

Angelman Syndrome (AS; Happy Puppet Syndrome) — Symptoms and Genetics

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Angelman syndrome (AS) is an infrequent, unusual autosomal neuro-developmental disease resulting from epigenetic sex-specific genomic imprinting and uniparental disomy of paternal chromosome 15 with a simultaneous functional loss of the maternal part 15q11-q13. With a focus on clinical, diagnostic and management aspects, this article encompasses a detailed discussion of the genetic mechanisms involved in AS.



Definition of the Angelman Syndrome

AS is an **infrequent neuro-developmental autosomal genetic disorder** in which specific segments of chromosome 15 are functionally silenced on the paternal chromosome. Literature attests to the fact that the **hypothalamus** is the organ of primary damage. The **cerebellum** is also grossly involved. The cascade of subsequent implications that follows affects a variety of organ systems in diverse proportions. Exacting evidence to determine the tendency for hypothalamic and cerebellar damage is yet to be unearthed.

History of the Angelman Syndrome

Literature attests to the fact that “Angelman syndrome” is christened after a British pediatrician by the name of **Harry Angelman**. He was the first one to describe the syndromic aggregation of this disease in three children in Warrington in 1965. He is believed to have nicknamed the patients as ‘**Puppet children**’ after a painting in the Castelvecchio Museum in Verona “A boy with a puppet”.

Earlier, these patients were known as ‘happy puppets’ and the syndrome as ‘**Happy**

puppet syndrome'. However, the latter term usage is usually discouraged. The patients also go by the name of 'angels' due to their seemingly cheerful demeanor and the syndrome's name.

Epidemiology of the Angelman Syndrome

AS epitomizes an unusual and rare constellation of symptoms and signs. Literature estimates a **prevalence of about 1000 cases in the US and Canada**. There is no sex discrimination and racial selective affliction seen in the natural course of the illness. The best epidemiological data hails from European countries. The reliable prevalence rate is estimated to be 1 in 10,000 to 1 in 20,000 live births from Swedish and Danish studies.

Genomic Imprinting and Angelman Syndrome

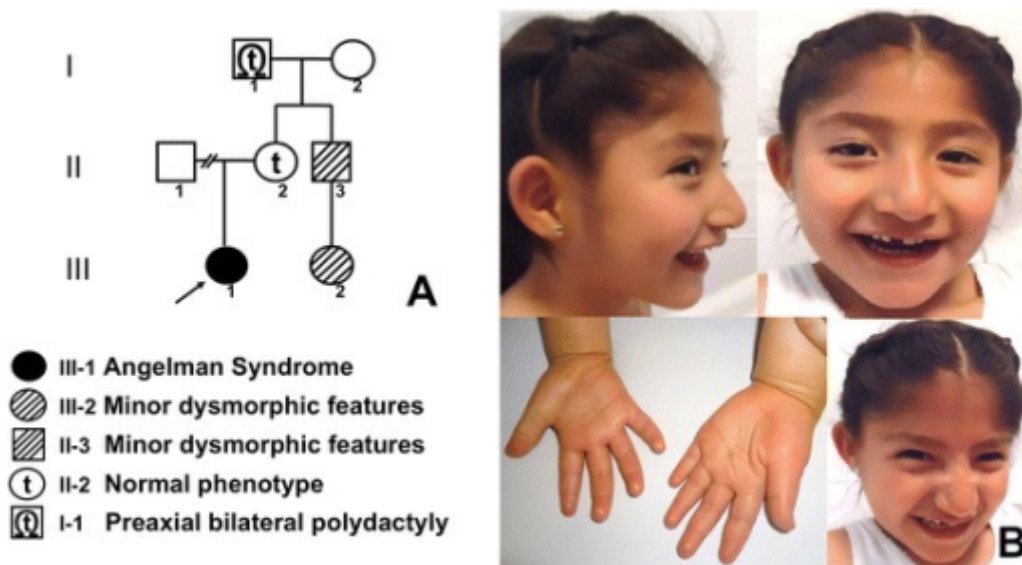


Image: "Available family members. A) Pedigree of the proband and her family, B) Proband (III-1) with telecanthus, bilateral epicanthal folds, wide mouth and an apparently happy demeanor, hands with tapered fingers, abnormal creases and broad thumbs," by Yokoyama-Rebollar E, Ruiz-Herrera A, Lieberman-Hernández E, Del Castillo-Ruiz V, Sánchez-Sandoval S, Ávila-Flores SM, Castrillo JL - Mol Cytogenet (2015). License: [CC-BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Genomic imprinting stands for expression of genes in a parent of origin-specific manner. Chromosome 15 encompasses a genomically imprinted sex-specific region. Genes are expressed only on the paternal and maternal chromosomes. Through hypermethylation, imprinting or specific turning of the corresponding alleles on the opposing homologous chromosomes takes place. Thus, DNA hypermethylation governs this epigenetic imprinting.

AS patients characteristically possess twice the normal amount of paternal chromosome 15 q segment (uniparental disomy) or absence of maternal homologous segment (microdeletion). Meiotic phase I non-disjunction culminates into heterodisomy and isodisomy. The maternal chromosomal segment is eliminated in heterodisomy as a desperate rescue attempt from the hazards of trisomy. The consequence is uniparental disomy of a paternally derived chromosome 15 segment.

Subsequent to genomic imprinting, only maternal copies of these genes are functional, and paternal alleles, even if present, are innately not expressed. About 70 % of the cases result from deletion of the maternal chromosomal segment, while the rest of the cases

are accounted for by paternal uniparental disomy. The latter has 2 copies from the father and none from the mother.

Human and experimental mice studies have pinned down the loss of functional allele of the gene “**UBE3A**” as the predominant critical cause of AS. In normal subjects, the maternal copy of UBE3A is part of the ubiquitin pathway, the protein scavenging system. The paternal allele is functionally silenced, especially in parts of the brain such as the hippocampus and the cerebellum.

The most common etiology of loss of the maternal functional copy of UBE3A is a **4Mb (megabase) maternal deletion**. This results in loss of function of E6-AP **ubiquitin ligase** which is primarily coded by the UBE3A gene. Ubiquitin ligase is a very selective enzyme. About 4 substrates of the same have been identified. Active research is still on to further elaborate the precise molecular mechanisms involved.

Single mutations, microdeletions can all silence the UBE3A functional allele. There are different mechanisms by which this functional loss occurs.

The same can be summarized in short as follows:

- Chromosome translocation
- Gene deletion
- Sporadic mutation
- Deletion and microdeletions within the gene segment
- Chance mutation, Uniparental disomy

The similar process when reversed, the existence of 2 copies from the mother and none from father, result in **Prader-Willi syndrome (PWS)**.

Animal studies also provide a testament to the affliction of hippocampus and memory formation impairment in AS. Studies have identified the disruption of hippocampal memory formation, long-term synaptic plasticity and contextual fear conditioning in mice whose UBE3A maternal allele has been knocked out.

Clinical Features of the Angelman Syndrome

AS patients are essentially normal at birth. They usually manifest developmental delay at about 6 months to 1 year of age. Patients usually have all the features of AS by the age of 3 years. These include seizures, inappropriate laughter, neurocognitive and neurodevelopmental delay, and speech impairment. Seizures can manifest early, at the age of about 24 months.

The key clinical features which help clinch the diagnosis are:

- Features
- Speech impairment
- Microcephaly
- Heat intolerance and sensitivity
- Balance and sleep issues
- Inappropriate frequent smiling and laughter
- Convulsions
- Hyperactivity
- Uplifted flexed arms

The spectrum of AS symptoms are rather vast. While a few characteristics are

consistently present, others are mere associations.

The symptoms can thus be segregated based on their relative frequency as follows:

Consistent (100 % occurrence) symptoms	Frequent (more than 80 % occurrence) clinical features	Associated features (incidence between 20-80 %)
Behavioral aberration in the form of inappropriate laughter, seemingly happy demeanor, short attention span.	Microcephaly by age 2	Strabismus
Lack of proper use of speech and relative higher use of non-verbal communication skills	Onset of seizures by 3 years of age	Hypopigmentation
Movement disorder as ataxia, fine tremors, jerky movements.	Abnormal EEG tracings.	Feeding problems, swallowing disorders
Severe developmental delay		Fascination with water
		Sleep disturbances
		Prominent mandible, flat head, and drooling protruded tongue can be characteristic

Diagnosis of the Angelman Syndrome

In association with the **Angelman syndrome foundation**, diagnostic criteria were objectively set in 1995 and further amended in 2005.

The key features of the same can be tabulated as follows:

- Diagnostic criteria
- History of neurodevelopmental, neurocognitive and speech development delay
- History of Epilepsy
- General happy demeanor
- Abnormal EEG tracing
- Inappropriate laughter
- Characteristic facies
- Weird limb movements such as hand flapping, fine tremors, jerky joint dispositions, seemingly spastic wide-based gait

While earlier medical personnel relied mainly on clinical features, the current trend is to use clinical features *prima facie* to suspect AS mainly in patients with developmental delay and then confirm the same with modern genetic testing armamentarium. Different cytogenetic analysis techniques can be implemented to diagnose AS.

Some of the most commonly used ones can be summarized as follows:

Technique	Explanation
aCGH (array comparative genomic hybridization) technique	Used to detect loss of the maternal allele on chromosome 15

FISH (fluorescence in situ hybridization)	FISH involves the use of fluorescence microscopy and fluorescent probes. It is instrumental in the determination of specific DNA sequences on the chromosomes of interest. Its usage is inclusive of defining the peculiar spatiotemporal gene profile in samples of AS patients.
BACs-on-Beads technology	Detects functional loss, inactivity, and deletion of the maternal UBE3A copy.
Methyl collector Ultrafast magnetic assay for specific isolation of CpG-methylated DNA	DNA methylation is crucial for the management of gene functions in various cellular cycles. In AS patients, this test detects methylation of a neighbor gene SNRPN, which in turn is functionally turned off by methylation of the maternal copy of the UBE3A gene.

Neurophysiological testing is increasingly being used to support the diagnosis of AS. Unfortunately, even though grossly abnormal, no particular features can be called pathognomonic of the disease.

The various abnormal interictal patterns observed can be summarized as:

- Patterns on EEG in AS patients
- 3-6 Hz spike and sharp waves in occipital leads on eye closure
- Large amplitude of 2-3 Hz rhythm characteristically in the prefrontal leads (most common)
- Symmetrical 4-6 Hz high voltage rhythm

Management of the Angelman Syndrome

A definite cure and treatment for AS are at best, enigmatic, at present. A circumferential multifaceted integrated approach is a prerequisite when one yearns to manage AS.

To ensure an independent future, the important elements to focus on can be summarized as follows:

- Speech and communication therapy
- Exercise and physical therapy
- Physical activity management
- Behavioral therapy
- Medical therapy with drugs for seizure control

Medical management in AS patients is far and largely limited.

Few drugs which are used commonly can be summarized as follows:

Drug used	Explanation
Antiepileptic drugs	Management of antiepileptic drugs is particularly challenging as AS is rather afflicted by a spectrum of a variety of seizures.
Melatonin	Melatonin is occasionally used to promote sleep in patients with AS.
Laxatives	Mild laxative use can be permitted to ensure normal regular bowel movements.

The education of parents and their cognizance of the disease and its behavioral repercussions are of critical significance. They need to understand the disease and their offspring and then decide on a management plan. Indeed, simple steps in this wake can be very helpful.

It is an unequivocal belief that comprehension of conversations is more advanced than

fluency and verbalization of speech in these patients. They are naturally inclined to use non-verbal cues to express themselves. **Most AS patients spontaneously generate a maximum of 5–10 words vocabulary.** Parents need to be made aware of such limitations and encouraged to use ancillary methods of non-verbal expression and conversations.

Puberty and sexual development are not hindered in these patients. With intensive behavioral therapy and speech therapy, these individuals can be encouraged to lead a near-normal average lifespan. **Health disturbances seen in adult AS patients include obesity and scoliosis.** Interestingly, epilepsy becomes relatively tamed in adulthood.

Genetic Testing and Counseling of the Angelman Syndrome

In an attempt to predict the clinical evolution of these patients and determine the risk to future offspring and family members, genetic testing and counseling is a must. Curiously, albeit the existence of the basis of this syndrome in chromosomes, AS appearance is not hereditary, it is, literally, not a genetic disease.

The genetic dent occurs **either in the process of meiosis, haploid gamete synthesis or in the early embryonic period.** These alterations that culminate into the genetic aberrations of genomic imprinting are often spontaneous and sporadic. Thus, the risk estimate depends on the involved genetic aberration that occurs in the first place and can vary grossly accordingly.

The genetic turbulence can be situated in the sex-specific genomically-imprinted region. In these circumstances, AS takes on the traits of an **autosomal dominant** condition. Therefore, the odds that the next sibling will be affected are almost 50 %. In contrast, the prospective sibling is subjected to a risk of about 1 %, similar to the normal population, if the affected individual has uniparental disomy or gene deletion. This risk escalates to about 25 % when the etiology involves maternal chromosomal translocation. These risk estimates can be derived from the study of the morphology and pattern of the genetic aberration that exists in the first place.

Also, the genetic mechanism primarily involved determines the phenotypic infliction to some extent. Patients with UBE3A gene mutation have the mildest clinical symptoms, while patients with larger deletions on chromosome 15 have frank neurodevelopmental and neurocognitive damage.

Summary of the Angelman Syndrome

Angelman syndrome (AS) is an unusual genetic autosomal ailment where the loss of maternal alleles or duplication of paternal copies of the chromosome 15 q11-q13 segment results in loss of ubiquitin scavenging functions secondary to sex-specific genomic imprinting functional in this region. The reverse leads to Prader-Willi syndrome.

AS was, not a long time ago, a clinical diagnosis. Our diagnostic armamentarium now is inclusive of sophisticated genetic testing techniques like FISH and tests to detect hypermethylation to clinch the diagnosis of AS.

Integrated circumferential multi-targeted management therapy can often help an AS patient to lead an enhanced version of independent living. Complete cure, unfortunately,

is unheard of thus far.

In AS, genetic testing and counseling are available for risk estimation of potential infliction of potential prospective family members, siblings and the generations to come.

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