AWMGS
All Wales Medical Genomics Service

Non-syndromic Sensorineural Hearing Loss (DFNB1) – (OMIM 220290) and Aminoglycoside induced hearing loss (AIHL) (OMIM 561000)

Background

In the UK, about one in 2000 children is born with significant deafness, and half of these cases have a genetic basis. Non-syndromic hearing loss (NSHL), where no other medical problems are present, accounts for a large proportion of these inherited hearing loss cases. The majority of NSHL cases are inherited in an autosomal recessive manner and mutations at the DFNB1 locus (13q11-12), which contains the *GJB2* (*Connexin 26* – OMIM 121011) and *GJB6* (*Connexin 30* – OMIM 604418) genes, account for approximately 50% of autosomal recessive NSHL. Mutations in mitochondrial DNA (maternally inherited) are also implicated in NSHL and the most common mutation, m.1555A>G, accounts for 0.6-17% (varying in different populations) of NSHL. The MTRNR1 m.1555A>G mutation exhibits a wide range of penetrance, severity and age-of-onset, with aminoglycoside antibiotic exposure being a major modifier.

Recommended Clinical Referral Criteria

- DFNB1 – Non-syndromic hearing loss, particularly isolated cases or those with affected sibs, however other family history does not exclude the possibility of DFNB1 as deafness is relatively common)
- Mitochondrial MTRNR1 m.1555A>G – Non-syndromic hearing loss, particularly if matrilineal inheritance or aminoglycoside exposure

Molecular Analysis

Mutation screen: Bi-directional sequence analysis of the coding region plus the splice site mutation c.-23+1 G>A (previously called IVS1+1G>A) in intron 1 of the *GJB2* gene and analysis for the *GJB6*-D13S1830 and *GJB6*-D13S1854 deletions that include a portion of the *GJB6* gene by PCR across the deletion breakpoint; >95% of DFNB1 patients have 2 *GJB2* mutations; *GJB2/GJB6* gene re-arrangements, whole gene deletions/ duplications not detected; ~2% of DFNB1 patients have 1 *GJB2* mutation and 1 of the *GJB6* deletions. Pyrosequencing analysis for the mitochondrial MTRNR1 m.1555A>G mutation; 13-33% of patients with aminoglycoside ototoxicity (damage to the ear due to exposure to certain antibiotics) has this mutation.
Family follow-up: Testing for known familial mutations in *GJB2* and *GJB6* genes

Test (Price available on request)	**TAT (calendar days)**
Mutation screening (*GJB2*) and analysis of *GJB6* rearrangements	42
Familial testing for known mitochondrial MTRNR1 mutation (m.1555A>G)	42
Mutation screening (*GJB2*) and analysis of *GJB6* rearrangements **plus** test for known mitochondrial MTRNR1 mutation (m.1555A>G)	42
Test for known familial mutations in *GJB2* and *GJB6*	42
Pre-treatment testing in neonates for mitochondrial MTRNR1 mutation (m.1555A>G)	14
Pre-treatment testing for mitochondrial MTRNR1 mutation (m.1555A>G) in CF patients	14

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Sample Requirements

Blood – 5ml in EDTA (1ml neonates/infants);
Please contact lab prior to sending a prenatal sample.
Please label samples with three identifiers and date of collection.

All samples must be accompanied by request form

Consent for testing & DNA storage is assumed when request for test received

Links

Orphanet
http://www.orpha.net/
OMIM
http://www.omim.org/
Genetic Test Registry
http://www.ncbi.nlm.nih.gov/gtr/
Support
Deafness Research UK
www.deafnessresearch.org.uk