

# ANGELMAN SYNDROME

Angelman syndrome (AS) is characterized by severe developmental delay or intellectual disability, severe speech impairment, gait ataxia and/or tremors in the limbs. Microcephaly and seizures are common. Affected individuals also display a characteristic demeanor that includes inappropriate laughing, smiling, excitability and aggression. There are a number of genetic changes that cause AS, however each produces a similar clinical phenotype.

## GENETICS

DNA in the AS critical region is methylated. If the normal expression of genes in the critical region is altered, the methylation pattern is also changed. Abnormal methylation status of the *SNRPN* gene within the AS critical region therefore indicates a genetic alteration in the gene. Abnormal methylation of the maternally derived gene is diagnostic of Angelman syndrome.

Abnormal methylation results from a deletion in the maternally contributed chromosome 15q11-q13 region in ~70% of AS cases. Approximately 5% of cases have received two copies of chromosome 15 from their father and none from their mother; paternal uniparental disomy (patUPD). Like the patients with a deletion, patients with paternal UPD are deficient for maternally derived genes in the AS critical region. Approximately 3% of patients have an 'imprinting mutation', altering the expression of maternal genes in the AS critical region. Approximately 5-11% of AS patients have a mutation in the maternally inherited *UBE3A* gene.

## WHO SHOULD BE TESTED?

- Individuals clinically suspected of being affected with AS
- Pregnancies at risk due to a family history of AS

## POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS

<b>SNRPN Methylation Status</b>	<b>Explanation</b>
Normal	This result does not support a diagnosis of Angelman syndrome
Abnormal	This result supports a diagnosis of Angelman syndrome
Deletion detected	This result supports a diagnosis of Angelman syndrome

## TEST METHODS

- Quantitative testing to determine the methylation status of the *SNRPN* gene, using Multiplex Ligation-dependent Probe Amplification (MLPA)
- STR analysis can also be used in order to determine if the lack of maternal allele expression is due to paternal UPD or imprinting mutations. STR marker alleles associated with the AS critical region in the affected individual are compared to the marker patterns of the parents to determine the parental origin and genetic nature of the disorder.

## TEST SENSITIVITY

Deletion, paternal UPD, and imprinting mutations account for ~80% of abnormal expression of maternal alleles in those affected with AS. Approximately 20% of individuals affected with AS have a different genetic alteration than those listed above, such as point mutations in *UBE3A* or small deletions in the AS critical region of chromosome 15, or rare cases resulting from a subtle balance translocation involving one of the parents. These cases will not be detected by the diagnostic procedures described above.

## For More Information

Online Mendelian Inheritance in Man <http://www.ncbi.nlm.nih.gov/omim/> Item # 105830

GeneReviews online clinical information resource <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=angelman>

Angelman Syndrome Foundation <http://www.angelman.org/>

To locate a genetics centre near you, please visit the Canadian Association of Genetic Counsellors website at [www.cagc-accg.ca](http://www.cagc-accg.ca) or the National Society of Genetic Counsellors website at [www.nsgc.org](http://www.nsgc.org).



1. *Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of Angelman syndrome.*

2. *The clinical course or severity of symptoms cannot be predicted by molecular analysis.*

3. *Test results should be interpreted in the context of clinical findings, family history and other laboratory data.*

4. *This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.*