Molecular Test for Mitochondrial DNA 1555A>G Mutation Associated with Aminoglycoside-induced and Non-syndromic Hearing Loss

The UNC Hospitals Molecular Genetics Laboratory performs a molecular test to detect the mtDNA 1555A>G mutation in the mitochondrially encoded 12S RNA (*MT-RNR1*) gene, which is associated with aminoglycoside-induced and nonsyndromic hearing loss.

Disease Pathophysiology

Hearing loss is the most common sensory defect, with a birth incidence of ~1 in 1000. The mtDNA 1555A>G mutation in the *MT-RNR1* gene is the most common mitochondrial mutation in individuals with non-syndromic hearing loss. Affected individuals generally have bilateral, progressive sensorineural hearing loss of variable severity. The mutation alters the structure of the mitochondrial 12S rRNA to resemble that of the target *E. coli* 16S rRNA, thus enabling aminoglycoside binding and resulting in altered mitochondrial protein synthesis. It is transmitted by maternal inheritance and is generally present in a homoplasmic state. The mutation predisposes to early age onset of hearing loss after exposure to ototoxic aminoglycosides; hearing loss may develop in individuals with the mtDNA1555A>G mutation independent of exposure to aminoglycosides, but usually with a later age of onset. The 1555A>G mutation accounts only for ~33% of genetic predisposition to aminoglycoside ototoxicity, so additional predisposing mutations both in the mitochondrial and nuclear genomes are likely.

Clinical indications for mtDNA 1555A>G testing

Testing for the 1555A>G mutation should be considered in patients who develop hearing loss secondary to aminoglycoside exposure, independent of dosage. Detection of the mutation has implications for counseling maternal relatives of the affected individual regarding their risk for aminoglycoside-ototoxicity and the likelihood of later onset of hearing loss. Testing of patients prior to treatment with aminoglycosides and choosing alternative therapy may prevent hearing loss in predisposed individuals. The test is also useful for diagnosis of hearing loss independent of aminoglycoside exposure, even with a negative family history since penetrance is variable.

Laboratory testing for mtDNA 1555A>G mutation

The preferred sample is EDTA anticoagulated blood (lavender-top), which may be refrigerated up to 48 hrs before analysis by real-time PCR and allele-specific hybridization followed by melting curve analysis. Results are reported as either positive or negative for the mtDNA 1555A>G mutation.

References

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3. Prezant T.R. et al. Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness *Nat Genet.* 1993 4(3):289-94

Questions?

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