Angelman Syndrome (AS) Is a Rare and Severe Neurodevelopmental Disorder[1-4]

AS is a rare, monogenic, neurodevelopmental disorder that is caused by a loss of function in the maternally inherited ***UBE3A* gene**.[1-4] The majority of AS cases (~70%-75%) are caused by **deletions in the *UBE3A* gene**, leading to the **most severe symptoms**. Truncations or missense mutations, imprinting center defects, and paternal uniparental disomy can also cause AS.[3-7]

The diagnosed prevalence of AS is approximately 1 in 21,000 people worldwide.[3,7-9] AS symptoms and impairments present early in life and persist throughout a normal lifespan, resulting in medical challenges that require lifelong care.[3,5,10-13]

The lack of FDA-approved disease-modifying therapies, combined with the severity of the condition, results in **high unmet clinical needs** for individuals with AS and their families.[14,15]

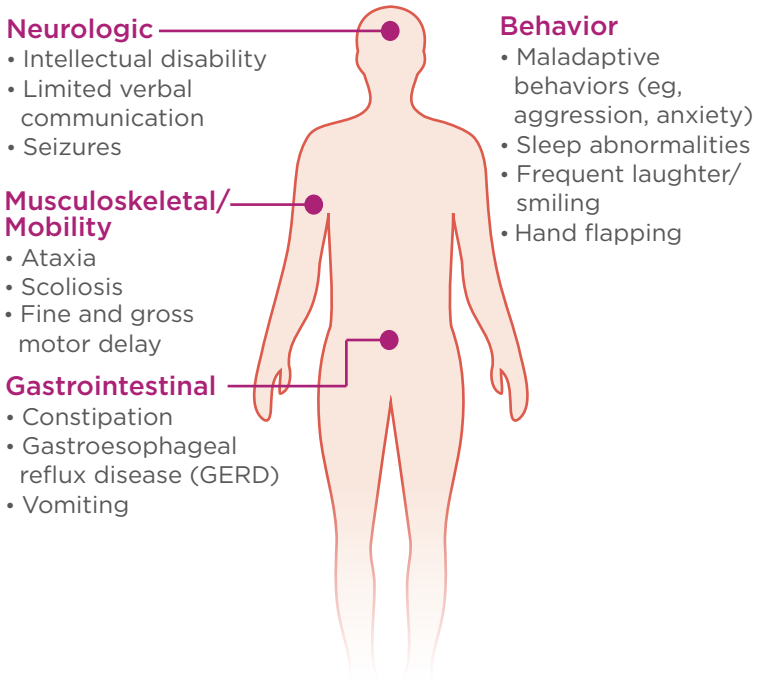
AS Is Characterized by a Range of Impairments, Including Communication, Cognitive, Motor, and Behavioral Manifestations[3,5,10]

AS is characterized by **intellectual disability, seizures, communication difficulty, a very happy demeanor with frequent laughter, sleep disturbances, delays in fine and gross motor milestones, and movement issues** (Figure 1).[3,5,10]

Individuals with AS may be asymptomatic at birth, but often have feeding problems in the first months of life, developmental delays between 6 and 12 months, and seizures beginning around 2 to 3 years of age.[3,5,10,16]

Clinical signs and symptoms of AS may vary based on genetic subtype. Expressive communication and cognitive impairment are universal features of AS, with most severe disability seen in those with deletion subtype. Epilepsy is also common in all subtypes, with higher rates in those with deletion subtype and later onset in the nondeletion subtype (>5 years of age). Microcephaly is often seen in those with deletion subtype but not as frequently noted in other subtypes, while hyperphagia is more common in those with uniparental disomy or imprinting defects.[11,17]

Figure 1: Primary Symptoms Associated With AS[3,5,10]



In adulthood, individuals with AS continue to experience AS-related impairments, including cognitive disability, communication difficulties, anxiety, issues with self-care, and further decline in mobility. Sleep, seizures, and hyperactivity often become less significant impairments as individuals with AS age.[3,5,11,12]

Individuals with AS have a near-normal life expectancy but require lifelong care[3,11]

FDA, US Food and Drug Administration; *UBE3A*, ubiquitin protein ligase E3A.

1. Kishino T, et al. *Nat Genet*. 1997;15(1):70-73. 2. Matsuura T, et al. *Nat Genet*. 1997;15(1):74-77. 3. Wheeler AC, et al. *Orphanet J Rare Dis*. 2017;12(1):164. 4. Larson AM, et al. *Am J Med Genet A*. 2015;167A(2):331-344. 5. Prasad A, et al. *Am J Med Genet A*. 2018;176(6):1327-1334. 6. Mertz LGB, et al. *Am J Med Genet A*. 2013;161A(9):2197-2203. 7. Hagenaar DA, et al. *J Intellect Disabil Res*. 2024;68(3):248-263. 8. Yakoreva M, et al. *Eur J Hum Genet*. 2019;27(11):1649-1658. 9. Luk HM, et al. *Eur J Med Genet*. 2016;59(6-7):315-319. 10. Clayton-Smith J, et al. *J Med Genet*. 2003;40(2):87-95. 11. Duis J, et al. *Mol Genet Genomics Med*. 2022;10:e1843. 12. Khan N, et al. *Qual Life Res*. 2023;32(7):2059-2067. 13. Willgoss T, et al. *Child Psychiatry Hum Dev*. 2021;52(4):654-668. 14. Wheeler AC, et al. *J Neurodev Disord*. 2023;15(1):37. 15. Angelman syndrome. National Organization for Rare Disorders. Updated February 14, 2018. Accessed August 22, 2024. https://rarediseases.org/rare-diseases/angelman-syndrome/?filter=ovr-ds-resources/ 16. Williams CA, et al. *Am J Med Genet*. 1995;56:237-238. 17. Keute M, et al. *Mol Psychiatry*. 2021;26(7):3625-3633.

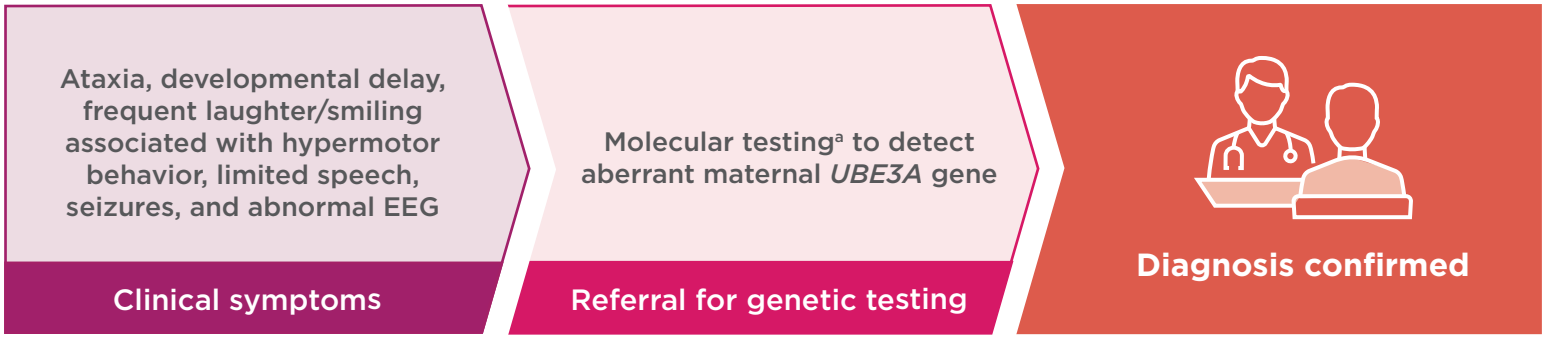
Prompt Diagnosis and Interventions Targeting the Underlying Pathophysiology of Angelman Syndrome (AS) Are Critical Unmet Needs[1-3]

On average, individuals are diagnosed **1 to 4 years** after symptom onset[5,6]

Disorders with overlapping symptomatology[4]

- Alpha-thalassemia
- Lennox-Gastaut syndrome
- Infant autism spectrum disorder
- Mowat-Wilson syndrome
- Rett syndrome
- X-linked intellectual disability

Figure 2: Diagnosis Is Made by Clinical Observation Followed by Confirmatory *UBE3A* Genetic Testing[1-4,7]



Further diagnostic and screening efforts are needed to identify individuals with AS early in life prior to symptomatic presentation (~2 years of age), as they often experience developmental delays in early childhood[6]

There Are No Disease-Modifying Treatment Options Available for Individuals With AS[2,3,5]

Current treatments provide only symptomatic relief...

Expressive communication[1,2,8]
- Speech therapy
- Augmentative and Alternative Communication
- Individualized education plan

Sleep[1,2,8]
- Treatment of contributing problems (eg, GERD, epilepsy, anxiety, obstructive sleep apnea)
- Sleep hygiene
- Medicinal and medical treatments

Behavior[1,2,8]
- Physical and occupational therapy
- Hydrotherapy

Seizures[8]
- Antiseizure medications
- Low carbohydrate diet
- Referral to epileptologist

...and poorly address the range of symptoms experienced by patients, as supported by reports from healthcare providers and caregivers[9,10,12-14]

[a]Tests include methylation studies, chromosome microarray, uniparental disomy studies, imprinting center studies, and gene sequencing.[3,4,11]

EEG, electroencephalogram; GERD, gastroesophageal reflux disease; *UBE3A*, ubiquitin protein ligase E3A.

1. Wheeler AC, et al. *Orphanet J Rare Dis*. 2017;12(1):164. 2. Angelman syndrome. National Organization for Rare Disorders. Updated February 14, 2018. Accessed August 22, 2024. https://rarediseases.org/rare-diseases/angelman-syndrome/?filter=ovr-ds-resources/ 3. Madaan M, Mendez MD. *StatPearls*. Treasure Island (FL): Stat Pearls Publishing; January 2024. 4. Maranga C, et al. *FEBS J*. 2020;287(11):2154-2175. 5. Wheeler AC, et al. *J Neurodev Disord*. 2023;15(1):37. 6. Williams CA, et al. *Am J Med Genet*. 1995;56:237-238. 7. Clayton-Smith J, et al. *J Med Genet*. 2003;40(2):87-95. 8. Duis J, et al. *Mol Genet Genomic Med*. 2022;10(3):e1843. 9. Willgoss T, et al. *Child Psychiatry Hum Dev*. 2021;52(4):654-668. 10. Connor-Ahmad S, et al. *Orphanet J Rare Dis*. 2023;18(1):156. 11. Testing and Diagnosis. Angelman Syndrome Foundation. Accessed August 27, 2024. https://www.angelman.org/what-is-as/testing-and-diagnosis/ 12. Hagenaar DA, et al. *J Intellect Disabil Res*. 2024;68(3):248-263. 13. Leader G, et al. *J Intellect Disabil Res*. 2022; 66(11):865-879. 14. Rogers M, et al. *Children (Basel)*. 2023;10(9):1462.