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Mitochondrial Hearing Loss

Non-syndromic mitochondrial hearing loss is characterized by moderate to profound hearing loss, and a maternally inherited mutation in either the *MTRNR1* or *MTTS1* gene. Individuals with an *MTRNR1* mutation may have a predisposition to aminoglycoside ototoxicity causing deafness and/or late onset sensorineural hearing loss. In these individuals, hearing loss associated with aminoglycoside ototoxicity is bilateral and severe to profound, and occurs within a few days to weeks after administration of any amount of aminoglycoside antibiotic. Individuals with an *MTTS1* mutation generally have an onset of sensorineural hearing loss during childhood. Variability in clinical findings may be due to the presence of variable numbers of mitochondria containing mutations in different tissues of the body (heteroplasmy).

Genetics

The *MTRNR1* gene encodes the 12S ribosomal RNA and the *MTTS1* gene encodes transfer RNA for serine; both are important in mitochondrial protein synthesis. Several recurrent mutations cause nonsyndromic mitochondrial hearing loss, including mutations in the *MTRNR1* gene (m.C1494T, m.A1555G, m.961delT+Cn) and *MTTS1* gene (m.A7443G, m.G7444A, m.A7445C, m.T7510C, m.T7511C).

Non-syndromic mitochondrial sensorineural hearing loss is due to mutations in mitochondrial DNA (mtDNA) and is transmitted by maternal inheritance. In most cases, the mother of a proband has a disease-causing mtDNA mutation, and may or may not have hearing loss. All offspring of females with a mtDNA mutation are at risk of inheriting the mutation. Offspring of males with a mtDNA mutation are not at risk of inheriting the mutation.

Who Should be Tested?

- Individuals clinically suspected of being affected with non-syndromic mitochondrial hearing loss
- Relatives of probands with identified *MTRNR1* or *MTTS1* mutations

Test Methods

- Complete mtDNA sequencing of the region encompassing nucleotides 860-1226 and 1313-1601 of the *MTRNR1* gene to identify point mutations
- Complete mtDNA sequencing of the coding region and flanking exon/intron boundaries of the *MTTS1* gene to identify point mutations

Test Sensitivity

Of individuals affected with mitochondrial non-syndromic hearing loss, three mutations in the *MTRNR1* gene (m.C1494T, m.A1555G, m.961delT+Cn) account for ~70% of mutations, while five mutations in the *MTTS1* gene (m.A7443G, m.G7444A, m.A7445C, m.T7510C, and m.T7511C) account for a further ~14% of mutations.

Note: Sequencing analysis may not detect low levels of heteroplasmic mutant mitochondria.

Potential Outcomes & Interpretation of Test Results

Reason for Referral	*MTRNR1 / MTTS1* Gene Mutations	Explanation
Diagnosis	None detected	This result does not support a diagnosis of non-syndromic mitochondrial hearing loss
Diagnosis	Mutation detected	This result supports a diagnosis of non-syndromic mitochondrial hearing loss

For More Information

Online Mendelian Inheritance in Man http://www.ncbi.nlm.nih.gov/omim/
- *MTRNR1* # 561000
- *MTTS1* # 590080

GeneReviews online clinical information resource http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=deafness-overview

The Canadian Association of the Deaf http://www.cad.ca/

To locate a genetics center near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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1. Current molecular testing may not detect all possible mutations for this disorder. A negative test does not rule out the possibility that the individual has a different MTRNR1 or MTTS1 mutation, or a mutation in another gene, not included in the assay and is affected with non-syndromic mitochondrial hearing loss.

2. Low levels of heteroplasmic mutant mitochondria may not be detected by this testing.

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 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.