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# ANGELMAN SYNDROME: A COMPREHENSIVE REVIEW OF GENETIC ABNORMALITY

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**ABSTRACT** Angelman syndrome is a rare genetic and neurological disorder. It is characterised by jerky movements, frequent and sometimes inappropriate laughter, a love of water, severe mental retardation and learning disabilities, ataxia, and susceptibility to seizures and sleep disorder. The facial features are subtle and include a wide, smiling mouth, prominent chin, and deepest eyes. It is caused by a variety of genetic abnormalities involving the chromosome 15q11-13 region, which is subject to genomic imprinting. The genetic mechanisms identified so far in AS are found in 85-90% of those with the clinical phenotype and all interfere with UBE3A expression.

**KEYWORDS :** Angelman syndrome, Genetic abnormalities, Delayed development.

## Introduction

Angelman syndrome (AS) is a complex genetic disorder that primarily affects the nervous system. It includes delayed development, intellectual disability, severe speech impairment, and problems with movement and balance (ataxia). Most affected children also have recurrent seizures (epilepsy) and a small head size (microcephaly). Delayed development becomes noticed by the age of 6 to 12 months, and other common signs and symptoms usually appear in early childhood period.[1]

Children with AS typically have a happy, excitable behaviour with frequent smiling, laughter, and hand-flapping movements. Hyperactivity, a short attention span, and intense interest with water are common. Most affected children also have difficulty sleeping and need less sleep than usual.[2]

With age, people with Angelman syndrome become less excitable, and the sleeping problems tend to improve. However, affected individuals continue to have intellectual disability, severe speech impairment, and seizures throughout their lives. Adults with Angelman syndrome have distinctive facial features that may be described as "coarse." Other common features include hair and an abnormal side-to-side curvature of the spine (scoliosis). The life expectancy of people with the condition arises to be nearly normal.[3]

## Causes

The causes of Angelman syndrome are unknown in 10 to 15 percent of affected individuals.

- Chromosomes may be responsible near about 70% occur when a segment of the maternal chromosome 15 containing that gene is deleted. In other cases 11%, AS due to mutation in the maternal copy of the UBE3A gene and loss of function that is UBE3A. People normally inherit one copy of the UBE3A gene from each parent. Both copies of this gene are turned on (active) in many of the body's tissues. In certain areas of the brain, however, only the copy inherited from a person's mother (the maternal copy) is active. If the maternal copy of the UBE3A gene is lost because of a chromosomal change or a gene mutation, a person will have no active copies of the gene in some parts of the brain.
- Maternal deletion, paternal uniparental disomy, imprinting defects, and point mutations or small deletions within the UBE3A gene, which lies within this region. UBE3A shows tissue specific imprinting, being expressed exclusively from the maternal allele in brain.
- In a small percentage of cases, Angelman syndrome results when a person inherits two copies of chromosome 15 from his or her father (paternal copies) instead of one copy from each parent that is paternal uniparental disomy.
- In some people who have Angelman syndrome, the loss of a gene called OCA2 is associated with light-coloured hair and fair skin. The OCA2 gene is located on the segment of chromosome 15 that is often deleted in people with this disorder. [4,5]

## Types

**1. Deletion (65-75%):** DNA (deoxyribonucleic acid) is the main component of chromosomes. It contains our unique genetic code. Most individuals with AS are missing a piece of DNA in region 15q11-13 on the maternal chromosome 15.

**2. Mutation (5-11%):** It occurs when there is a small abnormality in the DNA of the UBE3A gene. A mutation can happen anywhere on the gene.

**3. Uniparental Disomy (3-7%):** An individual with UPD has two copies of chromosome 15 from their father and mother. UPD usually happens if there is no chromosome 15 in the egg.

**4. Imprinting Defect (<3%):** The imprinting centre is a small stretch of DNA located in the q11-13 region of the chromosome. In rare cases, the mother's chromosome 15 is blank, and the center copies the father's chromosome 15. [6]

## Signs and symptoms

### Consistent (100%)

- Developmental delay, functionally severe speech impairment, minimal use of words; receptive and non-verbal communication skills higher than verbal ones.
- Movement disorder, usually ataxia of gait
- Behavioural uniqueness: any combination of frequent laughter/smiling; apparent happy behaviour(demeanor); easily excitable personality, often with hand flapping movements; hyper motoric behaviour; short attention span

### Frequent (more than 80%)

- Delayed growth in head circumference, usually resulting in microcephaly (absolute or relative) by age 2.
- Seizures, onset usually less than 3 years of age
- Abnormal EEG, characteristic pattern with large amplitude slow-spike waves
- Delayed motor development, such as delay in sitting, crawling and walking
- Speech problems
- Jerky, puppet-type movements
- Stiff-legged walking style
- Hand flapping, Hyperactive behaviour
- Loving, happy and social demeanour
- A child easily moved to laughter
- Intellectual disability

### Associated (20–80%)

- Strabismus
- Hypopigmented
- skin and eyes
- Tongue thrusting; suck/swallowing disorders
- Hyperactive tendon reflexes
- Uplifted, flexed arms during walking
- Prominent mandible
- Increased sensitivity to heat
- Sleep disturbance
- Fascination with water

- Excessive chewing
- Flat back of head
- Smooth palms
- deep-set eyes ,wide, ever-smiling mouth [7,8,9]

**EEG Findings in Angelman Syndrome**

There are specific EEG patterns in AS patients which appear in isolation or different combinations. They are similar patients both with and without seizures. In childhood mainly three characteristic patterns are:

1) Persistent rhythmic 4-6/s activity reaching more than 200 μV, not associated with drowsiness,
2) Prolonged runs of rhythmic (triphasic) 2-3/s activity with an amplitude of 200-500 μV, maximal over the frontal regions and normally mixed with spikes or sharp waves,
3) Spikes mixed with 3-4/s components, usually of more than 200 μV mainly posteriorly and facilitated by or only seen on eye closure.[10]

**Diagnostic Evaluation**

The diagnosis of Angelman syndrome is based on:

- A history of delayed motor milestones, general development and speech
- Unusual movements including fine tremors, jerky limb movements, hand flapping and a wide-based, stiff-legged gait.
- Characteristic facial appearance (but not in all cases).
- A history of epilepsy and an abnormal EEG tracing.
- A happy disposition with frequent laughter
- A deletion or inactivity on chromosome 15 by array comparative genomic hybridization (aCGH) or by BACs-on-Beads technology.
- Seizures are a consequence, but so is excessive laughter, which is a major hindrance to early diagnosis. [10,11]

**Treatment for Angelman syndrome**

There is no cure for Angelman syndrome, but the child can benefit from a range of treatments for some symptoms including:

- Speech therapy
- Behaviour modification
- Communication therapy
- Occupational therapy
- Physical therapy
- Special education
- Social skills training
- Anti-epileptic medication
- Back brace or spinal surgery may be recommended to prevent the spine from becoming more curved
- An ankle or foot orthosis (lower leg brace) may be recommended to help with walking independently

Angelman syndrome is not a degenerative disease. Children with Angelman syndrome can expect a normal lifespan.[10,12]

**Complications**

Complications associated with Angelman syndrome include:

**1.Feeding difficulties:** Difficulty coordinating sucking and swallowing problems in infants. The paediatrician may recommend a high-calorie formula to help the baby gain weight.

**2.Hyperactivity:** Children's move quickly from one activity to another, have a short attention span, and keep their hands or a toy in their mouths. Hyperactivity often decreases with age, and medication usually isn't necessary.

**3.Sleep disorders:** It have abnormal sleep-wake patterns and need less sleep than most people. Sleep difficulties may improve with age. Medication and behaviour therapy may help control sleep disorders.

**4.Curving of the spine (scoliosis):** Some people with Angelman syndrome develop an abnormal side-to-side spinal curvature over time.

**5.Obesity:** Older children with Angelman syndrome tend to have large appetites, which may lead to obesity[13,16]

**Prognosis**

The severity of the symptoms associated with Angelman syndrome varies significantly across the population of those affected. Some speech and a greater degree of self-care are possible among the least profoundly affected. Early and continued participation in physical, occupational and communication (speech) therapies are believed to significantly improve the prognosis of individuals affected by AS. The clinical features of Angelman syndrome alter with age. As adulthood approaches, hyperactivity and poor sleep patterns improve. The seizures decrease in frequency and often cease altogether and the EEG abnormalities are less obvious. Dressing skills are variable and usually limited to items of clothing without buttons or zippers. Most adults can eat with a knife or spoon and fork, and can learn to perform simple household tasks. General health is fairly good and life-span near average. [14,15]

**Conclusion**

AS presents a complex neurodevelopmental profile in which several aspects play a negative role in global development leading to a severe functional impairment. Intellectual disability is not the only component because neurovascular functions and behavioural disorders may worsen the global function and are needed of specific rehabilitation programs.

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