

Information Sheet No 67

“Genetic Testing For Angelman Syndrome”

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Genetic Testing For Angelman Syndrome

Angelman syndrome can be caused by a variety of different genetic abnormalities. They all involve chromosome 15, but different genetic tests must be used to detect the different types of abnormality. It's not surprising that parents and doctors are often confused about this. At the International Angelman Syndrome Organisation Meeting in July 2000, the participants of the scientific workshop discussed strategies for screening for Angelman syndrome and came up with the following plan as the ideal path to follow. It's important to remember however, that not all countries and not all regions within a country have access to the same resources. The actual screening plan that different doctors adopt may therefore vary from one place to another.

Step 1. Methylation Test

The most useful diagnostic test. If this is “positive” i.e. the methylation pattern is characteristic of Angelman syndrome, then the diagnosis is confirmed. The laboratory will then go on to determine whether the AS is due to a deletion, uniparental disomy or an imprinting defect.

Step 2 FISH test - a specialised type of chromosome analysis which will detect very tiny abnormalities, normally invisible on routine examination

The FISH test is a way of testing the chromosomes to check for a deletion. If the methylation test is positive and the FISH test is positive no further tests are needed as the diagnosis of deletion positive AS is confirmed.

Step 3 RFLP analysis (DNA test to check that a chromosome 15 has been inherited from each parent)

If methylation is positive but FISH is negative RFLP analysis will be used to differentiate between AS due to uniparental disomy and AS due to an imprinting defect. With UPD both chromosome 15s will have come from the father. With an imprinting defect both parents will have contributed a chromosome 15. If RFLP analysis confirms UPD no further tests are needed.

Step 4 Search for imprinting centre mutations

If methylation test was positive and neither deletion or UPD were present then there is an imprinting defect. In some families, in order to offer accurate genetic counselling, it is then necessary to look for the precise change or “mutation” on chromosome 15 which gave rise to the imprinting defect. Only a couple of laboratories in the world offer this type of testing at present. From the UK most samples are sent to a laboratory in Germany.

Step 5 UBE3A screening

If methylation was normal but Angelman syndrome is still strongly suspected clinically i.e. the movements and behaviour are typical and there is a characteristic EEG pattern then the next step is to screen the UBE3A gene to look for a tiny change

within the gene. This is a laborious and expensive process but worth trying in selected patients as mutations will be detected in 20% (80% if familial Angelman syndrome).

Step 6 Consider other possibilities

If all the tests above are negative, then Angelman syndrome is unlikely, though not impossible. Other diagnostic possibilities should be considered and it is recommended that patients be reviewed by a paediatrician/neurologist from time to time as the situation may change or new tests may become available over the years.