



Disease Information

Mutations in the mitochondrial 12S rRNA gene *MT-RNR1* are associated with hearing loss after aminoglycoside exposure and with non-syndromic hearing loss in the absence of aminoglycoside exposure. The aminoglycosides are a class of antibiotics including streptomycin, gentamicin, kanamycin, amikacin, neomycin, and tobramycin. The natural target of aminoglycosides is the bacterial ribosome, which is structurally similar to the mitochondrial ribosome. *MT-RNR1* mutations such as A1555G are thought to increase aminoglycoside binding to mitochondrial ribosomes and reduce mitochondrial protein synthesis, resulting in oxidative stress and death of sensitive cochlear hair cells.¹ Other mutations in this gene have been identified in individuals with post-exposure hearing loss.²

Hearing loss following aminoglycoside exposure in *MT-RNR1* mutation carriers may be sudden or delayed and varies in severity but is often severe to profound.³ Mutation carriers who are not exposed to aminoglycosides may also develop hearing loss.¹ Specific mutation carrier rates and risk figures for hearing loss with or without aminoglycoside exposure are not well established and vary by ethnicity.¹ The variability in onset and penetrance appears to be governed by a threshold model of environmental contributions, the mitochondrial background haplotype, and multiple nuclear modifier genes.¹

Hearing loss is a well-known side-effect of aminoglycoside therapy in the general population and patients who test negative for *MT-RNR1* mutations share a risk of hearing loss as a complication of therapy.

Testing Benefits & Indications

Determination of mutation status allows the greatest opportunity for prevention or minimization of hearing loss due to future aminoglycoside exposures, and helps define the etiology of existing hearing loss. Indications are:

- diagnostic testing for individuals with hearing loss after aminoglycoside exposure
- diagnostic testing for individuals with maternally-inherited hearing loss, with or without aminoglycoside exposure
- carrier testing for individuals with family history of maternally-inherited hearing loss, with or without aminoglycoside exposure
- carrier testing for relatives of known mutation carriers
- carrier testing for care planning in advance of aminoglycoside therapy

Test Description

This test is available separately or by reflex after a positive cystic fibrosis DNA test result in our laboratory. PCR-based double-stranded automated sequencing of the entire *MT-RNR1* gene at mitochondrial nucleotides 648-1601 is performed in the sense and antisense directions. Nucleotide numbering is according to the revised Cambridge Reference Sequence HUMMTCG J01415.2 (http://www.mitomap.org/euk_mitos.html). The three known gross deletions of approximate sizes 4.7 kb, 4.9 kb, and 3.9 kb that include the *MT-RNR1* gene may be detected due to lack of PCR amplification. Heteroplasmy (a mixture of normal and mutant mitochondria) is not reliably detected by this assay. Specific mutation analysis for known family mutations in *MT-RNR1* is also available.

Mutation Detection Rate

Approximately 99% of *MT-RNR1* mutations are detectable by this test. A negative result cannot rule out that the patient may carry a mutation in a tissue other than the one tested or that heteroplasmy may be present in the tissue that was tested.

Turn-Around-Time

Full gene analysis	10 – 21 days
Specific mutation analysis	10 – 14 days

Specimen Requirements

BLOOD: Collect 3-5 cc from adult or 2 cc minimum from child into EDTA purple-top tube (first choice) or ACD yellow-top tube (second choice). Store at room temperature or refrigerate. Ship at room temperature.

BLOOD SPOT: Minimum of one complete spot approximately 0.5 inch in diameter on S&S 903 collection paper or similar. Store in a clean plastic bag at room temperature. Ship at room temperature.

SALIVA: Collect 2 ml into Oragene™ DNA Self-Collection container. Store and ship at room temperature.

DNA: Send 20 µg in TE at 50-100 ng/µl. Store frozen and ship on ice or dry ice.

Prenatal samples are not accepted for this test due to the inability to reliably assess heteroplasmy.

CPT Codes

Full gene analysis or specific mutation analysis83891, 83894, 83898, 83904, 83909, 83912

References

¹Fischel-Ghodsian N et al. *Mitochondrion*. 2004;4:675-694.

²Li R et al. *J Med Genet*. 2004;41:615-620.

³Fischel-Ghodsian N et al. *Am J Otolaryngology*.1997;18:173-178.