

## 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 ( <i>GJB2</i> ) and analysis of <i>GJB6</i> rearrangements	42
Familial testing for known mitochondrial MTRNR1 mutation (m.1555A>G)	42
Mutation screening ( <i>GJB2</i> ) and analysis of <i>GJB6</i> rearrangements <b>plus</b> test for known mitochondrial MTRNR1 mutation (m.1555A>G)	42
Test for known familial mutations in <i>GJB2</i> and <i>GJB6</i>	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

#### Contact Details

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Accredited to ISO 15189:2012  
(8988)

#### 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/>  
**EDDNAL**  
<http://www.eddnal.com/>  
**OMIM**  
<http://www.omim.org/>  
**Genetic Test Registry**  
<http://www.ncbi.nlm.nih.gov/gtr/>  
**Support**  
Deafness Research UK  
[www.deafnessresearch.org.uk](http://www.deafnessresearch.org.uk)