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 the 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 the 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 the Prader-Willi syndrome the deletion was always observed on the paternally derived one. This was an important discovery and ultimately paved the way for the delineation of several mechanisms that caused AS, all by disruption of a gene located on maternally inherited chromosome 15. It was learned that AS can be caused by two copies of the paternal chromosome 15 (1991) (paternal uniparental disomy (pUPD)) and that disruption of a regulatory region (the Imprinting Center) can also lead to AS (1993). 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 neural development.

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

syndrome is well represented by parent-based support groups in many countries, on individual family websites and on a host of medical and professional information websites. 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?

Angelman Syndrome 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.

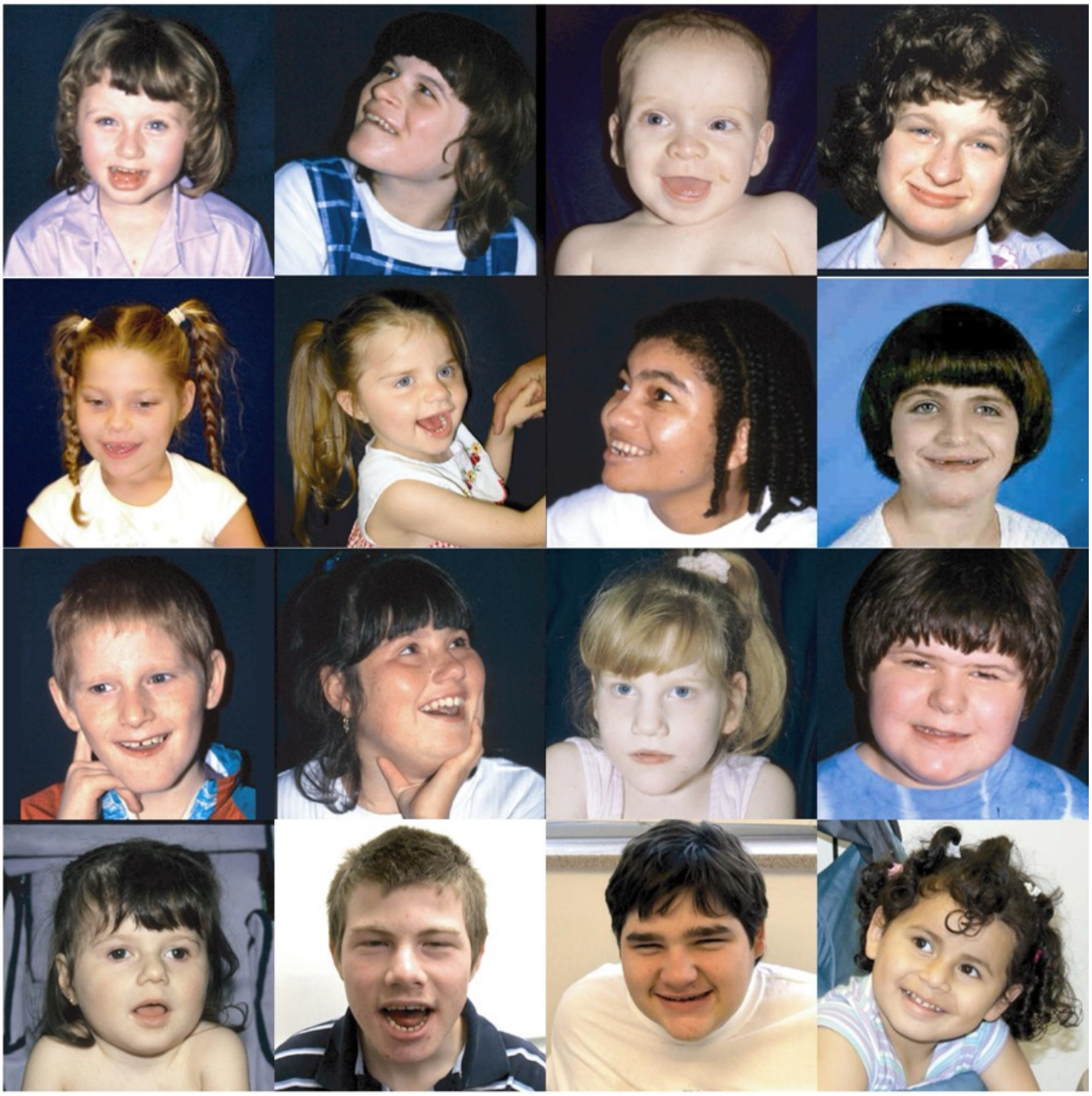
By searching the: (i) Danish National Patient Registry, which includes all Danish residents who have received inpatient and outpatient medical care; (ii) Danish Cytogenetic Central Registry, which includes all prenatal genetic testing and postnatal chromosome analysis; contacting all pediatrics and clinical 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 1:22,30 (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

Angelman syndrome 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 decrease). Children with *UBE3A* mutation and 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, and it is unusual for them to be considered to have a “dysmorphic” facial appearance. 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 genetically-proven AS.

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

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

- Developmental delay, meaning developmental milestones and skills develop much 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 < 3 yrs. of age. Seizure severity usually decreases with age after puberty, but the seizure disorder lasts throughout adulthood.

- Abnormal brain wave pattern (EEG), with a characteristic pattern, as mentioned in the text. The EEG abnormalities can occur in the first 2 years of life, can precede other clinical features, even if there are no clinical seizures.

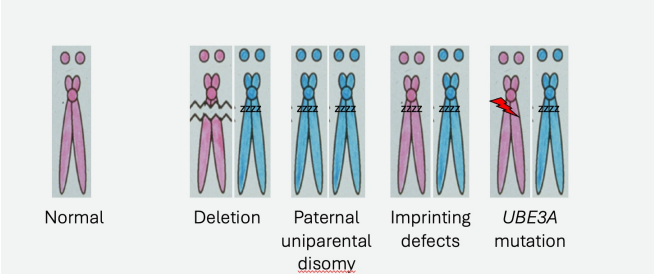
Associated features seen in some individuals (20 - 80%)

- Flattened back of the head
- Feeding problems, often related to low muscle tone in the trunk during infancy
- A prominent lower jaw
- Wide mouth, widely-spaced teeth
- Frequent drooling
- Excessive chewing/mouthing of non-food objects
- Crossed or misaligned eyes
- Hypopigmented skin, light 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 T 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 Y et al., 1999). These mechanisms are depicted in the illustration below.

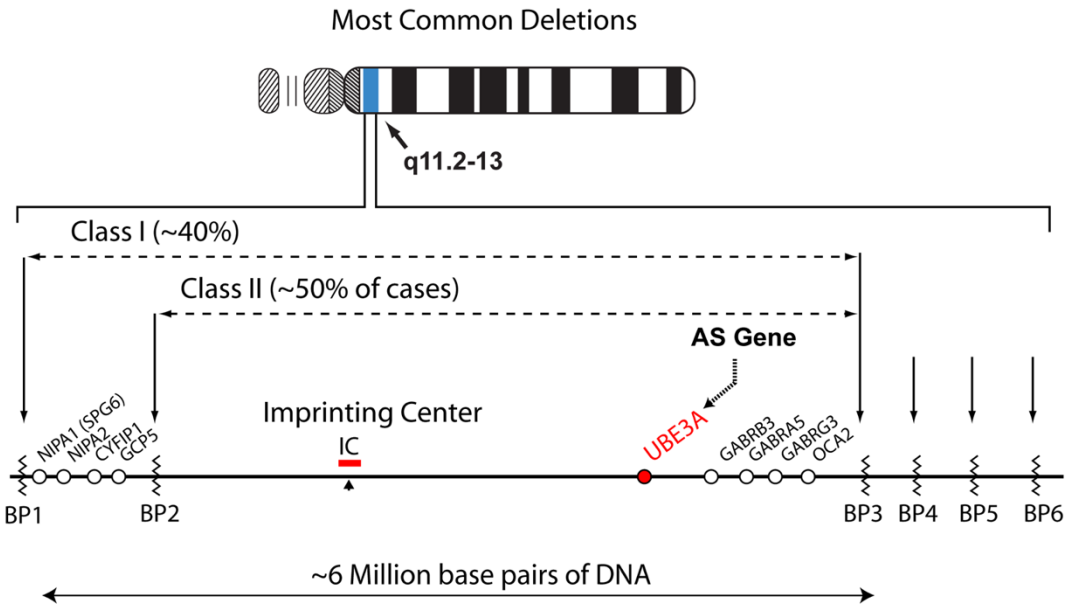


A chromosome 15 pair is illustrated for each mechanism and a normal chromosome pair is depicted on the left with a normal q12 chromosome region. In blue = paternally-derived chromosome and in pink = maternal derived chromosome. AS can be caused by a large deletion of the maternal chromosome 15q11.2 region (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. The imprinting center is located some distance from *UBE3A* but it is still able to regulate the gene by a complex mechanism that is the subject of intense research. Finally, AS can be caused by a mutation in *UBE3A* on the maternally derived chromosome 15.

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

The table above shows the prevalence of the different genetic subclasses. Individuals with a clinical diagnosis of AS without an identifiable molecular diagnosis probably have an alternative diagnosis, such as Phelan–McDermid syndrome, Pitt–Hopkins syndrome, or the GRINopathies. (Tan et al., 2014)

The typical deletion spans about 6 million building blocks (base pairs) of DNA. The common deletions extend from either breakpoint (BP) one (BP1) or BP2 to BP3 and are termed class I (BP1-BP3) and class II (BP2-BP3) deletions respectively. 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 methods of testing including fluorescent in situ hybridization (FISH) will detect a deletion. 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

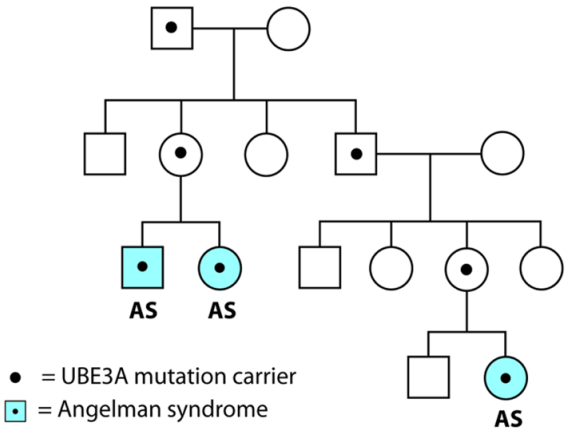
The *UBE3A* gene produces the UBE3A protein (also called E6-AP), which is an important component of the ubiquitin-proteasome pathway (pictured below). This pathway is extremely important to all cells. The pathway enables a small protein molecule, ubiquitin, to be attached to certain proteins, thereby 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 can have either a de novo mutation (i.e., not inherited from either parent) or a mutation inherited from the mother; since the paternally-inherited *UBE3A* is silenced, mutations in the paternally-inherited *UBE3A* gene would not result in any clinical symptoms. 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

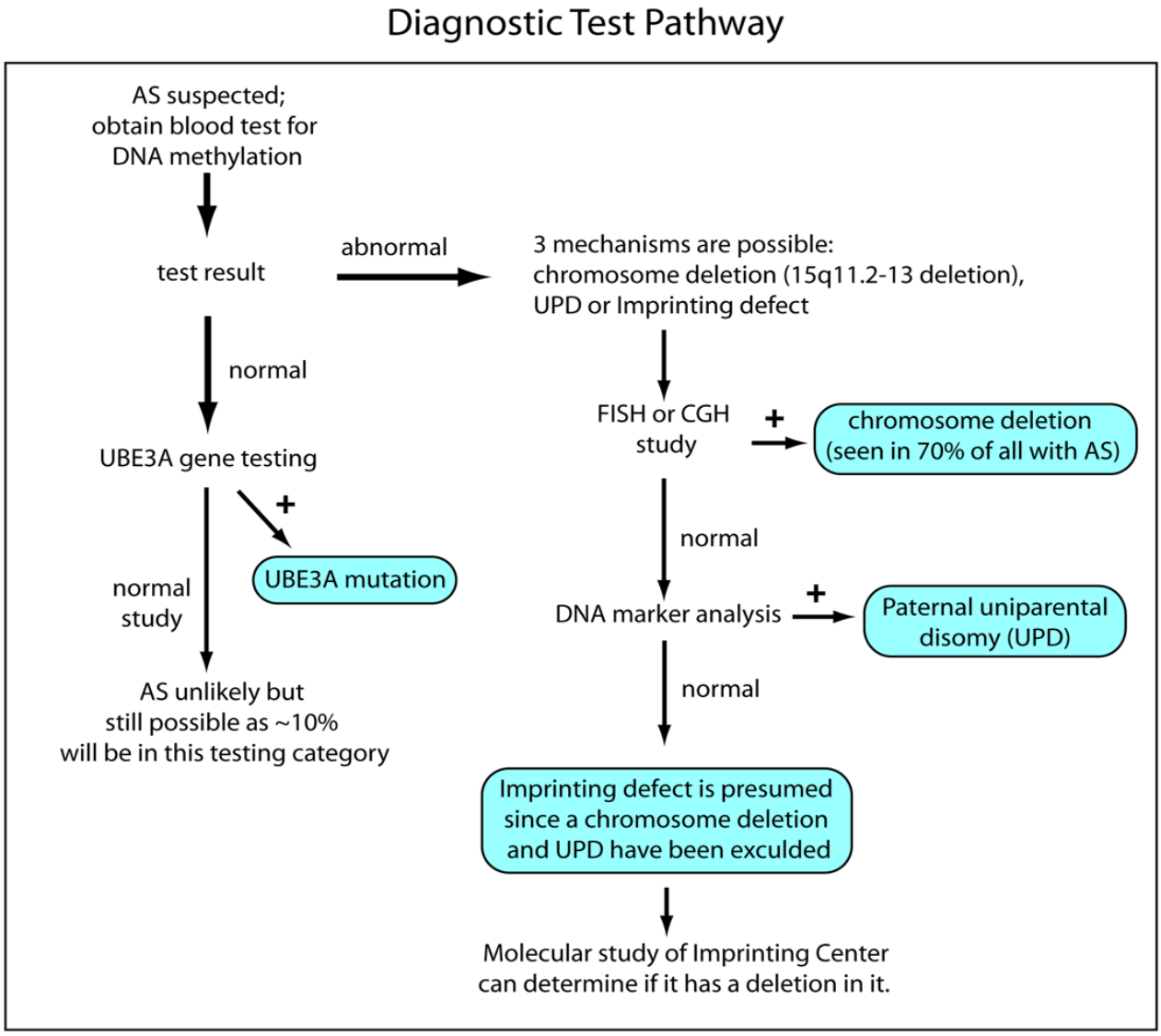
Regardless of the genetic mechanism causing AS, the syndrome is characterized by a reasonably uniform clinical picture of severe intellectual disability, characteristic behaviors, and severe limitations in speech and language. However, there are some clinical differences that correlate with the genotype,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

1. Those with a deletion 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 deletion classes 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 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. Some individuals with ImpD are mosaic for the imprinting error (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.

4. Those with a UBE3A mutation tend to have clinical severity between those with a deletion and an ImpD. Some of those with UBE3A mutations may have relatively high cognitive abilities, fine motor, and gross motor skills depending on the type of mutation. (Keute et al., 2021; Sadhwani et al, 2024).



Genetic Diagnostic Testing

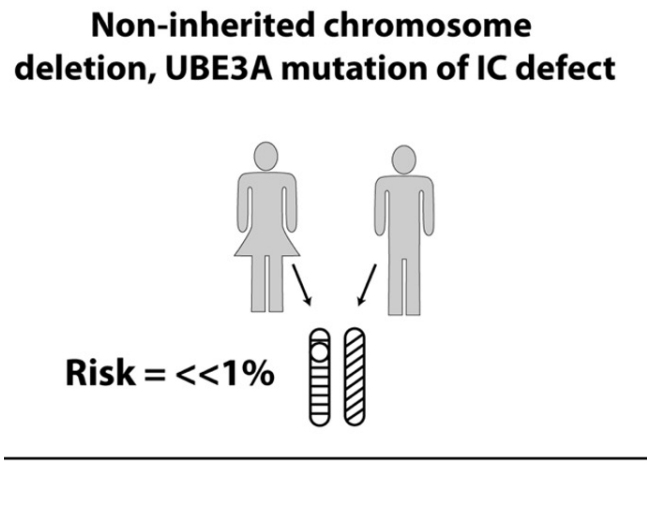
Laboratory diagnostic testing for AS can be complex. Evaluation of an individual in whom the diagnosis of AS is suspected (above) starts with a DNA methylation analysis of the AS/PWS region. A positive DNA methylation test confirms the diagnosis of AS. The DNA methylation test is positive in AS when 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. 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 shows no deletion, it may show that both chromosomes 15 are identical which indicates they came from the same parent (UPD). 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 fur-

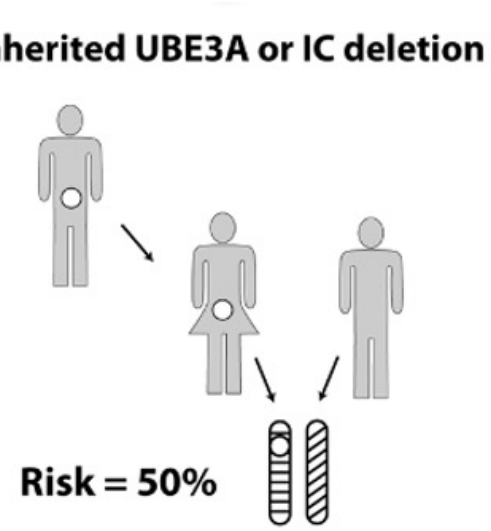
ther studied to determine if there is a DNA deletion involving the Imprinting Center (IC), which is one of the hereditary forms of AS. Molecular testing for IC deletions is available clinically from a small number of laboratories.

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 whole exome or whole genome sequencing. After a mutation is found, maternal testing should be performed to determine if the variant 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 smaller (<1%) risk of recurrence.

If all genetic testing for Angelman syndrome returns normal, another diagnosis should be sought using a broad investigational strategy such as genome sequencing if not yet done.

Understanding Genetic Risk in Angelman Syndrome





What This Means for Families

AS can happen for different genetic reasons, 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, (e.g., only a few cases reported in the literature), a child can have AS due to a very small, deletion that involves a small area around and including UBE3A. For these reasons, chromosome study of the mother, including FISH, is recommended to help rule out inherited chromosome changes.

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 nevertheless be considered to exclude the rare possibility that a chromosome change in one of the parents presents a predisposing factor. In summary, the recurrence risk is <1% if both parents have normal chromosome analyses.

3. Imprinting Defect (ImpD):

An ImpD means the *UBE3A* gene is present 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:

For those who have a change (mutation) in *UBE3A*, the mutation can either occur spontaneously (brand new error in the egg) or be maternally inherited (mutation present in mom on the copy of *UBE3A* she inherited from her father) and have a 50% risk of recurrence. If the mother carries the *UBE3A* mutation, there is a 50% chance of passing AS to each child.

5. Germline mosaicism:

This term refers to a phenomenon in which a genetic defect is present in the cells of the gonad (ovary in the mother's case) but not in other cells of the body. This occurrence can lead to errors in risk assessment because a genetic test, for example on a mother's blood cells, will be normal when in fact a genetic defect is present in the germ cells of her ovary (eggs). 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.

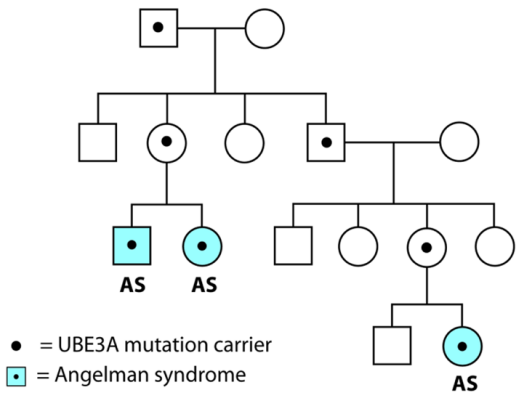
6. Imprinting inheritance:

Some AS-related genetic changes (such as *UBE3A* mutations or imprinting center deletions) can be silently passed through fathers without causing symptoms.

UBE3A mutations and IC deletions can be inherited wherein a carrier father can pass on the genetic defect to his children without causing any problems in the child, but if a carrier mother were to pass this same genetic defect on to her child (1-in-2 chance of doing so with every pregnancy), regardless of the sex of her child, that child would have AS. The carrier father or mother is unaffected. This pattern can cause AS to appear unexpectedly in a family, sometimes after passing through multiple generations without symptoms. When an inherited mechanism is identified, testing of other family members should be offered.

The pedigree diagram below illustrates inheritance of a paternally imprinted gene such as *UBE3A*. Here, AS has only occurred after a carrier mother passed on the gene defect (for example as in the two siblings with AS pictured on the left lower part of the pedigree). In addition, a distant cousin in this family also has AS due to inheritance of the *UBE3A* mutation that passed silently through two carrier males to a carrier female who then passed on the non-functioning *UBE3A* gene to her child resulting in AS. In the diagram, individuals with the light blue circles or squares have AS but everyone else in the family is clinically normal. 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.

Example of Imprinting Inheritance in Familial AS:
Inherited UBE3A Mutation



What This Means 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 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 discuss:

- Prenatal testing options in future pregnancies
- Preimplantation genetic testing 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.

Behavioral 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, mouthing of objects, sleep disturbances, and a fascination with water and plastic or paper items that make crinkly noises when manipulated (Dagli et al., 2012). Some individuals may also show behavioral challenges, especially during times of frustration. Caregivers most often report concerns relate 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 severe sleep issues, and severe GERD. Giggling, chuckling and laughing develop early in life and appear to represent reflexive behavior, but 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 prevailing behavior; crying, shrieking, screaming or short guttural sounds may also be heard.

It is not known why laughter is so frequent in AS, and although there is a type of seizure associated

with laughter, termed gelastic epilepsy, this is not what occurs in AS. 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.

In summary, researchers do not fully understand why laughter is so common in AS. Brain imaging studies suggest that differences in areas involved in emotion, reward, and movement may play a role. Importantly, this laughter is not a type of seizure and is different from conditions where laughter is caused by epilepsy.

Hyperactivity/Hypermotoric

Most children with AS are described as hyperactive, especially in infancy and early childhood. Essentially all young children with AS have some component of increased motor activity, with boys and girls equally affected and short attention span is often 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 system, adjustments to the environment to minimize distractors, 1:1 aide for educational activities, and occupational therapy. Preliminary studies reported poor tolerance to stimulant medication, 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.

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 is not something a child can control. With time, 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

Even though many individuals with AS have a happy or cheerful appearance, individuals with AS also display behaviors such as restlessness, irritability, temper tantrums, and repetitive movements, that can make it hard for them to interact well in social situations. 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 non-deletion subtypes. Behavioral challenges between males and females are for the most part comparable. Limited differences are noted between males and females in behavioral challenges. Females may be more lethargic and 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. As individuals with AS age, they may become more irritable and hyperactive. Across all subtypes aggressive behavior, hand flapping, and anxiety increased significantly with age. Increased irritability among non-deletion subtype may be linked to heightened awareness of their surroundings combined with the ongoing challenges in communication (Sadhwani et al., 2019).

What This Means for Families

For families these challenging behaviors can be stressful and exhausting, especially when they occur frequently or without an obvious trigger. It is important to understand that these challenging behaviors often serve a function: to get attention, to communicate, to escape or avoid a situation and to get additional sensory input. Many families find that trying to identify the triggers of these behaviors and providing alternative solutions help reduce the behavior. For example if a challenging behavior is used to get attention, families can learn ignore or redirect undesirable behaviors and give attention for desired behavior. In addition, these behaviors improve with structure, predictability, and support. Helpful strategies may include consistent routines, clear transitions, visual supports, communication tools, and behavioral guidance tailored to the child's needs. Addressing underlying issues, such as anxiety, sleep problems, or difficulty communicating, can also reduce behavioral challenges.

What Helps at Home and School Checklist

Structure & Predictability

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

Behavior Support Strategies

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

Environmental Modifications

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

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.

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 individuals with AS, and it is more commonly seen in older individuals. It is not known whether anxiety is truly less frequent in younger children with AS, or whether caregivers and providers have difficulty recognizing it. 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, Excessive distress or anxiety related to separating from a caregiver is very common in individuals with AS. Other possible manifestations of anxiety, triggered by separation from a caregiver or exposure to an unfamiliar environment, include being clingy, unable to relax, trembling, having nervous habits avoidance, head banging, 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).

Some individuals may have strong reactions to new environments, changes in routine, or unfamiliar people. In some cases, anxiety may contribute to vomiting or other physical stress responses.

Emotional & Anxiety Support Checklist

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

Individual Education Plan (IEP) language: Support for emotional regulation; anxiety-informed strategies.

The Angelman syndrome Behavioral Phenotype
A Quick Reference Table for Families

Typical pattern	What It Looks Like	Why It Happen	What may Help
High Social Drive	Frequent smiling or laughter; strong desire for interaction; affectionate; seeks closeness	Individuals with AS have 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	Understands more than they can say; frustration; pulling, pushing, grabbing, biting to communicate	Expressive language is more impaired than receptive skills	Early AAC; modeling gestures; visual supports; 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 in AS can be difficult to interpret as it is significantly impacted in AS individuals due to attention deficits, hyperactivity and lack of speech and motor control. In such situations, test results invariably fall in the severe to profound range of functional impairment. 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 and standardized psychometric testing seem to indicate a ceiling for developmental achievement at around the 24-30 month 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 tended 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, 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, and abilities are similar to those of a toddler (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 causes of Angelman syndrome. (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, However, 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 real 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, educational supports, 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 include receptive and expressive language, social (interpersonal), practical (activities of daily living, household, self-care) and motor abilities (Buntinix 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 and a relative weakness in their motor skills (Gwaltney et al.,2023; Peters et al., 2004).

Motor (Fine and Gross)

Individuals with AS have significant delays in achievement of motor milestones such as sitting and walking independently. AS individual also present 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). Individuals with AS have fine motor difficulties in precision and, dexterity with skills falling around the 15-month level (Beckung et al., 2004).

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 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, with a small minority requiring 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 Angelman syndrome and ASD. In many cases, this serves as a practical pathway to access medically necessary therapies, educational supports, or insurance-covered services, rather than reflecting a distinct or separate condition.

It is important to approach the interpretation of autism-related characteristics in AS with care. Many behaviors seen in AS are part of the syndrome's core profile 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.

Emerging evidence suggests that autism-related characteristics may be more commonly observed in those with deletions, and may vary in presentation and severity (Sahoo et al., 2006; Peters et al., 2008). Importantly, these differences are not solely explained by cognitive ability and highlight the need for individualized assessment.

For individuals with AS who do exhibit autism-related characteristics, supports 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 objects 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 Angelman syndrome, but it may influence which therapies and supports are most helpful.

A diagnosis of autism in a child with AS can sometimes help unlock additional services, such as ABA or social-communication supports. At the same time, families should know that many behaviors that look "autistic" are actually core features of AS, and these behaviors may change over time.

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 Angelman syndrome 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 supports, ensure access to services, and promote the best possible outcomes for each individual.

Speech and Language

Angelman Syndrome 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. The absence of speech in individuals with AS cannot be solely attributed to their level of intellectual disability, as most individuals have receptive language abilities which would typically correspond to development of expressive language (Pearson et al., 2019), Clayton-Smith & Laan, 2003; Buntinx et al., 2010). Individuals with a mosaic imprinting defect can use many 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, and particularly pronounced in individuals with the deletion genotype. Those with other genotypes, such as UPD and imprinting defects, often demonstrate stronger communication skills, both expressively and receptively, and have more favorable prognoses for communication and language development (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 de-

velopment 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 Augmentative and Alternative Communication (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 includes both unaided and aided communication methods, which together support a multimodal approach to communication.

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 interaction (Calculator, 2016; Calculator, 2023).

Natural Gestures and Enhanced Natural Gestures

Children with AS typically use self-select 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. While some individuals with AS 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 (AAC)

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).

Current research emphasizes several key principles for aided 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.

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.

Receptive vs. Expressive Language

Research documents that individuals with AS demonstrate stronger receptive language abilities than their expressive output suggests (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 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, communication instruction 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. Communica-

tion 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 likely understands 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, 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. Communication instruction should happen everywhere—at home, in school, on the playground, and in the community.

Communication Supports Checklist

AAC and Communication Systems

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

Daily Implementation

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

Functional Communication

- 0 System for expressing basic needs (help, break, all done, more)
- 0 Ability to make choices and preferences known
- 0 Methods for refusing/rejecting
- 0 Opportunities for social communication (greetings, comments)
- 0 Ways to ask questions and gain information
- 0 Collaboration and Support
- 0 Regular SLP services with AAC expertise
- 0 Communication goals integrated across IEP/educational program
- 0 Ongoing family training and support
- 0 Peer awareness and communication partner training
- 0 Regular assessment and system updates as skills develop

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. Parent reports and recent studies indicate that abnormal sleep/wake cycles are common in AS (Waltz 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 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 seems to decrease with age. This does not necessarily mean there has been an actual improvement in sleep quality. Our impression is that over time, caregivers develop methods to prevent the individual's nighttime awakenings from disturbing other family members.

Interestingly, even though the literature suggests that children with AS may require less sleep than children with typical neurodevelopment, 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.

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). Use of sedatives such as antihistamines may be helpful if wakefulness excessively disrupts home life. 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 are part of the standard of care and eligible for health insurance coverage.

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 protect both the child and the household.

Sleep Support Strategies Checklist

Routine & Environment

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

Medical & Nutritional Considerations

- 0 Screening for iron deficiency when sleep problems are significant
- 0 Treating gastroesophageal reflux disease (GERD), pain, or constipation that may disrupt sleep
- 0 Reviewing medications that may worsen sleep

Safety & Family Protection

- 0 Creating a safe bedroom environment for nighttime wakefulness
- 0 Use of enclosed/safety beds
- 0 Monitoring strategies that allow caregivers to rest

Medications

Some children may benefit from low-dose melatonin given about one hour before bedtime. Other medications are sometimes used, but there is limited research on their effectiveness in AS. Medication decisions should always be individualized and discussed with the medical team.

Sexuality

Sexual maturation occurs with normal development of secondary sexual characteristics, menarche usually occurs at around 11.6 years and post pubertal females with AS are fertile and pregnancy has been reported (Lossie et al., 1999, Bidels-de Heus et al., 2023).

The main issues associated with sexual development in individuals without AS are also seen in those with AS. The general approach to consideration of sexual issues in the AS is to recognize that sexual development will occur in a relatively normal physiologic manner for both young men and young women. Accordingly, issues of potential sexual abuse, normal masturbation behaviors, approach to contraception, and access to gynecological care are important. Gynecological care is advisable by age 21 years, and it should include a breast and pelvic examination. If a pelvic exam is not possible, ultrasound of pelvic organs may be indicated.

Sexual education is problematic in those with intellectual disability. Individuals with developmental challenges are at increased risk for sexual assault and abuse, and parents should be alert to 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 gynecologic 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. It is possible that increasing the GABA level without enhancing the GABA receptor function may be responsible for the ineffectiveness of vigabatrin. Single medication use 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 special attention should be reserved differentiating active seizures from the movement abnormalities, additionally the EEG signature that may persist even when seizures are

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 more medication.

Every family should have a clear plan for prolonged seizures. This usually includes 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 Behaviors

Feeding problems are frequent and usually manifest early as difficulties with sucking from the breasts or bottle, 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 often present as 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, and it may reduce the seizure threshold, thereby increasing the risk for seizures. Other gastrointestinal issues are cyclic vomiting episodes, and eosinophilic esophagitis.

Individuals with AS are notorious for putting everything into their mouths (mouthing behavior), but they do not generally swallow non-food objects (i.e., pica). 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; 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 the child and its family, and it is unclear if any treatments are effective.

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.

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, it can require consistent environmental supports.

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) and appears to increase with age. 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. However, the medications that have been tried with varying degrees of success include trihexyphenidyl, levetiracetam, propranolol, some benzodiazepines, and even baclofen.

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 is most frequently observed during voluntary, goal-directed activity such as reaching, feeding, or manipulating objects (Wil-

liams 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 tremor 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 tremor significantly interferes 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).

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 something 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).

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 related to increased activity of the vagus nerve (Saitoh et al, 1994; Vanagt et al, 2005; 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 if individuals with AS have an increased risk for cardiac rhythm disturbances. Anesthesiologist should certainly 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 isn't sufficient evidence to make specific anesthetic recommendations.

Temperature Sensitivity

Some individuals with AS appear to have increased sensitivity to high temperatures. In fact, increased sensitivity to outdoor temperatures has been commonly reported in individuals with AS. There may be difficulty regulating body temperature, with symptoms of flushing, increased irritability and hyperactivity when exposed to heat. Caregivers frequently employ water sprays, and portable fans and appropriate clothing to help manage this sensitivity. It is also common for the 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, 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 88% to 34% 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 however have head circumferences less than the 25th percentile by age 3 years, often accompanied by a flattened back of the head. Average height is lower than the mean for typical children, but most AS children 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. Overweight and obesity are associated with the ability to walk independently (Bindels-de Heus et al., 2024), which may indicate that improved mobility allows the individual with hyperphagia to acquire food, or could be a coincidental association since the genotypes most likely to exhibit hyperphagia (UPD and ImpD) show better development in general.

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 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 carefully. If your child is independently mobile and shows strong interest in food, structured meal routines and supervision may be important.

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 is something to think about 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.

Healthy Bones Checklist

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

Hypopigmentation, Strabismus and Ocular Albinism

When AS is caused by deletion, skin and eye hypopigmentation may result. This occurs 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 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 are usually normal. Children with AS who have hypopigmentation require photoprotective creams and clothing. Not all AS children with deletions of OCA2 are obviously hypopigmented but may have lighter skin color than expected.

Management of strabismus in AS is similar to that in other children: evaluation by an ophthalmologist, correction of any visual deficit, and where appropri-

ate, 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 and 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 difficulty 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.

Education

Education must be thoughtfully designed to be individualized, multidisciplinary, and focused on the whole child. Effective programs go beyond academics alone. They support communication, independence, social connection, and long-term quality of life. This approach is closely aligned with emerging Angelman syndrome Standards of Care, which emphasize early intervention, functional skill 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 plan such as an IEP or IFSP. 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 those 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, behavior 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.

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 designed 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 supports. Preparing for adulthood is not something that begins 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 supports, and that is okay. Children with AS benefit from being given opportunities to learn and succeed, rather than having expectations limited too early. Finally, you are not alone in this journey. There is a strong community, along with organizations like ASF, working to support families, improve systems, and ensure that every individual with AS has the opportunity to live a meaningful and fulfilling life.

Caregiver & School Collaboration Checklist

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

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).

There is a critical need to understand life-span issues impacting adults with AS to ensure they have continued access to appropriate services and therapeutic supports when needed and for as long as needed. Life-long learning should be presumed possible, even if gains are slow and benefits appear to be modest. Principles of therapy should be directed toward maintaining and if possible improving individuals' functioning with the goal of optimizing their personal and social competence, improving daily and practical living skills and enhancing their 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). While for the most part adults with AS present with the same range of conditions that affect them in childhood, symptomatic improvements can occur. Seizures may become less active or occur less often as individuals with AS move into adulthood (Prasad et al., 2018) but may recur for 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 supports 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) but 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 through responding in a consistent and appropriate manner. The situation may be different for students with AS who are accustomed to AAC devices at school. When this group transitions to the adult system, communication supports will be required to ensure the communication system meets their needs in different settings and the people they interact with have the skills to support successful communication. It is also critical to support individuals with AS in advancing their daily living skills and fostering independence in self-care and feeding routines as much as possible should be a key life-long learning goal.

What This Means for Families

When transitioning to adulthood, consider the availability of ongoing educational and therapeutic supports. This includes exploring access to specific behavioral therapies such as ABA and AAC device support. Additionally, it's essential to thoroughly research the process of applying for disability benefits, investigating state-specific waiver programs, and understanding the legal aspects of guardianship. Financial planning should include a special needs trust for the AS adult. Enrollment in vocational/ recreational opportunities should be considered early.

The Transition to Adulthood Checklist developed by the Angelman Syndrome Foundation provides practical guidance on healthcare transition, education and vocational planning, legal considerations, and long-term supports. 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

The good news regarding adult health in AS is that many health matters are the same as those encountered in the typical population. Young adults with AS continue to learn and are generally not expected to have deterioration in their mental abilities, and 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 although there are no actuarial data estimating life span [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. 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 SUDEP), respiratory infections likely related to aspiration, and postoperative complications. 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 Angelman syndrome but underscore the importance of protective supports for vulnerable individuals. (Gomes et al., 2024)

Physical health in AS appears to be remarkably good. 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.

Adults with AS, due to behavioral issues, are perhaps more likely to be given some type of neuroleptic medication, and side effects or sedative effects of these agents can be a problem.

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 chapter. 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 also that 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.

With coordinated medical care and appropriate supports, many individuals with AS live into adulthood and maintain meaningful participation in family and community life.

While AS is a lifelong condition, many individuals enjoy stable health and meaningful quality of life with appropriate support. Families are encouraged to plan early, ask for help, and work closely with healthcare providers to adapt care as needs change over time.

Standard of Care

"The multidisciplinary approach and consensus statement to establish standards of care for Angelman Syndrome" 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, controlled clinical trials, as high-quality evidence is limited for many aspects of AS management. As such, 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), and a few years later, in 1997, UBE3A was described as the re-

sponsible gene for AS (Kishino et al., 1997; Matsuura T et al., 1997).

Soon after, researchers created mouse models of Angelman syndrome. 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 events associated with AS and has been invaluable in exploring the interruption of the pathophysiology of AS through gene transcription and protein interactions (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 William provided a solid foundation of 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 this provide crucial information about the disease course over time and lay a foundation for treatment trials.

Early clinical trials tested supplements intended to change DNA methylation and increase UBE3A activity, such as folate and betaine. These studies did not show meaningful improvement in symptoms of AS, and this approach is no longer considered effective (Bird et al, 2011; Peters et al., 2011)

Medications already approved for other conditions were studied in AS in an effort to improve symptoms. One of these was minocycline, an antibiotic that also has effects on brain inflammation and synaptic function. Early studies suggested possible improvements in behavior or development, but larger and more rigorous trials did not show consistent benefit. As a result, minocycline is not recommended as a disease-modifying treatment for AS. Another medication studied was levodopa, a drug that affects dopamine signaling and is commonly used in Parkinson disease. Levodopa was tested to see whether it could improve movement, attention, or other neurologic features in AS. Clinical trials did not demonstrate clear or sustained benefit, and its use is not part of standard treatment for Angelman syndrome.

AS murine model data suggested that gaboxadol could improve cerebellar motor dysfunction. Trials of gaboxadol in humans had encouraging results in phase 2 studies (STARS trial), however the phase 3 (NEPTUNE trial) to evaluate the efficacy and safety of gaboxadol in pediatric individuals failed to demonstrate a positive treatment effect of gaboxadol in pediatric patients with AS, in part due to a high placebo response rate. Strong placebo responses have also been well documented in other neurodevelopmental disorders, such as Fragile X syndrome. (Keary et al., 2023)

A major breakthrough came when researchers discovered ways to turn on the silent paternal copy of UBE3A in brain cells. In 2012, Huang proposed topoisomerase inhibitors to “unsilencing” 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 particular mechanism led to exploration of ASOs as a potential therapy.

Two pharmaceutical companies are currently developing ASO treatments for AS. These include Ultragenyx (GTX-102, NCT04259281) and Ionis (ION582, NCT05127226), which have recently embarked on phase 3 studies. F. Hoffmann La Roche has halted their ASO development (RO7248824, NCT04428281), not due to safety concerns, and instead partnered with Oak Hill Bio to continue the development of Rugonersen. In 2024, Ultragenyx's phase 3 ASO trial began, shortly followed by Ionis' phase 3 trial launch in 2025. Oak Hill Bio plans a phase 3 trial of Rugonersen in 2026.

Another promising approach is gene replacement therapy, which delivers a working copy of the UBE3A gene to brain cells using a modified virus. Studies conducted on mice with AS have demonstrated promising outcomes using this method. A modified virus carrying a copy of the mouse Ube3a gene is injected into the brains of Ube3a-deficient mice. Ube3a protein is made from the transgene, which is stably integrated at random sites in the genome and can produce Ube3a indefinitely(Keary et al., 2023). Building on these preclinical results, gene replacement therapy is now being evaluated in humans. The ASCEND-AS study, a Phase 1/2 clinical trial investigating the safety and potential effectiveness of MVX-220 in individuals with AS. While this research is still in early stages, it represents an important step toward treatments aimed at addressing the underlying genetic cause of the condition.

In addition to the strategies mentioned above, there are additional trials involving downstream targets. In 2022, Neuren pharmaceuticals began a phase 1 trial of NNZ-2591 in Australia, and in 2023, and Roche began a phase 2a trial of alobagat for deletion AS patients.

What This Means for Families Today

Right now, care for a child with Angelman syndrome focuses on supporting development, health, and quality of life. 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.

Some medical concerns, such as seizures, sleep difficulties, feeding challenges, or drooling, can often be improved with targeted treatments. These issues may change over time, so care plans are usually adjusted as children grow.

It is also important to know that children with AS often continue to learn new skills, even if progress is slower or looks different from typical development. Gains may be small, but they are meaningful.
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.

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