What is Angelman Syndrome?
Angelman Syndrome (AS) is a non progressive neuro-genetic disorder named after an English paediatrician, Dr. Harry Angelman, who first described the syndrome in 1965. A syndrome is number of features which occur together as a group and indicate a particular condition. AS is characterised by severe intellectual disability, speech impediment, sleep disturbance, unstable jerky gait, seizures and usually a happy demeanour.

Is it difficult to diagnose?
Yes, but with increasing public awareness of the condition and more accurate diagnostic tests, more children are being diagnosed. It is estimated that Angelman Syndrome occurs about one in 20,000 births.

Testing
To test for Angelman Syndrome, blood is take for genetic testing. The most common test for the diagnosis of AS is a FISH (fluorescence in situ hybridization) test. This test will identify the deletion on the chromosome 15.

Genetics of Angelman Syndrome
Angelman Syndrome was known as a distinct clinical entity before the genetics were fully understood. It has taken years of research to elucidate the different genetic mechanisms that can lead to AS. There are 4 major genetic mechanisms that cause Angelman syndrome (figure 1):

1. del 15q11-q13  
2. UPD  
3. IC mutation  
4. UBE3A mutation

Figure 1
Mechanisms causing Angelman syndrome. 1. deletion 15q11-q13; 2. paternal UPD- uniparental disomy; 3. IC (imprinting center) mutation; 4. UBE3A mutation. 
M- maternally derived chromosome 15; P- paternally derived chromosome 15.

Chromosome 15q11 -q13 deletion (a very small piece missing) accounts for 65-75% of AS cases and has a less than 1% recurrence risk. It was first observed on high resolution chromosome analysis that some patients with AS had a very small piece missing from the long (q) arm of chromosome 15 between bands q 11-13. This led to the development of the FISH (fluorescence in-situ hybridization) test to readily diagnose this common deletion from the maternally derived chromosome 15.

Paternal uniparental disomy (UPD) accounts for 3-5% of AS cases and has less than 1% recurrence. Patients with UPD have two paternal copies of chromosome 15 and no maternal copy of chromosome 15. These observations suggest that each copy of chromosome 15 is marked with "a label" (an imprint) for its parental origin. This is thought to regulate expression of genes on each chromosome 15. Thus AS represents a loss of functionally important imprinted genes on chromosome 15 that are only expressed from the maternal chromosome 15.

Imprinting center (IC) mutations account for 7-9% of AS cases, and can have significant recurrence. The imprinting center acts as the 'switch' that turns on the maternal copy of the UBE3A gene and turns off the paternal copy in certain tissues of the central nervous system. If there is a mutation in the IC, it cannot perform its 'switch' function. If the IC mutation occurs sporadically in the affected individual, the
recurrence risk is less than 1%. However, if the patient's mother carries the IC mutation on her own paternally inherited chromosome 15, there is a 50% risk of recurrence.

UBE3A mutations account for 6-20% of AS cases. If it happens sporadically in the affected individual, the recurrence risk is less than 1%. However, if the patient's mother carries the UBE3A mutation on her own paternally inherited chromosome 15, there is a 50% recurrence risk. Let's talk more about the UBE3A gene.

The UBE3A Gene
In 1996/1997, the laboratories of Dr. Joseph Wagstaff from Children's Hospital in Boston and Harvard School of Medicine and Dr. Arthur Beaudet from Baylor College of Medicine found a single gene on chromosome 15q called UBE3A that caused Angelman syndrome (figure 2). They showed that some patients with AS have mutations in the UBE3A gene. The gene encodes a protein called E6-AP ubiquitin protein ligase (also known as ubiquitin ligase 3). The exact mechanism of how the deficiency of this protein causes the clinical features of AS is not completely understood. However, it is known that E6-AP acts as an enzyme necessary for normal protein turnover within cells. This may suggest that the clinical findings are due to failure to degrade various proteins, accumulation of which may be deleterious to an individual.

What makes the UBE3A gene unique, is that it demonstrates tissue specific imprinting. The gene is expressed from maternal and paternal alleles in all tissues (organs) except specific parts of the central nervous system. UBE3A is imprinted in the human brain with the paternal copy of the gene being naturally silenced. In other words, in the brain the UBE3A is only expressed from the maternal copy. If this does not happen due to a mutation or deletion of UBE3A, the enzyme is not made and it is thought that certain proteins are not degraded in the brain. Recent animal studies have shown that the gene is preferentially expressed from the maternal allele with silencing of the paternal allele in the hippocampus and cerebellum in mice brains. The tissue specific imprinting fits the clinical presentation of AS since affected individuals have various neurologic problems and complications, but do not have involvement of other organ systems.

As mentioned above, UBE3A is naturally silenced on the paternally inherited copy in certain parts of the brain. Therefore, if a UBE3A mutation is inherited from the father, the person is unaffected as the paternal copy is not expressed. If the carrier of the UBE3A mutation is a male, he has a 50% chance of passing on the mutation, but is not at risk of having children with AS. Again, it is because the paternally inherited copy of the UBE3A gene is naturally silenced in the brain. If the carrier of the UBE3A mutation is a female, she also has a 50% chance of passing on the mutation. However, in this case if the mutation is passed on, the child will have Angelman syndrome. This is due to the fact that the maternal copy of the UBE3A gene has to function in the brain as the paternal copy is naturally silenced.
Figure 2
Genetic map of 15q11-q13 region. cen- centromere (constriction on a chromosome that separates the short [p] and the long [q] arms of a chromosome); tel - telomere (end of a chromosome). The jagged lines indicate the two common centromeric breakpoints and one telomeric breakpoint. The distance between a centromeric breakpoint and the telomeric breakpoint represents the deleted DNA in the common deletion. Circles in gray indicate genes implicated in Prader-Willi syndrome (PWS). The black circle represents the UBE3A - the disease gene in Angelman syndrome (AS). The white circles represent other genes. IC - imprinting center.

(adapted from The UBE3A Gene and its Role in Angelman Syndrome
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Traits of Angelman Syndrome

Always Seen/Consistent (100%)

- Severe intellectual disability and developmental delay (failure to match developmental milestones of other children), eg. delays in sitting and walking, delay in fine motor skills development and delay in toilet training;
- Profound speech impairment: no speech or minimal use of words; receptive and non-verbal communication skills higher than verbal ones;
- Movement or balance disorder (tremulous movement of limbs, stiffness and jerkiness in limbs) and ataxia of gait (lack of muscular co-ordination when walking);
- Behavioural uniqueness: any combination of frequent laughter/smiling; happy demeanour; easily excitable personality, often with hand flapping movements; short attention span and hyperactivity.

Usually Seen/Frequent (More than 80%)

- Small head size - often by age two years;
- Seizures - onset usually before three years of age;
- Abnormal EEG (brain wave pattern irregularity).

Sometimes Seen/Associated (20% to 80%)

- Flat occiput (flattened back of head);
- Protruding tongue;
- Tongue thrusting; suck/swallowing disorders;
- Feeding problems during infancy;
- Wide mouth, widely spaced teeth;
- Frequent drooling;
- Excessive chewing/mouthing behaviours;
- Scoliosis (curvature of the spine);
- Strabismus (crossed eye);
- Hypo pigmented skin, light hair and eye colour (compared to family), a feature in deletion cases;
- Wide based gait (feet far apart with flat, out turned feet);
- Tendency to hold arms up and flexed while walking;
- Increased sensitivity to heat;
- Sleep disturbance;
- Attraction to/fascination with water.

Not all features may be present. A diagnosis of Angelman Syndrome is based on a combination of the clinical features as above, together with genetic diagnostic tests.
Is there a cure for Angelman Syndrome?
No, but some symptoms can be treated. The condition is permanent but is not degenerative. Research is continuing worldwide on the complex genetics of AS to better understand why it occurs. Males and females are affected equally.

AS children can look forward to a normal lifespan, when children with Angelman Syndrome are observed and studied, many educational and behavioural interventions have been shown to be effective in the areas of communication, behaviour modification, sleep disturbance, general conduct and social skills. Physical and occupational therapies, speech and language intervention assist AS children.

Further Research Update: (Ellie Smith - 23/2/98)
I recall saying to you this time last year - that we had a great start for AS for 1997 with the “finding” of the AS gene! In the first issue of Nature Genetics for 1997, there were 2 publications - 2 of a kind - back to back - detailing the work performed, the results and the claim that we now have the AS gene. The discovery of the AS gene - UBE3A - is still a very great achievement, but is not the whole story. UBE3A is situated exactly within the region previously narrowed down to be the AS Critical Region, it contains a promoter region (a CpG island in OP2, a DNA sequence previously identified in Sydney), there is a function known for the gene product and there is significant homology (similarity) to a mouse. The gene has a protein product which is a ubiquitin - protein ligase. All of this is consistent with the claim that UBE3A is the AS gene. In addition, mutations in UBE3A have been described in patients with AS and this is really a most critical finding for those families. These mutations have been shown in patients who had previously been tested and found to be nondeleted, nonUPD and nonimprinted. (NDUI or triple-non patients) Scientists have even shown that UBE3A is imprinted in brain tissue during early development but not in cells from peripheral blood and skin. In these latter tissues, UBE3A is expressed from both the maternal and paternal chromosomes 15. Thus lack of imprinting in the tissue most studied (blood) has not excluded UBE3A from being the AS gene. It is in this respect in particular, that I think that recent work has been most outstanding and the laboratories involved must be congratulated, because they went ahead and followed through with a lot of work to prove the concept that imprinting could be tissue and time specific.

So progress into understanding the AS gene has been made - however, now, only 12 months later, it seems that UBE3A is not the whole story. While mutations have been found in some patients, and for these families, this is the answer to their diagnostic dilemma, nevertheless this only seems to account for about 20% of triple-non patients. What about the rest? There must still be another factor(s) of crucial importance to account for the remaining AS patients - now termed “quadruple-non”. Science has been able to narrow down the field, with each new discovery, but we haven't got there yet. Molecular research is still continuing, with DNA sequencing going along close by but downstream to UBE3A. Research clinically into the features present in patients also is continuing, as it may be that partial phenotypes or atypical patients can be accounted for by the mechanisms which will be found to operate in the quadruple-non patients. I will keep you posted on further progress.............