Angelman syndrome (AS) is a neurodevelopmental disorder characterised by severe learning difficulties, ataxia, a seizure disorder with a characteristic EEG, subtle dysmorphic facial features, and a happy, sociable disposition. Most children present with delay in developmental milestones and slowing of head growth during the first year of life. In the majority of cases speech does not develop. Patients with AS have a characteristic behavioural phenotype with jerky movements, frequent and sometimes inappropriate laughter, a love of water, and sleep disorder. The facial features are subtle and include a wide, smiling mouth, prominent chin, and deep set eyes. It is caused by a variety of genetic abnormalities involving the chromosome 15q11-13 region, which is subject to genomic imprinting. These include maternal deletion, paternal uniparental disomy, imprinting defects, and point mutations or small deletions within the UBE3A gene, which lies within this region. UBE3A shows tissue specific imprinting, being expressed exclusively from the maternal allele in brain. The genetic mechanisms identified so far in AS are found in 85-90% of those with the clinical phenotype and all interfere with UBE3A expression.

In 1965, Harry Angelman, an English paediatrician, reported the clinical findings in three children with similar features of severe learning disability, ataxic, jerky movements, inability to speak, and easily provoked laughter. All three had epileptic seizures with a characteristic EEG appearance and subtle dysmorphic facial features. This condition, originally known as the “happy puppet” syndrome, is now known by the less pejorative term of Angelman syndrome. For over 20 years it was considered a rare disorder, and although the occurrence of families with affected sibs suggested a genetic aetiology, no known cause could initially be identified. In 1987 Magenis et al identified a deletion of chromosome 15q11-13 in two patients with Angelman syndrome and subsequent work has shown that Angelman syndrome can be caused by a variety of genetic mechanisms which involve this imprinted region of the genome. All of these mechanisms affect maternal expression of the UBE3A gene which lies at the 15q11-13 locus. In recent years clearer delineation of the clinical phenotype of Angelman syndrome and improved diagnostic testing has led to improved recognition of the condition and the incidence of Angelman syndrome is now estimated to be between 1 in 10 000 and 1 in 40 000.  

Studies of the specific cognitive and behavioural features associated with AS and of the seizure disorder have improved management of the condition and provided insight into the long term outlook for affected patients. Molecular genetic studies have begun to elucidate the role of genes within the 15q11-13 region in the pathophysiology of Angelman syndrome and have also shed light on the more general phenomenon of genomic imprinting. We review the clinical features, natural history, and current management of the condition and summarise the complex genetic mechanisms involved.

**Clinical features**

The original patients reported by Angelman all had severe learning disability, epileptic seizures, ataxia, absent speech, and dysmorphic facial features with a prominent chin, deep set eyes, wide mouth with protruding tongue, and microcephaly with a flat occiput. They were also hypopigmented with fair hair and blue eyes (fig 1). Although many patients with AS have these characteristics, it is now clear that the clinical spectrum of Angelman syndrome is much broader than was originally thought. Many patients are normally pigmented and some have a normal head circumference. Seizures are not present in every case and some speech may be present. Some patients may not have the characteristic dysmorphic facies and have minimal ataxia. Several patients with AS are able to speak, although speech is always limited. The behavioural features seen in AS are perhaps the most consistent clinical feature. It is necessary, therefore, to have a wide index of clinical suspicion in a child with the behavioural phenotype of the condition as described below. A summary of the main clinical features and their frequencies is given in table 1.

**Behavioural characteristics**

The behavioural characteristics of AS are striking and it is these which often prompt clinicians to consider the diagnosis. They are present in all patients irrespective of the type of genetic abnormality. Paroxysms of easily provoked laughter begin within the first few weeks of life and almost all patients are happy and smile frequently. Laughter is usually provoked, but the stimulus is often minimal and the laughter can be inappropriate. Hyperactivity and sleep disturbance are...
common in childhood and can pose major management problems. The sleep disorder can be improved by behaviour therapy with adherence to a strict bed time regimen and by the use of melatonin, which is effective in around 50% of patients. People with Angelman syndrome love water and have a fascination for reflective surfaces, plastic, and balloons. They enjoy being in the company of others and watching TV, especially slapstick humour. With progression into adulthood the behaviour becomes quieter and concentration span increases. The sociable disposition still persists and paroxysms of laughter may occur. Some adults have shown a tendency to aggressive behaviour, especially if frustrated because of difficulty with communication.

**COMMUNICATION AND SELF HELP SKILLS**

Communication difficulties are a prominent feature of Angelman syndrome. Speech does not develop and most AS patients have a vocabulary of only two or three words. Most patients will be able to understand simple commands within the context of their daily routine. A minority can communicate using a formal sign language such as Makaton or the Picture Exchange Communication System (PECS). Others use gestures to communicate. Some patients have been able to use augmented communication devices (for example, Dynavox) to good effect and acquisition of communication skills is often easier as patients get older and concentration span improves. Difficulties with communication can lead to frustration. Speech is present in a few patients (see Phenotype/genotype correlation), but even these will have difficulty in understanding complex commands and lack capacity for abstract thought.

Self-help skills in Angelman syndrome vary. Most patients learn to walk and to communicate their likes and dislikes. They can make choices, for example, regarding the food they eat and the clothes they wear. Help is needed with dressing and bathing, though undressing is easier. Toilet training is possible and about a third of patients will be dry by day, fewer
particularly atypical absences or myoclonic seizures. A large number of adults have epileptic seizures, although there may be a decreasing frequency of epileptic seizures with age, and tonic seizures to status epilepticus. Absence status and tonic status are raised and held flexed at the wrists and elbows. Hand flapping is common when walking and if excited. Muscle tone is abnormal with truncal hypotonia and hypertonicity of the limbs and reflexes are brisk. Thoracic scoliosis occurs in approximately 10% of children but is a major problem in the majority of adult patients. It may require orthopaedic treatment by physiotherapy or bracing and although these may be sufficient to resolve the scoliosis in some patients, in other patients the deformity is progressive and surgery is required. Many patients with AS have jerky movements and a discrete tremor of the fingers owing to cortical myoclonus. This phenomenon is worsened by stress and is more pronounced in adults, some of whom develop increasing tremor.

**SEIZURES IN ANGELMAN SYNDROME**
Epileptic seizures occur in 80% of patients. Age at onset varies between one and five years. The initial presentation of the epilepsy is with febrile convulsions in infancy. In childhood a variety of seizures can be observed, ranging from tonic-clonic seizures, atonic absences, complex partial, myoclonic, atonic, and tonic seizures to status epilepticus. Absence status and myoclonic status may also occur. Earlier reports suggested a decreasing frequency of epileptic seizures with age, but further follow up has shown that although there may be a relatively quiescent period during late childhood and adolescence, a large number of adults have epileptic seizures, particularly atypical absences or myoclonic seizures. The epilepsy of Angelman syndrome is difficult to control with anti-epileptic drugs, especially in childhood. The most effective drugs are sodium valproate or lamotrigine or in combination with clobazam or other benzodiazepines. Carbamazepine sometimes has an adverse effect. In adults, phenobarbitone is also effective. Experience with the newer antiepileptic drugs is very limited.

**NEUROLOGICAL FEATURES OF ANGELMAN SYNDROME**
All AS patients have severe mental retardation and delayed motor milestones. They sit unsupported at around 12 months, crawl (commando style) or bottom shuffle at 18-24 months, and walk at a mean age of 4 years (range 18 months to 7 years). The gait is slow, stiff legged, and ataxic and the arms are raised and held flexed at the wrists and elbows. Hand flapping is common when walking and if excited. Muscle tone is abnormal with truncal hypotonia and hypertonicity of the limbs and reflexes are brisk. Thoracic scoliosis occurs in approximately 10% of children but is a major problem in the majority of adult patients. It may require orthopaedic treatment by physiotherapy or bracing and although these may be sufficient to resolve the scoliosis in some patients, in other patients the deformity is progressive and surgery is required. Many patients with AS have jerky movements and a discrete tremor of the fingers owing to cortical myoclonus. This phenomenon is worsened by stress and is more pronounced in adults, some of whom develop increasing tremor.

**EEG FINDINGS IN ANGELMAN SYNDROME**
There are specific EEG patterns in AS patients which appear in isolation or in different combinations. They are similar in patients both with and without seizures. In childhood the three characteristic patterns are (1) persistent rhythmic 4-6/s activity reaching more than 200 μV, not associated with drowsiness, (2) prolonged runs of rhythmic (triphasic) 2-3/s activity with an amplitude of 200-500 μV, maximal over the frontal regions and normally mixed with spikes or sharp waves, and (3) spikes mixed with 3-4/s components, usually of more than 200 μV mainly posteriorly and facilitated by or only seen on eye closure. In patients over 10 years of age the background rhythm is slower than normal. There may be focal spikes and intermittent or continuous triphasic delta activity (fig 2), maximal over the frontal regions. There is no correlation between the EEG findings and the paroxysms of laughter seen in AS. The EEG features are specific to AS and are an important diagnostic feature. Unfortunately, these three components may not always be seen within the same EEG recording and may occur at different times in the same patient. It is therefore worth repeating the EEG if the diagnosis of AS is strongly suspected but the typical features are not seen initially.

**ANGELMAN SYNDROME IN ADULTS**
The phenotype of Angelman syndrome is an evolving one which changes with progression into adulthood (fig 3). Puberty occurs at a normal time and there are normal secondary sexual characteristics. Facial characteristics in adults are more pronounced with marked mandibular prognathism, pointed chin, macrostomia, and a prominent lower lip. Eyes appear more deeply set and in some patients keratoconus (because of eye rubbing) is observed. Mobility decreases because of limb hypertonicity, development of thoracic scoliosis, and a general reluctance to walk. Some patients develop contractures and in those with reduced mobility ataxia is less obvious. Many patients become obese and oesophageal reflux may occur and can be severe. Despite these problems a good quality of life is maintained into adulthood and in the majority of patients lifespan is not greatly reduced.

**GENETICS OF ANGELMAN SYNDROME**
There are four major genetic mechanisms which are now known to cause Angelman syndrome and AS patients have been divided into classes I to IV based on these mechanisms. A further group of patients, designated class V, have clinical features of AS but no demonstrable cytogenetic or molecular abnormality of chromosome 15q11-13. A summary of the

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**Table 1 Main clinical characteristics of AS**

<table>
<thead>
<tr>
<th>Consistent (100%)</th>
<th>Frequent (more than 80%)</th>
<th>Associated (20–80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe developmental delay</td>
<td>Delayed, disproportionate growth in head circumference, usually resulting in microcephaly by age 2</td>
<td>Flat occiput</td>
</tr>
<tr>
<td>Speech impairment, no or minimal use of words, receptive and non-verbal communication skills higher than verbal ones</td>
<td>Seizures, onset usually &lt;3 years of age</td>
<td>Occipital groove*</td>
</tr>
<tr>
<td>Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs</td>
<td>Characteristic EEG with large amplitude slow spike waves and triphasic waves</td>
<td>Promoting tongue</td>
</tr>
<tr>
<td>Behavioural uniqueness†</td>
<td>Tongue thrusting, suck/swallowing disorders</td>
<td>Tongue thrusting, suck/swallowing disorders</td>
</tr>
<tr>
<td>any combination of frequent laughter/smiling, apparent happy demeanour; easily excitable personality, often with hand flapping movements; hypermetric behaviour; short attention span</td>
<td>Feeding problems during infancy</td>
<td>Excessive chewing/mouthing behaviours</td>
</tr>
<tr>
<td>All AS patients have severe mental retardation and delayed motor milestones.</td>
<td>Cognitive impairment with IQ usually below 50</td>
<td>Strabismus</td>
</tr>
<tr>
<td>They sit unsupervised at around 12 months, crawl (commando style) or bottom shuffle at 18-24 months, and walk at a mean age of 4 years (range 18 months to 7 years).</td>
<td>Hypopigmented skin, light hair and eye colour (compared to family), seen only in deletion cases</td>
<td>Hypopigmented skin, light hair and eye colour (compared to family), seen only in deletion cases</td>
</tr>
<tr>
<td>The gait is slow, stiff legged, and ataxic and the arms are raised and held flexed at the wrists and elbows. Hand flapping is common when walking and if excited.</td>
<td>Hyperactive lower limb deep tendon reflexes</td>
<td>Hyperactive lower limb deep tendon reflexes</td>
</tr>
<tr>
<td>Muscle tone is abnormal with truncal hypotonia and hypertonicity of the limbs and reflexes are brisk. Thoracic scoliosis occurs in approximately 10% of children but is a major problem in the majority of adult patients.</td>
<td>Uplifted, flexed arm position especially during ambulation</td>
<td>Uplifted, flexed arm position especially during ambulation</td>
</tr>
<tr>
<td>Many patients with AS have jerky movements and a discrete tremor of the fingers owing to cortical myoclonus. This phenomenon is worsened by stress and is more pronounced in adults, some of whom develop increasing tremor.</td>
<td>Increased sensitivity to heat</td>
<td>Increased sensitivity to heat</td>
</tr>
<tr>
<td>SEIZURES IN ANGELMAN SYNDROME</td>
<td>Sleep disturbance</td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Epileptic seizures occur in 80% of patients. Age at onset varies between one and five years. The initial presentation of the epilepsy is with febrile convulsions in infancy. In childhood a variety of seizures can be observed, ranging from tonic-clonic seizures, atonic absences, complex partial, myoclonic, atonic, and tonic seizures to status epilepticus. Absence status and myoclonic status may also occur. Earlier reports suggested a decreasing frequency of epileptic seizures with age, but further follow up has shown that although there may be a relatively quiescent period during late childhood and adolescence, a large number of adults have epileptic seizures, particularly atypical absences or myoclonic seizures.</td>
<td>Attraction to/fascination with water</td>
<td>Attraction to/fascination with water</td>
</tr>
</tbody>
</table>

†The characteristic behavioural phenotype has been shown to be perhaps the most useful diagnostic marker for AS.

*Although emphasised particularly in Harry Angelman’s first description, we have not found this to be a particularly useful sign.


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various genetic mechanisms and their frequencies is shown in
Table 2 and a diagrammatic representation of the 15q11-13
region is shown in Fig 4.

The commonest genetic mechanism giving rise to Angel-
man syndrome, occurring in approximately 70-75% of
patients, is an interstitial deletion of chromosome 15q11-13.
The majority of deletions are of a similar size, approximately 4
Mb, and with common breakpoints. They are thought to occur
because of unequal crossing over between low copy repeats
duplicons) within the 15q11-13 region. The duplicons con-
tain the transcript of the HERC2 gene, a highly conserved gene
which, when mutated in mice, affects development and
fertility. Most deletions occur de novo and are of maternal
origin, in contrast to the 15q11-13 deletions observed in
Prader-Willi syndrome which are of paternal origin. The
common deletion can be detected by FISH analysis and by
methylation analysis of the SNRPN (small nuclear ribonucleo-
protein polypeptide N) promoter which lies within a CpG
island at 15q11-13. In the presence of a maternal deletion only
the paternal, unmethylated pattern will be detectable. Rarely,
patients with AS will have a different sized deletion, often in
association with an unbalanced translocation or chromosome
rearrangement. It is important to distinguish this group of
patients as the mother may carry the same chromosome rear-
rangement and therefore be at risk of having a further child
with AS. Several patients have been reported in whom a
supernumerary inv dup(15) was present in addition to a de
novo deletion of 15q11-13. It has been hypothesised that the
presence of such a marker predisposes to 15q11-13 deletion.
Cytogenetic analysis and FISH analysis to exclude cryptic
translocation should therefore be carried out on people with
AS where the families concerned have requested genetic
counselling.

A second class of AS patients, class II, have uniparental dis-
omy (UPD) for chromosome 15 and thereby fail to inherit a
maternal copy of UBE3A. The UPD is usually for the entire
chromosome and Robinson et al have studied in detail the
mechanisms by which it arises, concluding that in most cases
the error is postzygotic, although some cases have been shown
to arise through meiotic non-disjunction. Maternal and pater-
nal ages of patients with UPD are significantly higher than the
general population. This is likely to be responsible for a
higher rate of non-disjunction in patients where UPD has
arisen because of a meiotic error, but the mechanism by which
raised paternal age contributes to a postzygotic duplication of
chromosome 15 is unclear. In some cases UPD(15) arises in
association with a Robertsonian translocation or a reciprocal
translocation involving chromosome 15. The occurrence of
uniparental disomy is sporadic and accounts for only 2-3% of
cases of AS.

Class III patients are those without deletions or UPD, but
with abnormal chromosome 15 methylation, signifying a
defect in imprinting. Imprinting defects account for 3-5% of
patients with AS. This is the process by which epigenetic
Table 2 Genetic mechanisms giving rise to Angelman syndrome

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Methylation analysis*</th>
<th>Other diagnostic tests</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>De novo deletion</td>
<td>Abnormal</td>
<td>High resolution cytogenetics</td>
<td>70%</td>
</tr>
<tr>
<td>Ia</td>
<td>Deletion owing to chromosome rearrangement</td>
<td>Abnormal</td>
<td>FISH</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>II</td>
<td>Uniparental paternal disomy</td>
<td>Abnormal</td>
<td>High resolution cytogenetics</td>
<td>2%</td>
</tr>
<tr>
<td>IIIa</td>
<td>Imprinting defect owing to imprinting centre mutation</td>
<td>Abnormal</td>
<td>Screening of IC for mutations is positive</td>
<td>2%</td>
</tr>
<tr>
<td>IIIb</td>
<td>Imprinting defect without IC mutation</td>
<td>Abnormal</td>
<td>Screening of IC for mutations is negative</td>
<td>2%</td>
</tr>
<tr>
<td>IIIc</td>
<td>Mosaic imprinting defect</td>
<td>Abnormal</td>
<td>Screening of IC for mutations is usually negative</td>
<td>?</td>
</tr>
<tr>
<td>IV</td>
<td>UBE3A mutation</td>
<td>Faint maternal band</td>
<td>Screening of UBE3A for mutations</td>
<td>5–10%</td>
</tr>
<tr>
<td>V</td>
<td>No genetic abnormality identified</td>
<td>Normal</td>
<td>Consider other diagnoses</td>
<td>12–15%</td>
</tr>
</tbody>
</table>

Figure 4 The Angelman/Prader-Willi region on chromosome 15q11-13 which spans 4 Mb. The common breakpoints are represented by dashed lines. Paternally imprinted genes are depicted in blue and maternally imprinted genes in pink. Those depicted in white are not known to be imprinted. The imprinting centre (IC) is bipartite. The centromeric portion is responsible for the paternal to maternal imprint switch and deletions in this part cause AS. For further details see text.
Table 3  AS: differential diagnosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Useful investigations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22qter deletions involving 22q13.3</td>
<td>22qter FISH</td>
<td>Precht et al2</td>
</tr>
<tr>
<td>dup 15q11-13</td>
<td>Chromosome analysis, FISH test</td>
<td>Clayton-Smith et al22, Repetto et al23</td>
</tr>
<tr>
<td>del 2q22.q23</td>
<td>ZFH1X8 analysis</td>
<td>Schroer et al25</td>
</tr>
<tr>
<td>5p- Others: eq 17q23, 4q12, 4p15</td>
<td>FISH</td>
<td>Mowat et al22</td>
</tr>
<tr>
<td>Single gene disorders</td>
<td></td>
<td>Yamada et al23</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>MECP2 analysis, EEG</td>
<td>Laan et al23</td>
</tr>
<tr>
<td>Alphathalassaemia, retardation syndrome, (ATRX)</td>
<td>Hb inclusions, mutation/methylation studies of ATRX gene</td>
<td>Wilkie &amp; al21</td>
</tr>
<tr>
<td>Methyltetrahydrofolate reductase deficiency (MTHFR)</td>
<td>Urine amino acids for homocysteine</td>
<td>Arn et al23</td>
</tr>
<tr>
<td>Gurrieri syndrome</td>
<td>Ophthalmological examination</td>
<td>Battaglia and Gurrieri27</td>
</tr>
<tr>
<td>Heterogeneous neurodevelopmental disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>MRI of the brain</td>
<td>Laan et al25</td>
</tr>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>EEG</td>
<td>Loan et al5</td>
</tr>
<tr>
<td>Non-progressive encephalopathy</td>
<td></td>
<td></td>
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<tr>
<td>Childhood autism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pervasive developmental disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondrial encephalopathy</td>
<td>Blood/CSF lactate, MRI of the brain</td>
<td>Nissenkorn et al24</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial DNA studies</td>
<td></td>
</tr>
</tbody>
</table>


GENETIC COUNSELLING

Genetic counselling in AS families is complicated in view of the wide variety of genetic mechanisms which can all give rise to this condition. It is recommended that diagnostic investigation should begin with 15q11-13 methylation analysis, which is relatively inexpensive and will be abnormal in the majority of cases of AS. One can then move on to other tests to elucidate the specific genetic mechanism involved or to screen for UBE3A mutations in patients with suggestive clinical features, EEG, and normal methylation. An algorithm for genetic testing is shown in fig 5. Recurrence risks in AS will depend on the genetic mechanism involved and on whether the mother is shown to carry a genetic abnormality of 15q11-13. For patients with de novo deletions of 15q11-13 and uniparental disomy, recurrence risks are low, although there has been one reported incidence of recurrence owing to possible gonadal mosaicism.50-52 Where imprinting centre mutations and UBE3A mutations are concerned, the situation is complicated further by the high levels of gonadal mosaicism which appear to be present in the mothers.50-52 In these situations, even if the mother tests negative for a mutation identified in a child there is still an appreciable risk of recurrence owing to gonadal mosaicism and prenatal testing should be offered. If the mother carries the same mutation, the recurrence risk is 50%. Recurrence has been reported within families of class V patients and genetic counselling needs to reflect this. This group is likely to include some patients with X linked or autosomal recessive disorders. In some families prenatal diagnosis has been offered by haplotyping the fetus during a future pregnancy to determine whether the fetus has inherited the same maternal chromosome 15 as the affected child. However, this can only be offered in families where the clinical diagnosis of AS is very secure and parents should be made fully aware of the limitations of this type of testing.50-52

PHENOTYPE/GENOTYPE CORRELATION

Delineation of the different genetic mechanisms giving rise to AS has helped to explain some of the phenotypic differences between patient groups (fig 1).5 6 10 7274 It has been shown, for example, that patients with chromosome 15 deletions are in general the most severely affected. They have a higher incidence of seizures, microcephaly, and hypopigmentation,
Finally, milder AS phenotypes have been reported in patients with incomplete imprinting defects or mosaicism. Gillessen-Kaesbach et al described the clinical phenotype in seven AS patients who presented initially with features of the Prader-Willi syndrome but were subsequently shown to have a chromosome 15 methylation pattern in keeping with AS. These patients presented with hypotonia, obesity, and a milder degree of mental retardation. Methylation analysis in some of these patients showed an atypical pattern with only a faint maternal band. Tékin et al have also reported a patient with milder clinical features of AS who was proven to have mosaicism for a 15q11-13 deletion, which was detectable on fluorescence in situ hybridisation but where methylation analysis had proven normal.

**MANAGEMENT OF ANGELMAN SYNDROME**

The management of AS revolves around appropriate therapies for the physical and neurological problems encountered in this condition and provision for special educational needs, given the very specific cognitive profiles and behavioural features of the condition. In some cases AS patients have undergone courses of intensive therapies similar to the conductive education which has been carried out in many children with cerebral palsy. While some children undergoing this type of treatment have shown short term improvement, for example, in mobility and communication, there are no data as yet to suggest that this will offer long term benefit in Angelman syndrome. There is evidence from parents, albeit anecdotal, that massage and aromatherapy can improve hyperactivity and concentration. The UK study suggested that AS people appear to need continuous reinforcement of their skills if they are not to lose them. Treatment of the epilepsy in AS is often difficult, especially in the early years, and the advice of a paediatric neurologist should be sought. Seizures can take many forms and taking a short video clip of suspected seizures to show to the neurologist is helpful. AS children have global developmental problems, but the most marked problem is with acquisition of language. No single communication method works best in AS so every attempt should be made to find a communication system which works for an individual AS child. There remain some children who have very limited communication skills however much input they receive from parents and therapists. AS children have relatively good social skills and fit in well with others within their peer group. Their inherent inquisitiveness and childhood hyperactivity can be improved by a consistent approach, with help from a behavioural therapist if necessary. In adults with recent onset of behavioural problems the possibility of oesophageal reflux should be considered.

**ANGELMAN SYNDROME RESOURCES**

A large amount of knowledge has been gathered over the last 10 years about the clinical features, natural history, and genetic mechanisms involved in Angelman syndrome. Studies of the condition have also been carried out by a variety of professionals involved in the management of patients with AS. Many countries worldwide now have support groups for those with AS and their families and these groups have produced a large amount of information on different aspects of the condition and have in many cases been instrumental in bringing together parents and professionals involved in the care of AS people. An international umbrella organisation now exists (www.iaso.com) and can guide parents and professionals to a variety of AS resources and information about the individual national AS groups. ASSERT, the UK support group, has a free telephone line for parents and a professional helpline.

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**Figure 5** Simple algorithm for genetic testing in Angelman syndrome.

1. **In practice blood is usually taken for methylation analysis and FISH analysis at the same time. In some laboratories FISH analysis is not undertaken until the results of the methylation analysis are known.**

2. An abnormal result is where the methylation analysis shows an absent or reduced maternal band.

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greater delay in motor milestones, and absent speech. The more severe features are thought to be the result of haploinsufficiency for a number of genes within the 15q11-13 region. Minassian et al suggested that the severe epilepsy seen in AS patients with deletions is the result of the absence of one copy of the GABA receptor genes. The locus for the P gene which is implicated in type II oculocutaneous albinism also lies within this region. Recent studies have shown that AS deletion patients with hypopigmentation frequently have a mutation of the P gene on the remaining chromosomal homologue and some patients have the characteristic ocular findings of albinism with misrouting of optic nerve fibres at the optic chiasm. Patients with uniparental disomy of chromosome 15 have a low incidence of seizures, microcephaly, and hypopigmentation. Many of these patients are able to say a few words and their growth parameters are also greater than the deletion group, often being in the upper half of the normal range. Dysmorphic features are less obvious in this group, although the behavioural characteristics are quite typical. AS subjects with imprinting defects are less likely to have microcephaly, hypopigmentation, or seizures and, again, they are more able than the deletion group with less delay in motor milestones and better communication skills. Growth is better than in deletion patients and obesity is relatively common within this group. The abilities of patients with UBE3A mutations fall somewhere in between those of the deletion group and the UPD group. They frequently have seizures and microcephaly but are not hypopigmented and have better motor and communication skills than the deletion group. Lossie et al pointed out that this group have a particularly high frequency of obesity as they get older.


Clayton-Smith, Jahn

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