Hearing Loss: Targeted Mitochondrial Mutation Panel

**Test Code:** QJ  
**Turnaround time:** 3 weeks  
**CPT Codes:** 81254 x1

### Condition Description

Approximately 1 in 1000 children are diagnosed with prelingual hearing loss (HL) or deafness. Approximately half of prelingual hearing loss or deafness is attributed to environmental exposures and the remaining half to genetic causes. Approximately 30% of hereditary hearing loss is estimated to be syndromic (associated with other birth defects) while the remaining 70% is non-syndromic (isolated and not associated with other findings). Non-syndromic deafness is mainly due to recessive genes (75-80%), and over 20 such genes have been identified. Non-syndromic hearing loss may also be inherited in autosomal dominant, X-linked, or mitochondrial patterns.

In the presence of specific mitochondrial DNA mutations, moderate to severe hearing loss can result from exposure to aminoglycoside antibiotics such as gentamycin, tobramycin, amikacin, kanamycin, or streptomycin [1]. Bilateral severe hearing loss can occur within a few days to weeks of exposure to an aminoglycoside. Aminoglycoside ototoxicity mitochondrial mutations cause sensorineural hearing loss during childhood or early adulthood even in the absence of aminoglycoside exposure. Patients may or may not have a family history of hearing loss and typically do not have any other physical findings [2]. Mutations in the mitochondrial MTRNR1 and MTTS genes have been associated with aminoglycoside ototoxicity in an estimated 2% of deaf individuals in the US [3, 4]. The prevalence is higher, 15-30%, among deaf persons with a history of aminoglycoside exposure [5].

One of the most common mitochondrial mutations is the A1555G substitution in the 12S ribosomal RNA subunit gene (MTRNR1 gene) which can be found in 0.6-2.5% of Caucasian, 3-5% of Asian and as high as 17% of Spanish population with non-syndromic hearing loss [6]. Approximately 21% of individuals with mitochondrial nonsyndromic hearing loss have the 1555A>G mutation in MTRNR1 and 50% have the 961delT+(C)n. The 1555A>G mutation occurs in a homoplasmic state and the penetrance of hearing loss following aminoglycoside exposure is 100%. Without aminoglycoside exposure the penetrance of 1555A>G at age 65 is 80%.

The 7,445A>G/7,443A>G/7,444G>A mutations in the tRNA serine gene (MTTS1) have been found in patients with maternally inherited sensorineural hearing loss, but they are less likely to cause aminoglycoside hypersensitivity. Of individuals with mitochondrial nonsyndromic hearing loss, 14% have MTTS1 mutations 7443A>G, 7444A>G, or 7445A>G.

Most mitochondrial DNA mutations causing non-syndromic hearing loss are maternally inherited. Heteroplasmic states (uneven distribution of mitochondrial DNA during cell division) and variable penetrance may be related to the level of mutant mitochondria present, and is not quantitated by this assay. MTTS1 mutations may occur in heteroplasmic states and penetrance may be related to the level of mutant mitochondria (not quantitated by this assay).

This test analyzes four different mutations in the MTRNR1 and MTTS1 genes that have been shown to be involved in non-syndromic hearing loss. Please click here for the GeneReviews summary on this condition.

### References:

### Genes

MTRNR1, MTTS1

### Indications

This test is indicated for:
- Individuals with clinical symptoms of non-syndromic hearing loss especially if triggered by aminoglycoside antibiotics.
- Carrier testing in individuals with a maternal family history of aminoglycoside related hearing loss.

### Methodology

1555 (12S rRNA) and 7443/7444/7445 (tRNA Serine) mutations are assayed by PCR and restriction fragment analysis.

### Detection

The A1555G substitution in the MTRNR1 gene can be found in 0.62.5% of Caucasian, 3-5% of Asian and as high as 17% of Spanish population with non-syndromic HL [7]. This assay is estimated to detect about 35% cases of all mitochondrial non-syndromic hearing loss.

### Reference Range

Qualitative assay.
Specimen Requirements

Submit only 1 of the following specimen types

Type: DNA, Isolated

Specimen Requirements:
- Microtainer
- 8µg
- Isolation using the Perkin Elmer™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
- Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:
- Oragene™ Saliva Collection Kit
- Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
- Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: Whole Blood (EDTA)

Specimen Requirements:
- EDTA (Purple Top)
- Infants and Young Children (2 years of age to 10 years old): 3-5 ml
- Older Children & Adults: 5-10 ml
- Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
- Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Related Tests

- **Hearing Loss: Comprehensive Panel (HL)** is indicated for patients who have not have previous molecular testing and includes sequencing of the GJB2 and GJB6 genes, targeted mutation analysis of the GJB6 common 342kb deletion, and testing for mitochondrial mutations associated with aminoglycoside sensitivity.
- **Known Mutation Testing (KM)** is available to family members if mutations are identified by sequencing.
- **Prenatal testing** is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.