angelman
SYNDROME FOUNDATION

Facts About Angelman Syndrome

Clear, accessible information for parents and professionals.



8th Edition

Facts About Angelman Syndrome began in 1987 as a small, foundational booklet—created to help launch the Angelman Syndrome Foundation and to provide parents and professionals with clear, accessible information about a then-little-understood condition. What started as a modest educational pamphlet has evolved alongside the community it was created to serve.

Now in its eighth edition, Facts About Angelman Syndrome reflects nearly four decades of scientific progress, clinical learning, and—most importantly—lived experience. This edition marks a significant evolution of the document, both in substance and in form. The former pamphlet has been fully reimagined for a web-based platform, allowing for greater depth, accessibility, and real-time relevance.

This new edition captures the profound advances made since earlier versions, including expanded understanding of genetics, epilepsy, sleep, behavior, communication, and medical management. Equally important, it reflects a deliberate shift toward family-centered, functionally meaningful, and lifespan-oriented content. Angelman syndrome is no longer framed solely through early childhood milestones, but as a lifelong condition that unfolds across childhood, adolescence, and adulthood.

Substantially revised and newly added sections address how Angelman syndrome presents and evolves over time, with particular attention to behavior, sleep, anxiety, communication, adaptive functioning, and quality of life. Throughout the document, new “What This Means for Families” sections and practical strategy callouts translate research and clinical knowledge into real-world guidance—supporting caregiving decisions, educational planning, and medical care in everyday life.

This edition is not simply an update—it is a statement of where the Angelman community is today and how knowledge must evolve to meet it.

“Facts About Angelman Syndrome is more than an educational resource—it’s a reflection of our community’s collective knowledge and lived experience. This document is meant to be used, shared, and revisited over time by families, clinicians, educators, and researchers alike. It bridges science and real life, and it affirms that the voices of families matter just as much as the data. Our hope is that this resource empowers better care, better research, and a deeper understanding of Angelman syndrome across the entire lifespan.” — Amanda Moore, CEO, Angelman Syndrome Foundation

Together, this edition serves as both a trusted reference and a living framework—grounded in science, shaped by families, and designed to support the Angelman community now and into the future.

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Dr. Angelman and the History of AS

In 1965, Dr. Harry Angelman, an English physician, first described three children with characteristics now known as Angelman syndrome (AS) (Angelman, 1965). 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 (Angelman, 1991).

"The history of medicine is full of interesting stories about the discovery of illnesses. The saga of Angelman 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."

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 1987, Ellen Magenis, a physician at the Oregon Health Science Center, identified children with microdeletions of chromosome 15 who were expected to have Prader-Willi syndrome (PWS). However, these children had seizures and severe developmental delay, features not expected for PWS. It was quickly realized that these children had microdeletions on the maternally derived number 15 chromosome whereas in 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 maternally inherited chromosome 15. It was learned that AS can be caused by two copies of the paternal chromosome 15 (paternal uniparental disomy (pUPD)) and that disruption of a regulatory region (the Imprinting Center) can also lead to AS. In 1997, 10 years after the chromosome deletion was discovered, the AS gene, UBE3A, was identified. This quickly led to the development of animal models and to active neuroscience research aimed at discovering how abnormalities of UBE3A cause impairment in neuronal development.

During the last 40 years, there has been increasing awareness of AS throughout the world. Angelman

syndrome is well represented by parent support groups in many countries, on individual family websites and on a host of medical and professional information websites. Some of these resources are:
https://www.angelman.org/
https://cureangelman.org/
https://www.ncbi.nlm.nih.gov/books/NBK1144/

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 AS?

AS has been reported throughout the world among all ethnic and racial groups. The exact incidence of AS is unknown, and until AS is included in state newborn screening programs, it can never be determined accurately. Nonetheless, some studies have attempted to estimate the birth prevalence of AS.

By searching the: (i) Danish National Patient Registry, which includes all Danish residents who have received inpatient and outpatient medical care; (ii) Danish Cytogenetic Central Registry, which includes all prenatal genetic testing and postnatal chromosome analysis; contacting all pediatrics and clinical genetics departments, and through the AS patient advocacy groups in Denmark, 51 patients with AS were born between 1991 and 2009. There were 1,253,599 births in Denmark in that period, so the birth incidence of AS in that population was 1:24,580 (Mertz et al., 2013).

In another study on AS in Hong Kong, 55 patients with AS were evaluated between 1995 and 2015 through the records of the Department of Health Clinical Genetic Service. There were 1,226,780 live births during this period, so the prevalence of AS was estimated to be 1:22,305 (Luk et al., 2016).

A retrospective review of the records of patients evaluated between 1998 and 2016 and prospectively collected data from 2014 to 2018 at the only genetic referral center in Estonia identified 15 patients with AS, giving a birth prevalence of 1:27,198 (Yakoreva et al., 2019).

Consensus Criteria for Diagnosis of AS

AS is not easily recognized in early infancy since the developmental problems are nonspecific at that time. The most common age of diagnosis is 18 months (though with increasing awareness and availability of molecular testing, average age at diagnosis will likely decrease). Children with UBE3A mutation or pUPD are diagnosed significantly later than those with deletion (Mertz et al., 2013; Wheeler et al., 2023). Parents may first suspect the diagnosis after reading about AS or meeting a child with the condition, or it may be suggested by a therapist who treats individuals with AS. Children with AS may have a relatively wide mouth, sometimes associated with a prominent chin (see figure). Most children also share the facial traits of their family. More often, AS is recognized by distinctive behaviors and a characteristic developmental profile. 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 (Williams et al., 2006). Not all the features need to be present for the diagnosis to be made, and the diagnosis is often first suspected when the typical behaviors emerge.



Composite photograph of facial appearances of individuals with AS.

Developmental and Physical Findings (modified from 2005 Consensus Criteria document)

Consistent features seen in almost all individuals (>95%)

- Developmental delay, meaning acquiring developmental milestones and skills more slowly than expected
- Movement or balance differences, usually tremulous movement of limbs, often affecting gait. This may look like unsteadiness, clumsiness, leaning forward while walking, shaky movements, or jerky movements rather than obvious loss of balance.
- Behavioral uniqueness: a combination of frequent laughter/smiling, apparent happy demeanor, easily excitable personality, often with uplifted hand-flapping or waving movements, and near-constant movement of the body.
- Speech impairment, none or minimal use of words; non-verbal communication (such as gestures, facial expressions, or use of picture-exchange systems) is often stronger than verbal language; receptive language (i.e., understanding of what others are saying to them) tends to be stronger than expressive language, although it is still below expectations for age.

Frequent features, seen in most individuals (more than 80%)

- Delayed, disproportionate growth in head circumference, usually resulting in below average head size by age 2 years, mainly in those with AS due to a deletion on chromosome 15.
- Seizures, usually starting between 1 and 3 years of age. Seizure frequency and severity may decrease after puberty, although epilepsy can persist or recur in adulthood.
- Abnormal brain wave pattern (EEG), with a characteristic pattern, as mentioned in the text. The EEG abnormalities can precede other clinical features, even if there are no clinical seizures.

Associated features seen in some individuals (20 - 80%)

- Flattened back of the head
- Feeding problems, often related to low muscle tone in the trunk during infancy
- A prominent lower jaw
- Wide mouth and widely spaced teeth
- Frequent drooling

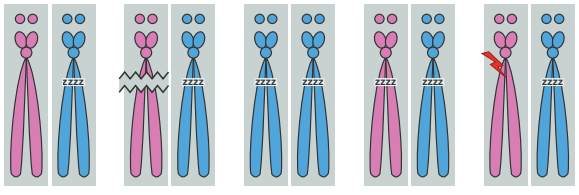
- Excessive chewing/mouthing of non-food objects
- Crossed or misaligned eyes
- Hypopigmented skin, lighter hair and eye color (compared to family)
- Increased lower extremity deep tendon reflexes
- Uplifted, flexed arm position especially while walking
- Wide-based walking pattern with ankles that roll inward or outward
- Increased sensitivity to heat
- Disrupted sleep pattern
- Attraction to/fascination with water; fascination with crinkly items such as certain papers and plastics
- Unusual food-related behaviors
- Overweight / obesity (in the older child and adults)
- Curvature of the spine
- Constipation

Genetics of AS

Genetic Mechanisms that Cause AS

In 1997, mutations in UBE3A located on chromosome 15 were identified as the cause of AS (Kishino et al., 1997; Matsuura et al., 1997). The mechanisms known to cause AS either disrupt, inactivate, or lead to the absence of this gene on the maternally-derived chromosome 15. There are four genetic "subclasses" or mechanisms that can disrupt UBE3A and thus cause AS (Jiang et al., 1999). These mechanisms are depicted in the illustration below.

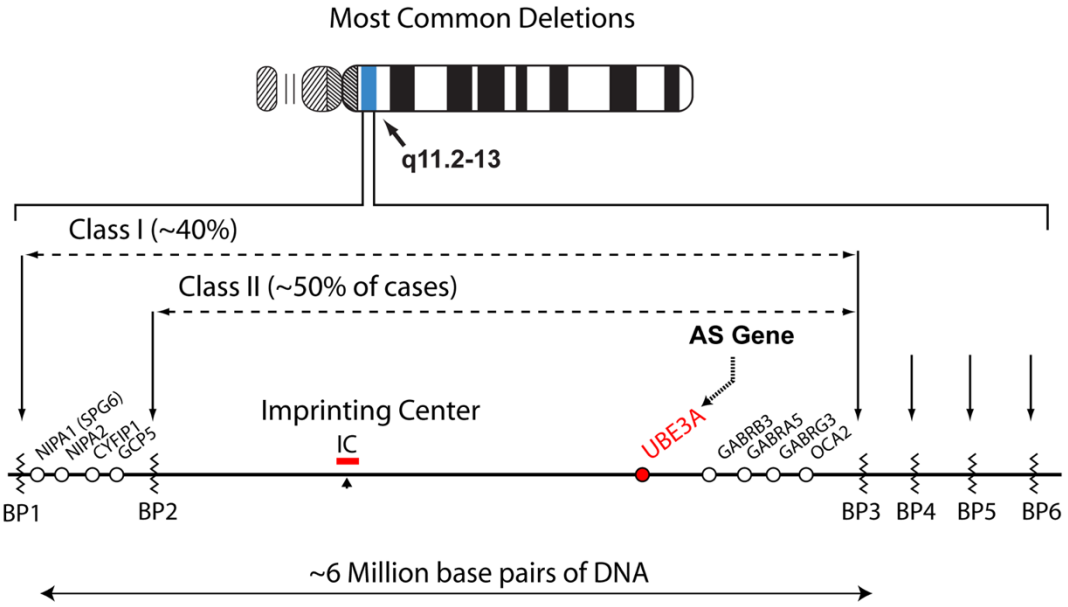
A chromosome 15 pair is illustrated for each mechanism, with a normal chromosome pair depicted on the left. The paternally inherited chromosome is shown in blue, and the maternally inherited chromosome is shown in pink. AS can be caused by a large deletion of the maternal chromosome 15q11.2 region (where the active UBE3A resides). AS can also be caused by inheritance from the father of two paternal chromosomes 15, a phenomenon termed paternal uniparental disomy (pUPD). Another cause, referred to as an imprinting defect (ImpD), occurs when the chromosome 15 inherited from the mother has the paternal pattern of gene functioning so that UBE3A expression is prevented. Finally, AS can be caused by a mutation in UBE3A on the maternally derived chromosome 15.



Mechanism	Frequency (%)
Deletion	~65-70%
pUPD	5-10%
Imprinting defect	5-10%
UBE3A mutation	~15%

The table above shows the prevalence of the different genetic subclasses.

The typical deletion spans approximately either 5 million or 6 million building blocks (base pairs) of DNA. Two common deletion classes have been identified. Class I deletions extend from breakpoint 1 (BP1) to BP3 and span approximately 6 million base pairs. Class II deletions extend from BP2 to BP3 and span approximately 5 million base pairs. About 10% of the deletions are atypical in that they either extend beyond BP3 or are smaller than the class II deletions. Chromosomal microarray (CMA), also known as comparative genomic hybridization (CGH), is a genetic test that can determine the precise size of the deletion (but not whether it affects



the paternally- or maternally-inherited copy of the chromosome). Older testing methods, including fluorescence in situ hybridization (FISH), can also detect deletions. The typical deletion includes UBE3A and other genes in the region, as shown in the figure, but it is the loss of UBE3A that results in most of the clinical manifestations in those with AS due to a deletion.

UBE3A and the Ubiquitin Pathway

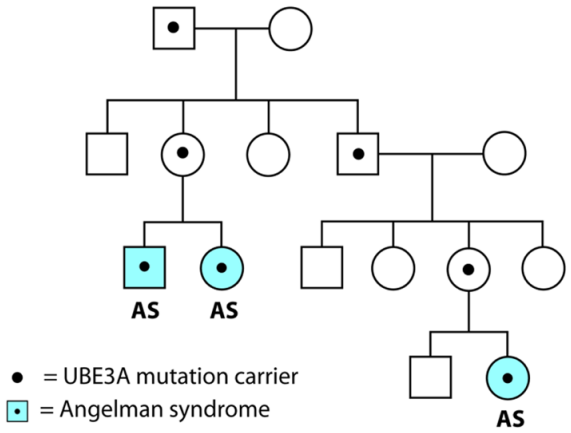
The UBE3A gene produces the UBE3A protein (also called E6-AP), which is an important component of the ubiquitin-proteasome pathway. This pathway is extremely important to all cells. The pathway enables a small protein molecule, ubiquitin, to be attached to certain proteins, thereby causing those proteins to be degraded (Scheffner et al., 1995).

UBE3A and Imprinting

UBE3A is known to be paternally imprinted in neurons (Yamasaki et al., 2003). This means that UBE3A on the paternally-inherited chromosome 15 is almost completely inactive while the maternally-inherited gene is active. When UBE3A on the maternally-inherited chromosome 15 is deleted or mutated, the only active copy of the gene is lost. Deletions in the same chromosomal region of the paternally-inherited chromosome 15 cause another developmental disorder, Prader-Willi syndrome (PWS), due to the loss of other imprinted gene(s) in the region.

Individuals with a UBE3A mutation (pathogenic variant) can have either a de novo mutation (i.e., not inherited from either parent) or a mutation inherited from the mother. Because the paternally-inherited UBE3A is silenced, mutations in the paternally-inherited UBE3A gene do not cause AS. Therefore, the mother and her siblings could have inherited the same UBE3A mutation from their father (i.e., the child's maternal grandfather); these asymptomatic individuals are "carriers" of the UBE3A mutation. The pedigree illustrates how imprinting inheritance can cause recurrence of AS in somewhat distantly related relatives. However, should a carrier daughter transmit the UBE3A mutation to her child, that child will have AS. The same type of inheritance pattern can also be seen in some families with a deletion of the Imprinting Center.

Example of Imprinting Inheritance in Familial AS:
Inherited UBE3A Mutation



Most individuals with AS due to a deletion, UPD, or an imprinting defect without an imprinting center deletion did not inherit the condition from either parent.

Genetic Mechanisms and Severity of Symptoms

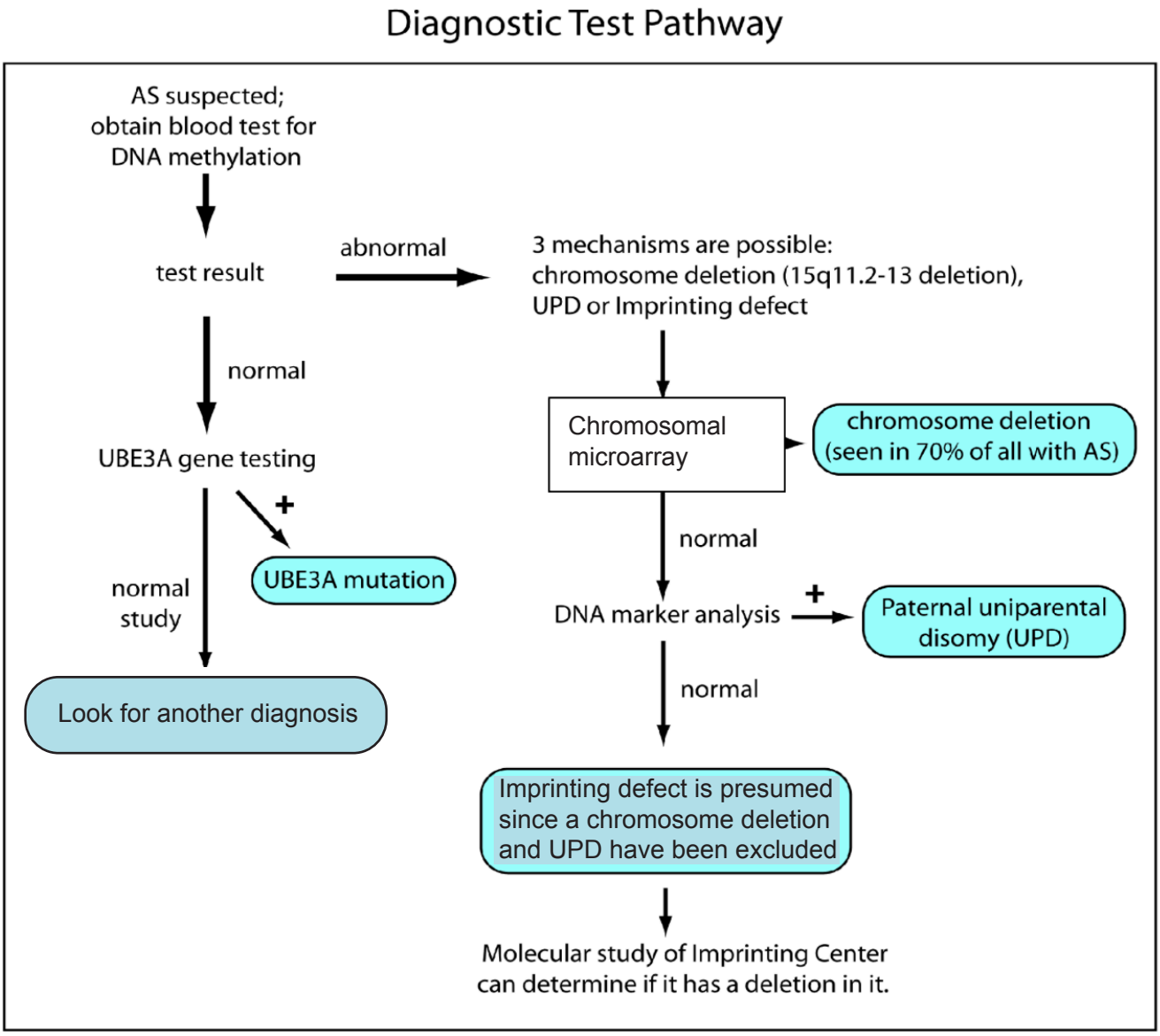
Regardless of the genetic mechanism causing AS, the syndrome is characterized by a reasonably uniform clinical picture of severe intellectual disability, characteristic behaviors, and severe limitations in speech and language. There are some clinical differences that correlate with the genotype, although there is great variability within each genotype. These correlations are broadly summarized below:

1. Individuals with deletions are more severely affected with seizures, motor difficulties (e.g., ataxia, hypotonia), feeding difficulties, and global developmental delay. While those with larger deletions tend to be more impaired, the practical differences between the two common deletion classes (i.e., class I and class II) are minor. (Keute et al., 2021; Sadhwani et al., 2024).

2. UPD and ImpD individuals have better physical growth and better motor and language skills, and they have a lower prevalence (but not necessarily absence) of seizures. Individuals with UPD and ImpD have a higher risk of obesity than those with a deletion (Yang et al., 2021).

3. Individuals with a UBE3A mutation tend to have clinical severity between those with a deletion and ImpD. Some individuals with UBE3A mutations may demonstrate relatively stronger cognitive, fine motor, and gross motor abilities. The clinical presentation may also vary depending on the specific variant. (Keute et al., 2021; Sadhwani et al., 2024).

4. Some individuals are mosaic for the genetic defect (i.e., having some cells that are imprinted correctly among the cells that are imprinted incorrectly). These individuals may speak up to 50-60 words and use simple sentences.



Genetic Diagnostic Testing

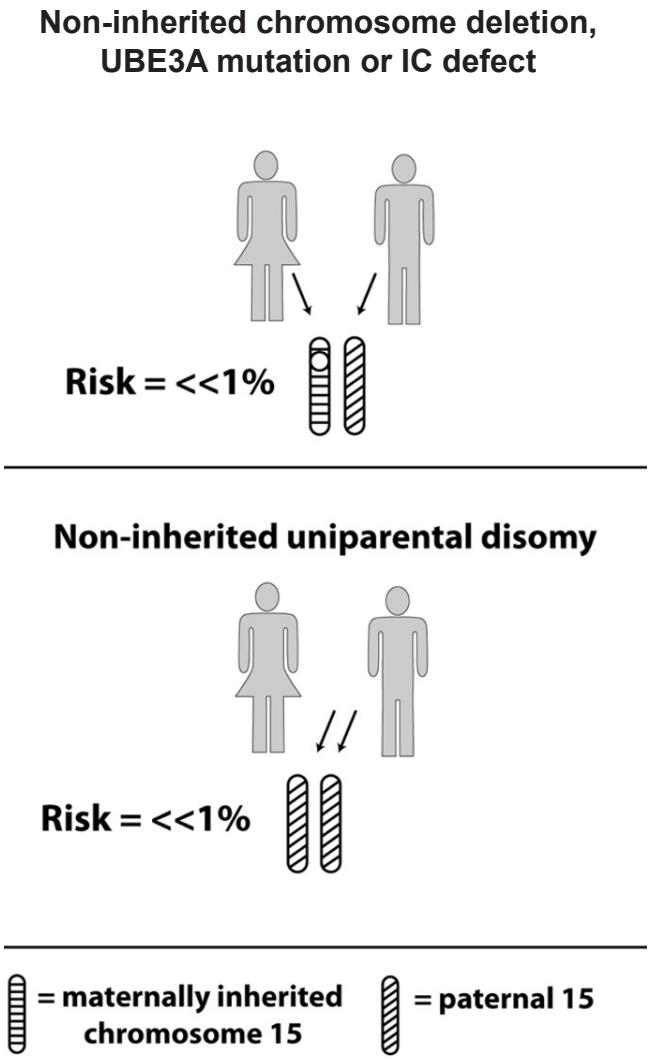
Laboratory diagnostic testing for AS can be complex. Evaluation of an individual in whom the diagnosis of AS is suspected starts with a DNA methylation analysis of the AS/PWS region. A positive (abnormal) DNA methylation test confirms the diagnosis of AS. The DNA methylation test is positive in AS when one of three mechanisms is present: deletion, UPD, and ImpD. When the methylation test is positive, additional studies are recommended to define the specific genetic mechanism (maternal 15q11.2-q13 deletion, paternal UPD, or an imprinting defect). In such situations, the next step typically is to perform a chromosomal microarray (CMA) to determine if the common 15q11.2-13 deletion is present. If the CMA test is normal, the next step is to look for UPD by additional molecular testing involving parental blood samples. Individuals with a positive AS DNA methylation study who have normal CMA and normal UPD studies are then presumed to have an ImpD. Those cases should be further studied to determine if there is a deletion involving the Imprint-

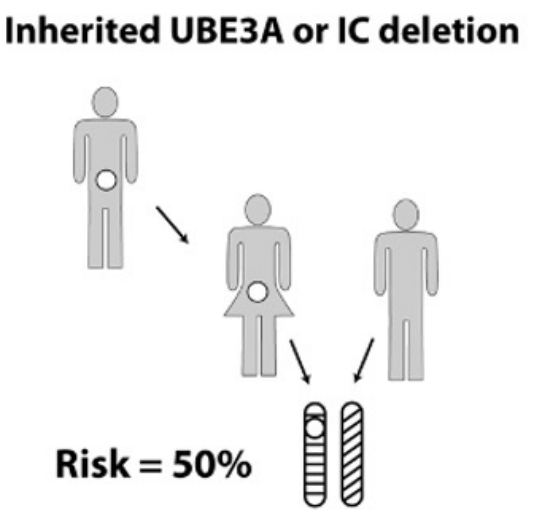
ing Center (IC), which is one of the hereditary forms of AS.

If the methylation test is negative, this rules out deletion, UPD and ImpD. Sequencing of UBE3A is then indicated to look for a mutation. Sequencing can be done with targeted gene sequencing, gene panels that include UBE3A or by exome or genome sequencing. After a mutation is found, maternal testing should be performed to determine if the mutation is carried by the mother (on the chromosome she inherited from her father). If the mother carries the mutation, recurrence risk is 50%. If the mother does not carry the mutation, it is de novo and carries a much lower recurrence risk (<1%).

Individuals with a clinical phenotype suggestive of AS but without an identifiable molecular diagnosis should be evaluated using a broad investigational strategy such as genome sequencing for alternative Angelman-like neurodevelopmental disorders, such as Phelan-McDermid syndrome, Pitt-Hopkins syndrome, and GRIN-related disorders (Tan et al., 2014). However, a small proportion of individuals with a classic AS phenotype remain without an identifiable molecular mechanism despite comprehensive testing.

Understanding Genetic Risk in Angelman Syndrome





What This Means for Families

AS can occur through different genetic mechanisms, and the chance of it happening again in a family depends on which genetic mechanism caused it. Because this can be complex, families are strongly encouraged to meet with a genetic counselor who is familiar with AS to review results and discuss recurrence risk.

Below is an overview of the main genetic causes and what they usually mean for families. (https://www.ncbi.nlm.nih.gov/books/NBK1144/#angelman.Genetic_Counseling)

1. Common chromosome deletion:

The vast majority (>98%) of AS deletions are not inherited. For these families, the chance of having another child with AS is <1%. However, 1-2% of deletions occur because the mother carries a chromosomal change that does not affect her health. Very rarely, a child can have AS due to a very small deletion that involves a small area around and including UBE3A (e.g., only a few cases reported in the literature). For these reasons, additional parental studies may be recommended to evaluate for a rare inherited chromosomal rearrangement or deletion, depending on the characteristics of the child's deletion.

2. Paternal uniparental disomy (pUPD):

In pUPD, the child receives both copies of chromosome 15 from the father instead of one from each parent. This usually occurs as a spontaneous, non-inherited event. If an individual has AS due to pUPD and has a normal karyotype, a chromosomal analysis of both parents may be considered to exclude the rare possibility that a chromosome change in one of the parents may predispose to this outcome. In summary, the recurrence risk is <1% if both parents have normal chromosome analyses.

3. Imprinting Defect (ImpD):
An ImpD means that UBE3A is present on the maternally-inherited chromosome, but not properly turned on. There are two types of ImpDs: those that occur spontaneously (~90%) (and have a <1% recurrence risk) and those that are caused by an IC deletion (~10%). If the IC deletion is inherited from the mother, this confers a 50% risk for recurrence. Distinguishing between these two types is very important for family planning.

4. *UBE3A* mutations:
Mutations in UBE3A may occur de novo or be inherited from the mother. When the mother carries the mutation, each pregnancy has a 50% chance of inheriting it. When the variant occurs de novo and is not detected in either parent, the recurrence risk is generally low, although germline mosaicism remains possible.

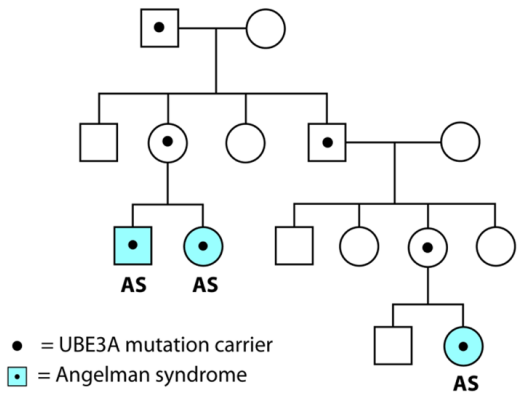
5. Germline (also known as gonadal) mosaicism:
This term refers to a phenomenon in which a genetic defect is present in the germ cells of the gonad (egg cells in the ovary in the mother's case) but not in other cells of the body. Germline mosaicism can complicate recurrence-risk assessment. For example, a mother's blood test may be normal even when a genetic change is present in some of her egg cells. Fortunately, germline mosaicism occurs very infrequently. Nevertheless, it has been observed in AS caused by deletion, IC deletion and UBE3A mutation (Tang et al., 2019). Because of this, recurrence risk is never zero.

6. Imprinting inheritance:
Some AS-related genetic changes, including UBE3A mutations and imprinting center deletions, can be transmitted through unaffected family members. A carrier father may pass the genetic change to his children without causing AS. However, when a carrier mother transmits the same genetic change, the child will generally have AS, regardless of sex. A carrier mother has a 50% chance of transmitting the genetic change in each pregnancy. This inheritance pattern can explain why AS sometimes appears unexpectedly in families after several generations without affected individuals. When an inherited genetic mechanism is identified, genetic testing and counseling should be offered to appropriate family members.

The pedigree diagram below illustrates inheritance of a paternally imprinted gene such as UBE3A.

Here, AS has occurred only after a carrier mother transmitted the genetic change, as illustrated by the two siblings with AS shown in the lower-left portion of the pedigree. A first cousin once removed in this family also has AS. In this branch of the family, the UBE3A mutation was transmitted through two unaffected male carriers before reaching a female carrier. She subsequently transmitted the variant to her child, resulting in AS. In the diagram, individuals represented by light blue circles or squares have AS, but everyone else in the family is clinically normal.

Example of Imprinting Inheritance in Familial AS:
Inherited UBE3A Mutation



The black dots represent asymptomatic, normal carriers of the AS mutation. When an AS genetic mechanism is determined to be inherited, genetic testing of family members can identify healthy individuals who carry the gene defect. As you might imagine, professional genetic counseling is advised in these situations.

What Does This Mean for Future Pregnancies?

For most families, the chance of having another child with AS is low. In the majority of cases, AS happens due to a spontaneous (de novo) genetic change that is not inherited and is unlikely to happen again. However, the exact risk depends on the specific genetic cause identified in the child. Some genetic mechanisms carry a higher chance of recurrence, particularly when a parent, in this case the mother, carries a genetic change that does not affect her health but can be passed on to a child. Because of this, genetic testing of the parents is often recommended. These tests help clarify whether the genetic change occurred by chance or was inherited, which directly affects recurrence risk.

If a higher recurrence risk is identified, families should be informed of:

- Prenatal testing options in future pregnancies
- Preimplantation genetic testing option if using in vitro fertilization (IVF)
- Early testing after birth to guide medical care

Even when testing suggests a very low recurrence risk, it is important to know that no genetic risk can ever be considered zero. Rare situations, such as changes present only in egg cells (germline mosaicism, discussed above), can occasionally occur.

Families planning future pregnancies are strongly encouraged to meet with a genetic counselor familiar with AS. This allows families to receive personalized information, ask questions, and make informed decisions that align with their values and goals.

Behavior and Development

Characteristic behaviors

Children and adults with AS often show a recognizable pattern of behaviors. Common features include frequent laughter that is easily provoked, increased social smile and hypersocial behavior, apparent happiness, mouthing of objects, and a fascination with water and plastic or paper items that make crinkly noises when manipulated (Dagli et al., 2012; Stoppel et al., 2017). Some individuals may also show challenging behaviors, especially during times of frustration. Caregivers most often report concerns related to hyperactivity, short attention span, and irritability/aggression. These issues are linked to higher stress for parents and lower quality of life (Sadhwani et al., 2019).

Laughter and happiness

One of the earliest signs of AS may be early and persistent smiling, sometimes beginning in the first few months of life. Additional early signs are sleep problems, gastroesophageal reflux disease (GERD), and difficulties with breast or bottle feeding. Giggling, chuckling and laughing develop early in life and appear to represent reflexive behavior. Cooing and babbling are often reduced. A few individuals have pronounced laughing that is truly paroxysmal or contagious (Buntinx et al., 1995). More often, happy grimacing and a happy disposition are predominant. In rare cases, the apparent happy disposition is fleeting as irritability and hyperactivity become the prevailing behavior; crying, shrieking, screaming or short guttural sounds may also be common.

The reason laughter is so frequent in AS is not fully understood. Although laughter can occur during

certain types of seizures, known as gelastic seizures, the characteristic laughter associated with AS is generally not epileptic in origin. The laughter in AS seems mostly to be an expressive motor event; most reactions to stimuli, physical or mental, are accompanied by laughter or laughter-like facial grimacing. Brain imaging studies suggest that differences in areas involved in emotion, reward, and movement may play a role.

Hyperactivity

Most children with AS are described as hyperactive, especially in infancy and early childhood. Short attention spans are also frequently reported. Infants and toddlers may have seemingly ceaseless activity, constantly moving from object to object. In early childhood, attention abilities may increase, often associated with apparent curiosity. Attentiveness may then become sufficient to begin teaching sign-gesture language and other communication techniques. However, hyperactivity may interfere with educational activities and limit forward progress. Increase in hyperactivity from childhood until young adulthood has been documented across all molecular subtypes (Sadhwani et al., 2019). Behavioral approaches can help with regulation of attention and activity level and include providing frequent movement breaks, positive reinforcement or reward systems, adjustments to the environment to minimize distractors, 1:1 aide for educational activities, and occupational therapy. Medication may be considered when hyperactivity or impulsivity significantly interferes with learning, daily functioning, or safety despite appropriate environmental and behavioral supports. Alpha-2 adrenergic agonists, such as guanfacine and clonidine, are used to treat ADHD symptoms in children (Neuchat et al., 2023) and may be considered in selected individuals with AS. Preliminary studies have reported poor tolerance to stimulants, commonly used as first-line treatment in attention-deficit/hyperactivity disorder (Keary et al., 2022). Use of calming or sedating medications is not generally advised but may be useful in extreme cases. There is a tendency toward weight gain with the use of certain neuroleptics, and these drugs are also associated with more side effects. Thus far, there are no formal clinical trials examining the efficacy of stimulant medications or neuroleptics to treat hyperactivity/impulsivity in AS. Medication decisions should therefore be individualized and monitored carefully for sedation, irritability, sleep disturbance, blood pressure, and other medication-specific effects.

What This Means for Families

For families, hyperactivity can make daily life more demanding. Children need constant supervision, frequent redirection, and regular opportunities to move. This can be tiring for caregivers and may affect routines at home, school, and in the community. It is important to know that hyperactivity in AS is not due to poor parenting and reflects underlying neurodevelopmental differences rather than intentional behavior. Many families find that highly structured and predictable routines, clear expectations, and supportive school environments make a meaningful difference. Families often benefit from working closely with therapists and educators to build strategies that support attention and regulation, while also allowing for movement. Seeking help early and adjusting expectations can reduce stress and help families focus on their child's strengths and progress.

Challenging Behaviors

Although many individuals with AS are described as cheerful, they may also experience restlessness, irritability, tantrums, and aggression. These behaviors can interfere with social interactions and daily activities. Additionally, attention-seeking behaviors

are common and can become challenging and unsafe. These behaviors can look different from one person to another and may change over time. Behavior patterns can also vary depending on the underlying genetic cause of AS, but all individuals may experience periods of behavioral difficulty. Those with the deletion subtype show less irritability than those with UPD, ImpD and UBE3A mutations. However, they display more repetitive movements and mouthing behaviors than those with nondeletion subtypes. Behavioral challenges are generally comparable between males and females, although some sex-related differences have been reported. Females may exhibit more lethargy, whereas males are more likely to engage in hair pulling and biting compared to females. In addition, males tend to show progressively shorter attention spans and increased excitability over time compared to females (Sadhwani et al., 2019).

In individuals with the deletion genotype, interest in water and frequent laughter increase with age, while hair pulling remains largely unchanged. For the UPD and ImpD genotypes, interest in water increases with age, but hair pulling decreases. Individuals with AS become more irritable and hyperactive over time. Across all subtypes, aggressive behavior, hand flapping, and anxiety increase with age. Increased irritability among individuals with nondeletion subtype may be linked to heightened awareness of their surroundings combined with the ongoing challenges in communication (Sadhwani et al., 2019). Behavioral changes may represent an attempt to communicate anxiety, frustration, sensory overload, or other unmet needs. Transitions, routine disruption, separation from the caregiver, and preferred item removal are the most common precipitants of behavioral escalation in AS.

What Helps at Home and School (Checklist)

Structure & Predictability

- ☐ Consistent daily routines
- ☐ Visual schedules (pictures or icons)
- ☐ Use of timers
- ☐ Planning for transitions
- ☐ Advance warnings before transitions ("2 minutes left")
- ☐ Clear beginning and end to activities

Behavior Support Strategies

- ☐ Use of rewards and preferred items for engagement and calm behavior
- ☐ Clear expectations with simple, consistent language
- ☐ Visual choice boards to reduce frustration
- ☐ Redirecting behavior rather than punitive responses
- ☐ Frequent breaks

Environmental Modifications

- ☐ Preferential seating
- ☐ Small group or 1:1 support during learning tasks
- ☐ Predictable seating and materials

What This Means for Families

Challenging behaviors can be stressful for families, particularly when they occur frequently or without an obvious trigger. These behaviors often serve a function, such as communicating a need, seeking attention, avoiding an uncomfortable situation, or obtaining sensory input. Understanding what hap-

pens before and after a behavior can help families and professionals identify its likely function and develop individualized strategies. Helpful approaches include predictable routines, clear transitions, visual supports, communication tools, and positive behavioral interventions. Addressing contributing factors, such as anxiety, sleep difficulties, pain, or communication challenges, may also reduce behavioral difficulties.

Caregivers should not hesitate to seek support from behavioral specialists, therapists, and school teams. Connecting with other families who have children with AS can also be reassuring and provide practical ideas.

Emotional & Anxiety Support (Checklist)

- ☐ Consistent caregivers and staff when possible
- ☐ Preparation for new or unfamiliar situations
- ☐ Calm, reassuring responses during distress
- ☐ Recognizing signs of anxiety or overstimulation early

Suggested IEP language: Support for emotional regulation; anxiety-informed strategies.

Anxiety

Anxiety can affect individuals with AS, although it may be hard to recognize, especially due to the limited speech. Anxiety symptoms have been reported by caregivers of adolescents and adults with AS. It is not known whether anxiety is less frequent in younger individuals with AS, or whether caregivers and providers have difficulty recognizing it in children. Typical symptoms of anxiety are screaming and crying, increased restlessness and pacing, specific fears, somatic symptoms (like stomach discomfort), increase in repetitive or ritualistic behaviors, increase in agitation and aggression, self-injury, head banging, or excessive distress related to separating from a caregiver. Other possible manifestations of anxiety, often triggered by separation from a caregiver or exposure to an unfamiliar environment, include being clingy, unable to relax, trembling, slapping, pacing and cyclic vomiting (Prasad et al., 2018; Larson et al., 2015). Wheeler and colleagues found that older age and non-deletion-subtype are associated with more anxiety behaviors. Those with the deletion subtype show fewer anxiety behaviors, possibly due to reduced awareness or limited expressive abilities. An association between disruptive behaviors and elevated levels of anxiety in individuals with AS has been described (Grebe et al., 2022; Wheeler et al., 2019).

The Angelman syndrome Behavioral Phenotype
A Quick Reference Table for Families

Typical pattern	What It Looks Like	What May Contribute	What May Help
High Social Drive	High Social Drive Frequent smiling or laughter; strong desire for interaction; being affectionate; seeking closeness	Strong social motivation	Encourage/allow connection with structured peer interaction
Motoric Overflow	Constant movement; hand-flapping; pacing; difficulty staying still	Differences in motor control and regulation	Movement breaks; physical therapy; structured activity;
Communication Mismatch	Understanding more than ability to express; frustration; pulling, pushing, grabbing, biting to communicate	Expressive language is more impaired than receptive skills	Early AAC; modeling gestures; visual support; teaching functional communication
Anxiety Sensitivity	Distress with transitions; separation difficulty; irritability; self-injury; sleep disruption	Heightened sensitivity to unpredictability and environmental change	Predictable routines; visual schedules; preparation for changes; calm reassurance
Sensory Seeking / Sensory Sensitivity	Mouthing objects; fascination with water or textures; heat intolerance; overstimulation	Differences in sensory processing and regulation	Sensory-friendly environments; OT support

Cognitive Abilities and Developmental Testing

Developmental testing can be difficult to interpret in AS individuals. Traditional developmental test results often fall in the severe to profound range of functional impairment however, interpretation requires caution because performance may be substantially affected by cooperation, expressive-language limitations, motor impairment, hyperactivity, and difficulty demonstrating knowledge through conventional testing formats. It is possible that the cognitive abilities in AS may be higher than those estimated by traditional developmental testing. Nevertheless, the developmental delay is still consistently in the functionally severe range. (Peters et al., 2004). In general, individuals with AS have relative strengths in nonverbal reasoning skills and with social interactions that are based on non-verbal events (Sadhwani et al., 2024; Didden et al., 2004). Patients with deletion have lower developmental scores compared with non-deletion types of AS. Among non‐deletion subtypes, those with a UBE3A mutation tend to have better developmental scores and higher rates of skill attainment than those with imprinting defects or paternal UPD (Lossie et al., 2001; Clayton-Smith and Laan, 2003).

Developmental milestones

Development across all areas in AS, including movement, communication, learning, and coordination is significantly delayed. Most individuals experience global developmental delay, meaning that skills develop more slowly in all domains and developmental milestones such as sitting, standing, and walking independently are attained much later than the general population (Sadhwani et al., 2024). Progress occurs over time, but gains are often small and gradual. (Gentile et al., 2010; Peters et al., 2004; Sahoo et al., 2006). Children with deletion tend to have more significant delays than those with other genetic subtypes of AS. (Sadhwani et al., 2023; Bindels-de Heus et al., 2020; Gentile et al., 2010; Mertz et al., 2014; Wheeler et al., 2019). Across all genotypes, expressive language is the most affected area of development; understanding is often better than expression; and many children learn to communicate using gestures, signs, pictures, or communication devices. (Gentile et al., 2010; Mertz et al., 2014).

What This Means for Families

Families should know that progress in AS is steady but slow, and developmental testing may not capture all of a child's strengths. Learning often looks different and may depend more on routine, visual cues, and hands-on experience than on traditional educational methods. Therapies, various forms of educational support, and communication tools remain important throughout childhood and adulthood. While expectations need to be realistic, children with AS can continue to learn new skills, participate socially, and build meaningful connections over time.

Adaptive Functioning

The individual's level of adaptive functioning refers to the range of skills an individual uses in everyday life and includes receptive and expressive language, social (interpersonal), practical (activities of daily living, household, self-care), and motor abilities (Buntinx et al., 2010). Assessment of adaptive functioning is used to establish educational and treatment goals and determine the level of support needed (Tassé et al., 2012). Individuals with AS have delayed adaptive functioning commensurate with their overall cognitive functioning, with relative strength in their socialization. (Gwaltney et al.,2023; Peters et al., 2004). Independence in performing daily living skills such as brushing teeth, bathing, and dressing are challenging, with only a small minority of the individuals with AS achieving these skills, especially among deletion-positive individuals (Sadwani et al., 2019).

Motor (Fine and Gross)

Individuals with AS have significant delays in achieving motor milestones such as sitting and walking independently. Individuals with AS also present with significant impairments in balance and coordination (Buntinx et al., 1995; Clayton-Smith & Laan, 2003; Sadhwani et al., 2024). Hypotonia is common, particularly in infancy and early childhood, and it may persist into later life in some individuals. Ataxia of gait (impaired balance while walking) is also common (Thibert et al, 2013). Fine motor skills such as picking up an object are usually achieved during the first 3.5 years of life while gross motor skills such as walking with support are achieved within the first five years of life (Sadwani et al., 2019).

There are significant differences between the deletion and non-deletion groups in the acquisition of motor milestones. Individuals with UPD and UBE3A mutation sit and walk independently earlier than those with a deletion.

Motor Milestone Development by Genetic Subtype in Angelman Syndrome
(Sadhwani et al., 2024)

Milestone	*UBE3A* Mutation	UPD	Deletion
Sitting independently	~8.5 months	~10 months	~10–11 months
Walking independently	~28 months	~31 months	~40–47 months

Longitudinal natural history data indicate that most individuals with AS eventually walk, at least with support; a small minority require long-term assistance for mobility.

Autism and Related Traits

Some individuals with AS display behaviors that overlap with characteristics commonly associated with autism spectrum disorder (ASD). These may include repetitive, sensory interests (e.g., mouthing, licking, or sniffing objects), stereotypic motor movements (such as rocking or hand-flapping), and significant differences in expressive language (Clayton-Smith & Laan, 2003; Williams et al., 2006).
Because of this overlap, some individuals with AS receive a "dual diagnosis" of AS and ASD. Because communication impairment, sensory differences, repetitive behaviors, and motor stereotypies are also common features of AS itself, ASD assessment should consider the individual's overall developmental and social-communication profile rather than isolated behaviors. When criteria are met, an ASD diagnosis may also facilitate access to autism-specific services and supports.

It is important to approach the interpretation of autism-related characteristics in AS with care. Many behaviors seen in ASD are part of the core profile of AS and may reflect communication differences, sensory processing needs, or motor planning challenges rather than autism itself (Didden et al., 2004; Peters et al., 2004). Additionally, developmental trajectories in AS can change over time and some individuals who demonstrate autism-like features in early childhood may show increased social engagement and communication later in life (Clayton-Smith, 2001).

Research findings on autism in AS are mixed. Some studies suggest a low prevalence of autism diagnoses in individuals with AS, while others indicate that a subset of individuals do meet criteria for ASD (Trillingsgaard & Østergaard, 2004; Veltman et al., 2005; Bonati et al., 2007). Differences in findings are likely influenced by variability in study design, diagnostic tools, and the unique clinical presentation of AS.

For individuals with AS who do exhibit autism-related characteristics, specific types of support such as Applied Behavior Analysis (ABA) or other behavioral approaches may be helpful when they are adapted to the individual's needs. As emphasized throughout this toolkit, any behavioral support should prioritize communication, reduce frustration, and support safety and quality of life and not focus on compliance or suppression of personality.
Older or more cognitively advanced individuals may also display behaviors such as rituals, repetitive interests, or strong preferences (e.g., hoarding ob-

jects or specific routines) (Barry et al., 2005). These behaviors can overlap with features seen in other neurogenetic conditions.

What This Means for Families

For families, the overlap between AS and autism can be confusing and emotionally challenging. Some children with AS may receive an autism diagnosis, while others may show autism-like traits without meeting full criteria. Either situation does not change the underlying diagnosis of AS, but it may influence which therapies and types of support are available and/or helpful. Importantly, an autism diagnosis does not define a child's ability to connect, learn, or enjoy relationships. Many individuals with AS, whether or not they meet criteria for autism, continue to show strong social interest, affection, and responsiveness, especially when communication is supported and environments are predictable. Overall, autism-related characteristics in AS should be understood within the broader context of the condition. Careful, individualized evaluation by clinicians familiar with both AS and autism is essential to guide appropriate types of support, ensure access to services, and promote the best possible outcomes for each individual.

Speech and Language

AS almost always results in lack of speech, with a large majority of individuals (between 71% and 90%) never or rarely producing any speech. Even those with some speech have limited vocabulary, typically using only two to 15 words, with an average of five words. The absence of speech in individuals with AS cannot be solely attributed to the level of intellectual disability (Clayton-Smith & Laan, 2003; Buntinx et al., 2010). Individuals with mosaicism can use many more words (50 or 60), and a few can speak in simple sentences (Nazlican et al, 2004). The nonverbal language skills of children with AS vary greatly, with the children using gestures, manual signs, and AAC. Please refer to the section in this document on communication for more about the language and communications abilities, and the therapy approaches, for those with AS.

Communication

Communication challenges are universal in AS, especially in individuals with the deletion genotype. Those with other genotypes, such as UPD and imprinting defects, often demonstrate stronger communication skills, both in expressive and receptive language (Pearson et al., 2019; Wheeler et al., 2017). Regardless of the underlying genetic mechanism, most children with AS are unable to use speech as their primary method of communication. However, interventions that include efforts to support speech development may still be appropriate for some individuals, particularly those with non-deletion genotypes, as some may acquire a modest inventory of words or phrases (Calculator, 2013; Pearson et al., 2019).

Augmentative and Alternative Communication (AAC)

Given the limited prognosis for speech, most individuals with AS require alternative means of expressing themselves. Research consistently demonstrates that most individuals can successfully utilize at least one communication method, including gestures, symbolic systems, and AAC (Calculator & Black, 2009; Pearson et al., 2019; Calculator, 2023). According to the American Speech-Language-Hearing Association (ASHA), AAC encompasses all forms of communication other than speech used to express thoughts, needs, wants, and ideas.

AAC systems encompass both unaided methods (such as gestures and signs) and aided methods (such as communication boards, picture exchange systems, and speech-generating devices). These

components work together to form a multimodal communication system. Current best practice emphasizes that no single AAC approach is appropriate for all individuals with AS; systems that work well for one person may be of limited use to another. Comprehensive assessment and individualized planning are essential (Calculator & Black, 2009; Pearson et al., 2019).

Contemporary research strongly supports the early introduction of robust AAC systems rather than limiting individuals to simple requesting systems. Studies indicate that individuals with AS can learn to use AAC for multiple communicative functions beyond basic requests, including commenting, asking questions, and social interactions (Calculator, 2016; Calculator, 2023).

Natural Gestures and Enhanced Natural Gestures

Children with AS typically use self-selected gestures (Calculator & Black, 2009). Early in development, these behaviors often depend on physical contact with people and objects, such as pulling a parent's hand toward a desired item or pushing away something unwanted. More abstract, distal gestures emerge later, including extending arms to be picked up or pointing toward desired objects.

Most individuals with AS develop an inventory of natural gestures they use functionally, particularly with familiar communication partners. These natural gestures can be shaped and expanded using a system of Enhanced Natural Gestures (ENGs)—modifications that enable individuals to express a greater range of meanings more clearly and effectively (Calculator, 2002; Calculator & Black, 2009).

Given their natural propensity for gestures, some communication interventions incorporate sign language instruction for individuals with AS. While some may acquire anywhere from a few to over a hundred signs, motor difficulties often affect accuracy and intelligibility. For this reason, ENGs—which are by definition understandable to both familiar and unfamiliar communication partners—are often preferred and more functional (Calculator, 2002).

Aided vs. Aided Communication Systems

To improve clarity and consistency, communication supports are organized into two primary categories:

Unaided Communication

Unaided communication does not require external tools and relies solely on the individual's body. These methods are often the earliest to emerge and may serve as foundational components of a multimodal communication system. Examples include:

- Natural gestures (e.g., reaching, pointing, pulling, pushing away)
- Facial expressions and body language
- Vocalizations
- Sign language
- ENG

ENGs are structured adaptations of spontaneous gestures that allow individuals with AS to communicate more clearly and effectively. Because ENGs build upon naturally occurring behaviors, they are often intuitive and highly functional (Calculator, 2002; Calculator & Black, 2009).

Aided Communication

Aided communication involves the use of external supports or tools. These methods range from low-tech options to high-tech speech-generating devices and are commonly referred to as AAC in clinical and educational settings. Examples include:

- Communication boards and books
- Picture Exchange Communication System (PECS)

- Photographs and symbol-based systems
- Core word boards
- Tablet-based communication applications
- Speech-generating devices (SGDs)

These tools enable individuals with AS to communicate across environments and with a broad range of communication partners. Research supports the early introduction of robust aided AAC systems that provide access to a wide vocabulary and multiple communicative functions beyond simple requesting (Calculator, 2016; Calculator, 2023).

Terminology Note: In alignment with guidance from the American Speech-Language-Hearing Association (ASHA), Augmentative and Alternative Communication (AAC) includes both unaided methods (such as gestures and signs) and aided methods (such as communication devices). In this document, Enhanced Natural Gestures (ENGs) are categorized under unaided communication, while the term "AAC" is often used in practice to refer specifically to aided systems.

Current research emphasizes several key principles for AAC:
- Start early: AAC should be introduced as part of early intervention services, not delayed while "waiting to see" if speech develops.
- Presume competence: Assume individuals can learn to use robust communication systems with appropriate support.
- Provide robust vocabulary: Access to core words and diverse vocabulary supports broader communication functions.
- Model consistently: Communication partners should model AAC use throughout daily activities.
- Support multimodal communication: Encourage use of all available modalities – gestures, signs, aided AAC, vocalizations, and any speech that develops.

Identification of appropriate AAC systems requires comprehensive evaluation by trained professionals who can match the individual's skills, capabilities, and both immediate and long-term needs with available options that can be implemented effectively across settings (Calculator, 2013; Calculator, 2023).

AAC and Speech Development

Research consistently demonstrates that AAC does not hinder speech development—to the contrary, speech is generally fostered following the introduction of AAC (Millar et al., 2006; Romski & Sevcik, 2005). Families and professionals should not delay AAC introduction based on concerns about inhibiting speech. Early AAC intervention supports overall communication development and reduces frustration while providing individuals with immediate means of expression.

Receptive vs. Expressive Language

Studies have found that individuals with AS demonstrate stronger receptive language abilities than their expressive language would suggest (Calculator & Black, 2009; Pearson et al., 2019). Many individuals understand simple commands, sentences, and social situations even when unable to express comparable content. This discrepancy underscores the importance of presuming competence and providing robust communication supports that allow individuals to express what they understand.

However, receptive language should not be overestimated based on context-dependent responding. Comprehensive assessment should evaluate both receptive and expressive abilities across contexts (Calculator, 2013).

Research on expressive communication in AS has shown that individuals most frequently communicate to request desired items and activities or reject unwanted ones. Instances of commenting, labeling,

describing, and asking questions are less common but can be developed with appropriate instruction and AAC support (Calculator & Black, 2009; Calculator, 2016). Contemporary intervention approaches emphasize teaching multiple communication functions, not just requesting.

Effective communication has implications for virtually all aspects of education and daily living, and it should be a focal point in all instructional programs. Communication skills are essential for children to access curricula and participate actively in educational and community settings. Speech-language pathologists (SLPs) with expertise in AAC play a critical role in:

- Conducting comprehensive communication assessments
- Identifying appropriate AAC systems
- Training communication partners (family members, educators, peers)
- Supporting implementation across settings
- Monitoring progress and adjusting interventions

Communication services are best implemented through a combination of direct therapy and consultation. Critically, instruction on communication should not be confined to therapy rooms – it must be integrated throughout the school day and across all natural environments. SLPs should collaborate with families, teachers, and other team members to ensure consistent implementation and generalization of skills (Calculator, 2016; Wheeler et al., 2017).
While all individuals with AS experience communication challenges, severity varies considerably—even among those with the same genetic mechanism. It is essential to provide every individual with robust opportunities to communicate. Communication skills can be maximized through early and ongoing intervention, particularly when delivered by professionals with expertise in AAC and complex communication needs.

Intervention goals should focus on enabling individuals to communicate effectively with a broad range of partners across natural settings. A child's ability to communicate with their SLP in a therapy room has limited functional value compared to using those same skills with family members, teachers, peers, and community members in everyday environments (Wheeler et al., 2017).

Summary

Communication is central to learning, relationships, independence, and quality of life. SLPs, families, educators, peers, and others must collaborate to maximize individuals' abilities to communicate functionally and participate actively in their communities. Children need access to multiple communication modalities and robust AAC systems. Communication instruction should be integrated throughout daily routines—at home, school, and in the community. With consistent, evidence-based support beginning in early childhood and continuing throughout the lifespan, individuals with AS can build meaningful ways to connect with others and participate fully in their communities (Wheeler et al., 2017; Calculator, 2023).

What This Means for Families

Lack of speech does not mean lack of understanding. Many individuals with AS know what they want to communicate but need support to express it. Communication may look different—but it is still communication, and it can be developed and strengthened throughout life.

Key messages for families:

- Don't wait: Early introduction of AAC supports communication development and does not prevent speech from emerging.
- Presume competence: Your child may understand

more than they can express—provide robust communication tools.

- Be a communication partner: Model AAC use, gestures, and signs throughout daily activities.
- Advocate for expertise: Seek SLPs with experience in AAC and complex communication needs.
- Expect progress: With appropriate support, individuals with AS can develop meaningful communication skills.
- Communication happens everywhere: The best learning occurs during natural routines and activities (at home, in school, on the playground), not just in therapy.

Early and ongoing support using gestures, signs, pictures, and AAC can dramatically improve your child's ability to participate in daily life, reduce frustration, and strengthen relationships.

Stepping into AAC

The Angelman Syndrome Foundation's "Stepping into AAC" resource provides comprehensive guidance for families and professionals on supporting communication development in individuals with AS. This resource includes practical strategies, implementation guides, and family perspectives. Available at: www.angelman.org

Sleep Disorders

Sleep problems are very common in AS. Many infants, children, and adults have difficulty falling asleep, staying asleep, or maintaining a regular sleep–wake pattern. Parental reports and recent studies indicate that abnormal sleep/wake cycles are common in AS (Walz et al., 2005; Miano et al., 2004; Bruni et al., 2004). Only a small proportion of infants and children with AS sleep well, and sleep disturbances are reported as a major concern by caregivers of individuals with AS. Sleep deprivation is associated with greater levels of parental

Communication Supports Checklist

AAC and Communication Systems

- ☐ Comprehensive AAC evaluation completed by qualified SLP
- ☐ Appropriate AAC system(s) identified and implemented
- ☐ Access to robust vocabulary including core words
- ☐ AAC available across all settings (home, school, community)
- ☐ Backup/low-tech AAC options available

Daily Implementation

- ☐ Communication partners trained in AAC use
- ☐ Consistent modeling of AAC throughout the day
- ☐ Extra time provided for responses
- ☐ Multiple communication modalities accepted and encouraged
- ☐ Communication opportunities embedded in daily routines

Functional Communication

- ☐ System for expressing basic needs (help, break, all done, more)
- ☐ Ability to make choices and preferences known
- ☐ Methods for refusing/rejecting
- ☐ Opportunities for social communication (greetings, comments)
- ☐ Ways to ask questions and gain information

Collaboration and Support

- ☐ Regular SLP services with AAC expertise
- ☐ Communication goals integrated across IEP/educational program
- ☐ Ongoing family training and support
- ☐ Peer awareness and communication partner training
- ☐ Regular assessment and system updates as skills develop

stress and negatively impacts the quality of life for families (Wheeler et al., 2017). Iron deficiency has also been associated with sleep problems in AS, and one study found slight improvement of sleep with iron supplementation in those individuals with iron deficiency (Ryan et al., 2020).

Night awakenings, although still common, seem to decrease with age. We speculate that rather than an actual improvement in sleep quality, caregivers may develop methods to prevent the individual's nighttime awakenings from disturbing other family members.

Though conventional wisdom suggests that children with AS may require less sleep than children with typical neurodevelopment (e.g. https://www.angelmanuk.org/support/sleep/ and https://medlineplus.gov/genetics/condition/angelman-syndrome/), unpublished data from the Natural History Study reveal that around half of the participants experience physical exhaustion after a poor night of sleep. Specifically, 70% of the subgroup with deletion reported signs of physical exhaustion due to lack of sleep. Furthermore, approximately half of the patients in the UPD group and the ImpD group exhibit increased aggression after a poor night's sleep. These data suggest that, although there is a general belief that individuals with AS "need" less sleep, there are negative impacts of sleep deprivation on this population and their families.

Behavioral approaches and consistent sleep routines are important components of sleep management. Administration of a low dose of melatonin one hour before bedtime has also been shown to be of help in some children (Summers et al., 1992). There is very limited information about the efficacy of medications for sleep issues in AS. Some families construct safe and confining bedrooms to accommodate disruptive nighttime wakefulness, and fully enclosed beds can be an option for selected individuals following individualized safety assessment. Sleep hygiene and behavioral approaches are essential and can have great benefits to the sleep pattern. Even with these approaches, some individuals chronically struggle with sleep issues. Medication may be considered when sleep difficulties remain severe, although evidence supporting their use in AS is limited. Treatment should be individualized, with careful consideration of potential adverse effects.

What This Means for Families

Sleep problems are part of AS and are not caused by parenting practices. For families, sleep difficulties can be chronic and exhausting. Night awakenings, early morning waking, and irregular sleep schedules can affect parental sleep, work, and mental health. Children and adults with AS feel the effects of poor sleep, even if they appear active the next day. Addressing sleep is important not only for behavior and mood, but also for family well-being and safety.

Families should feel supported in seeking help and in using practical solutions to support both the child and the household.

Sexuality

Individuals with AS generally undergo typical pubertal development, including the development of secondary sexual characteristics. Menarche has been reported at an average age of approximately 11.6 years. Fertility is preserved, and pregnancy has been reported in at least one woman with AS (Lossie et al., 1999).

The main issues associated with sexual development in individuals without AS are also seen in those

Sleep Support Strategies Checklist

Routine & Environment

- ☐ Consistent bedtime and wake-up time
- ☐ Calm, predictable bedtime routine
- ☐ Dark, quiet, low-stimulation sleep environment
- ☐ Limiting stimulating activities before bedtime
- ☐ Not engaging in interactions during nighttime awakenings

Medical & Nutritional Considerations

- ☐ Screening for iron deficiency when sleep problems are significant
- ☐ Treating GERD, pain, or constipation that may disrupt sleep
- ☐ Reviewing medications that may worsen sleep

Safety & Family Protection

- ☐ Creating a safe bedroom environment for nighttime wakefulness
- ☐ Use of enclosed/safety beds

with AS. Sexual development will occur in a relatively normal physiologic manner for both young men and young women. Accordingly, issues of potential sexual abuse, developmentally appropriate sexual behaviors, including masturbation, approach to contraception, and access to gynecological care are important. Gynecological care is advisable by age 21 years, including developmentally appropriate gynecological care, menstrual management, with attention to consent, supported decision-making, privacy, and safeguarding. Pelvic examinations should be based on clinical indication and applicable screening recommendations, rather than performed automatically.

Sexual education requires individualized, accessible approaches for individuals with intellectual disability. Individuals with developmental challenges are at increased risk for sexual assault and abuse (Goddard et al., 2026), and parents should be aware of this and focus on prevention. Boundary issues are particularly difficult in individuals with AS because of their outgoing personality and fondness for hugging and wanting to be close to others.

Providing medical contraception may be important in some situations. For females, the contraceptive methods are the ones typically employed and may include oral contraceptives, progesterone only injections (e.g. Depo-Provera shot given once every three months), hormone-releasing implants and other methods.

What This Means for Families

Families should expect that puberty and sexual development will occur.

Key priorities include:

- Protecting against sexual abuse, with an emphasis on prevention
- Teaching simple, concrete concepts about privacy, body safety, and boundaries
- Ensuring access to appropriate gynecological care
- Implementing contraception when relevant, based on the individual's needs and circumstances

Medical Issues

Seizures

More than 90% of individuals with AS are reported to have seizures but this may be an overestimate. Less than 25% develop seizures before 12 months of age. Most have onset before 3 years, but onset in older children or in teenagers is not exceptional. The seizures can be of any type (e.g., major motor

involving jerking of all extremities, absence involving brief periods of lack of awareness, etc.) and they may require treatment with multiple anticonvulsant medications. Seizures may be difficult to recognize or distinguish from the child's usual tremulousness, hyperkinetic limb movements, or attention deficits. The typical EEG is often more abnormal than expected from the clinical appearance, and it may suggest seizures when in fact there are none (Boyd et al., 1988; Laan et al., 2005).

There is no agreement as to the optimal seizure medication although topiramate (Topamax), lamotrigine (Lamictal), levetiracetam (Keppra), and clonazepam (Klonopin) are more commonly used in North America. Due to a more favorable side effect profile, topiramate, lamotrigine, levetiracetam, and clobazam (slightly different chemical structure than other benzodiazepines) have emerged as more favorable options. Ethosuximide (Zarontin), phenytoin (Dilantin), phenobarbital, and ACTH are less commonly used. Vigabatrin (Sabril), an inhibitor of GABA metabolism, carbamazepine and oxcarbazepine can cause a worsening of seizures and should not be used in AS patients (Duis et al., 2022; Potter et al., 2026). It is possible that increasing the GABA level without enhancing the GABA receptor function may be responsible for the ineffectiveness of vigabatrin. Similarly, valproic acid (also known as sodium valproate – trade names include: Depakote, Depakene, Epilim) should be avoided when possible. Use of a single medication is preferred. Some children with difficult-to-control seizures have been placed on ketogenic diet, and this has been effective in many cases. A highly purified form of prescription cannabidiol (Epidiolex) has been approved for the treatment of drug-resistant seizures associated with other genetic disorders, and it has been reported to be also effective in children with AS. (Samanta, 2021). Children with AS are at risk for over-medicalization and active seizures should be differentiated from other movement abnormalities. Additionally, EEG abnormalities may persist even when seizures are well controlled clinically.

What this means for families

Seizures are common in AS. If your child has not had seizures in the first years, that is reassuring, but it does not eliminate future risk so continued observation is important. It is also important to establish care with a pediatric neurologist early, even if seizures are not yet present.

Not every unusual movement or staring spell is a seizure, and an abnormal EEG alone does not mean your child needs medication.

Every family should have a clear plan for prolonged seizures. This may include a rescue medication, such as:

- Rectal diazepam
- Intranasal or buccal benzodiazepines (depending on age and provider preference)

Rescue medication is typically used when a seizure lasts longer than 5 minutes and when multiple seizures occur without full recovery between them. Your neurologist should provide specific instructions on when to administer it, dosing guidance, and a written seizure action plan. Even if your child's seizures are rare, it is essential that you understand what to do in an emergency and feel prepared to act calmly and confidently if one occurs. All caregivers, school personnel, therapists, and family members should be informed about your child's seizure action plan, know where the rescue medication is stored, and receive clear instructions on when and how to administer it. The seizure action plan should be reviewed with your neurologist at least once a year, and updated as needed to reflect changes in your child's growth, medication doses, or seizure pattern.

Gastrointestinal Issues and Oral-motor (Oromotor) Behaviors

Feeding problems are frequent and usually manifest early as difficulties with breastfeeding or bottle-feeding, and with swallowing (Zori et al, 1992; Williams et al, 1995; Fryburg et al, 1991). Generalized oral-motor incoordination is relatively common, and bottle feeding may prove easier. Frequent spitting up may be due to formula intolerance or GERD. The feeding difficulties can result in poor weight gain. Very occasionally, feeding problems are severe enough that gastrostomy tube feeding is needed; GERD that is severe enough to require surgery is rare.

Constipation is common, and a significant proportion of individuals require medical management. The most commonly used treatments are stool softeners like Polyethylene Glycol (Miralax), magnesium sulfate, stimulant laxatives such as senna (e.g., Senokot), and a high fiber diet with sufficient fluid intake. Severe constipation appears to increase the risk of sleep disturbances and maladaptive behaviors. Constipation can cause discomfort, irritability and poor sleep, which may make seizures more likely in some individuals. Other gastrointestinal issues are cyclic vomiting episodes (which are rare), and eosinophilic esophagitis.

Mouthing behaviors are common in individuals with AS and likely represent increased sensory needs. Although mouthing is common, ingestion of non-food objects (pica) is less frequently reported. Later, most exploratory play is by oral manipulation and chewing. The tongue appears to be of normal shape and size, and persistent tongue protrusion is a distinctive feature in some individuals; some protrude their tongues only during laughter.

Drooling is frequently a persistent problem, often requiring bibs. The use of medications like scopolamine to reduce secretions generally does not produce an adequate long-term effect. Botulinum toxin injections into the salivary glands have been successful in improving drooling in some individuals with AS. It's important for those who opt for these interventions to be aware that decreased saliva production can negatively impact dental health.

Hyperphagia, including food seeking behavior, has been observed in AS. It has been reported more often in children with UPD and imprinting defects (Yang et al., 2021). Hyperphagia has a significant social impact on individuals and their families, and it is unclear if any treatment is effective. Strict control of the environment for those exhibiting hyperphagia is needed to prevent obesity and its complications.

What This Means for Families

Feeding and gastrointestinal issues are common and are part of the condition rather than the result of parenting or diet choices. Early feeding difficulties can be stressful, but many children improve over time with supportive therapies and careful monitoring.

Constipation should be treated proactively, as untreated constipation can worsen overall comfort. Families should feel comfortable discussing bowel patterns openly with their medical team.

Mouthing behaviors are typically sensory-driven and not dangerous in most cases, but supervision remains important. Blood lead levels should be checked at least once a year in the setting of environmental risk.

If drooling interferes with comfort, skin integrity, or social participation, treatment options can be discussed.

If food-seeking behaviors emerge, structured routines and supervision may be necessary. Hyperphagia does not occur in all individuals with AS, but when present, environmental controls may be needed.

Gait and Movement Disorders

Children with AS experience delayed gross motor development, including sitting, standing, and walking. Although the timing of these milestones is later than in children without AS, motor skills continue to develop over time, and meaningful progress is common.

Walking in AS is often unsteady and poorly coordinated, reflecting underlying challenges with balance and motor control. Even after walking is achieved, motor skills may remain immature, and children may continue to require support for stability, endurance, and safety.

Ongoing physical therapy is strongly recommended throughout childhood and into adolescence and adulthood. Therapy focuses on improving balance, coordination, strength, and functional mobility. Even when walking is slightly unsteady, physical therapy can enhance independence and participation in daily activities.

Importantly, gains in movement can continue for many years, and walking ability may improve well into later childhood and adolescence. Delayed motor milestones do not mean a lack of potential for continued development (Sadhwani et al., 2024).

Nonepileptic Myoclonus

Nonepileptic myoclonus (NEM) consists of abnormal movements that resemble epileptic seizures but are not caused by abnormal electrical activity in the brain. NEM presents as trembling movements of the hands and often spreads to the upper and/or lower extremities. The onset occurs during puberty and becomes more frequent in adulthood (Pollack et al., 2018). NEM can appear as brief, involuntary jerks or twitches, usually involving the arms, legs, and/or torso. NEM has an erratic pattern of movement and can last from seconds to hours. In adults with AS, NEM can occur in clusters or as discrete episodes, and it may be triggered by sensory stimuli. NEM does not result in an altered state of consciousness and does not cause developmental regression. The underlying cause of NEM in AS is unknown. NEM can be very challenging to treat, and no single medication has been proven to be effective. Several medications have been tried based largely on case reports and clinical experience. Management should therefore be individualized in consultation with a neurologist familiar with AS and movement disorders.

Tremor

Tremors are a common motor feature in AS and are part of the condition's movement presentation. They typically present as low-amplitude, irregular, and often jerky movements that most commonly affect the upper limbs. Tremor may be observed during voluntary, goal-directed activity such as reaching, feeding, or manipulating objects (Williams et al., 2006; Bird, 2014). Tremors are usually most evident during movement and are often described as intention tremors. This refers to the increased prominence of the tremor when an individual is actively attempting a task. In contrast, tremor at rest is typically minimal or absent (Bird, 2014; Tan et al., 2011).

Although tremors are not harmful, they may contribute to functional motor impairment. Difficulties may be observed in activities requiring fine motor coordination, including feeding, dressing, and the use of assistive communication devices. The severity and functional impact vary considerably between individuals (Bird, 2014; Pelc et al., 2008). Tremor severity may also change across the lifespan. Some individuals demonstrate improvement in tremor control with maturation and therapeutic

intervention, while others continue to exhibit persistent tremor into adolescence and adulthood. Fluctuations in tremor severity are common and may be influenced by fatigue, arousal, attention, and task demands (Tan et al., 2011; Pelc et al., 2008).

Management of tremors in Angelman syndrome is primarily supportive and function-oriented. Occupational therapy plays a central role in promoting motor coordination and adaptive skill development. The use of adaptive equipment, including modified utensils, weighted tools, and stabilizing devices, may improve functional independence. Environmental modifications, such as allowing additional time and reducing task-related pressure, may also be beneficial (Angelman Syndrome Foundation, 2023; Pelc et al., 2008).

Pharmacological intervention is not routinely indicated. In cases where tremors significantly interfere with functional ability or quality of life, neurological evaluation may be considered to determine whether targeted interventions are appropriate (Bird, 2014; National Institute of Neurological Disorders and Stroke, 2020). A Parkinson-like presentation that responds to levodopa has been reported in some adults with AS.

What This Means for Families

Tremors can look concerning, especially at first, but they are a well-known part of AS and are not causing harm. In everyday life, the goal is not to stop the tremor, but to help your child succeed. Small supports, like the right tools and extra time, can make a big difference.

It is also normal for tremors to vary. You might see more shaking when your child is tired, excited, or working hard on a task. That does not mean anything is getting worse.

However, new onset or significantly changing movement patterns should prompt clinical evaluation to differentiate tremor from other movement disorders or seizure activity. Video documentation is often helpful in supporting diagnostic assessment (National Institute of Neurological Disorders and Stroke, 2020).

Temperature Sensitivity

Some individuals with AS appear to have increased sensitivity to high temperatures. There may be difficulty regulating body temperature, with symptoms of flushing, increased irritability and hyperactivity when exposed to heat. Caregivers frequently employ water sprays, portable fans, and appropriate clothing to help manage this sensitivity. It is also common for families to limit time spent outdoors to prevent overheating. It's rare for individuals with AS to develop heat exhaustion or experience heat stroke, and sweating seems to be normal.

What This Means for Families

Your child may become uncomfortable in warm environments more quickly than other children. Behavioral changes such as irritability or increased activity may be early signs that your child is too warm. Planning ahead can make a significant difference. Bringing cooling tools, dressing in breathable clothing, scheduling outdoor activities during cooler parts of the day, encouraging drinking and ensuring access to shade or air conditioning can help prevent discomfort.

Physical Growth and Obesity

Newborns appear to be physically well formed, but by 12 months of age some show a deceleration of cranial growth which may lead to relative or absolute microcephaly (having a head circumference

lower than 2nd percentile). The prevalence of absolute microcephaly varies from 34% to 88% and may be as low as 25% when non-deletion cases are also included (Zori et al., 1992; Saitoh et al., 1994; Smith et al., 1992). Most AS individuals with a deletion, however, have head circumferences less than the 25th percentile by age 3 years, often accompanied by a flattened back of the head. Average height for deletion patients is lower than the mean for typical children, but most children with AS grow within the normal range, and height is influenced by parental size. The final adult height is significantly lower compared to parents and to the general population in those with the deletion genotype. Individuals with AS tend to grow more slowly during childhood and adolescence (Gruber N et al, 2024). Body mass index in the overweight and obese ranges are 23% and 20%, respectively, but severe (e.g., morbid) obesity is uncommon in AS.

What This Means for Families

If your child's head circumference begins to fall on the growth curve during infancy, this is a known feature of AS and does not necessarily indicate a new problem. Head growth patterns in AS follow a recognizable trajectory. Head size alone does not predict developmental potential, and children with similar head measurements may have very different abilities.

Children with AS due to deletion tend to grow more slowly during childhood and adolescence compared to typically developing peers. Average height is slightly below the population mean, but most children grow within the normal range when parental height is considered.

Weight gain in AS should be monitored. If your child is independently mobile and shows strong interest in food, structured meal routines and supervision may be needed.

Bone health

Individuals with AS may be at increased risk for reduced bone mineral density. Several factors, such as genetics, poor diet, lack of exercise, delayed puberty, medications, low vitamin D levels and hormonal imbalances can lead to low bone health (Ko A et al., 2020). A recent study looked at bone health specifically in children with AS between April 2010 and December 2021. Risk factors identified included deletion genotype, reduced mobility, and delayed onset of puberty. These findings suggest that bone health may require increasing attention as individuals grow older. The authors proposed monitoring bone health in AS adults, performing bone health assessment in case of fracture, and starting treatment when osteoporosis is diagnosed (Bindels-de Heus KGCB et al., 2023).

What This Means for Families

Bone health should be considered early, especially if your child has limited mobility, frequent falls, delayed puberty, or has had a fracture. Early attention to bone strength helps protect mobility, reduce fracture risk, and support long-term quality of life. Some bone health risks can be reduced with preventive care.

Hypopigmentation, Strabismus and Ocular Albinism

When AS is caused by a deletion, there may be skin and eye hypopigmentation because a pigment gene, OCA2, located close to the AS gene, is also deleted (Lee et al., 1994). The OCA2 gene produces an enzyme necessary for the synthesis of melanin, the main pigment molecule in our skin. In some children with AS, the hypopigmentation can be so severe that a form of albinism is suspected (King et al., 1993). When AS is caused by genetic mechanisms other than deletion, OCA2 is intact, and skin and eye pigmentation is usually normal. Children with AS who have hypopigmentation require photopro-

Healthy Bones Checklist

- ☐ Encourage safe weight-bearing activities (walking, supported standing, physical therapy)
- ☐ Ensure adequate dietary calcium (milk, yogurt, fortified foods, or supplements if needed)
- ☐ Consider vitamin D supplementation and ask about checking vitamin D level
- ☐ Consider bone density testing with DEXA scan if there are recurrent fractures or significant decline in mobility

tective cream and clothing. Not all AS children with deletions of OCA2 are obviously hypopigmented, but they may have lighter skin color than expected for their family background.

Management of strabismus (misalignment of the eyes) in AS is similar to that in other children and includes evaluation by an ophthalmologist, correction of any visual deficit, and where appropriate, patching, spectacles, and surgical adjustment of the extraocular muscles.

What This Means for Families

If your child has lighter skin or eye color than other family members, this is a known and expected feature in deletion-type AS. Children with hypopigmentation may be more sensitive to sun exposure and should use sunscreen regularly, protective clothing, hats, and sunglasses when appropriate.

If you notice that your child's eyes do not appear aligned consistently, it is important to seek evaluation by a pediatric ophthalmologist. Management may include:

- Correcting refractive errors with glasses
- Patching therapy
- Surgical adjustment of eye muscles when necessary

Some children with AS may have difficulties tolerating eye patches or glasses due to sensory sensitivities or high activity levels. This is common and different treatment approaches should be considered. All children with AS should have regular ophthalmology evaluations, regardless of genotype to evaluate for refractive errors. Early treatment improves visual development.

Surgical Procedures and Anesthesia

There are several literature reports of individuals with AS undergoing general anesthesia without any difficulties, and parent reports are generally favorable regarding successful general anesthesia and surgical intervention. Some scientific reports mention concern for those with deletion AS because these individuals also lack GABA receptor genes, which are known to be targets of certain anesthetic agents such as benzodiazepines and halogenated ethers. However, the weight of experience thus far indicates that individuals with AS tolerate anesthetic agents well. Convalescence from surgical procedures, even significant interventions such as spinal fusion and rod placement, also appears to occur relatively normally in AS.

Reports of bradycardia in individuals with AS were presumed to be related to increased activity of the vagus nerve (Gardner et al., 2008). These reports are difficult to interpret because of the complexities associated with hospitalization such as multiple medication use and the variables of the surgical procedure. At this point, it is unclear whether individuals with AS have an increased risk for cardiac rhythm disturbances. Anesthesiologist should be aware of these case reports and the possibility that agents increasing vagal tone may not be well tolerated in individuals with AS.

There is no evidence that a surgical procedure or anesthetic event leads to an exacerbation of seizures in AS. There is insufficient evidence to make specific anesthetic recommendations.

Education

Educational programs should be individualized, multidisciplinary, and focused on the whole child. Effective programs go beyond academics. They support communication, independence, social connection, and long-term quality of life. This approach is closely aligned with the AS Standards of Care, which emphasize early intervention, functional skills development, and preparation for meaningful participation across the lifespan.

Under the Individuals with Disabilities Education Act (IDEA), students with AS are entitled to an education that provides access to the general education curriculum to the greatest extent appropriate, delivered in the least restrictive environment, and guided by an individualized education plan (IEP) [typically for age 3 to 21 years] or individualized family service plan (IFSP) [typically for those under the age of 3]. These protections are critical, but how they are implemented matters just as much. Educational placement should never be the starting point. Instead, a student's strengths, needs, and goals should guide decision-making, with placement determined only after priorities are clearly defined. The ultimate goal is not a specific classroom setting, but meaningful progress, engagement, and inclusion.

One of the most important priorities in education for individuals with AS is communication, and AAC should be introduced early and used consistently across all environments. Communication is not simply an educational tool; it is foundational to autonomy, behavioral regulation, social connection, and overall development. When students are given reliable ways to express themselves, they are more engaged, less frustrated, and better able to participate in learning. Best practice supports providing access to robust communication systems without waiting for prerequisites, and ensuring that everyone in the student's environment, educators, therapists, aides, and peers understands how to support their use.

Caregiver & School Collaboration Checklist

- ☐ Regular communication between home and school
- ☐ Shared behavior strategies across settings
- ☐ Data collection focused on what helps, not just problem behaviors
- ☐ Flexibility as needs change over time

Students with AS learn best when instruction is embedded into meaningful, real-life contexts rather than isolated tasks. Skills such as communication, mobility, and self-care are most effectively developed when they are integrated into the natural flow of the day. For example, communication opportunities can be built into social interactions and classroom routines, mobility skills can be practiced during transitions, and independence skills can be reinforced during daily activities like dressing or mealtime. This type of integrated approach helps students generalize skills across settings and promotes greater independence over time. It also reflects Standards of Care priorities that emphasize functional learning and participation in everyday life.

Supporting a student with AS requires a coordinated, team-based approach. Most students

benefit from a combination of services, including speech-language therapy (with a strong emphasis on AAC), occupational therapy, physical therapy, and behavioral supports, along with other services based on individual needs. The most effective teams work collaboratively, with consistent communication between educators, therapists, paraprofessionals, and families. Families play a central role in this process not only as advocates, but as partners whose insights help shape meaningful goals and long-term planning. This level of coordination is essential to ensuring consistency across environments and maximizing outcomes.

Many students with AS require significant levels of support to access their education, often including one-on-one assistance. When implemented effectively, these supports enable participation, communication, and safety while promoting engagement in learning. It is important, however, that supports are implemented with the goal of building independence over time. Aides and paraprofessionals should be guided by trained professionals, with a focus on gradually reducing prompts and fostering more independent skills whenever possible.

A strength-based approach is critical when working with individuals with AS. Many students demonstrate strong social interest, a joyful disposition, and a natural motivation for movement and interaction. When instruction is built around these strengths, students are more engaged and better able to sustain attention. Rather than focusing solely on areas of challenge, effective educational programs recognize and leverage what motivates and connects the student to the world around them.
There is wide variability in abilities among individuals with AS, and educational outcomes will look different for each student. Some individuals may require high levels of lifelong support, while others, particularly those with non-deletion genotypes, may achieve greater independence and use more advanced communication systems. Regardless of ability level, it is essential that educators and families maintain high expectations. Students should be given opportunities to learn, make choices, and participate meaningfully in their communities. Education should also include early and ongoing conversations about transition to adulthood, including community participation, employment opportunities, and long-term support. Preparing for adulthood does not begin at the end of schooling; it is a process that should be thoughtfully integrated throughout a student's educational journey.

What This Means for Families

For families, navigating the education system can feel overwhelming, but there are a few key principles to hold onto. First, you are an essential part of your child's team, and your voice matters in every decision. Your understanding of your child's needs, strengths, and future goals should help guide the direction of their education.

It is also important to remember that the goal is not simply placement in a specific classroom, but ensuring that your child is engaged, supported, and making meaningful progress. Functional skills and participation in daily life should be fully integrated into your child's program. Consistency across school, home, and therapy settings can make a significant difference, so alignment between teams is key.

At times, you may need to advocate for higher expectations or additional support. Children with AS benefit from being given opportunities to learn and succeed, rather than having expectations limited. Finally, you are not alone on this journey. There is a strong community, along with organizations like Angelman Syndrome Foundation (ASF), working to

support families, improve systems, and ensure that every individual with AS has the opportunity to live a meaningful and fulfilling life.

Transition to adult care

Adults with AS often continue to have significant health problems. A significant proportion of adults experience some degree of decline in mobility, but most remain mobile. Problems with movements such as tremors and NEM may increase in adulthood (Prasad et al., 2018). The main areas for clinical management in adults with AS are seizures, sleep, risk of aspiration, GERD, constipation, dental care, vision, obesity, scoliosis, bone density, communication, behavior, and anxiety (Larson et al., 2015).

Understanding the changing needs of adults with AS is essential to ensuring continued access to appropriate medical care, services, and therapeutic supports throughout adulthood. Lifelong learning should be presumed possible, even if gains are slow and benefits appear to be modest. Therapeutic interventions should aim to maintain and, when possible, improve functioning throughout adulthood. Priorities include strengthening social participation, supporting daily living skills, promoting independence, and enhancing quality of life. Also, preventive and proactive strategies should be utilized to reduce the impact of underlying conditions and impairments that can interfere with learning and lead to, or exacerbate, challenging behavior and mental health issues.

The limited information about adults with AS comes from cross-sectional studies, case reports, and retrospective reviews utilizing data from clinical sources and parent interviews (Clayton-Smith, 2001; Larson et al., 2015; Prasad et al., 2018). Although adults with AS may continue to experience many of the same medical and developmental challenges present during childhood, some symptoms may improve with age. Seizures may occur less often as individuals with AS move into adulthood (Prasad et al., 2018), but they may recur in a subset of those over the age of 25 years (Larson et al., 2015). Some parameters of sleep improve in a proportion of adults with AS (Larson et al., 2015; Prasad et al., 2018). It is reasonable to expect that parents and caregivers of adults with AS will need access to various types of support such as behavioral interventions and/or medications for dealing with sleep problems.

Communication and adaptive skills appear to be maintained into adulthood. Many adults with AS use unaided modes of communication (signs or natural gestures and vocalizations), whereas aided modes of communication such as pictures and AAC devices may be used less frequently (Larson et al., 2015). For this group, speech therapy could center on educating key people (parents, peers, support workers) to recognize, reinforce, and extend the adult's attempts to communicate by responding in a consistent and appropriate manner. The situation may be different for individuals who are accustomed to AAC devices at school. When this group transitions to the adult system, communication support will be required to ensure that the communication system meets their needs in different settings and the people they interact with have the skills to support successful communication. Supporting daily living skills and promoting independence in self-care and feeding routines should remain important lifelong learning goals.

What This Means for Families

When transitioning to adulthood, consider the availability of ongoing educational and therapeutic support. This includes exploring access to specific be-

havioral therapies such as ABA and AAC device support. Additionally, it is essential to thoroughly research the process of applying for disability benefits, investigating state-specific waiver programs, and understanding the legal aspects of guardianship. Families may wish to explore special needs trusts and other financial planning options for the AS adult. Enrollment in vocational / recreational opportunities should be considered early.

The Transition to Adulthood Checklist developed by the ASF provides practical guidance on healthcare transition, education and vocational planning, legal considerations, and various forms of long-term support. This checklist can be a valuable tool to help families plan proactively and navigate the transition from pediatric to adult systems of care.

Adult Health and Life Expectancy

Available evidence suggests that many individuals with AS live well into adulthood and older age. However, robust actuarial data are not available, and the average life expectancy of individuals with AS has not been established. Young adults with AS continue to learn and are generally not expected to have deterioration in their mental abilities, so a decline in performance should prompt investigation. There is no apparent increased risk for malignancy, and there are reports of AS individuals living beyond 70 years old (Philippart, 2005).

While long-term actuarial data are limited, AS is not generally considered a life-limiting condition. A recent study compiled mortality data from registry sources and community reports (Gomes et al., 2024). Reported ages at death ranged widely, from infancy through older adulthood. Because these data were collected from registries and social media–based sources, they may reflect reporting bias and do not represent population-level life expectancy estimates. Compared with the general population, individuals with AS may have increased risk of complications related to epilepsy (including sudden unexpected death in epilepsy (SUDEP)), respiratory infections likely related to aspiration, and postoperative complications, as well as risk for drowning. In rare and tragic cases, abuse or neglect has been reported, as is true for many individuals with severe disabilities. These events are not specific to AS but underscore the importance of protective support for vulnerable individuals (Gomes et al., 2024).

Although the severity or frequency of seizures may improve with age, there is likely to still be the need for some type of anticonvulsant medication. Mobility issues become a more predominant concern as the individual with AS ages, often associated with concerns about obesity, scoliosis, and low bone density. Individuals with AS who have severe ataxia may lose their ability to walk if ambulation is not encouraged. Hence, ongoing physical therapy is crucial to maintain mobility and movement. Scoliosis can develop in adolescence and is especially a problem in those who are non-ambulatory (Clayton-Smith, 2001; Clayton-Smith, 1993). Scoliosis can be treated with early bracing to prevent progression, and surgical correction or stabilization may be necessary for severe cases.

Some adults with AS may receive antipsychotic medications to manage challenging behaviors. Potential adverse effects, including sedation, should be carefully monitored. In a recent study, researchers examined the quality of life, medical history, and medication use among adolescents and adults with AS. The study found that self-care, mobility, and daily activities were the most affected areas. All

adolescents (100%) and most adults (93%) experienced at least moderate difficulties with self-care activities, such as washing or dressing themselves. More than half (55%) of the adolescents and adults had at least moderate issues with mobility and usual activities. Around 30% of adolescents and adults experienced moderate to extreme problems with anxiety, as mentioned in the previous section. Both age groups were found to use an average of five medications. This suggests that the clinical burden of AS persists throughout an individual's life (Khan et al., 2019).

What This Means for Families

Families can expect that their loved ones with AS will continue to need support throughout adulthood, but learning, engagement, and enjoyment of life can continue. Importantly, many of the medical risks associated with AS can be reduced with proactive care. Careful seizure management, monitoring for swallowing difficulties and GERD, attention to respiratory health, safe sleep practices, and thoughtful perioperative planning all contribute to improved long-term outcomes.

Although the disabilities in AS are lifelong, many individuals continue to participate meaningfully in family and community life as adults. Coordinated medical care, appropriate supports, and proactive planning can help maintain health, functioning, and quality of life as needs change over time.

Standards of Care

"A multidisciplinary approach and consensus statement to establish standards of care for Angelman Syndrome" was published in 2022 (Duis et al., 2022). These recommendations were developed by a group of experienced clinicians with long-standing expertise in AS and reflect a consensus approach to care. Many of the practices described are informed by clinical experience and expert opinion, rather than large observational studies, as high-quality evidence is limited for many aspects of AS management. As such, these recommendations should be interpreted as guidance rather than prescriptive standards, and clinical decisions should be individualized based on patient needs, family preferences, and evolving evidence.

Research and clinical trials

In 1993, about 30 years after Dr. Harry Angelman described AS, Huibregtse and colleagues identified E6-associated protein (E6-AP), which was later renamed Ubiquitin E3 ligase A (UBE3A). A few years later, in 1997, UBE3A was described as the responsible gene for AS (Kishino et al., 1997; Matsuura et al., 1997).

Soon after, researchers created mouse models of AS. The first animal models were created in 1998 (Jiang Y et al., 1998). The research using Ube3a-deficient mice has clarified the molecular and cellular origins of AS, and these animal models have been invaluable in exploring the pathophysiology of AS (Kiyonori Miura et al., 2002; Margolis et al., 2015). These models have been essential for understanding how AS affects the brain and for testing potential treatments before they are tried in people.

Clinical research led by Dr. Charles Williams provided foundational knowledge on the clinical presentation of AS.

In 2006, the Natural History Study (NHS) began enrolling children with AS to better understand the progression of various aspects of the disorder, including medical problems, developmental and behavioral characteristics, and family functioning throughout the lifespan. Funding has come from

a variety of sources (NIH 2003 – 2014, FDA 2017-2022, Angelman Biomarkers & Outcome Measures Consortium 2022-present), and patients are enrolled at various sites in North America. Efforts like these provide crucial information about the course of AS over time and lay a foundation for treatment trials.

Early clinical trials in AS focused primarily on increasing the methylation of the paternal UBE3A, hypothesizing that such interventions would result in re-activation of the silenced (i.e., imprinted) paternal UBE3A, and on improving the function of neuronal cells through modulation of the synapses (Peters et al., 2010; Bird et al., 2011). However, these approaches were unsuccessful, as was a trial of levodopa (Tan et al., 2018). More recently, there have been attempts to correct the cellular pathophysiology in AS, but there have not been any successful clinical trials of these compounds (Keary et al., 2023).

A major breakthrough came when researchers discovered ways to turn on the normally silenced paternal copy of UBE3A in brain cells. In 2012, Huang et al. proposed use of topoisomerase inhibitors to "unsilence" the paternal UBE3A in neurons, and in 2015, Meng et al. showed that an antisense oligonucleotide (ASO) can reactivate the imprinted allele in mice. The in-depth understanding of this mechanism led to exploration of ASOs as a potential therapy for AS, with several phase 3 trials ongoing. Topoisomerase inhibitors, which were designed to treat specific types of cancer, proved to be too toxic for long-term use in humans, so no therapeutic compounds have been developed to treat AS using topoisomerase inhibitors.

Another promising approach is gene replacement therapy, which delivers a working copy of UBE3A to brain cells using a modified virus. Studies conducted on AS mice have demonstrated promising outcomes using this method. Gene replacement therapy is now being evaluated in humans with an ongoing Phase 1/2 clinical trial evaluating the safety, tolerability, and preliminary efficacy of MVX-220 (MavriX Bio, LLC., 2026).

Research in AS is advancing rapidly. Clinical trials are designed to determine whether these approaches are safe and whether changes observed in early studies translate into meaningful benefits for individuals with AS. None of the investigational therapies should be considered proven treatment until efficacy and safety have been adequately established.

Because the clinical-trial landscape changes rapidly, families interested in current studies should consult the ASF's clinical trials resources https://angelman.org/clinical-trials/ and ClinicalTrials.gov https://clinicaltrials.gov/ for the most current information.

What This Means for Families Today

Right now, care for an individual with AS focuses on supporting the development, health, and quality of life of that individual. While research is moving quickly, most treatments today are aimed at managing symptoms and helping children reach their individual potential.

Your child should continue to receive regular medical follow-up, including care from specialists such as neurology, developmental pediatrics, and ophthalmology, depending on their needs.

Although new treatments are being studied, participation in research or clinical trials is always a personal decision. Families can talk with their child's medical team about whether a study is appropriate and what participation would involve.

Finally, families are not alone. Connecting with support organizations, other families, and advocacy groups can provide education, shared experience, and practical support throughout childhood and beyond. Families can also learn more about the latest developments in therapeutics for AS through the websites of these parent support organizations.

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