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Gentamicin Therapy and *MT-RNR1* Genotype

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Introduction

Gentamicin is an aminoglycoside antibiotic that is commonly used to treat sepsis in premature infants. Brand names include Garamycin, Cidomycin, and Setpopal. Gentamicin is administered by injection to treat serious infections caused by Gram-negative bacteria (e.g., *Pseudomonas aeruginosa*, *Proteus* species, *Escherichia coli*, *Klebsiella-Enterobacter-Serratia* species, and *Citrobacter* species), and is used as an adjuvant treatment for infections caused by Gram-positive bacteria (e.g., *Staphylococcus* species) (1). Gentamicin may also be used topically to treat ophthalmic and dermatological infections.

In most patients, prolonged exposure to high gentamicin levels will cause ototoxicity (damage to the inner ear). However, in individuals who carry specific variants in the mitochondrial gene, *MT-RNR1*, a single dose of gentamicin can result in hearing loss. This toxicity occurs in genetically susceptible individuals even though the serum drug level is within therapeutic range (2).

In most studies, 100% of individuals with the *MT-RNR1* variant known as m.1555A>G (NC_012920.1:m.1555A>G) developed hearing loss after receiving aminoglycoside therapy. The onset of hearing loss varies, but once it occurs, the hearing loss is usually moderate to profound, bilateral, and irreversible (3).

Currently, the FDA-approved drug label for gentamicin does not include a statement about *MT-RNR1* However, a 2014 American College of Medical Genetics and Genomics (ACMG) guideline includes the following recommendation: "Single-gene testing may be warranted in cases in which the medical or family history, or presentation of the hearing loss, suggests a specific etiology. For example, testing for mitochondrial DNA mutations associated with aminoglycoside ototoxicity may be considered for individuals with a history of use of aminoglycoside antibiotics" (4, 5).

Drug: Gentamicin

Aminoglycosides such as gentamicin are among the earliest formulations of antibiotics (6). They are effective against most aerobic bacteria, both Gram-positive and Gram-negative. But because they are inactive against anaerobes, they are often used in combination with another antibiotic, such as a beta-lactam antibiotic or a cephalosporin, to increase coverage (7).

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Six aminoglycoside drugs are currently approved for use by the FDA: amikacin, gentamicin, neomycin, paromomycin, streptomycin, and tobramycin. The ending of these drug names, -mycin or -micin, reflects from which genus of bacteria the aminoglycoside was derived from, *Streptomyces* or *Micromonospora* respectively (8).

Aminoglycosides exert antibacterial effects by binding to bacterial ribosomes and inhibiting bacterial protein synthesis. They bind to the 30s ribosomal subunit, which interferes with the decoding site—this is where the ribosome has to accurately select tRNA in accordance with the appropriate mRNA codon. Errors here lead to inappropriate translation of the mRNA codons, so that incorrect amino acids are inserted into the polypeptide chain. This can disrupt elongation of the peptide chain (9, 10).

Like all aminoglycosides, gentamicin is poorly absorbed from the gut, so it is not taken orally. It is either given by injection, with regular blood tests to monitor drug levels, or given topically in the form of drops, cream, or ointment, to treat infections of the eye or skin.

The toxicity of aminoglycosides, along with the discovery of equally potent but less toxic antibiotics, has meant that the use of aminoglycoside injections is reserved for serious infections that are proven, or strongly suspected to be, caused by susceptible bacteria. Aminoglycosides are most commonly used in the treatment of neonatal septicemia, especially in premature babies—over 90% need aminoglycoside therapy during the first weeks of life (11). Aminoglycosides are also used in combination with other antibiotics as surgical prophylaxis in patients who are allergic to penicillin, and for febrile neutropenia, septic shock, and drug-resistant tuberculosis (6).

The main toxicities of aminoglycoside injections are kidney damage (nephrotoxicity) and damage to the inner ear (ototoxicity) (12). Nephrotoxicity primarily involves the proximal tubules and is generally reversible (13). In contrast, aminoglycoside-induced ototoxicity is usually irreversible. Damage may occur to the cochlea—resulting in sensorineural hearing loss—or the vestibular system—causing problems with balance, vertigo, ataxia, nausea, and vomiting. Gentamicin is considered to be more toxic to the vestibular system so is used for vestibular ablation to treat Ménière's disease. Amikacin and neomycin are examples of aminoglycosides that are more toxic to the cochlea (12, 14).

Rarely, neuromuscular blockade can occur after aminoglycoside therapy. The boxed warning on the FDA-approved drug label recommends that aminoglycosides "be used with caution in patients with neuromuscular disorders, such as myasthenia gravis or parkinsonism, because they may aggravate muscle weakness (7)"; whereas the British National Formulary states that aminoglycosides should not be given to patients with myasthenia gravis (15).

Gene: *MT-RNR1*

Mitochondria are the main source of energy in most cells—they use oxygen, sugars, and fats to create energy in the form of ATP. This process is known as oxidative phosphorylation. Any genetic variation that disrupts normal mitochondrial function can have severe effects on health.

Mitochondria have their own genome—it is small, circular, and resembles the bacterial prokaryotes from which they evolved. The mitochondrial genome is passed down from mother to child (maternal inheritance) and contains 37 genes, one of which is the *MT-RNR1* gene ("mitochondrially encoded 12S RNA"). The ribosomal RNA (rRNA) encoded by *MT-RNR1* is essential in the synthesis of the proteins that carry out oxidative phosphorylation.

Consistent with their bacterial origin, mitochondrial rRNA more closely resembles bacterial rRNA than human rRNA. However, at a highly conserved decoding region in the *MR-RNR1* gene, the sequence in humans is distinct from the sequence in bacteria. This difference means that aminoglycosides, which target the decoding region in bacteria, normally do not bind to this region in humans (9).

However, genetic variation in the ribosomal decoding region can result in mitochondrial RNA becoming more similar to bacterial rRNA, thereby facilitating the binding of aminoglycosides. The mechanism is unclear, but aminoglycosides damage the sensory hair cells in the cochlea that mediate hearing (16-18).

The most common *MT-RNR1* variant is a single nucleotide substitution of a guanine at position 1555 for an adenine (m.1555A>G). Individuals with this variant are exquisitely sensitive to aminoglycoside-induced hearing loss, which is moderate to profound, bilateral, irreversible, and may have a rapid onset. Even a single dose of aminoglycoside can be sufficient to cause ototoxicity (2, 19).

Genetically susceptible individuals who are not exposed to aminoglycosides may nonetheless develop hearing loss, referred to as "non-syndromic mitochondrial hearing loss." The course of hearing loss may be affected by the presence of additional genetic factors as well as environmental factors, such as exposure to loud noise. However, normal hearing is usually preserved until at least 44 years of age (2).

The prevalence of the m.1555A>G variant varies among different populations. In the US, the population prevalence is estimated to be 0.09%, and in the UK, 0.20% (5, 20, 21). In hearing impaired populations, the prevalence is much greater, but the estimates vary widely based on study differences, such as the age of onset of hearing loss and whether there has been exposure to aminoglycosides. Estimates include a prevalence of 3.5% among the hearing impaired population in Japan (22), 5% among deaf individuals in Indonesia (23), and 6% of individuals with post-lingual hearing loss from the UK and Southern Italy (24). Additionally, a prevalence of 15% has been reported in "ethnically diverse patients in the United States with hearing loss after aminoglycoside exposure" (25), and in 15-20% of individuals from Spain with hearing loss (26).

The m.1555A>G variant is the most well studied *MT-RNR1* variant with regards to aminoglycoside ototoxicity, but other mitochondrial variants are also strongly associated with hearing loss. In 10 small studies, all individuals with the 1494C > T (NC_012920.1:m.1494C>T) variant developed hearing loss after receiving an aminoglycoside antibiotic. A 827A>G (NC_012920.1:m.827A>G) variant, and variants at position 961, have also been associated with non-syndromic hearing loss, both with and without the use of aminoglycosides (3).

Several studies have highlighted the complex issues raised by screening for pathogenic *MT-RNR1* variants. The aim of screening is to prevent avoidable hearing loss in genetically susceptible individuals by administering an alternative antibiotic whenever possible. Issues include the costs of universal screening, for example, as part of the newborn screening program—given that the prevalence of m.1555A>G is thought to be 1 in 385 Caucasians (2, 27, 28) —versus limiting genetic testing to a case-by-case basis (e.g., patients with tuberculosis, children with leukemia, individuals with cystic fibrosis, and surgical patients allergic to beta-lactam antibiotics)(5, 29).

In the US, aminoglycosides are most commonly used in the neonatal intensive care unit, where acute, life-threatening sepsis means that aminoglycoside therapy cannot be delayed to wait for the results of genetic testing (30). However, recent advances in screening has allowed for rapid, accurate and inexpensive testing (31-33). One potential alternative would be to screen all pregnant women, because mitochondrial variants are maternally inherited and m.1555A>G is almost always homoplasmic ("homoplasmy" is when all the mitochondrial DNAs in a cell are identical; when they are not, it is called "heteroplasmy") (5, 19, 34).

Genetic screening may provide more benefit if aminoglycoside use becomes more widespread because of growing resistance to other antibiotics. Or screening could be reserved for countries where aminoglycosides are still commonly used, despite their toxicity, because they are inexpensive (35). In countries where the use of aminoglycosides is more common, a quarter of people with aminoglycoside-induced hearing loss have maternal relatives who also have drug-related hearing loss (36, 37).

A report from the World Health Organization's Essential Medicines and Pharmaceutical Policies comments that "pre-treatment screening is an important consideration to prevent aminoglycoside related hearing loss but given cost and access issues, asking about a maternal family history of deafness may be more practical" (38).

Genetic Testing

The NIH's Genetic Testing Registry (GTR) provides examples of the genetic tests that are currently available for the *MT-RNR1* gene. Targeted mutation panels vary among testing laboratories, but most laboratories routinely test for m.1555A>G.

MT-RNR1 variants are associated with two conditions: aminoglycoside hypersensitivity resulting in post-exposure deafness and nonsyndromic mitochondrial hearing loss that tends to develop gradually over time. While the presence of an *MT-RNR1* variant indicates a high risk of aminoglycoside ototoxicity, the test results do not predict the age of onset or severity of nonsyndromic mitochondrial hearing loss (19).

Therapeutic Recommendations based on Genotype

Excerpt from the American College of Medical Genetics and Genomics (ACMG) Guideline for the Clinical Evaluation and Etiologic Diagnosis of Hearing Loss:

For individuals lacking physical findings suggestive of a known syndrome and having medical and birth histories that do not suggest an environmental cause of hearing loss, a tiered diagnostic approach should be implemented.

Pretest genetic counseling should be provided, and, with patient's informed consent, genetic testing should be ordered.

Single-gene testing may be warranted in cases in which the medical or family history, or presentation of the hearing loss, suggests a specific etiology. For example, testing for mitochondrial DNA mutations associated with aminoglycoside ototoxicity may be considered for individuals with a history of use of aminoglycoside antibiotics.

Please review the complete therapeutic recommendations that are located here: (4).

Nomenclature

Common allele name	Alternative names	HGVS reference sequence			dbSNP reference identifier for allele location
		Genomic	Coding	Protein	
m.1555A>G	A1555G	NC_012920.1:m.1555A>G	NA	NA (encodes ribosomal RNA)	rs267606617
m.1494C>T	C1494T	NC_012920.1:m.1494C>T	NA	NA (encodes ribosomal RNA)	rs267606619
m. 827A>G	A827G	NC_012920.1:m.827A>G	NA	NA (encodes ribosomal RNA)	rs28358569

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Version History

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