Facts About Angelman Syndrome

7th Edition

January 1, 2009

Facts about AS was initially a small booklet developed in 1987 to help launch the Angelman Syndrome Foundation organization and to help inform parents and professionals about the syndrome. The Facts document is now in its seventh edition. Over the years, it has grown in scope and complexity and this year the "pamphlet/brochure" has been reformatted for a web presence. Current authors are:

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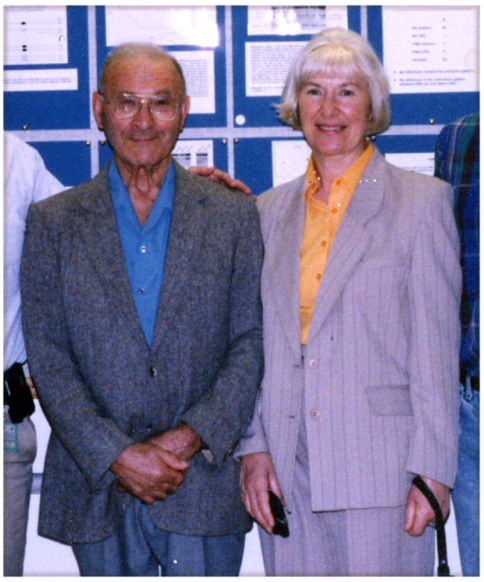
Dr. Angelman and the History of AS

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 1965, Dr. Harry Angelman, an English physician, first described three children with characteristics now known as the Angelman syndrome (AS) [1]. 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 [2].

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

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. However, these children had seizures and severe developmental delay, features not expected to be found for that syndrome. 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 chromosome 15. It was learned that the syndrome can be caused by two copies of the paternal chromosome 15 (1991) and that a regulatory region (the Imprinting Center) can be also be disrupted to the syndrome (1993). In 1997, 10 years after the chromosome deletion was identified, the AS gene, UBE3A, was isolated. This discovery 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 20 years, there has been increasing awareness of AS throughout the world. The 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. Angelman syndrome has emerged as one of the important syndromes causing neurological impairment and most pediatricians and neurologists now have some awareness of it.

How Common is AS?

AS has been reported throughout the world among divergent racial groups. In North America, the great majority of known cases seem to be of Caucasian origin. The exact incidence of AS is unknown but the best available data probably come from studies of school age children, ages 6-13 years, living in Sweden, and from Denmark where the diagnosis of AS children in medical clinics was compared to an 8 year period of about 45,000 births. The Swedish study showed an AS prevalence of about 1/12,000 [3] and the Danish study showed a minimum AS prevalence of about 1/10,000 [4]. Note that it is desirable to use the term *prevalence* since estimates of the AS diagnosis have been made in relatively small cohorts of children over various periods of time.

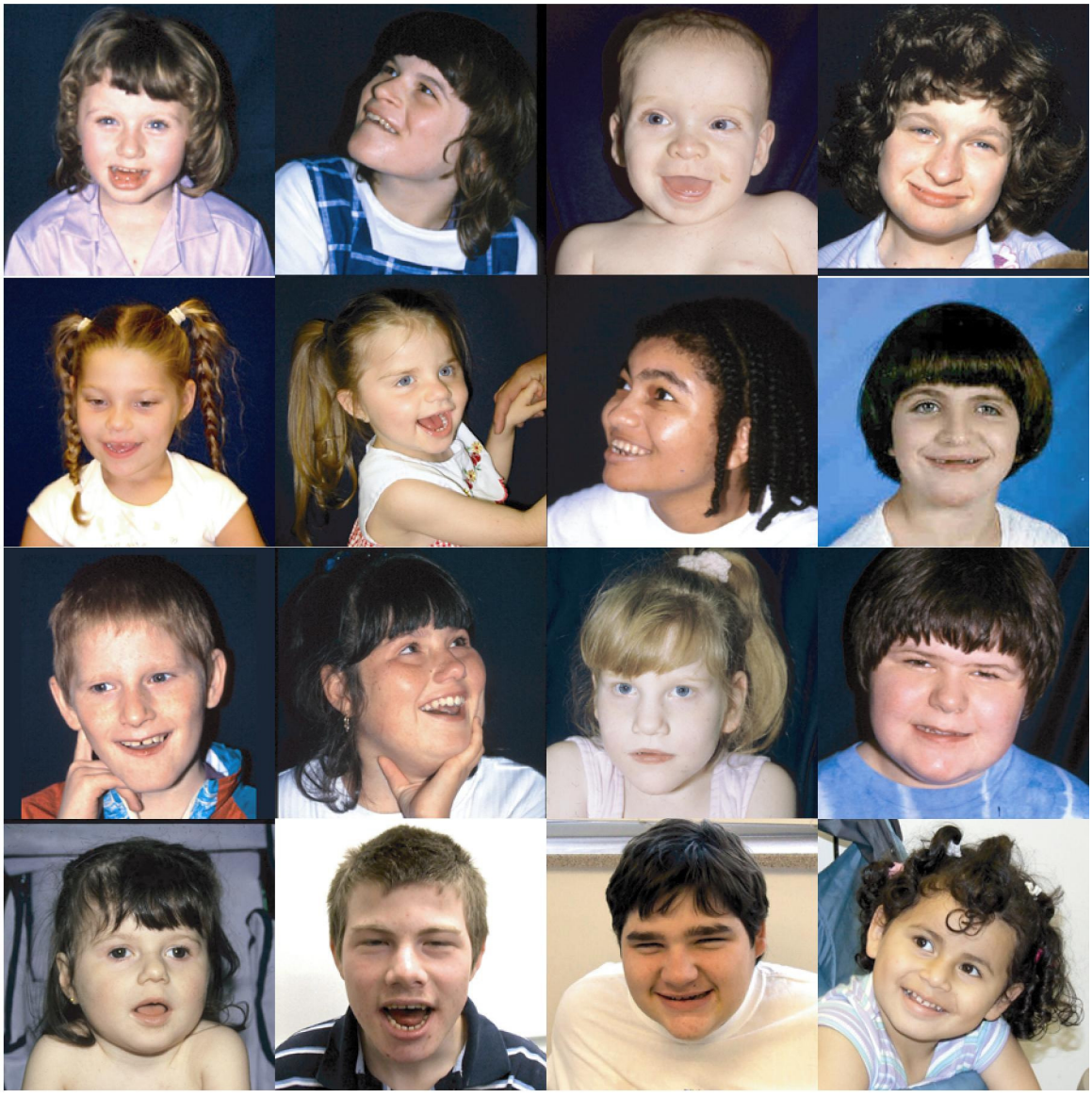
Several reports have tried to address the prevalence of AS among groups of individuals with established developmental delay. The results showed rates of 0% [5], 1.3% [6], 1.4% [7], and 4.8% [8]. The Buckley paper extrapolated their data in order to compare it to the population of the state of Washington (using 1997 Census Bureau figures) and obtained an estimate of 1/20,000, a number similar to that often quoted, but not referenced in terms of methodology, in a 1992 review paper [9].

There appear to be no reported prevalence studies that have screened newborns to detect rates of AS. Population wide prevalence figures would need to take into consideration that longevity in AS is probably reduced (severe mental delay and seizure presence would be risk factors) but no actuarial or other data are available on life span shortening. Likewise, it is not known what percent of individuals with AS are undiagnosed, although this is expected it to be significant. Accordingly, to estimate the number of people with AS living in the society, it would be inaccurate to divide any estimated AS prevalence figure into a total population number.

Given this information, it appears that the prevalence of AS among children and young adults is between 1/10,000 and 1/20,000. It is suggested to use a 1/15,000 figure if a single figure is needed. For population projections, estimates using birth rates can be used. For example, if an area has a birth rate of about 200,000/year it would be estimated that about 13 babies would be born each year with AS.

Consensus Criteria for Diagnosis of AS

Angelman syndrome is usually not recognized in early infancy since the developmental problems are nonspecific during this time. The most common age of diagnosis is between two and five years when the characteristic behaviors and features become most evident. Parents may first suspect the diagnosis after reading about AS or meeting a child with the condition. Children with AS may have a relatively wide mouth and a protruding tongue, sometimes associated with a prominent chin (see figure). Most children with AS also appear to share the normal familial facial traits of the family and so it is unusual for them to be considered to have a "dysmorphic" facial appearance. Angelman syndrome is a distinctive clinical condition however, mainly because of its distinctive behaviors and developmental course. 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 [10]. All of the features do not need to be present for the diagnosis to be made and the diagnosis is often first suspected when the typical behaviors are recognized.



Composite photograph of facial appearances of individuals with genetically-proven AS.

Developmental and Physical Findings (from 2005 Consensus Criteria document)

Consistent (100%)

- Developmental delay, functionally severe
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions
- Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping or waving movements; hypermotoric behavior
- Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones

Frequent (more than 80%)

- Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (≤2 S.D. of normal OFC) by age 2 years. Microcephaly is more pronounced in those with 15q11.2-q13 deletions.
- Seizures, onset usually < 3 yrs. of age. Seizure severity usually decreases with age but the seizure disorder lasts throughout adulthood.
- Abnormal EEG, with a characteristic pattern, as mentioned in the text. The EEG abnormalities can occur in the first 2 years of life and can precede clinical features, and are often not correlated to clinical seizure events.

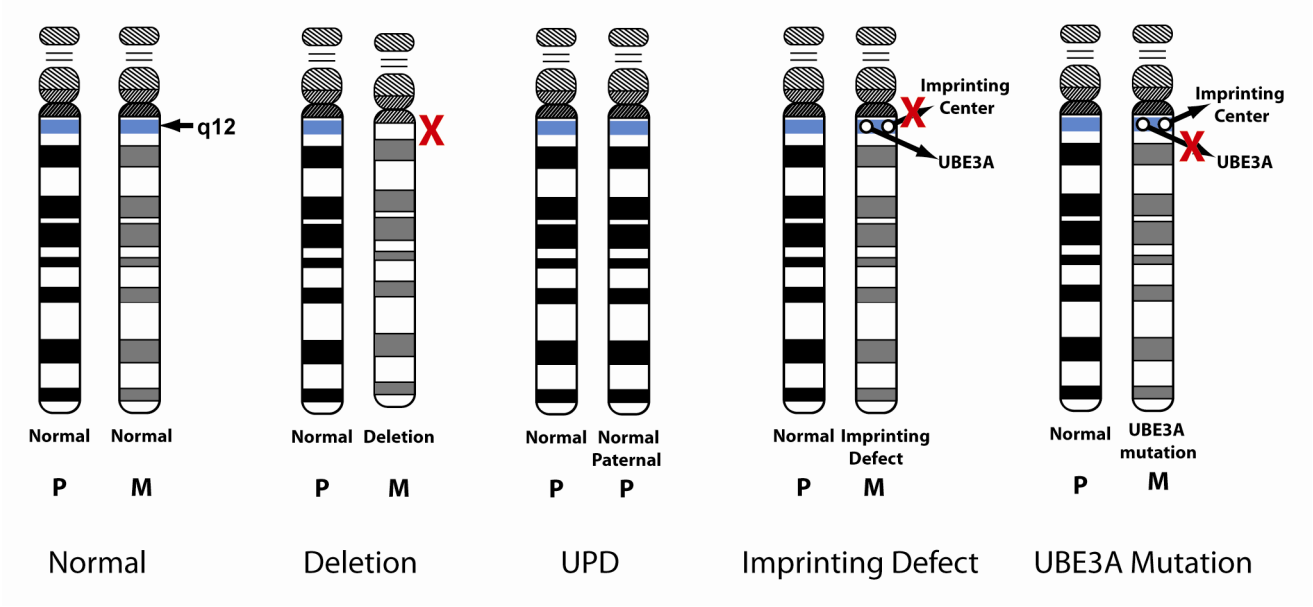
Associated (20 - 80%)

- Flat occiput
- Occipital groove
- Protruding tongue
- Tongue thrusting; suck/swallowing disorders
- Feeding problems and/or truncal hypotonia during infancy
- Prognathia
- Wide mouth, wide-spaced teeth
- Frequent drooling
- Excessive chewing/mouthing behaviors
- Strabismus
- Hypopigmented skin, light hair and eye color (compared to family), seen only in deletion cases
- Hyperactive lower extremity deep tendon reflexes
- Uplifted, flexed arm position especially during ambulation
- Wide-based gait with pronated or valgus-positioned ankles
- Increased sensitivity to heat
- Abnormal sleep wake cycles and diminished need for sleep
- Attraction to/fascination with water; fascination with crinkly items such as certain papers and plastics
- Abnormal food related behaviors

- Obesity (in the older child)
- Scoliosis
- Constipation

Genetic Mechanisms that Cause AS

In 1997, mutations in the gene, UBE3A located on chromosome 15, were identified as the cause of AS [11, 12]. All mechanisms known to cause AS either disrupt, inactivate or lead to absence of this gene on the maternally derived chromosome 15. There are several genetic "classes" or mechanisms that can disrupt UBE3A and thus cause AS [13, 14]. These mechanisms are depicted in this illustration.

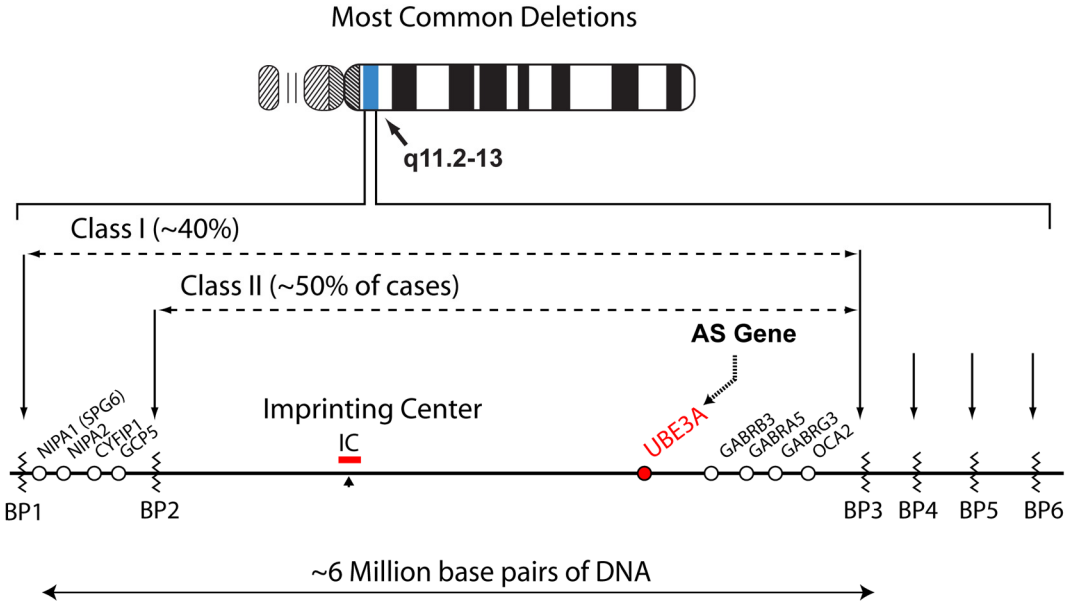


A chromosome 15 pair is illustrated for each mechanism and a normal chromosome pair is depicted on the left with a normal q12 chromosome region. P = paternally-derived chromosome and M = maternal derivation. AS can be caused by a large deletion of the maternal chromosome 15q12 region (where the active UBE3A gene resides). AS can also be caused by inheritance from the father of 2 paternal chromosomes; a phenomenon termed paternal uniparental disomy (UPD). Another cause, referred to as an imprinting defect (ID), occurs when the chromosome 15 inherited from the mother has the paternal pattern of gene functioning so that UBE3A expression is actually turned off. The IC is located some distance from the UBE3A gene but it is still able to regulate UBE3A by a complex mechanism that is the subject of intense research. Finally, AS can be caused by a mutation in the UBE3A gene on the maternally derived chromosome 15.

Mechanism	Frequency(%)
Deletion	~70
UPD	2-3
Imprinting defect	3-5
UBE3A mutation or deletion	5-10
Other chromosome Rearrangements	1-2
Unknown	10-15

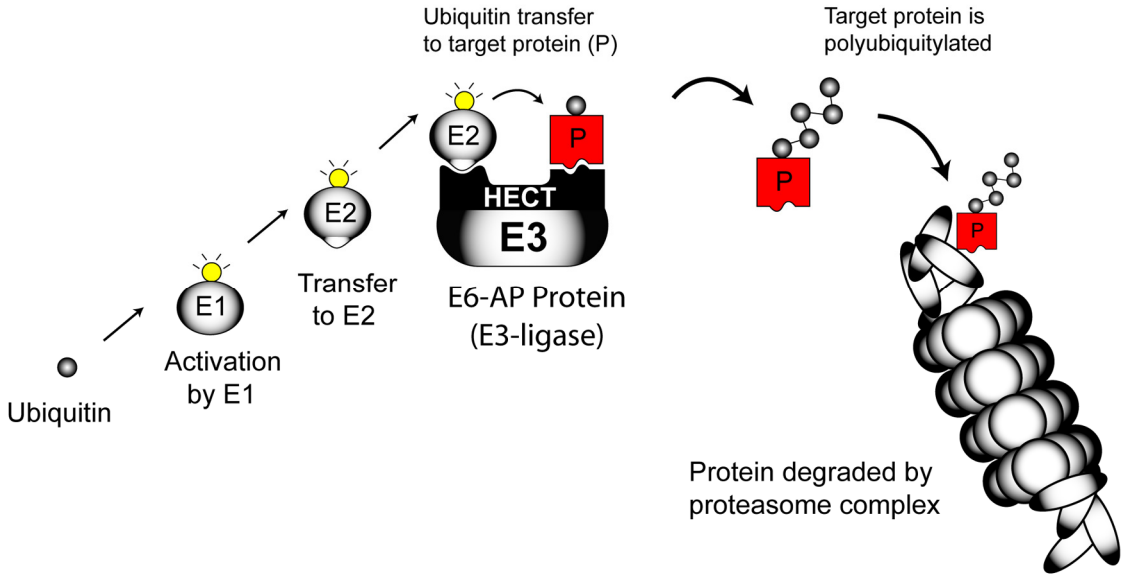
The table indicates the prevalence of each genetic mechanism and also notes that about 10-15% of individuals with the clinical features of AS actually will have normal genetic studies. At this time, it is unclear if these individuals have the correct diagnosis or if they have other yet-to-be-identified genetic defects that cause AS.

The most common genetic mechanism causing AS is the large chromosome deletion. The diagram explains more information about this. The typical deletion region is indeed large and spans about 6 million molecules (base pairs) of DNA. Most deletions extend from break point one (BP1) to either BP2 or BP3 and are termed class I or class II deletions. About 10% of the deletions extend further beyond BP3, for example, at site BP4. New methods of clinical testing such as array-based comparative genomic hybridization can distinguish between class I and class II deletions. However, the FISH test will not be able to determine this. All the large deletions remove UBE3A from the maternally derived chromosome. The deletions also remove additional genes as pictured (e.g., GABA receptor genes) but UBE3A deletion causes essentially all the problems associated with AS.



UBE3A and the Ubiquitin Pathway

The UBE3A gene makes the UBE3A protein (also called E6-AP) and this protein is an important component of the ubiquitin-proteasome pathway (pictured below). This pathway is extremely important to all cells, especially brain neurons. The pathway enables a small protein molecule, ubiquitin, to be attached to certain proteins, thereby causing them to be degraded [15]. Ubiquitin is a small protein (76 amino acids in length) that can be tagged onto other proteins in order to initiate their destruction. As pictured, E1 and E2 proteins activate (yellow) and transfer ubiquitin to E3. There are many different types of E3 proteins and UBE3A is one of them. UBE3A is able to chemically attach ubiquitin onto target proteins (red). Important in UBE3A's protein structure is the HECT domain, a molecular pocket that enables ubiquitin and the target protein to come into close proximity, allowing for attachment of the activated ubiquitin molecule [16]. Some protein targets for UBE3A are known but it is currently unknown which protein targets are linked to the precise brain dysfunction in AS. UBE3A is closely associated with neuronal synaptic function.



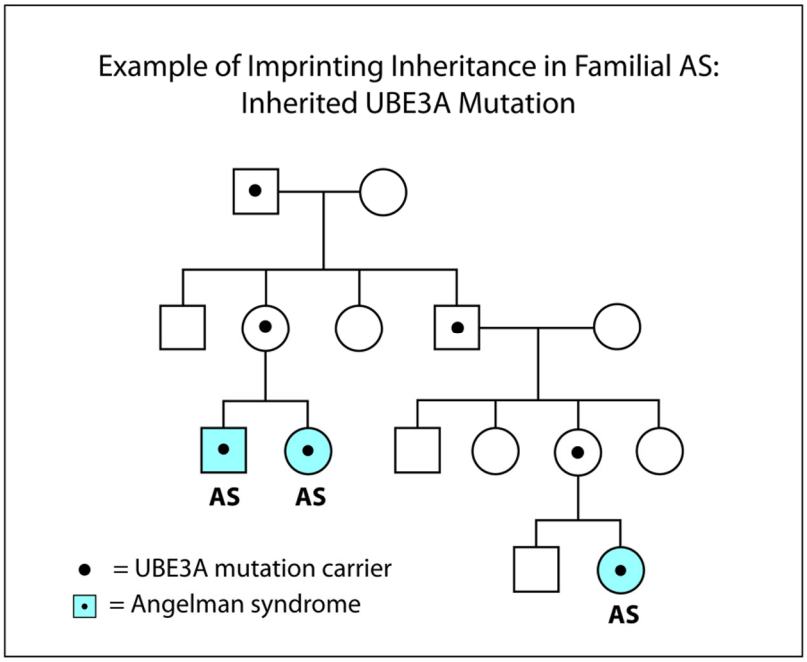
UBE3A and Imprinting

UBE3A is known to be "imprinted" in brain neurons [17]. This means that UBE3A gene from the paternally-derived chromosome 15 is almost completely *inactive* in many brain regions while the maternally-derived chromosome 15 gene is normally *active*. The brain neurons are normal even though they only have one active copy of the UBE3A gene. That chromosome deletions in AS occur only on the maternally-derived chromosome 15 indicate that UBE3A is active only on this chromosome, hence the deletion removes the only active copy of the gene. Disruptions of genes that are active on the paternally-derived chromosome 15 cause another developmental disorder, the Prader-Willi syndrome (PWS). PWS also involves imprinted gene(s) that are located close to but distinct from UBE3A. AS and PWS are quite unique because almost all other genetic disorders do not exhibit this type of imprinting effect.

The term "imprinting inheritance" can be difficult to understand. In order for an imprinted gene to be normally inherited and active on the correct parentally-derived chromosome (e.g., as occurs in normal individuals), there must be a mechanism for reversing the expression of genes at certain times of egg and

embryo development. For example, when a normal father produces sperm, regardless of whether the sperm end up having the maternally or paternally derived 15, all must now be "stamped" or "imprinted" so that their UBE3A genes will be turned off. The opposite occurs in the normal mother, whose eggs must have all their UBE3A genes turned on. Imprinted genes are thus capable of having their activity instructions erased and re-stamped.

The pedigree illustrates how imprinting inheritance can cause recurrence of AS in somewhat distantly related relatives. When a UBE3A mutation is inherited in a family, individuals who inherit the mutation may get AS but others can be normal! Inheritance of a UBE3A mutation from the father (top left of pedigree) has no detectable effect on his immediate children since he passed on an inactive UBE3A gene. It does not matter if this gene has a mutation since each of his immediate children also inherited a normal chromosome 15 (e.g., normal UBE3A gene) from their mother. However, should his carrier daughter transmit the UBE3A mutation to any child, it will have AS since that child would also get an inactivated UBE3A from her father so now there is essentially no UBE3A activity present. The same type of inheritance pattern can also be seen in some families with Imprinting Center defects. Refer to the Genetic Counseling page for more information.



Fortunately, most individuals with AS will have acquired their condition through a non-inherited, spontaneous mutation. This is the situation in almost all cases of the large common deletion and thus imprinting inheritance in not observed.

Genetic Mechanisms and Severity of Symptoms

In general, all of the AS genetic mechanisms lead to a somewhat uniform clinical picture of severe to profound mental retardation, 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 [18-24]. These correlations are broadly summarized below:

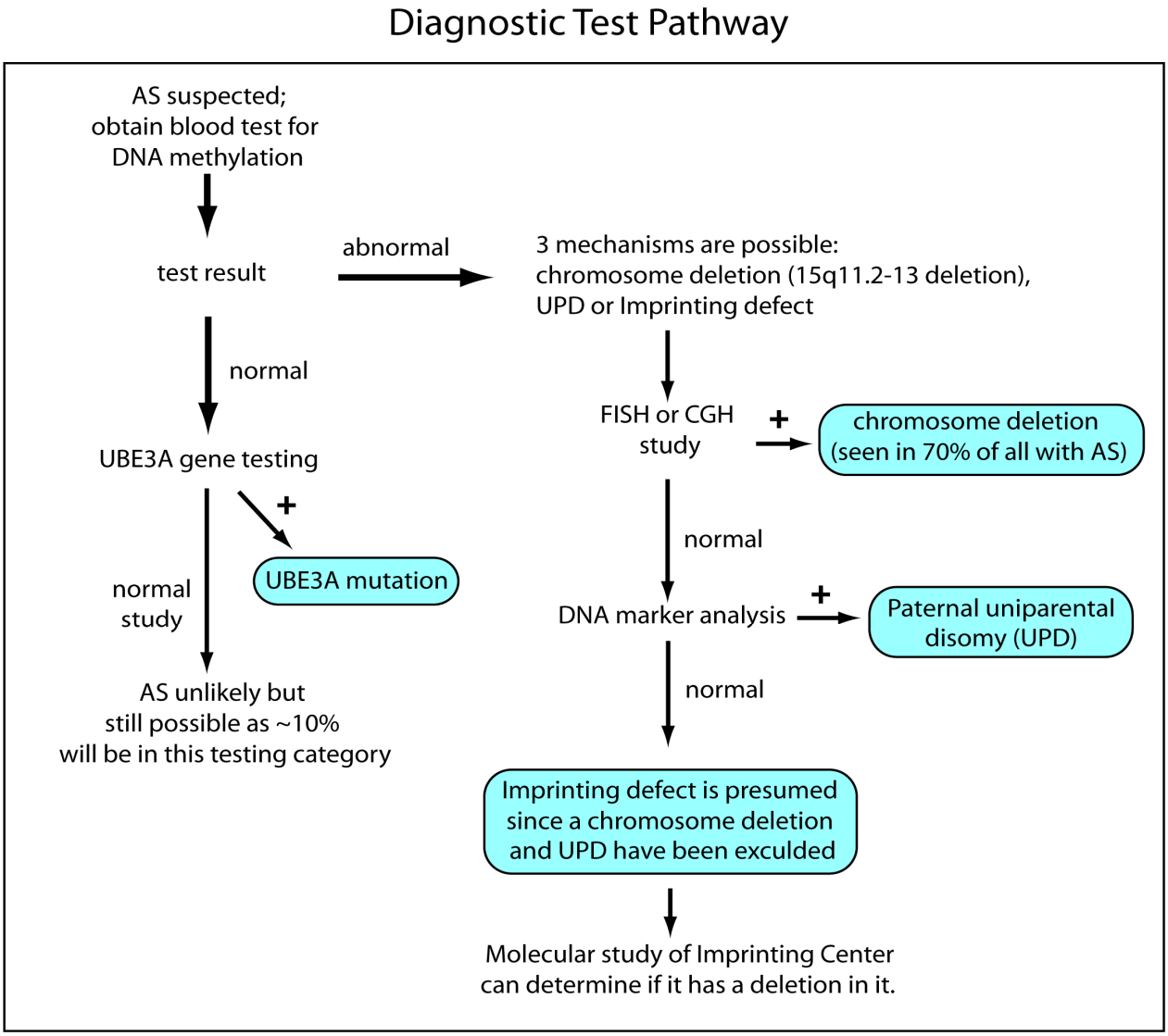
1. The deletion class is the most severely involved regarding microcephaly, seizures, relative hypopigmentation, motor difficulties (e.g., ataxia, muscular hypotonia, feeding difficulties), and cognition and language impairment.

2. UPD and ID individuals have better physical growth (e.g., less likely to have microcephaly) and have less movement and ataxia abnormalities and have a lower prevalence (but not absence) of seizures.

3. The ID group tends to have the highest cognitive, receptive language, fine motor, and gross motor abilities compared to other subtypes. The most advanced speech abilities occur in the ID group that is mosaic for the non-deletion imprint defect (about 20% of the ID group) [25]. These individuals may speak up to 50-60 words and use simple sentences.

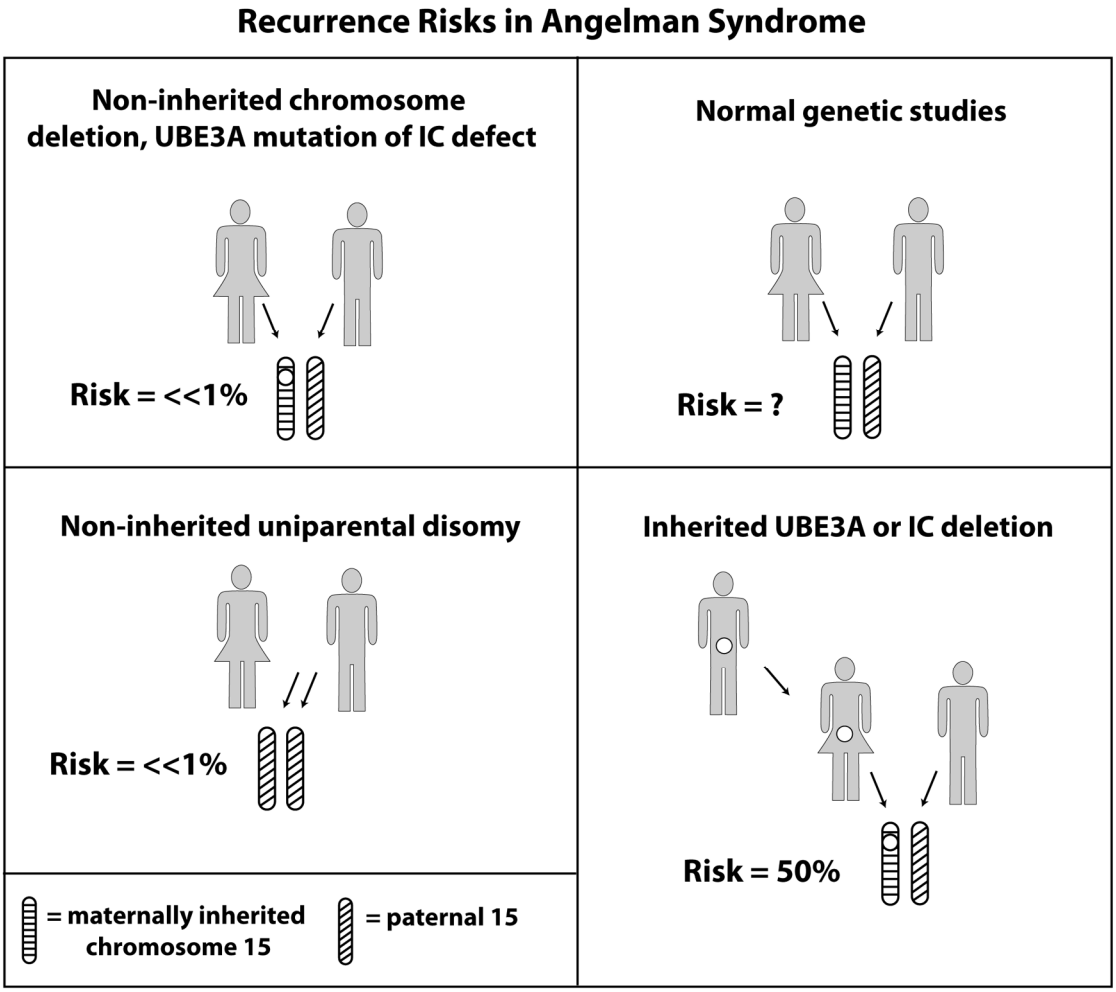
4. The UBE3A mutation group generally is intermediate between the deletion and the ID classes in terms of microcephaly, seizures, motor difficulties, and language ability. Some with UBE3A may have relatively high cognitive abilities, fine motor, and gross motor skills as presumably the effect of their mutation (e.g., location and type of DNA change within the gene) causes less severe clinical problems. ,

Genetic Diagnostic Testing



Laboratory diagnostic testing for AS can be complex. One approach to laboratory evaluation of an individual in whom the diagnosis of AS is suspected (above) starts with a DNA methylation analysis of the AS/PWS imprinting center region. The DNA methylation test is positive in AS when one of three mechanisms is present: the large common deletion, uniparental disomy, and defects in the imprinting center. If the methylation test is positive, additional studies are needed to define the specific genetic mechanism. In such situations, the next step typically is to perform a FISH (fluorescent in situ hybridization) chromosome test in order to see if the common 15q11.2-13 deletion is present (other methods can detect this deletion, such as array-based comparative genomic hybridization [CGH]). If the FISH test is normal, the next step is to rule out paternal uniparental disomy (UPD) by additional molecular testing involving parental bloods. Individuals with a positive AS DNA methylation study who have normal FISH and normal uniparental disomy studies are then presumed to have an imprinting defect. The imprinting defect can be further studied to determine if there is a DNA deletion involving the imprinting center. If the methylation test is negative, mutation analysis of the UBE3A gene may detect an abnormality. Molecular testing for IC region deletions is available clinically from a small number of laboratories.

Genetic Counseling and Recurrence Risk



The following aspects must be considered in understanding AS genetic risk. Because of the complexities of evaluating recurrence risk, genetic counseling from an expert familiar with AS is strongly advised. [26, 27]

1. Common chromosome deletion:

More than 98% of the chromosome deletion instances occur by a spontaneous event and thus they are not inherited; the recurrence risk is <<1% for these families. However, 1-2% of deletions occur because of an inherited abnormality in the maternal chromosome 15, such as a balanced chromosome translocation. Another very small group (e.g., only a few cases reported in the literature), can have AS due to a very small, maternally inherited chromosome deletion that involves a small area around and including the UBE3A gene. For these cases, the maternal recurrence risk is increased depending on the type of abnormality present. Chromosome study of the mother, including FISH, helps rule out inherited chromosome 15 abnormalities.

2. Paternal uniparental disomy (patUPD):

More than 99% of patUPD cases occur as an apparent spontaneous, non-inherited, event. If an individual has AS due to patUPD and has a normal karyotype, a chromosomal analysis of the mother should nevertheless be offered in order to exclude the rare possibility that a Robertsonian translocation or marker chromosome was a predisposing factor (e.g., via generation of maternal gamete that was nullisomic for chromosome 15, with subsequent post-zygotic "correction" to paternal disomy).

3. Imprinting Center (IC) Defect:

There are two types of IC defects: deletions and non-deletions. Non-deletion events do not appear to be inherited and have a <1% recurrence risk. Most deletions are not inherited but a significant proportion of them are (i.e., maternally inherited), and these confer a 50% risk for recurrence.

4. UBE3A mutations:

UBE3A mutation can either occur spontaneously (e.g., not inherited and with no increased recurrence risk) or be maternally inherited and have a 50% risk of recurrence (see below for imprinting inheritance).

5. Individuals with no known mechanism (all 4 above mechanisms have been eliminated):

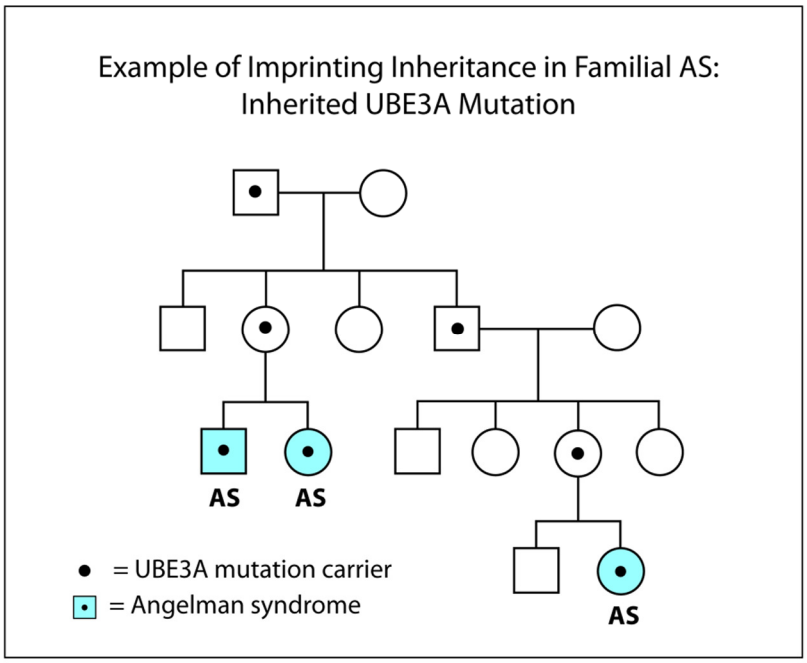
For parents of AS individuals who have apparent normal genetic tests (no evidence for deletion, imprinting defect, UPD or UBE3A mutation), and thus their children are only clinically diagnosed, it is not known what the recurrence risk is. An increased risk seems likely but probably does not exceed 10%.

6. Germ cell 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 germline cells of her ovary. Fortunately, germ cell mosaicism occurs very infrequently. Nevertheless, it has been observed in AS caused by the mechanisms of large chromosome deletion, Imprinting Center deletion and UBE3A mutation.

7. Imprinting inheritance:

UBE3A mutations and Imprinting Center deletions can exhibit imprinting inheritance wherein a carrier father can pass on the genetic defect to his children without it causing any problems, but whenever a female passes this same genetic defect on to her children, regardless of the sex of her child, that child will have AS. The pedigree diagram below illustrates imprinting inheritance. 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 the imprinting inheritance. 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 usually identify carriers of the gene defect. As you might imagine, professional genetic counseling is advised in these situations.



Hyperactivity

Hyperactivity is a very common behavior in AS and it is best described as hypermotoric. Essentially all young AS children have some component of this increased motor activity [28] and males and females appear equally affected. Infants and toddlers may have seemingly ceaseless activity, constantly keeping their hands or toys in their mouth, moving from object to object. In extreme cases, the constant movement can cause accidental bruises and abrasions. Grabbing, pinching and biting in older children have also been noted and may be heightened by the hypermotoric activity. Persistent and consistent behavior modification helps decrease or eliminates these unwanted behaviors.

In infants, the attention span can be short and social interaction is hindered because the AS child cannot seemingly attend to facial and other social cues. In childhood however attention abilities may increase, often associated with apparent curiosity as well. Attentiveness may then become sufficient to begin teaching sign-gesture language and other communication techniques. Observations in young adults suggest that the hypermotoric state decreases with age. Most AS children do not receive drug therapy for hyperactivity although some may benefit from use of such medications. Use of calming or sedating medications like Risperidone (Risperdal) is not generally advised but may be useful in rare 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.

Laughter and happiness

It is not known why laughter is so frequent in AS. More recently, advances in neuroimaging have assisted researchers in uncovering the cortical and subcortical regions of the brain that are associated with laughter in normal individuals. Specifically, the results of these studies indicate that the humor-processing pathway includes parts of the frontal lobe brain area, important for cognitive processing; the supplementary motor

area, important for movement; and the nucleus accumbens, associated with pleasure. The supplementary motor area is most involved in the motor aspects of humor (laughing and smiling). Recent neuroimaging studies show that increased activation in the supplementary motor area is correlated with laughter [29, 30], as is activation in the dorsal anterior cingulate area. Both of these regions receive rich dopamine input from the ventral striatum. A recent functional imaging study also showed that the cortical structures involved with humor and laughter include: the temporo-occipital junction, inferior frontal gyrus/temporal pole, and the supplementary motor area/dorsal anterior cingulate, all in the left hemisphere [31]. The same study also implicated that several subcortical structures, including the amygdala, ventral striatum/nucleus accumbens, ventral tegmental area, thalamus, and hypothalamus are also involved in humor and laughter. Taken together, the results suggest that the left hemisphere plays a distinct role in the humor processing pathway, and subcortical, dopaminergic structures play an important role in humor and laughter.

Studies of the brain in AS, using MRI or CT scans, have not shown any defect suggesting a site for a laughter-inducing abnormality. Recent neuroimaging studies in deletion positive patients with AS do reveal some abnormalities within the humor processing pathway. Specifically, individuals with AS exhibit reduced volume in the nucleus accumbens as well as the globus pallidus within the left hemisphere, and these regions are associated with both the reward mechanisms associated with humor/laughter as well as the motor aspects of laughter. The results of diffusion tensor imaging studies also reveal abnormalities (reduced fiber density and coherence) within white matter pathways in the limbic system in patients with AS, as well as prefrontal regions, and differences in the fibers projecting to and from the internal capsule that may account for difficulties with the regulation of laughter. The results of magnetization transfer imaging studies reveal differences in the thalamus (fibers projecting to/from the thalamus) that could also account for some of these difficulties[32]. 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. Although AS children experience a variety of emotions, apparent happiness predominates.
The first evidence of this distinctive behavior may be the onset of early or persistent social smiling at the age of 1-3 months. Giggling, chortling and constant smiling soon develop and appear to represent normal reflexive laughter but cooing and babbling are delayed or reduced. Later, several types of facial or behavioral expressions characterize the infant's personality. A few have pronounced laughing that is truly paroxysmal or contagious and “bursts of laughter” occurred in 70% in one study [28]. More often, happy grimacing and a happy disposition are the predominant behaviors. In rare cases, the apparent happy disposition is fleeting as irritability and hyperactivity are the prevailing personality traits; crying, shrieking, screaming or short guttural sounds may then be the predominant behaviors.

Mental Deficiency and Developmental Testing

Developmental testing is compromised in AS individuals due to attention deficits, hyperactivity and lack of speech and motor control. In such situations, test results are invariably in the severe to profound range of functional impairment. It is possible however that the cognitive abilities in AS are higher than indicated from developmental testing. Nevertheless the developmental delay is still consistently in the functionally severe range and formal psychometric testing seem to indicate a ceiling for developmental achievement at around the 24-30 month range [33-35]. In general, Angelman syndrome individuals have relative strengths in nonverbal reasoning skills and with social interactions that are based on non-verbal events.

As we learn more about the different genetic classes of AS it appears that patients with the common chromosome deletion type of AS have relatively more severe developmental impairment. [21, 36] Older

individuals with AS have been evaluated in terms of their adaptive functioning and the table, adapted from Summers and Pittman, lists some aspects of these studies [37].

Studies of Adaptive Functioning in AS

Study and Details	Findings
Smith et al., 1996 [38] Ages 3-34 years, all had deletions	Teenager and adults were all dependent on assistance with feeding, toileting and dressing
Moncla et al., 1999 [23] Ages 15-36 years; compared deletion to non-deletion cases	Vast majority with deletions were dependent on assistance for feeding, toileting and dressing; majority of non-deletion cases did not need assistance for dressing and feeding
Clayton-Smith, 2001 [39] Adults 20-53 years; not in institutions and 82% had deletions	85% could perform a simple task such as holding a utensil 50% helped to undress themselves 57% remained dry during the day (clock-trained) and 11% overnight
Sandanam et al, 1997 [40] Adult 24-36 years, all in institutions and all had deletions	All were dependent for activities of daily living

Many young adults with AS learn to respond to personal cues and interactions. Because of their interest in people, they express a broad repertoire of feelings and sentiments and form close bonds/attachments to others. Individuals with AS participate in group activities, household chores and in the activities and responsibilities of daily living. Like others, they enjoy most recreational activities such as TV/movies, listening to music, physical activity, going to the beach, etc. There is a wide range, however, in the developmental outcome so that not all individuals with AS attain the above noted skills. A few will be more impaired in terms of their mental retardation and lack of attention, and this seems especially the case in those with difficult to control seizures or those with extremely pronounced ataxia and movement problems. Fortunately, most children with AS do not have these severe problems, but even for the less impaired child, inattentiveness and hyperactivity during early childhood often give the impression that profound functional impairment is the only outcome possible. However, with a secure home and consistent behavioral intervention and stimulation, the AS child begins to overcome these problems and developmental progress occurs.

Autism and Related Traits

Some of the associated clinical features of AS (e.g. hand-flapping, stereotypic behaviors, deficits in expressive language), overlap with certain features of autism. Generally speaking, clinicians should exercise caution when examining symptoms of autism within AS, because some AS patients have been mistakenly identified as having autism in lieu of AS [41], and some patients who exhibit features of autism when they are younger, may no longer exhibit these features as their cognition and their language skills improve.

There are, however, some studies that specifically examine the frequency and magnitude of autistic traits in individuals with AS. While some researchers demonstrate a lack of autistic traits or very low incidence of autism in individuals with AS [42, 43], several other studies have demonstrated that a percentage of individuals with AS do also meet criteria for autism [34, 35, 44]. Individuals with AS and co-morbid autism are more likely to show decreased eye gaze, fewer social overtures, use fewer nonverbal gestures, use another person's body as a "tool" to communicate "for" them, have decreased shared enjoyment in interactions, and fewer socially directed vocalizations [34, 44].

In considering the differences in findings and clinical opinions across these studies, it is important to note that differences in sample selection, including differences in autism symptom severity across molecular subtypes of AS play a major role. Specifically, recent studies demonstrate that it is primarily deletion positive individuals with AS that exhibit greater symptom severity associated with autism, and within the deletion positive group, primarily children with larger, Class 1 deletions [45] [46]. Most recent findings indicate that these differences in symptoms of autism between the deletion subgroups are not related to differences in cognition (i.e. children with greater symptom severity were not necessarily lower functioning).

To summarize, studies seem to indicate that severity of autism symptoms in AS only affects a small proportion of AS patients, is associated with deletion size, and with a more aloof/withdrawn behavioral phenotype. There are four genes (*NIPA 1*, *NIPA 2*, *CYFIP1*, & *GCP5*) missing in Class I and present in Class II deletions (refer to diagram in Genetic Mechanisms that Cause AS section), one or more of which may have a role in the development of socialization skills and symptoms related to autism. For the small percentage of patients with AS who do exhibit more features of co-morbid autism, specific therapies such as applied behavioral analysis are quite helpful.

Repetitive behaviors (e.g. using objects or toys inappropriately), sensory interests (licking/mouthing, sniffing objects), and stereotypic motor movements (rocking, hand-flapping) are common to all individuals with AS and do not differentiate between those individuals who also have co-morbid autism [34, 44, 47]. In fact, some individuals with AS do exhibit some compulsions, rituals (e.g. hoarding, hiding of food or objects, food fads), and repetitive interests/playing with unusual objects [48]. These behaviors are primarily noted in older, and/or higher functioning individuals with AS and do seem to overlap with behaviors associated with Prader-Willi Syndrome; but the degree to which these associated behaviors are prevalent across the different molecular subclasses of individuals with AS has not yet been investigated. Additionally, the degree to which these behaviors may be responsive to pharmacological treatment has also not been investigated in formal clinical trials.

Speech and Language

Some AS children seem to have enough comprehension to be able to speak, but in even the highest functioning, conversational speech does not develop. Clayton-Smith [49] reported that a few individuals spoke 1-3 words, and in a survey of 47 individuals, Buntinx et al.[28] reported that 39% spoke up to 4 words, but it was not noted if these words were used meaningfully. Children with AS caused by uniparental disomy may have higher verbal and cognitive skills; at times use of 10-20 words may occur, although pronunciation may be awkward [18]. Finally, it is now clear that some AS individuals with a mosaic imprinting defect can have use of many words (up to 50 or 60) and a few of them can speak in simple sentences [25].

The speech disorder in AS has a somewhat typical evolution. Babies and young infants cry less often and have decreased cooing and babbling. A single apparent word, such as "mama," may develop around 10-18 months but it is used infrequently and indiscriminately without symbolic meaning. By 2-3 years of age, it is clear that speech is delayed but it may not be evident how little the AS child is verbally communicating; crying and other vocal outbursts may also be reduced. By 3 years of age, higher functioning children with AS are initiating some type of non-verbal language and use nonverbal gestures as a way in which to compensate for their expressive language deficits. Some point to body parts and indicate some of their needs by use of simple gestures, but they are much better at following and understanding commands. Others, especially those with severe seizures or extreme hyperactivity, cannot be attentive enough to achieve the first stages of communication, such as establishing sustained eye contact. The nonverbal language skills of AS children vary greatly, with the most advanced children able to learn some sign language and to use such aids as picture-based communication boards. Please refer to the section in this document on Communication for more details about the language and communications abilities, and the therapy approaches, for those with AS.

Communication

All children with AS communicate, some more effectively than others. [50, 51] Communicative attempts occur frequently in conjunction with individuals' overall desires to socially interact with others, an area of relative strength. When they are unable to communicate effectively, children may resort to problem behaviors such as pulling hair, pushing, hitting and biting to express their wants, needs, and feelings. It is important to recognize the vast majority of these behaviors are communicative attempts that occur when individuals lack access to other more conventional and socially appropriate methods of expressing themselves. [52] We can expect to see these behaviors fade once individuals learn alternative means of conveying the same intents, such as gestures and other forms of Augmentative and Alternative Communication (AAC). Children have no further need to scream if activating a message on a communication device results in the same desired outcome (e.g. gaining a teacher's attention) more efficiently and with less effort. Behavior problems more often reflect others' inabilities to provide children with effective and appropriate methods of communication than intrinsic limitations of the children.

Still all individuals with AS demonstrate communication difficulties to some extent. Problems in this area have implications for most aspects of education and daily living and should thus be a focal point in all instructional programs. Communication skills are critical in order for children to access the general education and special education curriculums and participate actively throughout the day. Whether we are referring to physical education, reading, writing (e.g. with line drawings), art, music, lunch, or science, all of these events have corresponding communication demands that must be met for students to be full participants. It is thus essential that speech-language pathologists (SLPs) are available to other educators to problem solve communication strategies needed for children to be included throughout the day.

Communication challenges are especially evident in individuals with large deletions of the 15th chromosome. Those whose problems are linked to other genetic mechanisms, such as uniparental disomy and imprinting defects, typically exhibit stronger communication skills, both expressively and receptively, and more favorable prognoses for communication and language development. [53] Irrespective of the underlying genetic mechanism, children with Angelman Syndrome are often unable to acquire and use speech as a primary method of communication. However, interventions including efforts to improve speech

may be appropriate in some cases, particularly for individuals exhibiting genetic mechanisms other than large deletions, as some of these children may acquire a modest inventory of words and even phrases. [52, 53] Oral motor programs with other populations have yielded marginal results in terms of generalization to improvements in speech. There are no current studies documenting the efficacy of oral motor training for children with AS.

Given their poor prognoses for speech, individuals with AS need other means of expressing themselves. AAC systems may include unaided (e.g. gestures and signs) and aided (e.g. communication boards and various speech generating devices [SGDs]) methods that together constitute a multimodal system of communication. No one AAC system is appropriate for all individuals with AS and systems that are ideal for one individual may be of limited use to others.

Children with Angelman Syndrome usually self-select gestures as their preferred method of communication. [50] Most of these behaviors, particularly early in their development, consist of 'contact gestures' which are dependent on physical contact with people and objects in order to be conveyed. Examples include pulling a parent by the hand toward a desired item that is out of reach or pushing away a non-preferred object offered to them. Distal gestures appear later and represent more abstract means of communication. These include extending their hands and arms to indicate a desire to be picked up and pointing toward a desired object that is out of reach. The vast majority of individuals with AS have an inventory of natural gestures they are able to use functionally, especially when interacting with familiar people. These natural gestures can be modified to express a greater range of meanings more clearly and effectively using a system of Enhanced Natural Gestures, or, ENGs. [51]

In light of their natural propensity to use gestures, communication interventions often rely on teaching individuals to use sign language. While they may indeed acquire anywhere from a few to more than a hundred signs, based heavily on the underlying genetic mechanism, individuals' motor problems often cause them to modify and distort targeted signs. This poses difficulty for others, particularly unfamiliar listeners, to understand. Listeners who are knowledgeable about sign language but not the versions of signs produced by some individuals may also encounter difficulty when interacting with these individuals. For this reason enhanced natural gestures (ENGs), which are by definition understandable to familiar as well as unfamiliar listeners, are often a preferred method of communication. [51]

Most individuals with AS supplement their gestures/signs with one or more types of aided communication. [50] They may use systems of tremendously varying complexity, ranging from touching a preferred object to make a request, selecting one of eight photographs to request a corresponding activity, or using a rather sophisticated electronic communication display with 50 or more pictures, photographs, line drawings, words and/ or other symbols to meet many of their daily communication demands. There are dozens of communication devices available; the identification of the 'right' system for a particular individual requires a comprehensive AAC evaluation by trained professionals. It is essential to match each individual's skills, capabilities, and immediate as well as long range needs to what is available and what is necessary to implement them effectively, using a process referred to as feature matching.

As indicated earlier, most children with AS, particularly those with deletions, do not acquire functional speech. Many parents report their child used words such as "mama" and "more" early on but these words later dropped out. Individuals' difficulties acquiring speech result from a combination of factors that include motor problems, such as low tone in the oral area, structural anomalies such as a protruding tongue;

intellectual disabilities, and possible apraxia. Efforts to teach speech to children with deletions have in most cases yielded marginal gains. Those presenting different genetic mechanisms offer better but still guarded prognoses. While no such investigations have been conducted on individuals with AS, those involving other populations have consistently found AAC does not hinder the development of speech. To the contrary, speech is generally fostered following introduction of AAC. It is extremely important to introduce AAC instruction as early as possible in conjunction with other early intervention services.

There have been several reports of individuals with AS demonstrating stronger abilities comprehending language than producing it. [50, 54] For example, many individuals have been reported able to understand simple commands and sentences even though they are unable to express such content. However variations appear in the literature, with some investigators failing to note consistent differences in individuals' production vs. comprehension of language. [55] Analyses of expressive language have demonstrated individuals with AS most often use language to *mand* (i.e. request desired objects and activities and/or reject undesired ones). Instances of *tacting* (e.g. labeling and describing) and echoing (i.e. imitation) are rare. [33] The difficulty with imitation suggests a need to proceed cautiously when relying on this method to teach communication and related skills.

While all individuals with AS experience difficulties with communication, the severity of these problems vary greatly among individuals with the same or different underlying genetic mechanisms. It is thus essential to maintain high expectations and give all individuals every opportunity to communicate. Communication skills can be maximized by early and ongoing interventions, including those carried out by experts in AAC. Interventions should target enabling individuals to communicate more effectively with a broad range of partners in various natural settings. A child's ability to communicate with his speech-language pathologist in a therapy room has little significance compared to the child's ability to demonstrate this same skill with teachers and peers in classrooms, playgrounds and other settings.

Communication services are best implemented through a combination of direct therapy and consultation. Direct therapy should always be accompanied by systematic probes designed to verify skills observed in therapy are generalizing to other settings as well. For example, an SLP may want to work on turn taking. In addition to direct time spent with the child, the SLP might ask the student's Aide to monitor and collect data on the child's application of this skill (i.e. turn taking) when she has opportunities and reasons to use it in real-life situations. For example, does the student wait her turn in going up to the blackboard? Does she wait her turn as objects are passed from one child to the next during circle time? Does she wait her turn as she stands in line and passes through the food line in the school cafeteria? Similarly, the SLP might teach the student to reject unwanted objects by gently pushing them away. The SLP would collaborate with the Aide and others to identify reasons and opportunities for the student to use this skill naturally and monitor whether or not the student is indeed doing so. For example, during art class the student might reach for and look at one of several crayons out of her reach. A peer might be asked to purposely offer her a differently colored crayon, setting up an opportunity for the student to push it away and repeat her initial request. (Please refer to the 'Education' section of this document for additional examples, and references, of how communication and other related skills can be integrated across the curriculum and throughout the school day).

In summary, it is essential that speech-language pathologists, parents, teachers, peers, employers and others collaborate to maximize individuals' abilities to communicate functionally and thus participate actively in their communities. Children need multiple means of communication and knowledge of when to use one

method vs. another depending on particular situations. Educators must understand that communication instruction must not be reserved for therapy rooms but should instead be targeted throughout the day. Themes such as membership, participation, and inclusion should be pervasive in all attempts to foster communication skills. It is through communication that children will establish and maintain friendships and networks of support that will be available throughout their lives.

Sleep Disorders

Parent reports and recent studies indicate that decreased need for sleep and abnormal sleep/wake cycles are common in AS [47, 56, 57]. An AS child, with abnormal sleep/wake cycles, has been reported to benefit from a behavioral treatment program [58]. Administration of a low dose of melatonin one hour before bedtime has also been shown to be of help in some children but this should not be given in the middle of the night if the child awakens [59]. Use of sedatives such a chloral hydrate or diphenylhydramine (Benadryl) may be helpful if wakefulness excessively disrupts home life. Some families construct safe but confining bedrooms to accommodate disruptive nighttime wakefulness. There are also many AS infants and children who apparently sleep fairly well and do not receive any sleep-related medications.

Sexuality

During adolescence, puberty may be delayed by 1-3 years but sexual maturation occurs with normal development of secondary sexual characteristics. Postpubertal females with AS are fertile and pregnancy has been reported [60].

The main issues associated with sexual development in normal individuals have an important component as well in the lives of those with AS. The general approach to consideration of sexual issues in the AS is to recognize the 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 some of the issues of importance.

Sexual education is problematic but important to the child with AS. Educational themes might address emphasis on body parts and on private and public components, differences between boys and girls, issues of how babies are made, understandings regarding acceptable social behaviors, and continued reinforcements and instruction about relationship boundaries. Individuals with developmental handicaps 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 some individuals with AS because of their outgoing personality and fondness of hugging or otherwise wanting to be close to others.

Since seizures are known to be affected by a menstrual periods, some individuals may require adjustment of seizure medications.

Providing medical contraception may be important in some situations. For females, the contraceptive methods are the ones employed in the normal population and may involve oral contraceptives or progesterone only injections (Depo-Provera shot given once every three months) and other methods.

Currently there is no report of a male with Angelman reported to have conceived a child although it appears that that is theoretically possible.

Gynecological care is advisable by age 21 years to include a breast and pelvic examination. If a pelvic exam is not possible, ultrasound of pelvic organs may be indicated. Menstrual hygiene is a concern and education should stress identifying body parts, hygienic habits such as washing hands, and of course this must be done in the most basic way due to the cognitive impairments of those with AS.

Seizures

More than 90% of individuals with AS are reported to have seizures but this may be an overestimate because medical reports tend to dwell on the more severe cases. Less than 25% develop seizures before 12 months of age. Most have onset before 3 years, but occurrence in older children or in teenagers is not exceptional. The seizures can be of any type (i.e. major motor involving jerking of all extremities; absence type involving brief periods of lack of awareness), and may require 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[36, 61, 62].

There is no agreement as to the optimal seizure medication although valproic acid (Depakote), topiramate (Topamax), lamotrigine (Lamictal), levetiracetam (Keppra), and clonazepam (Klonopin) are more commonly used in the North Amereica. Carbamazepine (Tegretol), ethosuximide (Zarontin), phenytoin (Dilantin), phenobarbital, and ACTH are less commonly used. Vigabatrin (Sabril), an inhibitor of GABA metabolism, should not be used. [63] Single medication use is preferred but seizure breakthrough is common. Some children with uncontrollable seizures have been placed on a ketogenic diet, and this may be helpful in some cases. Children with AS are at risk for medication over-treatment because their movement abnormalities or attention deficits can be mistaken for seizures and because EEG abnormalities can persist even when seizures are controlled.

Central Nervous System Structure

Individuals with AS are generally thought to have normal imaging studies although occasional abnormalities have been reported that probably are coincidental findings. The most common MRI or CT change, when any is detected, is mild cortical atrophy (i.e. a small decrease in the thickness of the cortex of the cerebrum) and/or mildly decreased myelination (i.e. the more central parts of the brain appear to have a slight degree of diminished white matter)[64, 65]. Several detailed microscopic and chemical studies of the brain in AS have been reported but the findings generally have been nonspecific or the number of cases has been too few to make meaningful conclusions.

A recent study using advanced neuroimaging techniques (diffusion tensor imaging [DTI], quantitative magnetic resonance imaging [MRI], and magnetization transfer ratio [MTR] imaging) revealed abnormalities in deletion positive individuals with AS [32, 66]. The DTI studies reveal significant differences between AS patients and controls for white matter pathways involving the frontal, temporal, parietal, and limbic areas. Those with AS had reduced white matter fiber density and coherence in these respective regions. Results of MTR, a measure of white matter integrity, showed differences between individuals with AS and controls in the global pallidus, thalamus, frontal white matter, and left temporal regions. Differences

in these regions appear to correlate with the language, cognitive, motor, and behavioral difficulties associated with AS. Quantitative MRI study, after controlling for total brain size, showed that those with AS had reduced white matter volumes in the cerebellum, cerebrum, hippocampus, accumbens, caudate, and corpus callosum. There was also subtle cortical thinning in gray matter in temporal, frontal, and occipital regions, primarily in the left hemisphere. The same regions are associated with increased cortical folding/gyrification. Findings in these regions appear to correlate with the clinical/behavioral anomalies (e.g., reduced hippocampal volume corresponds to lower cognitive and memory skills, reduced cerebellar volume corresponds to increased stereotypic behaviors, reduced fiber density and coherence in limbic regions corresponds to impairments in social communication and play).

These findings demonstrate that deletion positive AS patients exhibit microstructural changes in white matter fiber tracts that affect the development, wiring, and targeting of axons that link affected brain regions. They also exhibit reduced volume in brain regions that appeared to contribute to the clinical phenotype observed. It has not yet been determined if these abnormalities are present in other molecular subtypes of AS but it seems reasonable to expect that they will be.

Gastrointestinal Issues and Oral-motor Behaviors

Feeding problems are frequent but not generally severe and usually manifest early as difficulty in sucking or swallowing [67-69]. Tongue movements may be uncoordinated with thrusting and generalized oral-motor incoordination. There may be trouble initiating sucking and sustaining breast feeding, and bottle feeding may prove easier. Frequent spitting up may be interpreted as formula intolerance or gastroesophageal reflux. The feeding difficulties often first present to the physician as a problem of poor weight gain or as a "failure to thrive" concern. Infrequently, severe gastroesophageal reflux may require surgery.

AS children are notorious for putting everything in their mouths. In early infancy, hand sucking (and sometimes foot sucking) is frequent. Later, most exploratory play is by oral manipulation and chewing. The tongue appears to be of normal shape and size, but in 30-50%, persistent tongue protrusion is a distinctive feature. Some have constant protrusion and drooling while others have protrusion that is noticeable only during laughter. Some infants with protrusion eventually have no noticeable problem during later childhood (some seem to improve after oral-motor therapy). For the usual AS child with protruding tongue behavior, the problem remains throughout childhood and can persist into adulthood. Drooling is frequently a persistent problem, often requiring bibs. Use of medications such as scopolamine to dry secretions usually does not provide an adequate long term effect. Surgical procedures to ameliorate drooling are possible [70] but apparently rarely used in AS.

Gait and Movement Disorders

Hyperkinetic movements of the trunk and limbs have been noted in early infancy [69] and jitteriness or tremulousness may be present in the first 6 months of life. Voluntary movements are often irregular, varying from slight jerkiness to uncoordinated coarse movements that prevent walking, feeding, and reaching for objects. Gross motor milestones are delayed; sitting usually occurring after age 12 months and walking often delayed until age 3 to 5 years [28, 67].

In early childhood, the mildly impaired child can have almost normal walking. There may be only mild toe-walking or an apparent prancing gait. This may be accompanied by a tendency to lean or lurch forward. The tendency to lean forward is accentuated during running and, in addition, the arms are held uplifted. For these children, balance and coordination does not appear to be a major problem. More severely affected children can be very stiff and robot-like or extremely shaky and jerky when walking. Although they can crawl fairly effectively, they may "freeze up" or appear to become anxious when placed in the standing position. The legs are kept wide-based and the feet are flat and turned outward. This, accompanied by uplifted arms, flexed elbows and downward turned hands, produces the characteristic gait of AS. Some children are so ataxic and jerky that walking is not possible until they are older and better able to compensate motorically for the jerkiness; about 10% may fail to achieve walking. [9] In situations where AS has not been diagnosed, the nonspecific diagnosis of cerebral palsy is often given to account for the abnormal walking. Physical therapy is helpful in improving ambulation and sometimes bracing or surgical intervention may be needed to properly align the legs.

Surgical Procedures and Anesthesia

There are several literature reports of individuals with AS undergoing general anesthesia without any difficulties. Also, the experience reported by many parents on the web and from parent meetings is generally favorable regarding successful general anesthesia and other aspects of surgical intervention. Some scientific reports mention concern for those who have the deletion mechanism (present in 70% of those with AS) because these individuals also have a deletion of 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 also appears to occur relatively normally. For example, rather significant surgical interventions of scoliosis repair with rod replacement and bone grafting is not uncommon to be well tolerated in those with AS.

There have been recent reports of bradycardia in individuals with AS and the presumption has been that these rhythm problems were due to increased activity of the vagus nerve [71-73]. These reports are somewhat 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 seems unclear if individuals with AS have an increased risk for cardiac rhythm disturbances. Anesthesiologist should certainly be aware of these case reports however and of the possibility that agents that increase vagal tone may not be well tolerated in individuals with AS.

A final note should be made about seizures since precautions are always advised whenever someone with a seizure disorder undergoes general anesthesia or undergoes any type of operative procedure. At this point, it appears that the usual precautions that would be given for anyone with a seizure disorder would as well apply to someone with AS. The surgical procedure or the anesthesia event itself does not necessarily lead to an exacerbation of seizures and AS. This is not to say that a surgical procedure will not be complicated by the onset of seizures since that is always a possibility and it is generally known that significant health events predispose to exacerbation of seizures whether one has AS or any other type of seizure condition.

Temperature Sensitivity?

Increased sensitivity to outdoor or indoor temperatures has been mentioned on web chat sites and at AS parent meetings. These problems include apparent increased warmth to the skin or increased irritability and hyperactivity when a child with AS is in a warm room or in a room without air conditioning. In these situations, a bona fide fever (e.g., high core body temperature) is rarely ever observed. Individuals with AS appear to sweat normally and thus it appears that they are able to adequately cool themselves. It may be that the apparent increased sensitivity to heat is the result of a neuro-vascular or neuro-sensory phenomenon that affects only the microcirculation of the skin surface. This is only speculation however. At this time it seems fair to conclude that those with AS may have increased sensitivity to heat but it is uncertain if this is a problem unique to AS or if it is something observed in other conditions involving developmental delay.

Occasionally, a hypothermia event has been noted, often in the context of multiple medication use or associated with a common medical illness. In these observances, the core body temperature has been documented to be abnormally low. In these cases (which are very rare) it appears that the hypothermia is not a recurrent or chronic problem and it usually resolves in a day or two.

Physical Growth

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 (absolute microcephaly means having a head circumference in the lower 2.5 percentile). The prevalence of absolute microcephaly varies from 88% [67] to 34% [74] and may be as low as 25% when non-deletion cases are also included. [9] 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 normal children but most AS children will plot within the normal range. Final adult height has ranged from 4 foot 9 inches to 5 foot 10 inches in a series of 8 adults with AS. Familial factors will influence growth so that taller parents have AS children that tend to be taller than the average AS child. During infancy weight gain may be slow due to feeding problems but by early childhood most AS children appear to have near normal subcutaneous fat. In later childhood obesity can occur [49]. Food-related behaviors (e.g., eating non-food items, apparent increased appetite, increased behavioral orientation to food) are common in AS [48] and may contribute to obesity onset. Some weight gain can occur during young adulthood and obesity can be a management concern. Severe (e.g., morbid) obesity is a very uncommon occurrence in AS.

Hypopigmentation, Strabismus and Ocular Albinism

When AS is caused by the large deletion, skin and eye hypopigmentation usually result. This occurs because there is a pigment gene (the P gene, also termed OCA2), located close to the AS gene, that is also missing [75]. This pigment gene produces a protein that is believed to be crucial in melanin synthesis. Melanin is the main pigment molecule in our skin. In some children with AS, this hypopigmentation can be so severe that a form of albinism is suspected[76]. When AS is caused by the other genetic mechanisms, this gene is not missing and thus normal skin and eye pigmentation is seen. Children with AS who have hypopigmentation are sun sensitive, so use of a protective sun screen is important. Not all AS children with deletions of the P gene are obviously hypopigmented, but may only have relatively lighter skin color than either parent.

Surveys of individuals with AS demonstrate an increased incidence of strabismus. This problem appears to be more common in children with hypopigmentation (as above), since pigment in the retina is crucial to normal development of the optic nerve pathways. Management of strabismus in AS is similar to that in other children: evaluation by an ophthalmologist, correction of any visual deficit, and where appropriate,

patching and surgical adjustment of the extraocular muscles. The hypermotoric activities of some AS children will make wearing of patches or glasses difficult but many are able to accomplish this.

Education

As indicated elsewhere in this document, children with Angelman Syndrome (AS) present many unique physical, social, educational, cognitive, and communicative challenges which require interventions to be comprehensive in nature and scope. Educators, including teachers and related service providers (e.g. occupational therapists, physical therapists, speech-language pathologists), must have sufficient expertise in the area of severe disabilities (in general) and Angelman Syndrome (in particular) to meet these challenges and provide appropriate educational programs. Students' individualized programs should be aligned with the general education curriculum to the greatest extent possible, consistent with federal regulations (IDEA: Individuals with Disabilities Education Act).

Also consistent with IDEA, education should occur in the Least Restrictive Environment (LRE) in which individualized and appropriate instruction can be provided. For many students, this is a general education classroom where they learn along with children without disabilities. Other students may spend part of their day in a resource room, moving between this setting and the general education classroom. Other options include a self-contained classroom, where students are grouped with other children with special needs, and a separate school for children with special needs.

Decisions about the most appropriate placement for students with AS should follow much deliberation among the team, including the family. No particular placement is optimal for every student with AS. The appropriate placement is the least restrictive environment in which the student's needs can be effectively met and in which there are reasonable expectations the child can make meaningful progress. It is essential that students' educational needs and corresponding goals are determined first, with discussions about placement following. We must not work in reverse, determining where a child will be placed and then building goals around that placement. Finally, irrespective of where a student spends most of his or her time, whether it be an inclusive or a self-contained classroom, it is important that administrators and all staff share a common mission for all students, those with as well as those without disabilities. [77]

For children receiving some or all instruction in general education classrooms, it is essential that necessary types and levels of support are made available not only to students but also classroom teachers. This entails systematic and ongoing collaborations between special educators and general educators, with additional input from related service providers and, of course, parents. The team determines curriculum modifications and special accommodations that are necessary to meet each child's instructional needs. These are based on comprehensive evaluations conducted by a diagnostic team at school and/or in a specialized center. Families should play a central role in the selection of assessment instruments, interpretation of results and, perhaps most importantly, selection of instructional goals. [78] Educators should engage parents in discussions

about visions and dreams for their children post-graduation. [79] Educational goals should be aligned with these aspirations, irrespective of students' educational placements.

The resulting educational program should be conceived in a manner that enables students to derive benefit and demonstrate reasonable educational gains in relation to the general education curriculum. At the same time, it must also provide sufficient opportunities to address other skills noted in the child's Individual Education Plan (IEP) or, in the case of early intervention programs, Individual and Family Service Plan (IFSP).

Children with AS typically require a variety of related services, most commonly physical therapy, occupational therapy, and communication therapy (particularly Augmentative and Alternative Communication). It should be kept in mind that educators are expected to provide programs that are *appropriate* and not, necessarily *ideal.* Additional services such as adapted physical education, therapeutic recreation, behavioral interventions, music therapy, aquatics, and hippotherapy may be appropriate on a case by case basis. Related services enhance children's abilities to access and participate actively in the general education curriculum. This usually requires significant modifications of classroom instruction; academic expectations; and dual emphases on academic learning and the acquisition of functional skills (e.g. indicating food preferences to a cafeteria employee).

Children with AS typically require one on one instructional support from an aide or paraprofessional. Aides should work under the direction of general education and special education teachers, and related service providers. Although Aides may carry out programs, it is the responsibility of other professionals (Teachers, SLPs, etc.) to determine what is to be worked on, when, and in what manner and to monitor aides' implementation of programs on a regular basis. Similarly, although Aides may collect performance data, it is the responsibility of teachers and others to interpret these data and then make additional program recommendations.

Aides must be used in that capacity, as Aides, and not as teachers or other specialists. This requires sufficient levels of support from other staff. Team input is critical in identifying accommodations and modifications that must be made for students' frequent laughing, hypermotoric behavior, shortened attention span, and other disabilities commonly seen in AS. Modifications should also play into children's strengths, which often include a pleasant disposition, interest in people and social interactions; movement, and active engagement.

Calculator and others provide rationale as well as practical strategies for targeting students' IEP goals in the context of the general education curriculum using integrated models of service delivery in the classroom and other natural settings. [80-83] For example, rather than pulling a child out of the classroom to work on 'walking' in a therapy room, the Physical Therapist consults with the Aide and teachers and instructs them, through role release, how to foster acquisition of this skill in the context of the child's getting from one meaningful location to another. This could involve walking from the classroom to the gym for a PE class or navigating around the playground during recess. Similarly, rather than working with a speech-language pathologist on a choice making program, the Aide, teachers and others are taught and encouraged to instead integrate opportunities for children to make meaningful choices such as with whom they wish to play, whom they wish to be seated next to, and where they wish to play, throughout the day. Dressing skills can be worked on when the child arrives and leaves school and needs to put on and take off a coat, uses the bathroom, and changes in and out of gym clothes for a physical education class.

In order for an integrated model to be effective, assistive technology such as mobility aides and AAC devices must be available to students and educators at all times. Assistive technology needs are determined by multiple team members who seek to maximize students' independence and participation in a full range of meaningful activities throughout the day. School personnel should be trained how to use and maintain this equipment in good working order.

As discussed in another section of this document, Applied Behavior Analysis (ABA) has been found to be an effective instructional method for many children with AS. Programs employing other teaching methods, such as those found in general education instruction, often incorporate behavioral methods such as reinforcement, modeling, shaping, multiple trials, and so forth. Skills targeted should be appropriate chronologically and developmentally. [84-86] For example, puzzles intended for preschoolers should be used with preschoolers and not older children despite their perhaps being perceived to exhibit skills typically associated with preschool aged children. For example, an adolescent who is learning to make meaningful choices might be given an opportunity to select one of two books a classmate is prepared to read to him/her during silent reading, rather than choosing between bubbles and a pinwheel in a play setting.

Academic skills should be supplemented with attention paid to fostering independence and self-determination (i.e. students having maximum control over their lives, making choices and decisions). Whenever possible, functional skills should be integrated within the curriculum, as previously discussed.

Students with AS usually require high levels of assistance, such as physical prompting, when learning new skills. Verbal prompts should be kept to a minimum as these are very difficult to fade and often result in children's overly relying on them in order to act. This is referred to as prompt dependence. The goal should always be spontaneous behavior, with minimal reliance on prompts and cues.

Many children with AS demonstrate difficulties orienting to and then sustaining attention on task. This relates directly to students' levels of active engagement, interest and motivation. Unless instructional content and delivery appeal to students, and they value the consequences of this instruction, students may be distracted and/or seek stimulation elsewhere. Conversely, when meaningfully and actively engaged in activities as active, and not passive, learners students with AS can remain on task for up to an hour or more. The use of picture schedules and other aids that cue students to transitions from one activity to the next are often helpful in keeping students oriented and on task.

Amounts and rates of learning vary greatly in students with AS. Some students may complete school still highly dependent on others in most life skills, using relatively simple communication aids that enable them to express basic wants and needs, with a limited range of leisure interests, and requiring high levels of support to participate in their communities. Other students, particularly those without large deletions, may possess life skills that enable them to be more independent at school, home, and in the community, with less reliance on prompts and other external supports. They may utilize complex voice output communication aids (i.e. speech generating devices) to express hundreds of different meanings with a variety of listeners in numerous settings. Regardless of the severity of their disabilities, employment and a happy life can be a goal for all individuals with AS, so long as the necessary types and levels of support are readily available.

Finally, it is important that educators, families, and others set and maintain high expectations for all students with AS. It is preferable to provide students with opportunities to experience and succeed rather than withholding instruction in anticipation of failure.

Adult Health and Life Expectancy

Young adults with AS continue to learn and are generally not expected to have deterioration in their mental abilities. 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 child with AS ages, often associated with concerns about obesity. Individuals with AS who have severe ataxia may lose their ability to walk if ambulation is not encouraged. Scoliosis can develop in adolescence and is especially a problem in those who are non-ambulatory [36, 49]. Scoliosis is treated with early bracing to prevent progression, and surgical correction or stabilization may be necessary for severe cases.

The main adult problems in those with AS are essentially continuation of problems present in childhood. These include problems of seizure control, difficult behaviors and abnormal physical movements. The movement problems cover areas of ataxia, diminished ambulation and scoliosis. 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 health problem. The good news regarding adult health in AS is that many health matters are the same as those encountered in the normal population.

It does not appear that there is any major neurodegeneration event and that the brain per se (as determined by MRI) is able to withstand chronic seizure problems without obvious morphologic changes. There appears to be no apparent increased risk for malignancy or tumor problems and it appears that if longevity is diminished, it is only to a mild extent. Life span does not appear to be dramatically shortened in AS but may be decreased by 10-15 years. There are reports of AS individuals living beyond 70 years although there is as of yet no actuarial data that estimates life span [87, 88]. Hopefully, the results of a current study on natural history, funded by NIH, will provide important information in the near future.

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