Facts About AS

What is Angelman Syndrome

Dr. Harry Angelman (1915-1996) and his wife, Audrey (1936-1999)

Harry and Audrey attended several ASF meetings and Audrey corresponded with many US families.

In 1965, Dr. Harry Angelman, an English physician, first described three children with characteristics now known as the Angelman syndrome (AS). He noted that all had a stiff, jerky gait, absent speech, excessive laughter and seizures. Other cases were eventually published but the condition was considered to be extremely rare at that time, and many physicians doubted its existence. The first reports from North America appeared in the early 1980s. Dr. Angelman relates the following regarding his discovery of this syndrome.

""The history of medicine is full of interesting stories about the discovery of illnesses. The saga of Angelman's syndrome is one such story. It was purely by chance that nearly thirty years ago (e.g., circa 1964) three handicapped children were admitted at various times to my children's ward in England. They had a variety of disabilities and although at first sight they seemed to be suffering from different conditions I felt that there was a common cause for their illness. The diagnosis was purely a clinical one because in spite of technical investigations which today are more refined I was unable to establish scientific proof that the three children all had the same handicap. In view of this I hesitated to write about them in the medical journals. However, when on holiday in Italy I happened to see an oil painting in the Castelvecchio museum in Verona called . . . A Boy with a Puppet. The boy''s laughing face and the fact that my patients exhibited jerky movements gave me the idea of writing an article about the three children with a title of Puppet Children. It was not a name that pleased all parents but it served as a means of combining the three little patients into a single group. Later the name was changed to Angelman syndrome. This article was published in 1965 and after some initial interest lay almost forgotten until the early eighties."

Source: 7th edition Facts about Angelman Syndrome by Charles A. Williams, M.D., Sarika U. Peters, Ph.D., Stephen N. Calculator, Ph.D. in 2009

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In 1987, Ellen Magenis, a physician at the Oregon Health Science Center, identified children with microdeletions of chromosome 15 who were expected to have the Prader-Willi syndrome. However, these children had seizures and severe developmental delay, features not expected to be found for that syndrome. It was quickly realized that these children had microdeletions on the maternally derived number 15 chromosome whereas in the Prader-Willi syndrome the deletion was always observed on the paternally derived one. This was an important discovery and ultimately paved the way for the delineation of several mechanisms that caused AS, all by disruption of a gene located on chromosome 15. It was learned that the syndrome can be caused by two copies of the paternal chromosome 15 (1991) and that a regulatory region (the Imprinting Center) can be also be disrupted to the syndrome (1993). In 1997, 10 years after the chromosome deletion was identified, the AS gene, UBE3A, was isolated. This discovery quickly led to the development of animal models and to active neuroscience research aimed at discovering how abnormalities of UBE3A cause impairment in neural development.

Source: 7th edition Facts about Angelman Syndrome by Charles A. Williams, M.D., Sarika U. Peters, Ph.D., Stephen N. Calculator, Ph.D. in 2009

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How common is Angelman Syndrome?

During the last 20 years, there has been increasing awareness of AS throughout the world. The syndrome is well represented by parent-based support groups in many countries, on individual family websites and on a host of medical and professional information websites. Angelman syndrome has emerged as one of the important syndromes causing neurological impairment and most pediatricians and neurologists now have some awareness of it. How common is Angelman Syndrome. AS has been reported throughout the world among divergent racial groups. In North America, the great majority of known cases seem to be of Caucasian origin. The exact incidence of AS is unknown but the best available data probably come from studies of school age children, ages 6-13 years, living in Sweden, and from Denmark where the diagnosis of AS children in medical clinics was compared to an 8 year period of about 45,000 births. The Swedish study showed an AS prevalence of about 1/12,000 and the Danish study showed a minimum AS prevalence of about 1/10,000. Note that it is desirable to use the term prevalence since estimates of the AS diagnosis have been made in relatively small cohorts of children over various periods of time.

Several reports have tried to address the prevalence of AS among groups of individuals with established developmental delay. The results showed rates of 0%, 1.3%, 1.4%, and 4.8%. The Buckley paper extrapolated their data in order to compare it to the population of the state of Washington (using 1997 Census Bureau figures) and obtained an estimate of 1/20,000, a number similar to that often quoted, but not referenced in terms of methodology, in a 1992 review paper

There appear to be no reported prevalence studies that have screened newborns to detect rates of AS. Population wide prevalence figures would need to take into consideration that longevity in AS is probably reduced (severe mental delay and seizure presence would be risk factors) but no actuarial or other data are available on life span shortening. Likewise, it is not known what percent of individuals with AS are undiagnosed, although this is expected it to be significant. Accordingly, to estimate the number of people with AS living in the society, it would be inaccurate to divide any estimated AS prevalence figure into a total population number.

Given this information, it appears that the prevalence of AS among children and young adults is between 1/10,000 and 1/20,000. It is suggested to use a 1/15,000 figure if a single figure is needed. For population projections, estimates using birth rates can be used. For example, if an area has a birth rate of about 200,000/year it would be estimated that about 13 babies would be born each year with AS.

According to the Clinical Genetic Service, Department of Health, more than 50 cases were diagnosed in Hong Kong. On average three to five new cases were confirmed annually in the last 5 years.

Source: 7th edition Facts about Angelman Syndrome by Charles A. Williams, M.D., Sarika U. Peters, Ph.D., Stephen N. Calculator, Ph.D. in 2009

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Consensus Criteria for Diagnosis of Angelman Syndrome

Angelman syndrome is usually not recognized in early infancy since the developmental problems are nonspecific during this time. The most common age of diagnosis is between two and five years when the characteristic behaviors and features become most evident. Parents may first suspect the diagnosis after reading about AS or meeting a child with the condition. Children with AS may have a relatively wide mouth and a protruding tongue, sometimes associated with a prominent chin (see figure). Most children with AS also appear to share the normal familial facial traits of the family and so it is unusual for them to be considered to have a "dysmorphic" facial appearance. Angelman syndrome is a distinctive clinical condition however, mainly because of its distinctive behaviors and developmental course. A summary of the developmental and physical findings has been published for the purpose of establishing clinical criteria for the diagnosis and these are listed below. All of the features do not need to be present for the diagnosis to be made and the diagnosis is often first suspected when the typical behaviors are recognized.

Source: 7th edition Facts about Angelman Syndrome by Charles A. Williams, M.D., Sarika U. Peters, Ph.D., Stephen N. Calculator, Ph.D. in 2009

Facts About AS

Developmental and Physical Findings

Consistent (100%)

- Developmental delay, functionally severe
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions
- Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand---flapping or waving movements;

hypermotoric behavior

- Speech impairment, none or minimal use of words; receptive and non---verbal communication skills higher than verbal ones

Frequent (more than 80%)

- Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (≤2 S.D. of normal OFC) by age 2 years. Microcephaly is more pronounced in those with 15q11.2-q13 deletions
- Seizures, onset usually < 3 yrs. of age. Seizure severity usually decreases with age but the seizure disorder lasts throughout adulthood.
- Abnormal EEG, with a characteristic pattern, as mentioned in the text. The EEG abnormalities can occur in the first 2 years of life and can precede clinical features, and are often not correlated to clinical seizure events.

Associated (20 - 80%)

- Flat occiput
- Occipital groove

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- Protruding tongue
- Tongue thrusting; suck/swallowing disorders
- Feeding problems and/or truncal hypotonia during infancy
- Prognathia
- Wide mouth, wide-spaced teeth
- Frequent drooling
- Excessive chewing/mouthing behaviors
- Strabismus
- Hypopigmented skin, light hair and eye color (compared to family), seen only in deletion cases
- 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)
- Scoliosis
- Constipation

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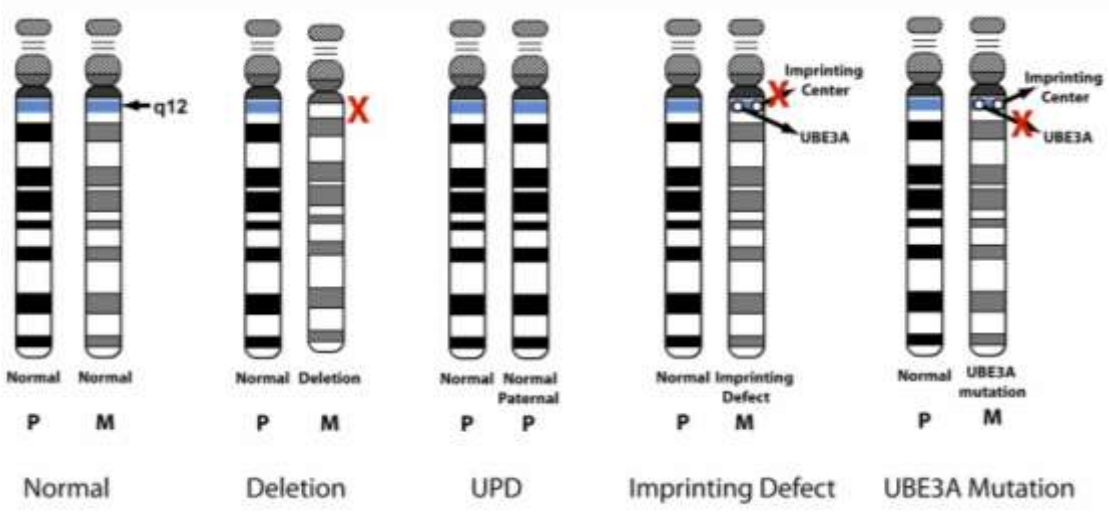
Genetic Mechanisms that Cause AS

In 1997, mutations in the gene, UBE3A located on chromosome 15, were identified as the cause of AS. All mechanisms known to cause AS either disrupt, inactivate or lead to absence of this gene on the maternally derived chromosome 15. There are several genetic "classes" or mechanisms that can disrupt UBE3A and thus cause AS. These mechanisms are depicted in this illustration.



A chromosome 15 pair is illustrated for each mechanism and a normal chromosome pair is depicted on the left with a normal q12 chromosome region. P = paternally---derived chromosome and M = maternal derivation. AS can be caused by a large deletion of the maternal chromosome 15q12 region (where the active UBE3A gene resides). AS can also be caused by inheritance from the father of 2 paternal chromosomes; a phenomenon termed paternal uniparental disomy (UPD). Another cause, referred to as an imprinting defect (ID), occurs when the chromosome 15 inherited from the mother has the paternal pattern of gene functioning so that UBE3A expression is actually turned off. The IC is located some distance from the UBE3A gene but it is still able to regulate UBE3A by a complex mechanism that is the subject of intense research. Finally, AS can be caused by a mutation in the UBE3A gene on the maternally derived chromosome 15.

Mechanism	Frequency (%)
Deletion	~70
UPD	2 - 3
Imprinting defect	3 - 5
UBE3A mutation or deletion	5 - 10
Other chromosome Rearrangements	1 - 2
Unknown	10 - 15

The table indicates the prevalence of each genetic mechanism and also notes that about 10-15% of individuals with the clinical features of AS actually will have normal genetic studies.

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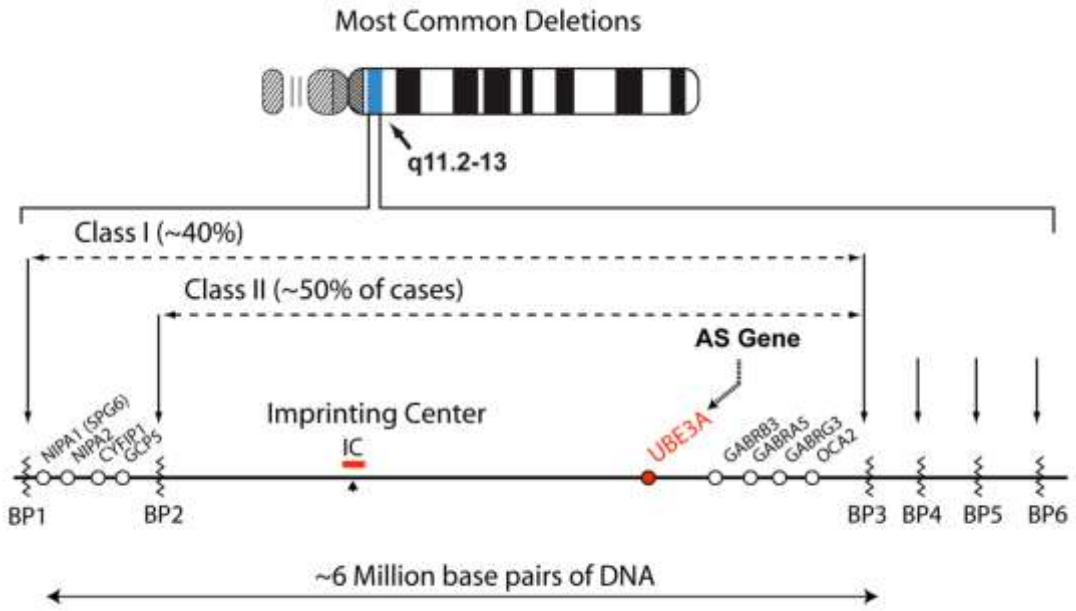
At this time, it is unclear if these individuals have the correct diagnosis or if they have other yet-to-be-identified genetic defects that cause AS. The most common genetic mechanism causing AS is the large chromosome deletion. The diagram explains more information about this. The typical deletion region is indeed large and spans about 6 million molecules (base pairs) of DNA. Most deletions extend from break point one (BP1) to either BP2 or BP3 and are termed class I or class II deletions. About 10% of the deletions extend further beyond BP3, for example, at site BP4. New methods of clinical testing such as array---based comparative genomic hybridization can distinguish between class I and class II deletions. However, the FISH test will not be able to determine this.

All the large deletions remove UBE3A from the maternally derived chromosome. The deletions also remove additional genes as pictured (e.g., GABA receptor genes) but UBE3A deletion causes essentially all the problems associated with AS.



UBE3A and the Ubiquitin Pathway

The UBE3A gene makes the UBE3A protein (also called E6-AP) and this protein is an important component of the ubiquitin-proteasome pathway (pictured below). This pathway is extremely important to all cells, especially brain neurons. The pathway enables a small protein molecule, ubiquitin, to be attached to certain proteins, thereby causing them to be degraded. Ubiquitin is a small protein (76 amino acids in length) that can be tagged onto other proteins in order to initiate their destruction. As pictured, E1 and E2 proteins activate (yellow) and transfer ubiquitin to E3. There are many different types of E3 proteins and UBE3A is one of them. UBE3A is able to chemically attach ubiquitin onto target proteins

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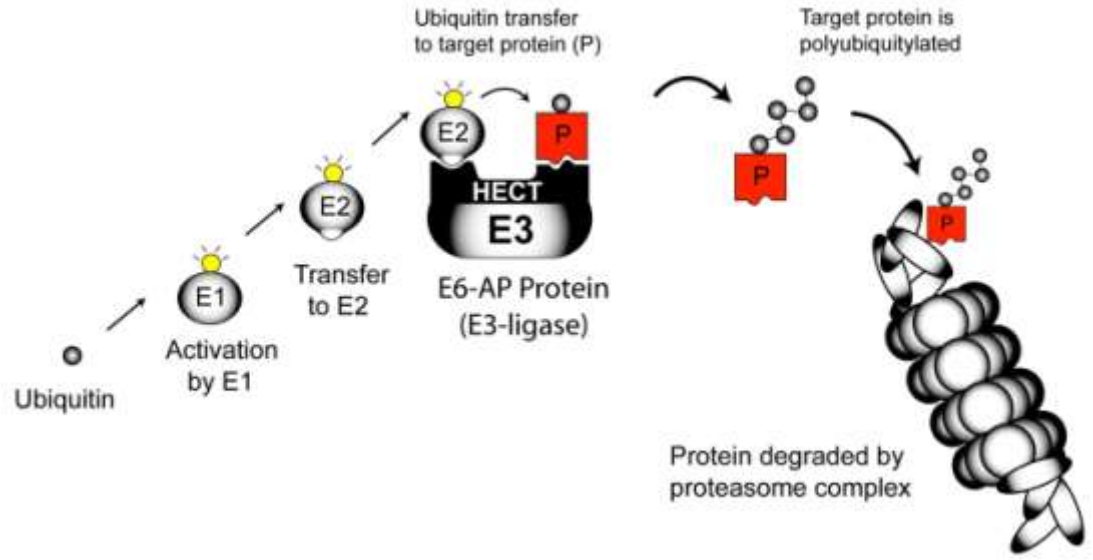
(red). Important in UBE3A''s protein structure is the HECT domain, a molecular pocket that enables ubiquitin and the target protein to come into close proximity, allowing for attachment of the activated ubiquitin molecule. Some protein targets for UBE3A are known but it is currently unknown which protein targets are linked to the precise brain dysfunction in AS. UBE3A is closely associated with neuronal synaptic function.



UBE3A and Imprinting

UBE3A is known to be "imprinted" in brain neurons. This means that UBE3A gene from the paternally‐derived chromosome 15 is almost completely inactive in many brain regions while the maternally‐derived chromosome 15 gene is normally active. The brain neurons are normal even though they only have one active copy of the UBE3A gene. That chromosome deletions in AS occur only on the maternally‐derived chromosome 15 indicate that UBE3A is active only on this chromosome, hence the deletion removes the only active copy of the gene. Disruptions of genes that are active on the paternally‐‐‐derived chromosome 15 cause another developmental disorder, the Prader‐‐‐Willi syndrome (PWS). PWS also involves imprinted gene(s) that are located close to but distinct from UBE3A. AS and PWS are quite unique because almost all other genetic disorders do not exhibit this type of imprinting effect.

The term "imprinting inheritance" can be difficult to understand. In order for an imprinted gene to be normally inherited and active on the correct parentally‐‐‐derived chromosome (e.g., as occurs in normal individuals), there must be a mechanism for reversing the expression of genes at certain times of egg and 10 embryo development. For example, when a normal father produces sperm, regardless of whether the sperm end up having the maternally or paternally derived 15, all must now be "stamped" or "imprinted" so that their

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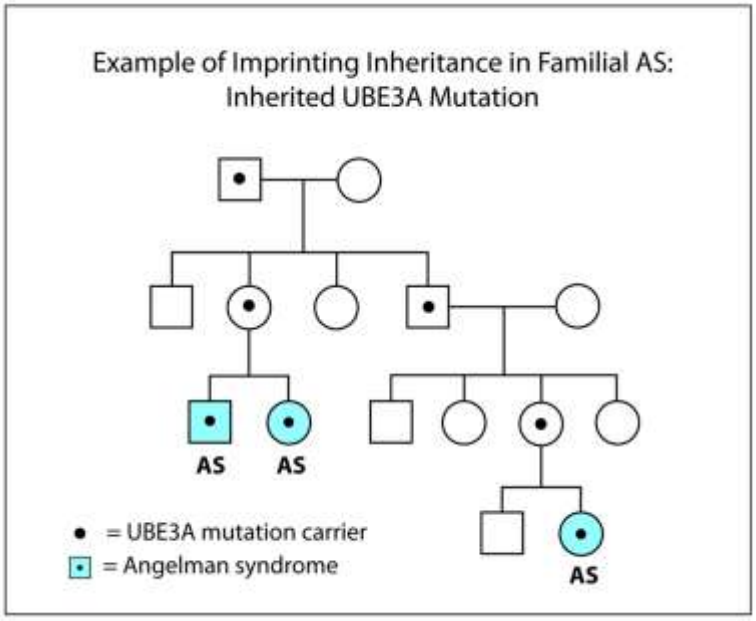
UBE3A genes will be turned off. The opposite occurs in the normal mother, whose eggs must have all their UBE3A genes turned on. Imprinted genes are thus capable of having their activity instructions erased and re-stamped.

The pedigree illustrates how imprinting inheritance can cause recurrence of AS in somewhat distantly related relatives. When a UBE3A mutation is inherited in a family, individuals who inherit the mutation may get AS but others can be normal! Inheritance of a UBE3A mutation from the father (top left of pedigree) has no detectable effect on his immediate children since he passed on an inactive UBE3A gene. It does not matter if this gene has a mutation since each of his immediate children also inherited a normal chromosome 15 (e.g., normal UBE3A gene) from their mother. However, should his carrier daughter transmit the UBE3A mutation to any child, it will have AS since that child would also get an inactivated UBE3A from her father so now there is essentially no UBE3A activity present. The same type of inheritance pattern can also be seen in some families with Imprinting Center defects. Refer to the Genetic Counseling page for more information.



Fortunately, most individuals with AS will have acquired their condition through a non-inherited, spontaneous mutation. This is the situation in almost all cases of the large common deletion and thus imprinting inheritance in not observed.

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Genetic Mechanisms and Severity of Symptoms

In general, all of the AS genetic mechanisms lead to a somewhat uniform clinical picture of severe to profound mental retardation, characteristic behaviors, and severe limitations in speech and language.

However, there are some clinical differences that correlate with the genotype, although there is great variability within each group. These correlations are broadly summarized below:

1. The deletion class is the most severely involved regarding microcephaly, seizures, relative hypopigmentation, motor difficulties (e.g., ataxia, muscular hypotonia, feeding difficulties), and cognition and language impairment.

2. UPD and ID individuals have better physical growth (e.g., less likely to have microcephaly) and have less movement and ataxia abnormalities and have a lower prevalence (but not absence) of seizures.

3. The ID group tends to have the highest cognitive, receptive language, fine motor, and gross motor abilities compared to other subtypes. The most advanced speech abilities occur in the ID group that is mosaic for the non-deletion imprint defect (about 20% of the ID group). These individuals may speak up to 50-60 words and use simple sentences.

4. The UBE3A mutation group generally is intermediate between the deletion and the ID classes in terms of microcephaly, seizures, motor difficulties, and language ability. Some with UBE3A may have relatively high cognitive abilities, fine motor, and gross motor skills as presumably the effect of their mutation (e.g., location and type of DNA change within the gene) causes less severe clinical problems.

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