cases of somatic and germline mosaicism for a *UBE3A* pathogenic variant have been noted [Malzac et al 1998, Hosoki et al 2005]. If a proband's mother has a *UBE3A* pathogenic variant, 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* pathogenic variant, IC deletion, or structural chromosome rearrangement has been identified in the mother (or father in the case of UPD and Robertsonian translocations) of a proband, the sibs of the carrier parent should be offered genetic counseling and the option of genetic testing:

- **IC deletions or *UBE3A* pathogenic variants.** If a proband's mother carries a known IC deletion or *UBE3A* pathogenic variant, the mother's sibs are also at risk of carrying the IC deletion or the pathogenic variant. Each child of the unaffected carrier sister 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 inherited the IC deletion or *UBE3A* pathogenic variant from them.

Related Genetic Counseling Issues

Family planning

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

DNA banking 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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Prenatal testing and preimplantation genetic testing (PGT) for high-risk pregnancies require prior identification of the disease-causing mechanism in the family.

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 chromosome/FISH analysis of fetal cells obtained by chorionic villus sampling (usually performed at ~10-12

weeks' gestation) or amniocentesis (usually performed at ~15-18 weeks' gestation) [Kubota et al 1996, Glenn et al 2000, Chang et al 2014].

DNA methylation analysis (for 5- to 7-Mb deletions, UPD, and IC defects) on cells obtained by CVS is theoretically possible [Kubota et al 1996, Glenn et al 2000]. However, the few clinical laboratories doing prenatal testing using DNA methylation analysis prefer using amniocytes because 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 Establishing the Diagnosis).

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

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 analysis or chromosomal microarray analysis (CMA) 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 supernumerary chromosome 15 marker is detected,** FISH analysis or CMA and parent-of-origin studies should be considered to evaluate for a possible deletion (of variable size) or UPD.

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

Other

Assisted reproductive technology (ART). In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have been demonstrated to increase the chance of certain imprinting disorders, like Beckwith-Wiedemann syndrome, in offspring. However, recent studies demonstrate that there is no significant association between AS and IVF or ICSI [Vermeiden & Bernardus 2013].

Fertility. Research from the Netherlands and Germany demonstrate an association between fertility issues and incidence of AS. The percent of couples who experienced fertility issues before having a child with AS ranged from 19% to 25%. There was no positive association with fertility issues and AS in families queried in the United Kingdom [Ludwig et al 2005, Doornbos et al 2007, Vermeiden & Bernardus 2013].

Resources

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

- **Angelman Syndrome Foundation, Inc. (ASF)**
  4255 Westbrook Drive
  Suite 219
  Aurora IL 60504
  Phone: 800-432-6435 (toll-free); 630-978-4245
  Fax: 630-978-7408
  Email: info@angelman.org
  www.angelman.org
- **Foundation for Angelman Syndrome Therapeutics (FAST)**
  PO Box 608
  Downers Grove IL 60515
  Phone: 630-852-FAST; 866-783-0078
  Fax: 630-852-3270
  Email: info@CureAngelman.org
  www.cureangelman.org
- **My46 Trait Profile**
  Angelman syndrome
- **National Library of Medicine Genetics Home Reference**
  Angelman syndrome
- **NCBI Genes and Disease**
  Angelman syndrome
- **American Epilepsy Society (AES)**
  www.aesnet.org
- **Epilepsy Foundation**
  8301 Professional Place East
  Suite 200
  Landover MD 20785-7223
  Phone: 800-332-1000 (toll-free)

Email: ContactUs@efa.org

www.epilepsy.com

- **Medical Home Portal**

  The Parents & Families section of the Medical Home Portal provides information and resources to help families learn how to better care for a child with chronic and complex conditions and to become more effective partners in their child's care.

  Department of Pediatrics University of Utah

  P.O. Box 581289

  Salt Lake City UT 84158

  Phone: 801-213-3920

  Email: info@medicalhomeportal.org

  For Parents & Families

Molecular Genetics

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

Table A. Angelman Syndrome: Genes and Databases

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

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

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

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

Molecular Pathogenesis

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, mitral cells of the olfactory bulb, and visual cortex [Albrecht et al 1997, Jiang et al 1998, Yashiro et al 2009]. It is possible that there is widespread, if not global, *UBE3A* allele-specific expression in mouse and in human brain neurons. 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* expression.

Gene structure. *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. The functions of the different protein isoforms are unknown.

- Isoform I (NM_130838.1, NP_570853.1) corresponds to the open reading frame for E6-AP (see **Normal gene product**).
- Isoform II (NM_000462.3, NP_000453.2) has an additional 20 amino acids.
- Isoform III (NM_130839.2, NP_570854.1) has an additional 23 amino acids at the amino terminus.

For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants

- **Deletions of 15q11.2-q13 (65%-75%).** Three chromosome break points (proximal BP1, BP2, and a distal BP3) are involved in most AS-causing deletion events involving 15q11.1-q13. These deletions span approximately 5-7 Mb [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 (*HERC2*) genes [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.

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

- **Genomic abnormalities of 15q11.1-q13**. It is possible that in otherwise normal individuals preexisting genomic abnormalities may predispose to deletion of 15q11.1-q13 in the germline resulting in offspring with AS.
  - A proportion of mothers who have a child with 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].

- A kindred in which two individuals had deletions (one deletion causing PWS and the other causing AS) has been previously reported to be associated with an inherited inverted intrachromosomal insertion of 15q11.2-q13 [Collinson et al 2004].

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

- **Imprinting defects (3%).** This subset of individuals with AS have a defect in the IC that disrupts the resetting of the normal imprint during gametogenesis. Even though these individuals have biparental inheritance of chromosome 15, the maternal 15q11.2-q13 region has a paternal epigenotype and is, therefore, transcriptionally incompetent for the maternal-only expressed gene(s) in this region [Glenn et al 1993, Buiting et al 2001, Buiting et al 2003].

  Mapping of these deletions (as well as mapping of the IC deletions that are associated with PWS) has delineated two small regions of deletion overlap (SRO) that define two critical elements in the IC region, the AS-SRO and the PWS-SRO [Buiting et al 1995] (see Figure 2). The PWS-SRO is 4.3 kb in size and overlaps with the *SNURF-SNRPN* exon1/promoter region [Ohta et al 1999]. IC deletions found in individuals with AS affect the more centromeric *SNURF-SNRPN* promoter/exon 1 region. The smallest region of overlap in patients with AS and an IC deletion (AS-SRO) is 880 bp in size and maps 35 kb proximal to *SNURF-SNRPN* exon 1 [Buiting et al 1999, Horsthemke & Buiting 2008]. 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%).** More than 150 pathogenic variants have been reported and 60%-70% of these involve small deletions and duplications leading to frameshifts [Camprubí et al 2009, Stenson et al 2009, Abaied et al 2010, Sadikovic et al 2014]. Another approximately 25% involve missense and nonsense pathogenic variants with the remainder representing splicing defects, gross deletions, and complex rearrangements [Stenson et al 2009, Sadikovic et al 2014].

  Most pathogenic variants noted thus far are predicted to disrupt the HECT ligase domain. Exons 9 and 16, which code for part of the HECT domain, account for a high percentage of all pathogenic variants but these coding regions are disproportionately large so the high percentage probably does not represent true hot spots for mutation. It is possible that individuals with milder-effect pathogenic variants (e.g., certain missense and in-frame deletions or duplications) 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].

For more information, see Table A.

Normal gene product. *UBE3A* produces an 865-amino acid E6-associated protein (E6AP). E6AP was first recognized as a protein that binds to p53 and mediates its association with human papilloma virus E6 protein. This binding leads to degradation of the p53 tumor suppressor via the ubiquitin proteasome pathway and thus promotes development of cervical carcinoma [Huibregtse et al 1991, Huang et al 1999]. E6AP facilitates the transfer and covalent linkage of activated ubiquitin (a 76-amino acid protein) to the target protein. The polyubiquitylated substrates are then identified and degraded by the 26S proteasome pathway. E6AP belongs to the HECT (homologous to E6AP COOH-terminus) class of E3 enzymes that share a 40-kd conserved COOH-terminal catalytic domain. The HECT domain of E6AP is a bi-lobed structure with a broad catalytic cleft at the junction of the two lobes. The domain is encoded by exons 9 through 16. The E6-binding site is encoded by exon 9 and the active site cysteine residue that accepts ubiquitin from the E2 ubiquitin-conjugating enzyme is encoded within exon 16 [Yamamoto et al 1997, Kishino & Wagstaff 1998]. Pathogenic variants within the cleft

interfere with ubiquitin-thioester bond formation. Indeed, most AS pathogenic variants occur in the HECT domain region or are predicted to ablate HECT domain function [Huang et al 1999].

A steroid receptor coactivation domain is located upstream of the HECT region but its role in neuronal development is uncertain. E6AP appears to have at least two independent functions since the ligase region and the HECT domain are not required for function of the coactivation domain [El Hokayem & Nawaz 2014].

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

Several E6AP protein targets have been discovered [Kühne & Banks 1998, Kumar et al 1999, Oda et al 1999, Khan et al 2006, Li et al 2006, Reiter et al 2006, Louria-Hayon et al 2009, Shimoji et al 2009, Margolis et al 2010, Scheiffele & Beg 2010, Gossan et al 2014].

The guanine exchange protein, ephexin-5, is known to regulate activity of EphB receptor signaling that is a crucial component of dendritic growth [Margolis et al 2010]. Eph receptors are known to be enriched at synapses and are important in regulating dendritic spine density. The EphB receptors interact with ephrin ligands and regulate dendritic development through small GTPases of the Rho family (Rho, Rac, and Cdc42) by activation of guanine nucleotide exchange factors (GEFs) [Murai & Pasquale 2003]. It is unknown how abnormalities in E6AP-target protein interactions lead to AS but the recently identified targets strongly indicate that the E6AP protein is crucial to development of normal synapses and neural plasticity.

References

Published Guidelines / Consensus Statements

American Society of Human Genetics/American College of Medical Genetics Test and Technology Transfer Committee. Diagnostic testing for Prader-Willi and Angelman syndromes: Report of the ASHG/ACMG Test and Technology Transfer Committee (pdf). 1996. Available online. Accessed 2-21-20.

Shaffer LG, Agan N, Goldberg JD, Ledbetter DH, Longshore JW, Cassidy SB. American College of Medical Genetics statement on diagnostic testing for uniparental disomy (pdf). 2001. Available online. Accessed 2-21-20.

Williams CA, Beaudet AL, Clayton-Smith J, Knoll JH, Kyllerman M, Laan LA, Magenis RE, Moncla A, Schinzel AA, Summers JA, Wagstaff J. Angelman syndrome 2005: updated consensus for diagnostic criteria. 2006.

Literature Cited

Abaied L, Trabelsi M, Chaabouni M, Kharrat M, Kraoua L, M'rad R, Tebib N, Maazoul F, Chaabouni H. A novel UBE3A truncating mutation in large Tunisian Angelman syndrome pedigree. Am J Med Genet A. 2010;152A:141–6. PubMed PMID: 20034088.

Albrecht U, Sutcliffe JS, Cattanach BM, Beechey CV, Armstrong D, Eichele G, Beaudet AL. Imprinted expression of the murine Angelman syndrome gene, Ube3a, in hippocampal and Purkinje neurons. Nat Genet. 1997;17:75–8. PubMed PMID: 9288101.

Amos-Landgraf JM, Ji Y, Gottlieb W, Depinet T, Wandstrat AE, Cassidy SB, Driscoll DJ, Rogan PK, Schwartz S, Nicholls RD. Chromosome breakage in the Prader-Willi and Angelman syndromes involves recombination between large, transcribed repeats at proximal and distal breakpoints. Am J Hum Genet. 1999;65:370–86. PubMed PMID: 10417280.

Arn PH, Williams CA, Zori RT, Driscoll DJ, Rosenblatt DS. Methylenetetrahydrofolate reductase deficiency in a patient with phenotypic findings of Angelman syndrome. Am J Med Genet. 1998;77:198–200. PubMed PMID: 9605586.

Bird LM. Angelman syndrome: review of clinical and molecular aspects. Appl Clin Genet. 2014;7:93–104. PubMed PMID: 24876791.

Boyar FZ, Whitney MM, Lossie AC, Gray BA, Keller KL, Stalker HJ, Zori RT, Geffken G, Mutch J, Edge PJ, Voeller KS, Williams CA, Driscoll DJ. A family with a grand-maternally derived interstitial duplication of proximal 15q. Clin Genet. 2001;60:421–30. PubMed PMID: 11846734.

Boyd SG, Cross JH, Dan B (1997) EEG features in Angelman syndrome. Eur J Ped Neurol 1:4, A1

Brunetti-Pierri N, Berg JS, Scaglia F, Belmont J, Bacino CA, Sahoo T, Lalani SR, Graham B, Lee B, Shinawi M, Shen J, Kang SH, Pursley A, Lotze T, Kennedy G, Lansky-Shafer S, Weaver C, Roeder ER, Grebe TA, Arnold GL, Hutchison T, Reimschisel T, Amato S, Geragthy MT, Innis JW, Obersztyn E, Nowakowska B, Rosengren SS, Bader PI, Grange DK, Naqvi S, Garnica AD, Bernes SM, Fong CT, Summers A, Walters WD, Lupski JR, Stankiewicz P, Cheung SW, Patel A. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet. 2008;40:1466–71. PubMed PMID: 19029900.

Bruni O, Ferri R, D'Agostino G, Miano S, Roccella M, Elia M. Sleep disturbances in Angelman syndrome: a questionnaire study. Brain Dev. 2004;26:233–40. PubMed PMID: 15130689.

Buiting K. Prader-Willi syndrome and Angelman syndrome. Am J Med Genet C Semin Med Genet. 2010;154C:365–76. PubMed PMID: 20803659.

Buiting K, Barnicoat A, Lich C, Pembrey M, Malcolm S, Horsthemke B. Disruption of the bipartite imprinting center in a family with Angelman syndrome. Am J Hum Genet. 2001;68:1290–4. PubMed PMID: 11283796.

Buiting K, Dittrich B, Gross S, Lich C, Färber C, Buchholz T, Smith E, Reis A, Bürger J, Nöthen MM, Barth-Witte U, Janssen B, Abeliovich D, Lerer I, van den Ouweland AM, Halley DJ, Schrander-Stumpel C, Smeets H, Meinecke P, Malcolm S, Gardner A, Lalande M, Nicholls RD, Friend K, Schulze A, Matthijs G, Kokkonen H, Hilbert P, Van Maldergem L, Glover G, Carbonell P, Willems P, Gillessen-Kaesbach G, Horsthemke B. Sporadic imprinting defects in Prader-Willi syndrome and Angelman syndrome: implications for imprint-switch models, genetic counseling, and prenatal diagnosis. Am J Hum Genet. 1998;63:170–80. PubMed PMID: 9634532.

Buiting K, Gross S, Lich C, Gillessen-Kaesbach G, el-Maarri O, Horsthemke B. Epimutations in Prader-Willi and Angelman syndromes: a molecular study of 136 patients with an imprinting defect. Am J Hum Genet. 2003;72:571–7. PubMed PMID: 12545427.

Buiting K, Lich C, Cottrell S, Barnicoat A, Horsthemke B. A 5-kb imprinting center deletion in a family with Angelman syndrome reduces the shortest region of deletion overlap to 880 bp. Hum Genet. 1999;105:665–6. PubMed PMID: 10647904.

Buiting K, Saitoh S, Gross S, Dittrich B, Schwartz S, Nicholls RD, Horsthemke B. Inherited microdeletions in the Angelman and Prader-Willi syndromes define an imprinting centre on human chromosome 15. Nat Genet. 1995;9:395–400. PubMed PMID: 7795645.

Bürger J, Horn D, Tonnies H, Neitzel H, Reis A. Familial interstitial 570 kbp deletion of the UBE3A gene region causing Angelman syndrome but not Prader-Willi syndrome. Am J Med Genet. 2002;111:233–7. PubMed PMID: 12210318.

Camprubí C, Guitart M, Gabau E, Coll MD, Villatoro S, Oltra S, Roselló M, Ferrer I, Monfort S, Orellana C, Martínez F. Novel UBE3A mutations causing Angelman syndrome: different parental origin for single nucleotide changes and multiple nucleotide deletions or insertions. Am J Med Genet A. 2009;149A:343–8. PubMed PMID: 19213023.

Cassidy SB, Dykens E, Williams CA. Prader-Willi and Angelman syndromes: sister imprinted disorders. Am J Med Genet. 2000;97:136–46. PubMed PMID: 11180221.

Castro-Gago M, Gómez-Lado C, Eirís-Puñal J, Rodríguez-Mugico VM. Abnormal myelination in Angelman syndrome. Eur J Paediatr Neurol. 2010;14:292. PubMed PMID: 19720548.

Chang CW, Hsu HK, Kao CC, Huang JY, Kuo PL. Prenatal diagnosis of Prader-Willi syndrome and Angelman syndrome for fetuses with suspicious deletion of chromosomal region 15q11-q13. Int J Gynaecol Obstet. 2014;125:18–21. PubMed PMID: 24434231.

Christian SL, Fantes JA, Mewborn SK, Huang B, Ledbetter DH. Large genomic duplicons map to sites of instability in the Prader-Willi/Angelman syndrome chromosome region (15q11-q13). Hum Mol Genet. 1999;8:1025–37. PubMed PMID: 10332034.

Christianson AL, Stevenson RE, van der Meyden CH, Pelser J, Theron FW, van Rensburg PL, Chandler M, Schwartz CE. X linked severe mental retardation, craniofacial dysmorphology, epilepsy, ophthalmoplegia, and cerebellar atrophy in a large South African kindred is localised to Xq24-q27. J Med Genet. 1999;36:759–66. PubMed PMID: 10528855.

Ciechanover A. The ubiquitin-proteasome pathway: on protein death and cell life. EMBO J. 1998;17:7151–60. PubMed PMID: 9857172.

Clayton-Smith J. Clinical research on Angelman syndrome in the United Kingdom: observations on 82 affected individuals. Am J Med Genet. 1993;46:12–15. PubMed PMID: 7684188.

Clayton-Smith J, Pembrey ME. Angelman syndrome. J Med Genet. 1992;29:412–5. PubMed PMID: 1619637.

Collinson MN, Roberts SE, Crolla JA, Dennis NR. A familial balanced inverted insertion ins(15)(q15q13q11.2) producing Prader-Willi syndrome, Angelman syndrome and duplication of 15q11.2-q13 in a single family: Importance of differentiation from a paracentric inversion. Am J Med Genet A. 2004;126A:27–32. PubMed PMID: 15039970.

Dagli A, Buiting K, Williams CA. Molecular and clinical aspects of Angelman syndrome. Mol Syndromol. 2012;2:100–12. PubMed PMID: 22670133.

DeSanto C, D'Aco K, Araujo GC, Shannon N, Study DDD, Vernon H, Rahrig A, Monaghan KG, Niu Z, Vitazka P, Dodd J, Tang S, Manwaring L, Martir-Negron A, Schnur RE, Juusola J, Schroeder A, Pan V, Helbig KL, Friedman B, Shinawi M. WAC loss-of-function mutations cause a recognisable syndrome characterised by dysmorphic features, developmental delay and hypotonia and recapitulate 10p11.23 microdeletion syndrome. J Med Genet. 2015;52:754–61. PubMed PMID: 26264232.

Didden R, Korzilius H, Duker P, Curfs L. Communicative functioning in individuals with Angelman syndrome: a comparative study. Disabil Rehabil. 2004;26:1263–7. PubMed PMID: 15513724.

Doornbos M, Sikkema-Raddatz B, Ruijvenkamp CA, Dijkhuizen T, Bijlsma EK, Gijsbers AC, Hilhorst-Hofstee Y, Hordijk R, Verbruggen KT, Kerstjens-Frederikse WS, van Essen T, Kok K, van Silfhout AT, Breuning M, van Ravenswaaij-Arts CM. Nine patients with a microdeletion 15q11.2 between breakpoints 1 and 2 of the Prader-Willi critical region, possibly associated with behavioural disturbances. Eur J Med Genet. 2009;52:108–15. PubMed PMID: 19328872.

Doornbos ME, Maas SM, McDonnell J, Vermeiden JP, Hennekam RC. Infertility, assisted reproduction technologies and imprinting disturbances: a Dutch study. Hum Reprod. 2007;22:2476–80. PubMed PMID: 17586835.

El Hokayem J, Nawaz Z. E6AP in the brain: one protein, dual function, multiple diseases. Mol Neurobiol. 2014;49:827–39. PubMed PMID: 24091829.

Fang P, Lev-Lehman E, Tsai TF, Matsuura T, Benton CS, Sutcliffe JS, Christian SL, Kubota T, Halley DJ, Meijers-Heijboer H, Langlois S, Graham JM Jr, Beuten J, Willems PJ, Ledbetter DH, Beaudet AL. The spectrum of

mutations in UBE3A causing Angelman syndrome. Hum Mol Genet. 1999;8:129–35. PubMed PMID: 9887341.

Fiumara A, Pittalà A, Cocuzza M, Sorge G. Epilepsy in patients with Angelman syndrome. Ital J Pediatr. 2010;36:31. PubMed PMID: 20398390.

Fridman C, Varela MC, Kok F, Diament A, Koiffmann CP. Paternal UPD15: further genetic and clinical studies in four Angelman syndrome patients. Am J Med Genet. 2000;92:322–7. PubMed PMID: 10861661.

Friez MJ, Jones JR, Clarkson K, Lubs H, Abuelo D, Bier JA, Pai S, Simensen R, Williams C, Giampietro PF, Schwartz CE, Stevenson RE. Recurrent infections, hypotonia, and mental retardation caused by duplication of MECP2 and adjacent region in Xq28. Pediatrics. 2006;118:e1687–95. PubMed PMID: 17088400.

Galván-Manso M, Campistol J, Conill J, Sanmarti FX. Analysis of the characteristics of epilepsy in 37 patients with the molecular diagnosis of Angelman syndrome. Epileptic Disord. 2005;7:19–25. PubMed PMID: 15741136.

Gentile JK, Tan WH, Horowitz LT, Bacino CA, Skinner SA, Barbieri-Welge R, Bauer-Carlin A, Beaudet AL, Bichell TJ, Lee HS, Sahoo T, Waisbren SE, Bird LM, Peters SU. A neurodevelopmental survey of Angelman syndrome with genotype-phenotype correlations. J Dev Behav Pediatr. 2010;31:592–601. PubMed PMID: 20729760.

Gilfillan GD, Selmer KK, Roxrud I, Smith R, Kyllerman M, Eiklid K, Kroken M, Mattingsdal M, Egeland T, Stenmark H, Sjøholm H, Server A, Samuelsson L, Christianson A, Tarpey P, Whibley A, Stratton MR, Futreal PA, Teague J, Edkins S, Gecz J, Turner G, Raymond FL, Schwartz C, Stevenson RE, Undlien DE, Strømme P. SLC9A6 mutations cause X-linked mental retardation, microcephaly, epilepsy, and ataxia, a phenotype mimicking Angelman syndrome. Am J Hum Genet. 2008;82:1003–10. PubMed PMID: 18342287.

Gimelli G, Pujana MA, Patricelli MG, Russo S, Giardino D, Larizza L, Cheung J, Armengol L, Schinzel A, Estivill X, Zuffardi O. Genomic inversions of human chromosome 15q11-q13 in mothers of Angelman syndrome patients with class II (BP2/3) deletions. Hum Mol Genet. 2003;12:849–58. PubMed PMID: 12668608.

Giroud M, Daubail B, Khayat N, Chouchane M, Berger E, Muzard E, Medeiros de Bustos E, Thauvin-Robinet C, Faivre L, Masurel A, Darmency-Stamboul V, Huet F, Bejot Y, Giroud M, Moulin T. Angelman syndrome: a case series assessing neurological issues in adulthood. Eur Neurol. 2015;73:119–25. PubMed PMID: 25472600.

Gitiaux C, Ceballos-Picot I, Marie S, Valayannopoulos V, Rio M, Verrieres S, Benoist JF, Vincent MF, Desguerre I, Bahi-Buisson N. Misleading behavioural phenotype with adenylosuccinate lyase deficiency. Eur J Hum Genet. 2009;17:133–6. PubMed PMID: 18830228.

Glenn CC, Deng G, Michaelis RC, Tarleton J, Phelan MC, Surh L, Yang TP, Driscoll DJ. DNA methylation analysis with respect to prenatal diagnosis of the Angelman and Prader-Willi syndromes and imprinting. Prenat Diagn. 2000;20:300–6. PubMed PMID: 10740202.

Glenn CC, Nicholls RD, Robinson WP, Saitoh S, Niikawa N, Schinzel A, Horsthemke B, Driscoll DJ. Modification of 15q11-q13 DNA methylation imprints in unique Angelman and Prader-Willi patients. Hum Mol Genet. 1993;2:1377–82. PubMed PMID: 8242060.

Gossan NC, Zhang F, Guo B, Jin D, Yoshitane H, Yao A, Glossop N, Zhang YQ, Fukada Y, Meng QJ. The E3 ubiquitin ligase UBE3A is an integral component of the molecular circadian clock through regulating the BMAL1 transcription factor. Nucleic Acids Res. 2014;42:5765–75. PubMed PMID: 24728990.

Harlalka GV, Baple EL, Cross H, Kuhnle S, Cubillos-Rojas M, Matentzoglu K, Patton MA, Wagner K, Coblentz R, Ford DL, Mackay DJ, Chioza BA, Scheffner M, Rosa JL, Crosby AH. Mutation of HERC2 causes developmental delay with Angelman-like features. J Med Genet. 2013;50:65–73. PubMed PMID: 23243086.

Harpey JP, Heron D, Prudent M, Lesourd S, Henry I, Royer-Legrain G, Munnich A, Bonnefont JP. Recurrent meiotic nondisjunction of maternal chromosome 15 in a sibship. Am J Med Genet. 1998;76:103–4. PubMed PMID: 9508076.

Harting I, Seitz A, Rating D, Sartor K, Zschocke J, Janssen B, Ebinger F, Wolf NI. Abnormal myelination in Angelman syndrome. Eur J Paediatr Neurol. 2009;13:271–6. PubMed PMID: 18573670.

Hershko A, Ciechanover A. The ubiquitin system. Annu Rev Biochem. 1998;67:425–79. PubMed PMID: 9759494.

Herzing LB, Cook EH Jr, Ledbetter DH. Allele-specific expression analysis by RNA-FISH demonstrates preferential maternal expression of UBE3A and imprint maintenance within 15q11- q13 duplications. Hum Mol Genet. 2002;11:1707–18. PubMed PMID: 12095913.

Herzing LB, Kim SJ, Cook EH Jr, Ledbetter DH. The human aminophospholipid-transporting ATPase gene ATP10C maps adjacent to UBE3A and exhibits similar imprinted expression. Am J Hum Genet. 2001;68:1501–5. PubMed PMID: 11353404.

Horsthemke B, Buiting K. Genomic imprinting and imprinting defects in humans. Adv Genet. 2008;61:225–46. PubMed PMID: 18282508.

Horsthemke B, Maat-Kievit A, Sleegers E, van den Ouweland A, Buiting K, Lich C, Mollevanger P, Beverstock G, Gillessen-Kaesbach G, Schwanitz G. Familial translocations involving 15q11-q13 can give rise to interstitial deletions causing Prader-Willi or Angelman syndrome. J Med Genet. 1996;33:848–51. PubMed PMID: 8933339.

Hosoki K, Takano K, Sudo A, Tanaka S, Saitoh S. Germline mosaicism of a novel UBE3A mutation in Angelman syndrome. Am J Med Genet A. 2005;138A:187–9. PubMed PMID: 16100729.

Huang HS, Allen JA, Mabb AM, King IF, Miriyala J, Taylor-Blake B, Sciaky N, Dutton JW Jr, Lee HM, Chen X, Jin J, Bridges AS, Zylka MJ, Roth BL, Philpot BD. Topoisomerase inhibitors unsilence the dormant allele of Ube3a in neurons. Nature. 2011;481:185–9. PubMed PMID: 22190039.

Huang L, Kinnucan E, Wang G, Beaudenon S, Howley PM, Huibregtse JM, Pavletich NP. Structure of an E6AP-UbcH7 complex: insights into ubiquitination by the E2-E3 enzyme cascade. Science. 1999;286:1321–6. PubMed PMID: 10558980.

Huibregtse JM, Scheffner M, Howley PM. A cellular protein mediates association of p53 with the E6 oncoprotein of human papillomavirus types 16 or 18. EMBO J. 1991;10:4129–35. PubMed PMID: 1661671.

Jiang Y, Lev-Lehman E, Bressler J, Tsai TF, Beaudet AL. Genetics of Angelman syndrome. Am J Hum Genet. 1999;65:1–6. PubMed PMID: 10364509.

Jiang YH, Armstrong D, Albrecht U, Atkins CM, Noebels JL, Eichele G, Sweatt JD, Beaudet AL. Mutation of the Angelman ubiquitin ligase in mice causes increased cytoplasmic p53 and deficits of contextual learning and long-term potentiation. Neuron. 1998;21:799–811. PubMed PMID: 9808466.

Khan OY, Fu G, Ismail A, Srinivasan S, Cao X, Tu Y, Lu S, Nawaz Z. Multifunction steroid receptor coactivator, E6-associated protein, is involved in development of the prostate gland. Mol Endocrinol. 2006;20:544–59. PubMed PMID: 16254014.

Kishino T, Lalande M, Wagstaff J. UBE3A/E6-AP mutations cause Angelman syndrome. Nat Genet. 1997;15:70–3. PubMed PMID: 8988171.

Kishino T, Wagstaff J. Genomic organization of the UBE3A/E6-AP gene and related pseudogenes. Genomics. 1998;47:101–7. PubMed PMID: 9465301.

Knoll JH, Nicholls RD, Magenis RE, Glatt K, Graham JM Jr, Kaplan L, Lalande M. Angelman syndrome: three molecular classes identified with chromosome 15q11q13-specific DNA markers. Am J Hum Genet. 1990;47:149–54. PubMed PMID: 1971993.

Kokkonen H, Leisti J. An unexpected recurrence of Angelman syndrome suggestive of maternal germ-line mosaicism of del(15)(q11q13) in a Finnish family. Hum Genet. 2000;107:83–5. PubMed PMID: 10982040.

Korff CM, Kelley KR, Nordli DR Jr. Notched delta, phenotype, and Angelman syndrome. J Clin Neurophysiol. 2005;22:238–43. PubMed PMID: 16093895.

Kubota T, Aradhya S, Macha M, Smith AC, Surh LC, Satish J, Verp MS, Nee HL, Johnson A, Christan SL, Ledbetter DH. Analysis of parent of origin specific DNA methylation at SNRPN and PW71 in tissues: implication for prenatal diagnosis. J Med Genet. 1996;33:1011–4. PubMed PMID: 9004133.

Kühne C, Banks L. E3-ubiquitin ligase/E6-AP links multicopy maintenance protein 7 to the ubiquitination pathway by a novel motif, the L2G box. J Biol Chem. 1998;273:34302–9. PubMed PMID: 9852095.

Kumar S, Talis AL, Howley PM. Identification of HHR23A as a substrate for E6-associated protein- mediated ubiquitination. J Biol Chem. 1999;274:18785–92. PubMed PMID: 10373495.

Kuroda Y, Ohashi I, Saito T, Nagai J, Ida K, Naruto T, Wada T, Kurosawa K. Deletion of UBE3A in brothers with Angelman syndrome at the breakpoint with an inversion at 15q11.2. Am J Med Genet A. 2014;164A:2873–8. PubMed PMID: 25099823.

Larson AM, Shinnick JE, Shaaya EA, Thiele EA, Thibert RL. Angelman syndrome in adulthood. Am J Med Genet A. 2015;167A:331–44. PubMed PMID: 25428759.

Lawson-Yuen A, Wu BL, Lip V, Sahoo T, Kimonis V. Atypical cases of Angelman syndrome. Am J Med Genet A. 2006;140:2361–4. PubMed PMID: 17036311.

Li L, Li Z, Howley PM, Sacks DB. E6AP and calmodulin reciprocally regulate estrogen receptor stability. J Biol Chem. 2006;281:1978–85. PubMed PMID: 16314411.

Lossie AC, Driscoll DJ. Transmission of Angelman syndrome by an affected mother. Genet Med. 1999;1:262–6. PubMed PMID: 11258627.

Lossie AC, Whitney MM, Amidon D, Dong HJ, Chen P, Theriaque D, Hutson A, Nicholls RD, Zori RT, Williams CA, Driscoll DJ. Distinct phenotypes distinguish the molecular classes of Angelman syndrome. J Med Genet. 2001;38:834–45. PubMed PMID: 11748306.

Louria-Hayon I, Alsheich-Bartok O, Levav-Cohen Y, Silberman I, Berger M, Grossman T, Matentzoglu K, Jiang YH, Muller S, Scheffner M, Haupt S, Haupt Y. E6AP promotes the degradation of the PML tumor suppressor. Cell Death Differ. 2009;16:1156–66. PubMed PMID: 19325566.

Low D, Chen KS. UBE3A regulates MC1R expression: a link to hypopigmentation in Angelman syndrome. Pigment Cell Melanoma Res. 2011;24:944–52. PubMed PMID: 21733131.

Ludwig M, Katalinic A, Gross S, Sutcliffe A, Varon R, Horsthemke B. Increased prevalence of imprinting defects in patients with Angelman syndrome born to subfertile couples. J Med Genet. 2005;42:289–91. PubMed PMID: 15805153.

Lugtenberg D., Reijnders MR, Fenckova M, Bijlsma EK, Bernier R, van Bon BW, Smeets E. Vulto-van Silfhout AT, Bosch D, Eichler EE, Mefford HC, Carvill GL, Bongers EM, Schuurs-Hoeijmakers JH, Ruivenkamp CA, Santen GW, van den Maagdenberg AM, Peeters-Scholte CM, Kuenen S, Verstreken P, Pfundt R, Yntema HG, de Vries PF, Veltman JA, Hoischen A, Gilissen C, de Vries BB, Schenck A, Kleefstra T, Vissers LE. De novo loss-of-function mutations in WAC cause a recognizable intellectual disability syndrome and learning deficits in Drosophila. Eur J Hum Genet. 2016;24:1145–53. PubMed PMID: 26757981.

Lugtenberg D, Kleefstra T, Oudakker AR, Nillesen WM, Yntema HG, Tzschach A, Raynaud M, Rating D, Journel H, Chelly J, Goizet C, Lacombe D, Pedespan JM, Echenne B, Tariverdian G, O'Rourke D, King MD, Green A, van Kogelenberg M, Van Esch H, Gecz J, Hamel BC, van Bokhoven H, de Brouwer AP. Structural variation in Xq28: MECP2 duplications in 1% of patients with unexplained XLMR and in 2% of male patients with severe encephalopathy. Eur J Hum Genet. 2009;17:444–53. PubMed PMID: 18985075.

Malzac P, Webber H, Moncla A, Graham JM, Kukolich M, Williams C, Pagon RA, Ramsdell LA, Kishino T, Wagstaff J. Mutation analysis of UBE3A in Angelman syndrome patients. Am J Hum Genet. 1998;62:1353–60. PubMed PMID: 9585605.

Margolis SS, Salogiannis J, Lipton DM, Mandel-Brehm C, Wills ZP, Mardinly AR, Hu L, Greer PL, Bikoff JB, Ho HY, Soskis MJ, Sahin M, Greenberg ME. EphB-mediated degradation of the RhoA GEF Ephexin5 relieves a developmental brake on excitatory synapse formation. Cell. 2010;143:442–55. PubMed PMID: 21029865.

Masurel-Paulet A, Andrieux J, Callier P, Cuisset JM, Le Caignec C, Holder M, Thauvin-Robinet C, Doray B, Flori E, Alex-Cordier MP, Beri M, Boute O, Delobel B, Dieux A, Vallee L, Jaillard S, Odent S, Isidor B, Beneteau C, Vigneron J, Bilan F, Gilbert-Dussardier B, Dubourg C, Labalme A, Bidon C, Gautier A, Pernes P, Pinoit JM, Huet F, Mugneret F, Aral B, Jonveaux P, Sanlaville D, Faivre L. Delineation of 15q13.3 microdeletions. Clin Genet. 2010;78:149–61. PubMed PMID: 20236110.

Matsuura T, Sutcliffe JS, Fang P, Galjaard RJ, Jiang YH, Benton CS, Rommens JM, Beaudet AL. De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. Nat Genet. 1997;15:74–7. PubMed PMID: 8988172.

Meng L, Ward AJ, Chun S, Bennett CF, Beaudet AL, Rigo F. Towards a therapy for Angelman syndrome by targeting a long non-coding RNA. Nature. 2015;518:409–12. PubMed PMID: 25470045.

Mertz LG, Christensen R, Vogel I, Hertz JM, Nielsen KB, Gronskov K, Ostergaard JR. Angelman syndrome in Denmark. birth incidence, genetic findings, and age at diagnosis. Am J Med Genet A. 2013;161A:2197–203. PubMed PMID: 23913711.

Murai KK, Pasquale EB. 'Eph'ective signaling: forward, reverse and crosstalk. J Cell Sci. 2003;116:2823–32. PubMed PMID: 12808016.

Nazlican H, Zeschnigk M, Claussen U, Michel S, Boehringer S, Gillessen-Kaesbach G, Buiting K, Horsthemke B. Somatic mosaicism in patients with Angelman syndrome and an imprinting defect. Hum Mol Genet. 2004;13:2547–55. PubMed PMID: 15385437.

Nicholls RD, Knepper JL. Genome organization, function, and imprinting in Prader-Willi and Angelman syndromes. Annu Rev Genomics Hum Genet. 2001;2:153–75. PubMed PMID: 11701647.

Nygren AO, Ameziane N, Duarte HM, Vijzelaar RN, Waisfisz Q, Hess CJ, Schouten JP, Errami A. Methylation-specific MLPA (MS-MLPA): simultaneous detection of CpG methylation and copy number changes of up to 40 sequences. Nucleic Acids Res. 2005;33:e128. PubMed PMID: 16106041.

Oda H, Kumar S, Howley PM. Regulation of the Src family tyrosine kinase Blk through E6AP-mediated ubiquitination. Proc Natl Acad Sci U S A. 1999;96:9557–62. PubMed PMID: 10449731.

Ohta T, Buiting K, Kokkonen H, McCandless S, Heeger S, Leisti H, Driscoll DJ, Cassidy SB, Horsthemke B, Nicholls RD. Molecular mechanism of angelman syndrome in two large families involves an imprinting mutation. Am J Hum Genet. 1999;64:385–96. PubMed PMID: 9973277.

Peippo MM, Simola KO, Valanne LK, Larsen AT, Kähkönen M, Auranen MP, Ignatius J. Pitt-Hopkins syndrome in two patients and further definition of the phenotype. Clin Dysmorphol. 2006;15:47–54. PubMed PMID: 16531728.

Pelc K, Boyd SG, Cheron G, Dan B. Epilepsy in Angelman syndrome. Seizure. 2008a;17:211–7. PubMed PMID: 17904873.

Pelc K, Cheron G, Boyd SG, Dan B. Are there distinctive sleep problems in Angelman syndrome? Sleep Med. 2008b;9:434–41. PubMed PMID: 17765640.

Peters SU, Bird LM, Kimonis V, Glaze DG, Shinawi LM, Bichell TJ, Barbieri-Welge R, Nespeca M, Anselm I, Waisbren S, Sanborn E, Sun Q, O'Brien WE, Beaudet AL, Bacino CA. Double-blind therapeutic trial in Angelman syndrome using betaine and folic acid. Am J Med Genet A. 2010;152A:1994–2001. PubMed PMID: 20635355.

Precht KS, Lese CM, Spiro RP, Huttenlocher PR, Johnston KM, Baker JC, Christian SL, Kittikamron K, Ledbetter DH. Two 22q telomere deletions serendipitously detected by FISH. J Med Genet. 1998;35:939–42. PubMed PMID: 9832042.

Procter M, Chou LS, Tang W, Jama M, Mao R. Molecular diagnosis of Prader-Willi and Angelman syndromes by methylation-specific melting analysis and methylation-specific multiplex ligation-dependent probe amplification. Clin Chem. 2006;52:1276–83. PubMed PMID: 16690734.

Pujana MA, Nadal M, Guitart M, Armengol L, Gratacos M, Estivill X. Human chromosome 15q11-q14 regions of rearrangements contain clusters of LCR15 duplicons. Eur J Hum Genet. 2002;10:26–35. PubMed PMID: 11896453.

Ramsden SC, Clayton-Smith J, Birch R, Buiting K. Practice guidelines for the molecular analysis of Prader-Willi and Angelman syndromes. BMC Med Genet. 2010;11:70. PubMed PMID: 20459762.

Reiter LT, Seagroves TN, Bowers M, Bier E. Expression of the Rho-GEF Pbl/ECT2 is regulated by the UBE3A E3 ubiquitin ligase. Hum Mol Genet. 2006;15:2825–35. PubMed PMID: 16905559.

Robinson WP, Christian SL, Kuchinka BD, Penaherrera MS, Das S, Schuffenhauer S, Malcolm S, Schinzel AA, Hassold TJ, Ledbetter DH. Somatic segregation errors predominantly contribute to the gain or loss of a paternal chromosome leading to uniparental disomy for chromosome 15. Clin Genet. 2000;57:349–58. PubMed PMID: 10852369.

Rosenfeld JA, Stephens LE, Coppinger J, Ballif BC, Hoo JJ, French BN, Banks VC, Smith WE, Manchester D, Tsai AC, Merrion K, Mendoza-Londono R, Dupuis L, Schultz R, Torchia B, Sahoo T, Bejjani B, Weaver DD, Shaffer LG. Deletions flanked by breakpoints 3 and 4 on 15q13 may contribute to abnormal phenotypes. Eur J Hum Genet. 2011;19:547–54. PubMed PMID: 21248749.

Rougeulle C, Cardoso C, Fontes M, Colleaux L, Lalande M. An imprinted antisense RNA overlaps UBE3A and a second maternally expressed transcript. Nat Genet. 1998;19:15–6. PubMed PMID: 9590281.

Rougeulle C, Glatt H, Lalande M. The Angelman syndrome candidate gene, UBE3A/E6-AP, is imprinted in brain. Nat Genet. 1997;17:14–5. [letter]. PubMed PMID: 9288088.

Rubin DI, Patterson MC, Westmoreland BF, Klass DW. Angelman's syndrome: clinical and electroencephalographic findings. Electroencephalogr Clin Neurophysiol. 1997;102:299–302. PubMed PMID: 9146490.

Runte M, Huttenhofer A, Gross S, Kiefmann M, Horsthemke B, Buiting K. The IC-SNURF-SNRPN transcript serves as a host for multiple small nucleolar RNA species and as an antisense RNA for UBE3A. Hum Mol Genet. 2001;10:2687–700. PubMed PMID: 11726556.

Sadikovic B, Fernandes P, Zhang VW, Ward PA, Miloslavskaya I, Rhead W, Rosenbaum R, Gin R, Roa B, Fang P. Mutation Update for UBE3A variants in Angelman syndrome. Hum Mutat. 2014;35:1407–17. PubMed PMID: 25212744.

Sahoo T, Bacino CA, German JR, Shaw CA, Bird LM, Kimonis V, Anselm I, Waisbren S, Beaudet AL, Peters SU. Identification of novel deletions of 15q11q13 in Angelman syndrome by array-CGH: molecular characterization and genotype-phenotype correlations. Eur J Hum Genet. 2007;15:943–9. PubMed PMID: 17522620.

Sahoo T, Peters SU, Madduri NS, Glaze DG, German JR, Bird LM, Barbieri-Welge R, Bichell TJ, Beaudet AL, Bacino CA. Microarray based comparative genomic hybridization testing in deletion bearing patients with Angelman syndrome: genotype-phenotype correlations. J Med Genet. 2006;43:512–6. PubMed PMID: 16183798.

Saitoh S, Wada T, Okajima M, Takano K, Sudo A, Niikawa N. Uniparental disomy and imprinting defects in Japanese patients with Angelman syndrome. Brain Dev. 2005;27:389–91. PubMed PMID: 16023557.

Sánchez J, Fernández R, Madruga M, Bernabeu-Wittel J, Antiñolo G, Borrego S. Somatic and germ-line mosaicism of deletion 15q11.2-q13 in a mother of dyzigotic twins with Angelman syndrome. Am J Med Genet A. 2014;164A:370–6. PubMed PMID: 24311297.

Sato K, Iwakoshi M, Shimokawa O, Sakai H, Ohta T, Saitoh S, Miyake N, Niikawa N, Harada N, Saitsu H, Mizuguchi T, Matsumoto N. Angelman syndrome caused by an identical familial 1,487-kb deletion. Am J Med Genet A. 2007;143A:98–101. PubMed PMID: 17152063.

Scheiffele P, Beg AA. Neuroscience: Angelman syndrome connections. Nature. 2010;468:907–8. PubMed PMID: 21164477.

Schroer RJ, Holden KR, Tarpey PS, Matheus MG, Griesemer DA, Friez MJ, Fan JZ, Simensen RJ, Strømme P, Stevenson RE, Stratton MR, Schwartz CE. Natural history of Christianson syndrome. Am J Med Genet A. 2010;152A:2775–83. PubMed PMID: 20949524.

Sharkey FH, Morrison N, Murray R, Iremonger J, Stephen J, Maher E, Tolmie J, Jackson AP. 17q21.31 microdeletion syndrome: further expanding the clinical phenotype. Cytogenet Genome Res. 2009;127:61–6. PubMed PMID: 20110647.

Shimoji T, Murakami K, Sugiyama Y, Matsuda M, Inubushi S, Nasu J, Shirakura M, Suzuki T, Wakita T, Kishino T, Hotta H, Miyamura T, Shoji I. Identification of annexin A1 as a novel substrate for E6AP-mediated ubiquitylation. J Cell Biochem. 2009;106:1123–35. PubMed PMID: 19204938.

Spiegel EK, Colman RF, Patterson D. Adenylosuccinate lyase deficiency. Mol Genet Metab. 2006;89:19–31. PubMed PMID: 16839792.

Stalker HJ, Williams CA. Genetic counseling in Angelman syndrome: the challenges of multiple causes. Am J Med Genet. 1998;77:54–9. PubMed PMID: 9557895.

Steffenburg S, Gillberg CL, Steffenburg U, Kyllerman M. Autism in Angelman syndrome: a population-based study. Pediatr Neurol. 1996;14:131–6. PubMed PMID: 8703225.

Stenson PD, Mort M, Ball EV, Howells K, Phillips AD, Thomas NS, Cooper DN. The Human Gene Mutation Database: 2008 update. Genome Med. 2009;1:13. PubMed PMID: 19348700.

Takano K, Lyons M, Moyes C, Jones J, Schwartz CE. Two percent of patients suspected of having Angelman syndrome have TCF4 mutations. Clin Genet. 2010;78:282–8. PubMed PMID: 20184619.

Tan WH, Bacino CA, Skinner SA, Anselm I, Barbieri-Welge R, Bauer-Carlin A, Beaudet AL, Bichell TJ, Gentile JK, Glaze DG, Horowitz LT, Kothare SV, Lee HS, Nespeca MP, Peters SU, Sahoo T, Sarco D, Waisbren SE, Bird LM. Angelman syndrome: Mutations influence features in early childhood. Am J Med Genet A. 2011;155A:81–90. PubMed PMID: 21204213.

Tan WH, Bird LM, Thibert RL, Williams CA. If not Angelman, what is it? A review of Angelman-like syndromes. Am J Med Genet A. 2014;164A:975–92. PubMed PMID: 24779060.

Thibert RL, Conant KD, Braun EK, Bruno P, Said RR, Nespeca MP, Thiele EA. Epilepsy in Angelman syndrome: a questionnaire-based assessment of the natural history and current treatment options. Epilepsia. 2009;50:2369–76. PubMed PMID: 19453717.

Thibert RL, Larson AM, Hsieh DT, Raby AR, Thiele EA. Neurologic manifestations of Angelman syndrome. Pediatr Neurol. 2013;48:271–9. PubMed PMID: 23498559.

Thibert RL, Pfeifer HH, Larson AM, Raby AR, Reynolds AA, Morgan AK, Thiele EA. Low glycemic index treatment for seizures in Angelman syndrome. Epilepsia. 2012;53:1498–502. PubMed PMID: 22779920.

Valente KD, Varela MC, Koiffmann CP, Andrade JQ, Grossmann R, Kok F, Marques-Dias MJ. Angelman syndrome caused by deletion: a genotype-phenotype correlation determined by breakpoint. Epilepsy Res. 2013;105:234–9. PubMed PMID: 23352739.

van Bon BW, Koolen DA, Brueton L, McMullan D, Lichtenbelt KD, Adès LC, Peters G, Gibson K, Moloney S, Novara F, Pramparo T, Dalla Bernardina B, Zoccante L, Balottin U, Piazza F, Pecile V, Gasparini P, Guerci V,

Kets M, Pfundt R, de Brouwer AP, Veltman JA, de Leeuw N, Wilson M, Antony J, Reitano S, Luciano D, Fichera M, Romano C, Brunner HG, Zuffardi O, de Vries BB. The 2q23.1 microdeletion syndrome: clinical and behavioural phenotype. Eur J Hum Genet. 2010;18:163–70. PubMed PMID: 19809484.

Van Esch H, Bauters M, Ignatius J, Jansen M, Raynaud M, Hollanders K, Lugtenberg D, Bienvenu T, Jensen LR, Gecz J, Moraine C, Marynen P, Fryns JP, Froyen G. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. Am J Hum Genet. 2005;77:442–53. PubMed PMID: 16080119.

Varela MC, Kok F, Otto PA, Koiffmann CP. Phenotypic variability in Angelman syndrome: comparison among different deletion classes and between deletion and UPD subjects. Eur J Hum Genet. 2004;12:987–92. PubMed PMID: 15470370.

Vermeiden JP, Bernardus RE. Are imprinting disorders more prevalent after human in vitro fertilization or intracytoplasmic sperm injection? Fertil Steril. 2013;99:642–51. PubMed PMID: 23714438.

Vu TH, Hoffman AR. Imprinting of the Angelman syndrome gene, UBE3A, is restricted to brain. Nat Genet. 1997;17:12–3. PubMed PMID: 9288087.

Walz NC. Parent report of stereotyped behaviors, social interaction, and developmental disturbances in individuals with Angelman syndrome. J Autism Dev Disord. 2007;37:940–7. PubMed PMID: 17019625.

Watson P, Black G, Ramsden S, Barrow M, Super M, Kerr B, Clayton-Smith J. Angelman syndrome phenotype associated with mutations in MECP2, a gene encoding a methyl CpG binding protein. J Med Genet. 2001;38:224–8. PubMed PMID: 11283202.

Willemsen MH, Vulto-van Silfhout AT, Nillesen WM, Wissink-Lindhout WM, van Bokhoven H, Philip N, Berry-Kravis EM, Kini U, van Ravenswaaij-Arts CM, Delle Chiaie B, Innes AM, Houge G, Kosonen T, Cremer K, Fannemel M, Stray-Pedersen A, Reardon W, Ignatius J, Lachlan K, Mircher C, Helderman van den Enden PT, Mastebroek M, Cohn-Hokke PE, Yntema HG, Drunat S, Kleefstra T. Update on Kleefstra Syndrome. Mol Syndromol. 2012;2:202–12. PubMed PMID: 22670141.

Williams CA, Beaudet AL, Clayton-Smith J, Knoll JH, Kyllerman M, Laan LA, Magenis RE, Moncla A, Schinzel AA, Summers JA, Wagstaff J. Angelman syndrome 2005: updated consensus for diagnostic criteria. Am J Med Genet A. 2006;140:413–8. PubMed PMID: 16470747.

Williams SR, Mullegama SV, Rosenfeld JA, Dagli AI, Hatchwell E, Allen WP, Williams CA, Elsea SH. Haploinsufficiency of MBD5 associated with a syndrome involving microcephaly, intellectual disabilities, severe speech impairment, and seizures. Eur J Hum Genet. 2010;18:436–41. PubMed PMID: 19904302.

Yamamoto Y, Huibregtse JM, Howley PM. The human E6-AP gene (UBE3A) encodes three potential protein isoforms generated by differential splicing. Genomics. 1997;41:263–6. PubMed PMID: 9143503.

Yamasaki K, Joh K, Ohta T, Masuzaki H, Ishimaru T, Mukai T, Niikawa N, Ogawa M, Wagstaff J, Kishino T. Neurons but not glial cells show reciprocal imprinting of sense and antisense transcripts of Ube3a. Hum Mol Genet. 2003;12:837–47. PubMed PMID: 12668607.

Yashiro K, Riday TT, Condon KH, Roberts AC, Bernardo DR, Prakash R, Weinberg RJ, Ehlers MD, Philpot BD. Ube3a is required for experience-dependent maturation of the neocortex. Nat Neurosci. 2009;12:777–83. PubMed PMID: 19430469.

Zweier C, Peippo MM, Hoyer J, Sousa S, Bottani A, Clayton-Smith J, Reardon W, Saraiva J, Cabral A, Gohring I, Devriendt K, de Ravel T, Bijlsma EK, Hennekam RC, Orrico A, Cohen M, Dreweke A, Reis A, Nurnberg P, Rauch A. Haploinsufficiency of TCF4 causes syndromal mental retardation with intermittent hyperventilation (Pitt-Hopkins syndrome). Am J Hum Genet. 2007;80:994–1001. PubMed PMID: 17436255.

Zweier C, Thiel CT, Dufke A, Crow YJ, Meinecke P, Suri M, Ala-Mello S, Beemer F, Bernasconi S, Bianchi P, Bier A, Devriendt K, Dimitrov B, Firth H, Gallagher RC, Garavelli L, Gillessen-Kaesbach G, Hudgins L, Kaariainen H, Karstens S, Krantz I, Mannhardt A, Medne L, Mucke J, Kibaek M, Krogh LN, Peippo M,

Rittinger O, Schulz S, Schelley SL, Temple IK, Dennis NR, Van der Knaap MS, Wheeler P, Yerushalmi B, Zenker M, Seidel H, Lachmeijer A, Prescott T, Kraus C, Lowry RB, Rauch A. Clinical and mutational spectrum of Mowat-Wilson syndrome. Eur J Med Genet. 2005;48:97–111. PubMed PMID: 16053902.

Chapter Notes

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