Angelman Syndrome

Contact details

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Samples required

- 5ml venous blood in plastic EDTA bottles (>1ml from neonates)
- Prenatal testing must be arranged in advance, through a Clinical Genetics department if possible.
- Amniotic fluid or CV samples should be sent to Cytogenetics for dissecting and culturing, with instructions to forward the sample to the Regional Molecular Genetics laboratory for analysis
- A completed DNA request card should accompany all samples

Patient details

To facilitate accurate testing and reporting please provide patient demographic details (full name, date of birth, address and ethnic origin), details of any relevant family history and full contact details for the referring clinician

Introduction

Angelman syndrome (MIM 105830) occurs in 1/15000 - 1/20000 individuals. It is characterized by severe motor and intellectual retardation, seizures associated with characteristic EEG traces, microcephaly, ataxia, frequent jerky limb movements and flapping of the arms and hands, hypotonia, hyperactivity, hypopigmentation (39%), absence of speech, characteristic face shape, and episodes of paroxysmal laughter. The AS phenotype results from the lack of a maternal contribution at chromosome 15q11-q13. This can be caused by deletion (~75%), paternal uniparental disomy (UPD) (~2%) or mutations in the imprinting centre (IC) (~5%) that cause abnormal methylation at exon alpha of the SNRPN gene at 15q11-13. These mutations are all detected by disrupted methylation. About 20% of AS patients have a normal methylation pattern and are believed to have a mutation in a putative Angelman gene (UBE3A). Deletions and UPD are usually de novo events, associated with low recurrence risks, although it is important to determine whether either parent of an affected child has a predisposing chromosome translocation. There is a recurrence risk of up to 50% in families with **confirmed** AS who do not show maternal deletion or UPD.

Referrals

- Confirmation of clinically suspected AS in children/adults.
- Investigation of the molecular defect in genetically confirmed AS cases (parental samples required).
- Carrier testing in adult relatives of confirmed (genetic) AS patients who are suspected of having an IC mutation (samples from appropriate family members are required).

Prenatal testing

Prenatal diagnosis is available to couples where AS has been confirmed in the family and to couples at risk of having a child affected with AS due to a balanced chromosomal rearrangement involving chromosome 15 in one of the parents. Please contact the laboratory to discuss, prior to sending prenatal samples.

Service offered

Confirmation of AS by methylation analysis and microsatellite analysis to determine the underlying cause in confirmed cases and carrier testing for adults (requires samples from appropriate family members). UBE3A mutation analysis is not offered in this laboratory.

Technical

For diagnostic referrals the initial test is to determine the methylation status of exon alpha of the SNRPN gene. Methylation analysis is performed by methylation specific PCR following bisulphite modification of genomic DNA. Normal individuals yield a 313bp maternally derived fragment and a 221bp paternally derived fragment. Patients with AS show a single 221bp paternal fragment only. Positive results are confirmed by either MS-MLPA or aCGH analysis. Chromosome 15 microsatellite markers from within and flanking the commonly deleted region can also be used to characterise the mechanism in patients shown to have abnormal methylation. Cytogenetic analysis is also helpful in identifying deletions and predisposing parental translocations. NB. Similar analysis is undertaken for Prader-Willi syndrome

Target reporting time

Routine analysis - the initial methylation test takes up to 4 weeks. Microsatellite marker analysis takes 8 weeks from receipt of parental samples. Please contact the laboratory for urgent cases.