

Use Case Template for ISCC Use Case Workgroup

- I. **Specialty/Professional Society:** American Academy of Pediatrics
American Academy of Otolaryngology-Head and Neck Surgery
- II. **Type of Use Case:** Gene-Based Intervention for Aminoglycoside Sensitivity - Pharmacogenomics/Family History
- III. **Title:** Mitochondrial DNA mutation A1555G and aminoglycoside-induced hearing loss and deafness

Key Takeaway

- Carriers of the mutation who undergo even one course of aminoglycoside antibiotic therapy can suffer severe and irreversible loss of hearing.

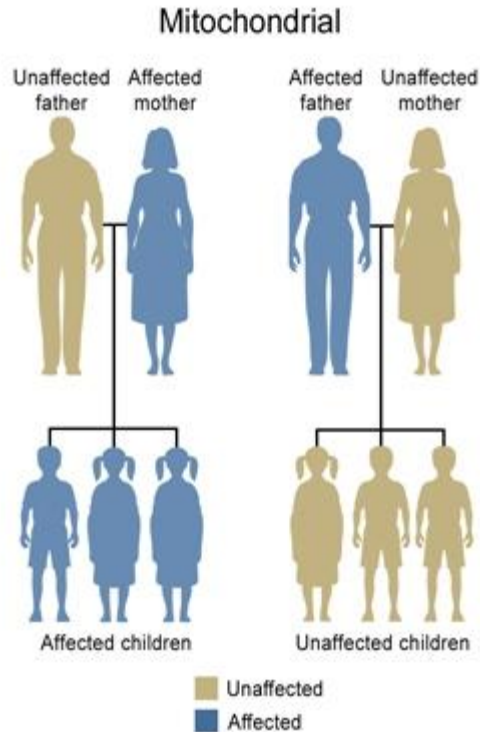
IV. **Clinical Scenario:**

A term newborn is noted to have an elevated temperature (39 C) and an elevated respiratory rate (45/minute). Sepsis is suspected, blood cultures and laboratory studies are obtained and the child is moved to the intermediate care unit for IV antibiotics (Clinical guidelines recommend Ampicillin and Gentamicin for rule out sepsis). When the mother is informed of the need to start antibiotics she tells the care team that she has hearing loss that she says occurred after receiving an antibiotic that she doesn't remember. "Some kind of mycin I was told," She is very concerned that this could happen to her child and asks that the baby be 'checked out'.

A quick PubMed search using the terms 'antibiotics' and 'hearing loss' identifies many articles that discuss the risk of hearing loss in individuals exposed to aminoglycoside antibiotics that have a specific mitochondrial pathogenic variant ('mutation'). Given this information the decision is made to start the baby empirically on Ampicillin and a cephalosporin and pursue investigation of the mitochondrial variant.

V. **Description of relevant genomic information and how this information would be used:**

Mitochondria undergo a special type of inheritance called maternal inheritance. Only the mother contributes mitochondria to her children. Thus, when a mitochondrial DNA mutation occurs in one of the maternal mitochondrial genes, she will pass it to **all** of her offspring. Males do not pass mitochondria to **any** of their offspring.



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Mitochondria are involved in the intermediate metabolism of many ingested substances and drugs. Mutations in two mitochondrial genes, MT-RNR1 and MT-TS1, confer susceptibility to nonsyndromic mitochondrial hearing loss or deafness after treatment with aminoglycoside antibiotics (e.g. gentamicin, kanamycin, streptomycin). Specifically a change from alanine to glycine in position 1555 (“A1555G mutation”) in the MT-RNR1 gene has been associated with aminoglycoside-induced (as well as late onset nonsyndromic) sensorineural hearing loss. There are population differences in the prevalence of the A1555G mutation: 2.9% - 5.3% in Asian, 0.6% - 2.5 % of Caucasian and as high as 17% of the Spanish population with nonsyndromic hearing loss. Therefore, Asian and Spanish populations have the highest frequency of the A1555G mutation followed by other populations of European ancestry. A higher frequency of the mutation is found among the deaf population with a history of aminoglycoside exposure accounting for 15-30%. Both males and females are affected equally. The hearing loss is generally bilateral and in the moderate to profound range. Once exposed to aminoglycoside antibiotics, most individuals with the variant go on to develop hearing loss or deafness³⁻⁶.

- VI. Recommended clinical action:** Genetic testing for the A1555G mutation should be performed in individuals with moderate to profound hearing loss in the presence of either a family history of hearing loss suggestive of maternal inheritance or onset of hearing loss following administration of an aminoglycoside antibiotic such as gentamicin. For women who carry the A1555G mutation, with or without hearing loss, carrier testing is recommended for other maternal family members with instructions for their children and all

other maternal members to strictly avoid the administration of aminoglycoside antibiotics if they carry the mutation. Carriers of the mutation who undergo even one course of aminoglycoside antibiotic therapy can suffer severe and irreversible loss of hearing. As a cautionary note, lack of identification of the mutation does not rule out hearing loss attributable to other variants within mitochondrial genes (e.g. the MT-RNR1 gene) or due to other genes known to be involved in hearing loss⁹.

a. Practice based learning activities:

- In a clinical practice that routinely uses aminoglycoside antibiotics (e.g. neonatology, infectious disease) perform review of 10 charts of patients receiving an aminoglycoside to see if family history of hearing loss is documented prior to initiation of antibiotics. If this is not documented, develop a system to capture family history of hearing loss prior to use of aminoglycoside antibiotics [particularly if your population has a significant proportion of Hispanic (especially Spanish) or Asian patients].
- Identify laboratories that perform testing for this mutation⁸

VII. Family Implications: Hearing loss caused by this pathogenic variant (A1555G) is consistent with a maternal pattern of inheritance.

VIII. Evidence to support the use of genomic information in this scenario:

ACMG Practice Guideline: Genetics Evaluation Guidelines for the Etiologic Diagnosis of Congenital Hearing Loss

http://www.ncbi.nlm.nih.gov/books/NBK55827/bin/Hearing_Loss.pdf

http://www.ncbi.nlm.nih.gov/books/NBK55827/bin/Visio-hearing_loss.pdf

<http://www.ncbi.nlm.nih.gov/pubmed/18595997>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110944/>

IX. References and Resources:

1. Fischel-Ghodsian, N., Prezant, T.R., Bu X., Oztas, S. Mitochondrial ribosomal RNA gene mutation in a patient with sporadic aminoglycoside ototoxicity. 1993. *Am Journal of Otolaryngology*, Nov.-Dec 14(6) 399-403.
2. Liu XZ, Angeli S., Ouyang, XM, LIU, W., Ke, X.M., Liu, Y.H., Liu, S.X., Deng, X.W., Yuan, H., Yan, D. . 2008. Audiological and genetic features of mtDNA deafness. *Acta Otolaryngologica*, Jul 128(7):732-8.
3. Pandya, Arti. Nonsyndromic Hearing Loss and Deafness, Mitochondrial Includes: MT-RNR1- Related Hearing Loss and Deafness (Aminoglycoside Ototoxicity), MT-TS1-Related Hearing Loss and Deafness. Last update April 21, 2011. GeneReviews. <http://www.ncbi.nlm.nih.gov/books/NBK1422/>.
4. Understanding the Genetics Of Deafness – A Guide for Patients and Families. Harvard Medical School Center for Hereditary Deafness. <http://hearing.harvard.edu/info/GeneticDeafnessBookletV2.pdf>

5. Vivero R.J., Ouyang X., Yan D., Du L., Liu W., Angeli S.I., Liu X.Z. . 2012. Mitochondrial DNA Mutation Screening in an Ethnically Diverse Nonsyndromic Deafness Cohort. *Genet Test Mol Biomarkers*. Sept, 16(9):1146-8.
6. Xing G., Chen Z., Cao X. 2007. Mitochondrial rRNA and tRNA and hearing function. *Cell Res*. Mar, 17(3): 227-239.
7. Yan D, Tekin M, Blanton SH, Liu XZ. 2013. Next Generation Sequencing in Genetic Hearing Loss *Genet Test Mol Biomarkers* 17:581-7.
8. NIH Genetic Testing Registry.
Aminoglycoside-induced deafness:
<http://www.ncbi.nlm.nih.gov/gtr/conditions/C1838854/>
Aminoglycoside response:
<http://www.ncbi.nlm.nih.gov/gtr/conditions/CN184091/>
9. Guan MX et al. Mutation in TRMU related to transfer RNA modification modulates the phenotypic expression of the deafness-associated mitochondrial 12S ribosomal RNA mutations. *Am J Hum Genet*. 2006 Aug;79(2):291-302.
<http://www.ncbi.nlm.nih.gov/pubmed/16826519/>
10. Consumer resources: Genetics Home Reference
<http://ghr.nlm.nih.gov/condition/nonsyndromic-deafness>

X. Additional Information:

<http://ghr.nlm.nih.gov/handbook/inheritance/inheritancepatterns>