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Nonsyndromic Hearing Loss and Deafness, Mitochondrial

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Summary

Clinical characteristics

Mitochondrial nonsyndromic hearing loss and deafness is characterized by sensorineural hearing loss (SNHL) of variable onset and severity.

Pathogenic variants in *MT-RNR1* can be associated with predisposition to aminoglycoside ototoxicity and/or late-onset SNHL. Hearing loss associated with aminoglycoside ototoxicity is bilateral and severe to profound, occurring within a few days to weeks after administration of any amount (even a single dose) of an aminoglycoside antibiotic such as gentamycin, tobramycin, amikacin, kanamycin, or streptomycin.

Pathogenic variants in *MT-TS1* are usually associated with childhood onset of SNHL that is generally nonsyndromic – although the *MT-TS1* substitution m.7445A>G has been found in some families who also have palmoplantar keratoderma (scaling, hyperkeratosis, and honeycomb appearance of the skin of the palms, soles, and heels).

Diagnosis/testing

The diagnosis of mitochondrial nonsyndromic hearing loss and deafness is established in a proband with hearing loss and identification of a pathogenic variant in *MT-RNR1* or *MT-TS1*, or one of the eight additional mitochondrial genes known to cause nonsyndromic hearing loss and deafness.

Management

Treatment of manifestations: Appropriate rehabilitation (hearing aids, speech therapy, culturally appropriate language training, cochlear implantation, educational programs for the hearing impaired). Electric acoustic stimulation for individuals with mitochondrial hearing loss with residual hearing in the lower frequencies. Lotions and emollients for mild keratoderma; dermatology referral for severe keratoderma.

Prevention of primary manifestations: Avoidance of aminoglycosides.

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Surveillance: Annual audiometric assessment to evaluate stability/progression of hearing loss. Annual physical exam for related clinical findings.

Agents/circumstances to avoid: Aminoglycosides and noise exposure, especially in those with normal hearing who have the m.1555A>G or m.1494C>T *MT-RNR1* pathogenic variants.

Evaluation of relatives at risk: Molecular genetic testing of at-risk maternal relatives allows for early detection of those who have inherited the mtDNA pathogenic variant and would benefit from avoiding aminoglycosides and appropriate early support and management.

Genetic counseling

Mitochondrial nonsyndromic hearing loss and deafness is caused by pathogenic variants in mitochondrial DNA (mtDNA) and is transmitted by maternal inheritance. The mother of a proband (usually) has the mtDNA pathogenic variant and may or may not have hearing loss. All offspring of females with a mtDNA pathogenic variant are at risk of inheriting the pathogenic variant. Offspring of males with a mtDNA pathogenic variant are not at risk of inheriting the pathogenic variant. Prenatal diagnosis for pregnancies at increased risk is possible if the mtDNA pathogenic variant in the family is known. Because of mitotic segregation, the mtDNA pathogenic variant load in amniocytes and chorionic villi is unlikely to correspond to that of other fetal or adult tissues. Furthermore, the presence of the mtDNA pathogenic variant does not predict the age of onset or severity of hearing loss.

Diagnosis

Suggestive Findings

Mitochondrial nonsyndromic hearing loss and deafness **should be suspected** in a proband with the following:

- Moderate-to-profound hearing loss

  Hearing loss graded by level of severity:

  - Mild (26-40 dB)
  - Moderate (41-55 dB)
  - Moderately severe (56-70 dB)
  - Severe (71-90 dB)
  - Profound (90 dB)

  Hearing is assessed by a variety of methods; see Hereditary Hearing Loss and Deafness Overview.
- Mild-to-moderate high-frequency hearing loss
- No other systemic findings on history or physical examination
- A family history of hearing loss suggestive of maternal inheritance (i.e., no transmission through a male)
- Onset of hearing loss following administration of an aminoglycoside antibiotic such as gentamycin, tobramycin, amikacin, kanamycin, or streptomycin

Establishing the Diagnosis

The diagnosis of mitochondrial nonsyndromic hearing loss and deafness **is established** in a proband with the above suggestive findings and a pathogenic variant in one of the genes associated with mitochondrial nonsyndromic hearing loss and deafness identified by molecular genetic testing (see Table 1a, Table 1b).

Molecular genetic testing approaches can include **targeted testing**, a **multigene panel**, and **complete mtDNA sequencing**:

- **Targeted testing.** In individuals with hearing loss following aminoglycoside exposure, molecular testing for the pathogenic variants m.1555A>G and m.1494C>T in *MT-RNR1* and m.7445A>C/T/G in *MT-TS1* can be done first.
- **A multigene panel** that includes the mitochondrial genes listed in Table 1a and other genes of interest (see Table 1b and Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (4) Some mitochondrial nonsyndromic deafness-causing pathogenic variants are heteroplasmic (i.e., both wild type and mutated mtDNA are present in a cell and/or tissue). When selecting a multigene panel, it is necessary to confirm that the test methods can identify heteroplasmic mitochondrial pathogenic variants.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **Complete mtDNA sequencing** may be considered if use of targeted testing and/or a multigene panel did not identify a pathogenic variant, clinical suspicion remains high, and there is no evidence of paternal transmission. Massively parallel DNA sequencing-based techniques are useful for identifying heteroplasmic mitochondrial pathogenic variants.

  Note: This testing may be performed before a **multigene panel** in the case of a clear mitochondrial inheritance pattern.

Table 1a. Molecular Genetics of Mitochondrial Nonsyndromic Hearing Loss and Deafness: Most Common Genetic Causes

Gene [1]	Proportion of Mitochondrial Nonsyndromic Hearing Loss and Deafness Attributed to Pathogenic Variants in Mitochondrial Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
MT-RNR1	~71%	~100%	Unknown [5]
MT-TS1	~29%	~100%	Unknown [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Table 1b. Molecular Genetics of Mitochondrial Nonsyndromic Hearing Loss and Deafness: Less Common Genetic Causes

Gene [1, 2]	Pathogenic Variants [3] / Comments
MT-CO1	m.7444G>A; located on the boundary of MT-CO1 & MT-TS1; reported in 4 persons of Polish ancestry & 2 of Chinese ancestry w/nonsyndromic hearing loss or aminoglycoside-induced hearing loss [Zhu et al 2006, Rydzanicz et al 2011]

Table 1b. continued from previous page.

Gene [1, 2]	Pathogenic Variants [3] / Comments
MT-ND1	m.3388C>A; reported in a family w/maternally inherited mild-moderate hearing loss [Lévêque et al 2007]
MT-TH	m.12201T>C; reported in a 5-generation family w/maternally inherited hearing loss w/ average onset age 29 years [Yan et al 2011]
MT-TI	m.4295A>G; identified in a 3-generation family w/maternally inherited nonsyndromic hearing loss
MT-TK	m.8296A>G; reported in 1/ 717 persons w/hearing loss [Mori et al 2016]
MT-TL1	m.3243A>G; identified in 5/717 persons w/isolated hearing loss [Mori et al 2016; Author, personal communication]
MT-TS2	m.12236G>A; reported in persons from 1 family w/moderate-to-profound hearing loss; onset age 7-30 yrs [Lévêque et al 2007]

1. Pathogenic variants of any one of the genes listed in this table are reported in only a few families (i.e., <1% of mitochondrial nonsyndromic hearing loss and deafness).
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Mitochondrial gene variants for nonsyndromic deafness and hearing loss in this table are limited to variants classified as "Confirmed" or "Reported" in the MITOMAP database on the basis of one or more functional analyses such as tRNA stability, respiratory complex activity, or mitochondrial protein synthesis.

Clinical Characteristics

Clinical Description

MT-RNR1-Related Hearing Loss

Aminoglycoside ototoxicity. Hearing loss occurs within a few days to weeks after administration of any amount (including a single dose) of aminoglycoside antibiotic such as gentamycin, tobramycin, amikacin, kanamycin, or streptomycin.

Hearing loss is bilateral and severe to profound [Yelverton et al 2013]. Once it appears, hearing loss is irreversible but not progressive. Hearing loss associated with the m.1555A>G pathogenic variant results from hair cell loss and dysfunction and hence is cochlear in nature [Bravo et al 2006].

Aminoglycoside ototoxicity secondary to the presence of a predisposing mtDNA pathogenic variant appears to be related to the administration of aminoglycosides (independent of dose) in contrast to "dose-related" aminoglycoside ototoxicity, which is related to the dose and/or plasma concentration of aminoglycosides in individuals who do not have a predisposing mtDNA pathogenic variant.

Vestibular symptoms are uncommon [Lu et al 2010a].

Sensorineural hearing loss (SNHL) independent of aminoglycoside exposure. *MT-RNR1* pathogenic variants are also reported to be a common cause of nonsyndromic hearing loss without aminoglycoside exposure. The probability of hearing loss varies widely among reports and families (see Penetrance).

The severity, onset age, and audiometric configuration of m.1555A>G variant-related nonsyndromic hearing loss without aminoglycoside exposure are wide-ranging. The severity and onset of hearing loss in these individuals ranges from congenital profound deafness to mild-to-moderate progressive late-onset hearing loss. High-frequency-associated hearing loss is prevalent among individuals with mild-to-moderate hearing loss [Iwanicka-Pronicka et al 2015]. Zhu et al [2014] reported that the heteroplasmy level of the m.1555A>G pathogenic variant correlated with hearing loss penetrance in five families with different levels of heteroplasmy [Zhu et al 2014].

Many individuals with progressive hearing loss commonly experience episodes of tinnitus, but vestibular symptoms are rare in these individuals. A small percentage of individuals with the m.1555A>G pathogenic variant who did not develop hearing loss had subclinical findings of a lower amplitude of response to DPOAE (distortion-product otoacoustic emission), indicating a deficit in cochlear physiology [Bravo et al 2006].

Other. Although hearing loss associated with *MT-RNR1* pathogenic variants is considered nonsyndromic, a constellation of digital, spinal, and pigmentary disturbances has been reported in a family with the m.1555A>G substitution. Pigmentary findings in family members included development of gray hair with a salt-and-pepper distribution in teenagers and hypopigmented skin patches ranging in size from two to 10 cm on the wrist, knee, and groin [Nye et al 2000]. The correlation between the mitochondrial substitution and the presence of pigmentary changes remains unclear.

MT-TS1-Related Hearing Loss

SNHL. *MT-TS1* is another hot spot for pathogenic variants associated with nonsyndromic hearing loss as well as syndromic hearing loss [Guan 2004, Zheng et al 2012]. A large number of *MT-TS1* variants have been reported to cause nonsyndromic hearing loss in multiple population groups (see Molecular Genetics).

Onset of SNHL caused by the m.7445A>G pathogenic variant occurs during childhood [Yelverton et al 2013]. The severity of hearing loss is highly variable, ranging from mild to severe. Progression in the severity of hearing loss is characteristic.

Other. The m.7445A>G substitution has also been associated in some families with palmoplantar keratoderma as well as hearing loss [Sevior et al 1998, Martin et al 2000, Caria et al 2005]. The skin changes can appear as early as age four to five years and consist of scaling, hyperkeratosis, and honeycomb appearance of the skin of the palms, soles, and heels [Sevior et al 1998]. Callus formation occurs on the heels and toes. Hyperkeratosis of palms with erythema is reported in a few individuals; marked variability in the severity and extent of involvement is characteristic. Caria et al [2005] described a family with this variant; dermatosis appeared by age four to 11 years and worsened until age eight in one individual. Skin biopsy showed orthokeratotic hyperkeratosis, with some columns of parakeratosis in the inferior third of the epidermis, mild acanthosis, and focal absence of granular layer. Individuals who have both the m.7444G>A and m.1555A>G (*MT-RNR1*) pathogenic variants [Pandya et al 2004] or the m.7443A>G pathogenic variant alone do not have skin findings.

The m.7471dupC (previously described as m.7472insC) pathogenic variant in *MT-TS1* was identified as responsible for maternally inherited nonsyndromic hearing loss, and one individual reported by Tiranti et al [1995] had syndromic hearing loss with ataxia and myoclonus. Ensink et al [1998] reported a family with this variant with early-onset SNHL and late-onset neurologic complaints.

Other Forms of Mitochondrial Gene-Related Hearing Loss

The m.7444G>A pathogenic variant located on the boundary of *MT-CO1* and *MT-TS1* has been reported to be responsible for nonsyndromic hearing loss and aminoglycoside-induced hearing loss [Zhu et al 2006, Rydzanicz et al 2011].

In addition, this pathogenic variant was co-identified with *MT-RNR1* variants m.1555A>G [Pandya et al 1999, Yuan et al 2005] and m.1494C>T [Yuan et al 2007] in individuals with nonsyndromic hearing loss and aminoglycoside-induced hearing loss.

Phenotype Correlations by Gene

See Clinical Description.

Genotype-Phenotype Correlations

MT-TS1. The m.7445A>G pathogenic variant is associated in some families with palmoplantar keratoderma in addition to hearing loss. Individuals who have both the m.7444G>A and m.1555A>G (*MT-RNR1*) pathogenic variants [Pandya et al 2004] or the m.7443A>G pathogenic variant alone do not have skin findings.

Penetrance

MT-RNR1

- Most m.1555A>G pathogenic variants occur as homoplasmic changes; the penetrance of hearing loss is believed to be 100% in those with the pathogenic variant who receive aminoglycoside antibiotics (i.e., all individuals with this pathogenic variant will become deaf with any amount of aminoglycoside in a single dose) – although neonates who were unaffected following treatment with aminoglycosides have been reported [Ealy et al 2011, Göpel et al 2014]. However, aminoglycoside exposure may increase the lifetime risk for developing deafness.
- The penetrance for hearing loss in individuals with the m.1555A>G pathogenic variant who are not exposed to aminoglycosides varies widely (0%-65%) [Bykhovskaya et al 1998, Estivill et al 1998, Ding et al 2009, Lu et al 2010b]. Zhu et al [2014] reported that the heteroplasmy level of the m.1555A>G pathogenic variant correlated with hearing loss penetrance in five families with different heteroplasmy levels; penetrance in these families was 52%, 18.2%, 10%, 26.7%, and 44%.
- The averaged penetrance of eight Chinese families harboring the m.1494C>T pathogenic variant was 31.7% when aminoglycoside-induced deafness was included and 17.5% when it was excluded [Zhao et al 2004, Chen et al 2007].
- Variants m.961T>G and m.961_962delTinsC(n) have been associated with SNHL [Guaran et al 2013] but may be either benign or low-penetrance pathogenic.

Note: It has been suggested that penetrance for hearing loss is lower in some families from China [Young et al 2005, Dai et al 2006, Tang et al 2007].

MT-TS1. The pathogenic variants exist as both homoplasmic and heteroplasmic; therefore, the severity of hearing loss and age of onset vary depending on the mutational load in an individual.

Prevalence

The prevalence of mitochondrial nonsyndromic hearing loss and deafness has been well studied for *MT-RNR1* and *MT-TS1* in many populations.

In a prospective study in the Tianjin Province in China in which 58,000 newborns were screened with both audiologic and genetic methods, Zhang et al [2013] identified a pathogenic mtDNA variant in 1.8% of newborns; however, only one newborn was found to have hearing loss.

MT-RNR1. Hearing loss caused by *MT-RNR1* pathogenic variant m.1555A>G has been observed worldwide (e.g., in the Arab-Israeli, Japanese, Mongolian, Zairean, Spanish, Chinese, Turkish, Balinese, Moroccan, Greek, Polish, Tunisian, and American populations) and is identified in 15% of all individuals with hearing loss and a history of aminoglycoside administration [Fischel-Ghodsian et al 1997].

The prevalence of the m.1555A>G pathogenic variant varies by population (see Table 2).

Table 2. Prevalence of *MT-RNR1* Pathogenic Variant m.1555A>G by Population

Population	Prevalence	Reference(s)
Argentina	0/1,042 newborns	Gravina et al [2007]

Table 2. continued from previous page.

Population	Prevalence	Reference(s)
Australia (European descent)	6/2,856 (0.21%) general population >age 49 years	Vandebona et al [2009]
Brazil	0/8,974 newborns	Nivoloni Kde et al [2010]
China	• 0.14%-0.7% of general population • 1.9%-11% of persons w/NSHL	Lu et al [2010a], Lu et al [2010b], Chen et al [2011], Ji et al [2011], Shen et al [2011], Zhang et al [2012], Han et al [2013], Wei et al [2013], Zhang et al [2013], Xu et al [2014], Jiang et al [2015a], Jiang et al [2015b], Ding et al [2016], Ma et al [2016a]
Europe	18/9,371 (0.19%) children in Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort	Bitner-Glindzicz et al [2009]
Germany	12/7,056 (0.2%) LBW neonates	Göpel et al [2014]
Greece	2 of 478 (0.5%) persons w/early-onset HL	Kokotas et al [2009]
Italy (southern)	6% of persons w/postlingual deafness	Jacobs et al [2005]
Japan	• 1.4% of persons w/early-onset HL • 2% of persons w/late-onset HL • 4.3% of maternally inherited HL	Usami et al [2012b], Yano et al [2014]
Poland	1.1%-3.6% of persons w/HL	Rydzanicz et al [2010], Iwanicka-Pronicka et al [2015]
South Africa	1/204 (0.5%) general population	Bardien et al [2009]
Spain	17% of deaf persons	Bravo et al [2006]
Taiwan	1/1,017 (0.1%) newborns	Wu et al [2011]
Tunisia	2/226 (0.9%) persons w/mitochondrial disease	Mkaouar-Rebai et al [2013]
United Kingdom	6% of persons w/postlingual deafness	Jacobs et al [2005]
United States	• 2/703 (0.3%) neonates in the NICU • 3/1,473 (0.2%) general population • 0.8% of individuals w/adult-onset HL • 0.3%-0.9% of persons w/NSHL	Arnos et al [2003], Ealy et al [2011], King et al [2012], Yelverton et al [2013]

HL = hearing loss; LBW = low birth weight; NICU = neonatal intensive care unit; NSHL = nonsyndromic hearing loss

The prevalence of *MT-RNR1* pathogenic variant m.1494C>T varies by population (see Table 3).

Table 3. Prevalence of *MT-RNR1* Pathogenic Variant m.1494C>T by Population

Population	Prevalence	Reference(s)
Chinese	• 0.014%, 0.029%, & 0.25% of general population • 0.18%-0.64% of persons w/HL	Zhu et al [2009], Lu et al [2010a], Shen et al [2011], Li et al [2012], Zhang et al [2012], Han et al [2013], Wei et al [2013], Zhang et al [2013], Ma et al [2016b]
Japanese	0.7% of persons w/HL	Yano et al [2014]
Poland	1.3% of persons w/HL	Iwanicka-Pronicka et al [2015]
United States	0.07% general population	Ealy et al [2011]

HL = hearing loss

The prevalence of the m.961_962delTinsC(n) pathogenic variants in deaf probands, initially determined by screening of anonymized blood spots from newborns in the state of Texas, revealed a prevalence of approximately 1% [Tang et al 2002]. More recent literature has identified varying frequencies for the three changes in this region [Guaran et al 2013, Yelverton et al 2013, Zhang et al 2013].

MT-TS1. The prevalence of pathogenic variants is 0.8%-1.1% in deaf probands studied from the United States [Arnos et al 2003] and from Mongolia [Pandya et al 1999], and 0.68% in probands from China [Tang et al 2015]. A Japanese family with the m.7511T>C pathogenic variant has been reported [Li et al 2005].

The prevalence of pathogenic variant m.7444G>A was 0.86% in individuals with hearing loss from the United States [Yelverton et al 2013] and 0.4% in individuals with hearing loss of Polish ancestry [Rydzanicz et al 2011], but it was not identified among 513 Greek individuals [Kokotas et al 2010] or 701 Chinese individuals [Chen et al 2014].

The prevalence of m.7511T>C was 1.2% in Japanese individuals with maternally inherited hearing loss [Yano et al 2014], and 0.04% in Chinese individuals with hearing loss [Tang et al 2015].

Genetically Related (Allelic) Disorders

Mitochondrial DNA pathogenic variants are responsible for a heterogeneous group of inherited diseases (see Mitochondrial Disorders Overview) that often cause a progressive neurologic disorder in association with multiorgan involvement (e.g., diabetes mellitus, cardiomyopathy) [McFarland et al 2010, Lightowlers et al 2015].

Differential Diagnosis

Other genetic causes of nonsyndromic hearing loss and deafness need to be considered (see Hereditary Hearing Loss and Deafness Overview and Mitochondrial Disorders Overview).

Aminoglycoside drug toxicity. The hearing loss seen after use of aminoglycosides in individuals without the *MT-RNR1* pathogenic variants m.961_962delTinsC(n) or m.1555A>G results from drug toxicity and is related to the dose administered and the metabolism of the drug (i.e., the peak and trough serum concentrations).

Maternally inherited diabetes mellitus and deafness (MIDD; OMIM 520000). A single base-pair substitution of A to G at position 3243 (m.3243A>G) in *MT-TL1* (NC_012920.1), which encodes tRNA leucine, is associated with MIDD [Suzuki et al 2003, Wang et al 2006]. MIDD accounts for 0.5%-2.8% of diabetes mellitus. The onset of diabetes mellitus occurs in the third decade or later in non-obese individuals. The disease can be acute or slowly progressive with or without insulin dependence, and is characterized by absence of anti-GAD (glutamic acid decarboxylase) antibodies and by rapidly progressive advanced microvascular complications. The deafness is progressive and sensorineural [Suzuki et al 2003].

Maternally inherited diabetes mellitus and deafness (MIDD) is also caused by the *MT-TK* pathogenic variant m.8296A>G [Kameoka et al 1998], *MT-TE* pathogenic variants m.14709T>C and m.14692A>G [Rigoli et al 2001, Wang et al 2016], and *MT-TG* pathogenic variant m.10003T>C [Liu et al 2015]. The penetrance of deafness and diabetes in individuals with MIDD is incomplete and some individuals present with isolated nonsyndromic hearing loss. It is, therefore, important to obtain a family history not only for hearing loss but also for diabetes mellitus.

Management

Evaluations Following Initial Diagnosis

To establish the extent of hearing loss and needs in an individual diagnosed with mitochondrial nonsyndromic hearing loss and deafness, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Complete auditory assessment (See Hereditary Hearing Loss and Deafness Overview.)
- Examination of the skin for evidence of keratoderma

- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Treatment includes the following:

- Appropriate rehabilitation including hearing aids, speech therapy, culturally appropriate language training, and evaluation for eligibility for cochlear implantation [Sinnathuray et al 2003]
- Electric acoustic stimulation (EAS) for individuals with mitochondrial hearing loss with residual hearing in the lower frequencies [Usami et al 2012a]
- Enrollment in educational programs appropriate for the hearing impaired
- For mild keratoderma, use of lotions and emollients; for severe keratoderma, dermatologic evaluation

Prevention of Primary Manifestations

***MT-RNR1*-related aminoglycoside-induced ototoxicity.** Physicians can inquire about a family history of aminoglycoside-induced hearing loss prior to the administration of aminoglycosides, either systemically or locally (e.g., into the cochlea as treatment for Meniere's disease). In individuals with a family history of aminoglycoside-induced hearing loss, alternatives to aminoglycoside treatment should be considered when possible.

In the US, aminoglycoside use is most common in the neonatal intensive care unit; however, the therapeutic imperative of treatment with antibiotics in a neonatal intensive care unit setting does not always lend itself to pre-treatment screening by molecular genetic testing.

- Bitner-Glindzicz et al [2009] report a population frequency of 0.19% for the A to G change in a European cohort of children age seven to nine years who had the pathogenic variant but did not have hearing loss because they were not exposed to aminoglycosides; they make an argument for screening on demand to avoid a preventable cause of hearing loss.
- In a commentary by Boles & Friedlich [2010], the authors suggest a prospective study into the feasibility of screening for these mitochondrial pathogenic variants (especially in busy neonatal units) in order to identify a preventable form of hearing loss.
- In the Tianjin Province in China, screening of 58,000 newborns by audiometry and molecular genetic testing determined that 1.8% of newborns had a pathogenic mitochondrial DNA variant and only one newborn had hearing loss [Zhang et al 2013].

Surveillance

The following are appropriate:

- Annual audiometric assessment to evaluate stability or progression of hearing loss
- Annual examination by a physician to assess for related clinical findings (e.g., palmoplantar keratosis)

Agents/Circumstances to Avoid

Aminoglycosides and noise exposure should be avoided, particularly in individuals with normal hearing who have the m.1555A>G or m.1494C>T *MT-RNR1* pathogenic variant.

Evaluation of Relatives at Risk

In a family in which the mtDNA pathogenic variant is known, prospective molecular genetic testing of at-risk maternal relatives allows early detection of those who have inherited the mtDNA pathogenic variant and would benefit from:

- Avoiding aminoglycosides to prevent onset of hearing loss
- Appropriate early support and management

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Use of aminoglycoside antibiotics during pregnancy in a mother who has the *MT-RNR1* m.1555A>G or m.1494C>T pathogenic variants should be considered only in the absence of other treatment options, as these antibiotics exhibit incomplete placental transfer.

Of note, if the mother has the *MT-RNR1* m.1555A>G or m.1494C>T pathogenic variant, she will pass it on to the fetus; hence, use of aminoglycosides should be avoided in the newborn.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Mitochondrial nonsyndromic hearing loss and deafness is caused by pathogenic variants in mitochondrial DNA (mtDNA) and is transmitted by maternal inheritance.

Risk to Family Members

Parents of a proband

- The father of a proband is not at risk of having the mtDNA pathogenic variant.
- The mother of a proband (usually) has the mtDNA pathogenic variant and may or may not have hearing loss.
- Up to 85% of individuals with mitochondrial nonsyndromic hearing loss have no known family history of hearing loss. The explanation for apparently simplex cases may be the absence of a comprehensive and/or reliable family history or, in rare cases, a *de novo* mtDNA pathogenic variant in the proband.

Sibs of a proband

- The risk to the sibs depends on the genetic load of the mitochondrial pathogenic variant in the mother (e.g., a mother heteroplasmic for a mtDNA pathogenic variant may transmit a low level of mutated mtDNA to her offspring, thus conferring a lower disease risk than a mother homoplasmic for a mtDNA pathogenic variant).
- If the mother has the mtDNA pathogenic variant, all sibs will inherit the variant; however, the risk of hearing loss depends on (a) the mutational load (see Penetrance) and (b) exposure to aminoglycosides.

Offspring of a proband

- All offspring of females with a mtDNA pathogenic variant are at risk of inheriting the pathogenic variant.
- Offspring of males with a mtDNA pathogenic variant are not at risk of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's mother: if the mother of the proband has a mtDNA pathogenic variant, her sibs and mother are also at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Many culturally deaf individuals view medical advances in hearing loss as a threat to the existence of their culture; it is important to acknowledge this point of view. The counseling session provides an opportunity to educate the individual regarding the etiology and natural history of the hearing loss and to discuss appropriate resources for services and information; such counseling is generally well received. Issues of prevention, cochlear implants, reproduction, and family planning should be dealt with in a culturally sensitive manner [Arnos & Oelrich 2002]. (See also Hereditary Hearing Loss and Deafness Overview.)

The following points are noteworthy:

- Communication with individuals who are members of the Deaf community and who sign requires the services of a skilled interpreter.
- Members of the Deaf community may view deafness as a distinguishing characteristic and not as a handicap, impairment, or medical condition requiring a "treatment" or "cure," or to be "prevented."
- Many deaf people are interested in obtaining information about the cause of their own deafness, including information on medical, educational, and social services, rather than information about prevention, reproduction, or family planning.
- The use of certain terms is preferred: probability or chance vs risk; deaf and hard-of-hearing vs hearing impaired. Terms such as "abnormal" should be avoided.

Family planning

- The optimal time for the determination of genetic status and discussion of prenatal testing availability is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are deaf or have a family history of deafness.

Prenatal Testing

Once a mtDNA nonsyndromic hearing loss and deafness-causing variant has been identified in the mother, prenatal testing is possible; however, it is typically not performed.

If the mother is homoplasmic for a pathogenic variant, genetic testing is not needed to predict that the fetus inherited the variant (based on the maternally inherited pattern); therefore, the results of prenatal testing for mitochondrial nonsyndromic hearing loss and deafness do not provide additional information.

If the mtDNA pathogenic variant is identified in the fetal tissue sampled:

- The mtDNA mutational load in amniocytes and chorionic villi is unlikely to correspond to that of other fetal or adult tissues because of mitotic segregation.
- The presence of the mtDNA pathogenic variant does not predict the occurrence, age of onset, or severity of hearing loss.

If the mtDNA variant is not identified in the fetal tissue sampled, the pathogenic variant is likely present in fetal tissue not sampled.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Medical Home Portal**
  Hearing Loss and Deafness
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  Listening and Spoken Language Knowledge Center
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **American Speech-Language-Hearing Association (ASHA)**
  Phone: 800-638-8255; 301-296-5650 (TTY)
  Fax: 301-296-8580
  www.asha.org
- **BabyHearing.org**
  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.
  babyhearing.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org

- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Nonsyndromic Hearing Loss and Deafness, Mitochondrial: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
MT-RNR1	Mitochondrion	Not applicable	MT-RNR1
MT-TS1	Mitochondrion	Not applicable	MT-TS1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Nonsyndromic Hearing Loss and Deafness, Mitochondrial (View All in OMIM)

500008	DEAFNESS, NONSYNDROMIC SENSORINEURAL, MITOCHONDRIAL
561000	RIBOSOMAL RNA, MITOCHONDRIAL, 12S; MTRNR1
580000	DEAFNESS, AMINOGLYCOSIDE-INDUCED
590080	TRANSFER RNA, MITOCHONDRIAL, SERINE, 1; MTTS1

MT-RNR1

Gene structure. See Mitochondrial Disorders Overview. For a detailed summary of gene and protein information, see Table A, Gene.

Pathogenic variants. The m.1555A>G pathogenic variant lies in a highly conserved region of the *MT-RNR1* product, mitochondrial 12S rRNA, which is involved in the binding of aminoglycosides in bacteria. Many genetic factors are presumed to modify the severity and penetrance of hearing loss, although none have been identified [Guan 2011, Jing et al 2015]. Ballana et al [2006] suggested that the reduced penetrance observed in individuals with the m.1555A>G pathogenic variant results from an alteration in the secondary structure of RNA caused by additional sequence changes in *MT-RNR1*.

Variants m.961T>G and m.961_962delTinsC(n) have been described with varying frequencies in persons with hearing impairment and in control groups, suggesting an association with SNHL. Guaran et al [2013] reported varying degrees of hearing loss in six of seven individuals with the m.961T>G variant, hypothesizing that it may represent either a benign variant or a low-penetrance pathogenic allele.

Table 4. *MT-RNR1* Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequence
Pathogenic	m.1555A>G	NA	NC_012920.1
	m.1494C>T	NA	
Uncertain clinical significance	m.961T>G	NA	
	m.961_962delTinsC(n) (961delT+C^{n})	NA	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
NA = not applicable.
1. Variant designation that does not conform to current naming conventions

Normal gene product. See Mitochondrial Disorders Overview.

Abnormal gene product. Pathogenic variants in *MT-RNR1* alter the susceptibility of ribosomes to aminoglycosides by making the rRNA more similar to a bacterial rRNA, leading to increased binding of aminoglycosides to the mitochondrial rRNA, which results in destruction of the sensory hair cells in the inner ear that are involved with auditory function [Bates 2003]. Hamasaki & Rando [1997] demonstrated specific binding of aminoglycosides to the m.1555A>G variant in a 12S rRNA construct. However, the mechanism of action for hearing loss in the absence of exposure to aminoglycosides is unclear.

Pathogenic variants m.1555A>G and m.1494C>T are located in the decoding center of the mitochondrial ribosome, and cause: (1) conformational change of stem-loop structure of aminoglycoside binding site of 12S rRNA similar to the bacterial type ribosome; (2) reduction of mitochondrial protein synthesis; and (3) mis-incorporation of amino acids with or without aminoglycoside exposure [Hobbie et al 2008a, Hobbie et al 2008b]. See also Mitochondrial Disorders Overview.

MT-TS1

Gene structure. See Mitochondrial Disorders Overview. For a detailed summary of gene and protein information, see Table A, Gene.

Pathogenic variants. See Table 3 and Mitochondrial Disorders Overview. Nucleotide m.7445 is located in the precursor for tRNA-Ser(UCN), adjacent to the 3' endonuclease cleavage site.

Many variants in *MT-RNR1* are reported to cause nonsyndromic hearing loss in multiple populations:

- m.7445A>G [Reid et al 1994]
- m.7445A>C [Pandya et al 1999, Jin et al 2007, Chen et al 2008]
- m.7445A>T [Pandya et al 1999, Jin et al 2007, Chen et al 2008]
- m.7462C>T [Uehara et al 2010]
- m.7471dupC (reported as m.7472insC) [Verhoeven et al 1999, Jacobs et al 2005]
- m.7505T>C [Tang et al 2010]
- m.7510T>C [Hutchin et al 2000, del Castillo et al 2002]
- m.7511T>C [Sue et al 1999]

These variants are identified as homoplasmic or heteroplasmic. (For details regarding heteroplasmy refer to Mitochondrial Disorders Overview.)

Table 5. *MT-TS1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequence
m.7443A>G	NA	AC_000021.2
m.7444G>A	NA	
m.7445A>G	NA	
m.7445A>C	NA	
m.7445A>T	NA	
m.7462C>T	NA	
m.7471dupC	NA	
m.7505T>C	NA	
m.7510T>C	NA	
m.7511T>C	NA	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
NA = not applicable

Normal gene product. See Mitochondrial Disorders Overview.

Abnormal gene product. The pathogenic variants m.7445A>G, m.7505T>C, and m.7511T>C have been confirmed to cause a decrease in tRNASer(UCN), and these variants have an important effect on tRNA Ser(UCN) processing or stability [Guan et al 1998, Li et al 2004, Tang et al 2010]. In vitro studies indicate an endonucleolytic processing defect (caused by the placement of a non-cleavable C at the processing junction) as the basis of nonsyndromic hearing loss for the m.7445A>G mitochondrial pathogenic variant [Levinger et al 2001].

The two adjoining variants at positions m.7444 and m.7443 do not alter the cleavage or processing of the tRNA-Ser(UCN) in a similar fashion, therefore, they are unlikely to share this pathogenic mechanism. These three base pairs also encode the stop codon in MT-CO1 (mitochondrially encoded cytochrome *c* oxidase I gene) mRNA on the H strand, and each one converts this "stop" to a sense codon with elongation of the MT-CO1 reading frame by three amino acids, after which it encounters a stop codon.

Chapter Notes

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Published Guidelines / Consensus Statements

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