R.C.P.U. NEWSLETTER

Editor: Heather J. Stalker, M.Sc.
Director: Roberto T. Zori, M.D.

R.C. Philips Research and Education Unit
Vol. XXVI No. 2 **A statewide commitment to the problems of intellectual disabilities** **June 2015**

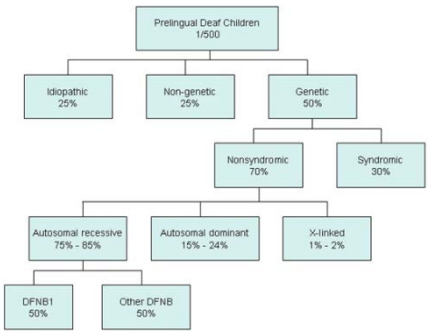
R.C. Philips Unit ♦ Division of Pediatric Genetics, Box 100296 ♦ Gainesville, FL 32610 ♦ (352)294-5050
E Mail: stalkhj@peds.ufl.edu; zorirt@peds.ufl.edu
Website: http://www.peds.ufl.edu/divisions/genetics/newsletters.htm

Genetic hearing loss in the pediatric setting: Common genetic etiologies, testing, and counseling implications.

Amy Jonasson, MS, CGC

Introduction: Hearing loss is a highly prevalent condition in the general population of the United States. The Newborn Screening Program estimates that 1.1 per 1,000 newborns have congenital hearing loss, and follow-up data suggests 3.1% of children have hearing loss within the frequencies necessary for speech (1,2). Hearing loss is highly variable in terms of both type, and underlying etiology. The different types of hearing loss are classified as conductive, sensorineural, central auditory dysfunction (auditory neuropathy), or mixed (a combination of conductive and sensorineural, for example). The type of hearing loss and any additional findings can help narrow down the possible underlying etiology for an individual's hearing loss.

Studies have shown that 50% of hearing loss is due to an underlying genetic etiology, 25% is acquired, and the remaining 25% is due to "idiopathic" or an unidentified cause (2,3). Of the 25% currently classified as idiopathic, a portion could have a multifactorial (genes combined with environment) cause, a digenic/multigenic mechanism, or an as yet unidentified genetic etiology underlying their hearing loss. Therefore, the 50% of cases attributed to genetic causes could actually be an underestimate. Within the 50% of hearing loss known to be genetic, there are also multiple classes. Hearing loss can be syndromic, meaning an individual has hearing loss along with other findings such as medical issues, developmental delay, dysmorphic features, or congenital malformations, or non-syndromic, meaning an individual has hearing loss without any other medical issues or features. Genetic hearing loss can also be divided into inheritance patterns (1,3). The majority (approximately 77%) of non-syndromic genetic hearing loss is due to autosomal recessive inheritance, 22% of non-syndromic hearing loss is autosomal dominant in inheritance, and the remaining 1% is inherited either by X-linked or mitochondrial inheritance.



Genetic Etiologies of Hearing Loss: When a child presents for a genetic evaluation of their hearing loss, multiple pieces of information are needed in order to determine the appropriate testing strategy. A complete medical history is important in order to rule out possible acquired etiologies such as CMV infections, postnatal bacterial meningitis, and/or otitis media. A thorough physical exam can help determine whether a syndromic or non-syndromic etiology is most likely, and a family history (pedigree) can help determine whether the individual is an isolated case within a family, whether there are siblings with hearing loss (autosomal recessive hearing loss), or whether one of the parents is affected (a dominantly inherited condition). Additionally, appropriate referrals may be necessary, such as to an ENT specialist, to rule out any physiologic issues such as pathology consistent with acquired hearing loss or finding suggestive of conductive hearing loss (2). Ophthalmology evaluations may also be helpful in identifying a potential dual-sensory impairment. The newborn hearing screen results can help clarify whether the hearing loss onset in the neonatal period, and a developmental history could help identify whether the onset is prelingual or postlingual. All of these factors can help determine the most appropriate testing strategy to determine the underlying etiology of hearing loss.

Common Syndromic Hearing Loss Conditions: Syndromic hearing loss conditions accounts for approximately 30% of hearing loss attributed to a genetic cause (1). Syndromic hearing loss are highly variable in the associated features. These conditions can be inherited in a variety of different patterns. Sometimes, the family history can suggest a particular syndrome or inheritance pattern, and other times the proband will be the only individual in the family.

Waardenburg syndrome: Waardenburg syndrome is an autosomal dominant condition characterized by hearing loss and pigmentation differences in the hair and skin. There are four different types of Waardenburg syndrome (called WS1, WS2, WS3, and WS4), and the hearing loss occurs in approximately 45-80% of individuals with this condition depending on the type. The hearing loss is typically congenital and can range from mild to profound. Additionally, individuals with Waardenburg syndrome may have a white forelock, pale colored eyes, heterochromia (differences in eye color), and premature grey hair. The genes associated with Waardenburg syndrome are PAX3 (WS1 and WS3), MITF (WS2), SNAI2 (WS2), SOX10 (WS2 and WS4), EDNRB (WS4), and EDN3 (WS4).

Pendred syndrome: Individuals with Pendred syndrome are seen with congenital sensorineural hearing loss that is generally in the severe or profound range of loss. Other features include: temporal bone abnormalities, cochlea hypoplasia, vestibular dysfunction, and euthyroid goiter. Pendred syndrome is highly variable even among family members with the same mutation. It is an autosomal recessive condition, and mutations in SLC26A4 account for approximately 50% of cases. Mutations in FOXI1 and KCNJ10 are less frequently reported. Of note, mutations in the SLC26A4 gene can also cause non-syndromic sensorineural hearing loss (called DFNB4) with similar vestibular issues to those seen in Pendred syndrome.

Usher Syndrome: Individuals presenting with both hearing and vision loss should be evaluated for Usher syndrome as it is the most common cause of dual-sensory impairment. Usher syndrome is an autosomal recessive condition characterized by hearing loss, which can range from profound congenital hearing loss to progressive postlingual hearing loss, balance issues, and a vision disorder called retinitis pigmentosa (RP). The degree of hearing loss, vision difficulties, and balance issues depends on the type of Usher syndrome. Thus far, 9 genes are implicated in Usher syndrome, and multiple additional loci have been identified as well. Type 1 is caused by mutations in CDH23, MYO7A, PCDH15, USH1C, and USH1G. Mutations in USH2A and GPR98 cause Usher syndrome type 2, and at least 2 more genes are yet unidentified. The gene CLRN1 is the only gene currently known to cause Usher syndrome type 3, but at least one other gene causing the type 3 phenotype remains unidentified.

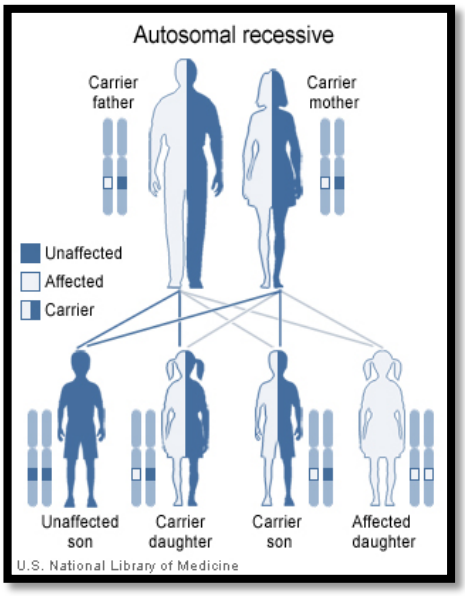
Alport syndrome: This condition affects multiple body systems, and is associated with progressive sensorineural hearing loss in childhood along with renal disease and ocular findings. Alport syndrome (AS) can be inherited in autosomal dominant, autosomal recessive, and X-linked patterns. The mode of inheritance plays a role in the age of onset and type, as well as the severity, of features a person will experience. Mutations in COL4A5 cause X-linked AS, and both the autosomal recessive and the autosomal dominant forms are caused by mutations in the COL4A3 and COL4A4 genes. The type of AS is determined in part by the clinical presentation of the patient, in combination with the family history to determine who else in the family is affected, the sex of the affected individual, and their relation to other affected family members.

Microdeletion and Microduplication syndromes: Some microdeletion and microduplication syndromes result in an increased incidence of hearing loss (4). One example of this is the 22q11.2 microdeletion syndrome, also called VCFS or DiGeorge syndrome. These individuals often have multiple system involvement including: dysmorphic facial features, developmental delay, medical issues, and/or congenital birth defects. If a child has hearing loss in addition to many, seemingly unrelated medical issues, developmental delay, or multiple problems at birth, a chromosomal microarray is appropriate to try and identify a microduplication or microdeletion underlying the complex presentation.

Non-syndromic Hearing Loss: Individuals with hearing loss without any additional complications such as birth defects, learning disability, developmental delay, or dysmorphic features are classified as having non-syndromic hearing loss. Non-syndromic hearing loss is mostly sensorineural, but can be central auditory dysfunction, conductive, or mixed in some instances. Additionally, autosomal recessive, X-linked, and dominant forms of non-syndromic hearing loss are reported. As with syndromic forms of hearing loss, not all the genes implicated in non-syndromic hearing loss are known. Therefore, a complete family history is important to try to narrow down the possible transmission/inheritance pattern.

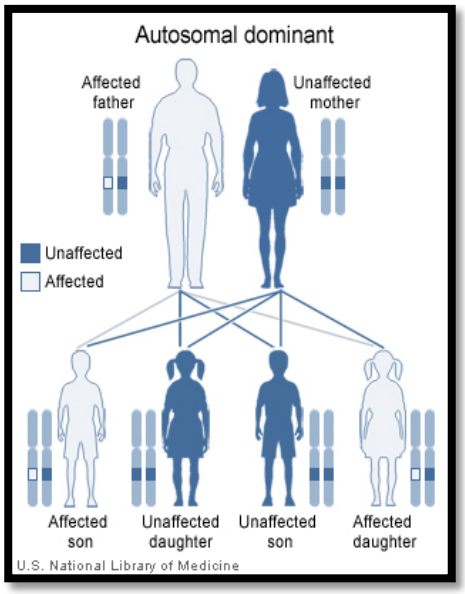
The majority of non-syndromic hearing loss is due to genes that are inherited in an autosomal recessive pattern (approximately 77%) (1). About 22% of non-syndromic hearing loss is autosomal dominant, and 1% is sex linked (either mitochondrial or X-linked). However, as our knowledge on mitochondrial disease has expanded, it appears that hearing loss due to mitochondrial inheritance appears to be greater than previously reported.

Autosomal Recessive non-syndromic Hearing Loss: Generally, autosomal recessive inheritance is considered when there is only one generation with hearing loss. Siblings to the proband may also have the condition, but multiple generations are rarely affected. When a child is affected with an autosomal recessive condition, both parents are carriers of the genetic condition, and do not typically display any of the condition's features. According to the Hereditary Hearing Loss Homepage (5) there are over 60 genes implicated in autosomal recessive hearing loss, and numerous other loci are identified as well.

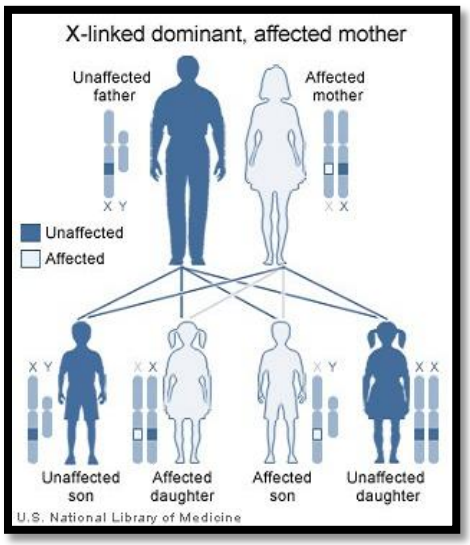


Approximately 50% of patients with non-syndromic sensorineural hearing loss and a negative family history will have a mutation in the GJB2 gene, or gap junction beta 2, also called Connexin26. Connexin26 is seen in many different types of cells, including the inner ear or cochlea. There are over 90 reported mutations within GJB2, and a minority of these mutations have been implicated in autosomal dominant hearing loss. Another gap junction protein, GJB6, works similarly to GJB2 and is implicated in autosomal recessive, and less frequently in autosomal dominant, hearing loss. As mentioned in the syndromic portion of this article, SLC26A4 mutations can cause autosomal recessive non-syndromic sensorineural hearing loss with some mutations. SLC26A4 is the second most common gene implicated in autosomal recessive non-syndromic sensorineural hearing loss. If a child presents with an auditory neuropathy type hearing loss, OTOF could be a consideration for testing. The OTOF gene codes for a protein called otoferlin, and is implicated in some cases of non-syndromic autosomal recessive auditory neuropathy.

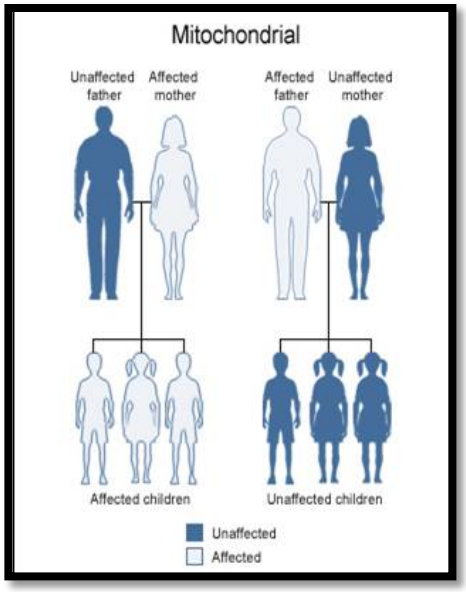
Autosomal Dominant non-syndromic Hearing Loss: There are over 30 genes implicated in autosomal dominant non-syndromic hearing loss, and there are multiple genes and/or loci that remain undiscovered. Generally, an autosomal dominant inheritance pattern means that the trait, in this case hearing loss, appears in every generation and is passed on from parent to child. However, autosomal dominant traits can also appear in an isolated individual within a family, called a "de novo" event and a family history is negative for the trait, such as hearing loss. Unlike recessive hearing loss, one gene in particular is not linked to a significant proportion of dominant hearing loss.



X-linked non-syndromic hearing loss: If there are multiple generations of males with hearing loss, and the genetic etiology for the hearing loss could be x-linked. Currently, there are 5 genes that are known to cause X-linked hearing loss, although as seen in the other inheritance patterns, there are multiple unidentified genes and/or loci segregating among families. Most of the genes implicated in X-linked hearing loss cause progressive sensorineural or mixed hearing loss in the severe to profound range. An X-linked loci, called DFNX3, causes mixed conductive-sensorineural hearing loss due to the stapes bone being fixated. Adult females with this condition sometimes manifest with bilateral mild to moderate sensorineural hearing loss in adulthood. This example highlights a common feature of X-linked inheritance, as females can manifest features of the condition, but they are generally less severe and are later in onset as compared to males with the condition.



Mitochondrial inherited non-syndromic hearing loss: Mitochondrial conditions have a unique pattern of inheritance, sometimes called "maternal inheritance". Genetic conditions due to mutations in the mitochondrial DNA affect both males and females, but can only be inherited through females. None of an affected male's children will have the condition, since mitochondria are not present in sperm cells. Hearing loss is one of the most frequent symptoms seen in mitochondrial disorders. One example is the 7510T->C and 7511T->C mutations which cause non-syndromic sensorineural hearing loss. Another example is the condition called "Maternally Inherited Diabetes and Deafness" (MIDD), which is characterized by hyperglycemia and high tone hearing loss in childhood to late adulthood. Mutations in the MT-TL1, MT0TK, and MT-TE subset of the mitochondrial genome are causative in MIDD.



There are a few particular mutations in the mitochondrial DNA that cause deafness, or a more severe level of hearing loss, when exposed to antibiotics containing aminoglycosides. For example, mutations at nucleotide 961 within the 12SrRNA are reported to cause this aminoglycoside exposure related deafness, as well as 1555A->G and 1494C->T.

Diagnostic Testing options in Hearing loss: Determining an underlying genetic etiology for a child's hearing loss is very dependent on whether it is syndromic or non-syndromic. If a child has syndromic hearing loss, the features seen in addition to the hearing loss generally point towards an appropriate testing strategy and the most likely candidate gene or genes. A microarray could be considered if a child has many nonspecific findings, such as dysmorphic features, multiple medical issues, or intellectual deficiency. If a child presents with non-syndromic or syndromic hearing loss, sometimes the family history can suggest an inheritance pattern. Additionally, the type of hearing loss, age at diagnosis, family history, and the severity of the loss can help determine the most appropriate genes to start with.

Next-generation Sequencing Panels: Testing single genes one at a time makes obtaining a genetic diagnosis very time intensive as well as expensive. There are many genetic laboratories that now offer panels of multiple genes implicated in hearing loss on a clinical basis. Depending on the situation, these panels of multiple genes, called next-generation sequencing panels, may be a more cost effective way to obtain a genetic diagnosis (6). When autosomal recessive hearing loss is suspected, these panels are generally considered as the next step after GJB2 is ruled out as a potential cause.

Some testing strategies begin with an audioprofile to distinguish high frequency loss from low frequency loss as well as progressive vs. non-progressive hearing loss (6,7), as many of the known genes implicated in autosomal dominant non-syndromic deafness are seen with a specific audioprofile. By narrowing down the number of genes tested for in the suspicion of an autosomal dominant hearing loss, testing costs can usually be cut and the test can be targeted to the proband.

Research Testing Options: There are many current studies describing the utility of whole exome sequencing and genome-wide copy number variant mapping to identify additional genetic causes of hearing loss. Research testing options do provide us with novel genes and loci that could be implicated in the genetic basis for individuals that have negative results on multi-gene panels. However, research results need to be confirmed by a clinical lab in order to be used for a patient's management. Additionally, research studies do not always report results, and if the study does report results, it could be months or years later in comparison to clinical testing.

Genetic Counseling Implications of a Confirmed Genetic Diagnosis: There are a wide variety of reasons why families are interested in learning the genetic etiology of a child's hearing loss. Sometimes, parents are interested in recurrence risks for future children, or they may feel as though something they did pre- or post-natally "caused" their child's hearing loss. A genetic diagnosis can sometimes alleviate these feelings of anxiety, guilt, or blame. Additionally, if there is a family history of hearing loss, this information can be distributed among family members, for individuals that are both unaffected and affected. There can sometimes be multiple different genetic etiologies of hearing loss within a family, particularly as deaf adults often marry other deaf adults. When two or more genetic types of hearing loss are present in one family, it is important to clarify through testing other family members which genetic etiology a family member's hearing loss is attributed to. Genetic testing becomes less cost-prohibitive for other affected family members once one individual has a confirmed genetic diagnosis. In the case of a negative family history, the parents will have concrete information on the underlying etiology, which may aid in coping with a child's hearing loss as well as an understanding of future recurrence risks.

When a genetic diagnosis for hearing loss is made, it gives both the proband and their family a specific recurrence risk for other individuals in the family to have future children with hearing loss. It could also help to identify individuals that may be at risk to develop hearing loss in some cases. For example, if a child is identified with a recessive hearing loss, it provides the parents with a 25% recurrence risk for any additional children to have hearing loss. Confirming the genetic diagnosis will also give the child the option for carrier testing in his or her future partners to further clarify to have a child with hearing loss. Other individuals in the family, such as siblings to a child with hearing loss, can utilize the information similarly, and receive carrier testing for both them and their partners.

Conclusion: Hearing loss is a variable condition caused by a multitude of etiologies, only one of which is genetics. Making a genetic diagnosis in a child presenting with hearing loss is difficult, as the underlying genetic etiologies are highly variable and not all genes associated with hearing loss are identified. As research studies identify additional genes and loci associated with both syndromic and non-syndromic hearing loss, we will be able to establish a genetic diagnosis in individuals with negative testing. By identifying a genetic etiology for an individual's hearing loss, we are able to counsel the individual and their family about the family's specific recurrence for hearing loss.

Resources for Families:

Alexander Graham Bell Association for the Deaf and Hard Of Hearing
Web: http://www.listeningandspokenlanguage.org

American Society for Deaf Children:
Web: www.deafchildren.org
e-mail: asdc@deafchildren.org

National Association of the Deaf (NAD):
Web: www.nad.org

Florida School for the Deaf and Blind:
Web: http://www.fsdb.k12.fl.us/index.php/contact-us/

References:

1. Mehra, S., Eavey, R., Keamy, D., *The epidemiology of hearing impairment in the United States: Newborns, children, and adolescents.* Otolaryngology- Head and Neck Surgery. 140:461-472; 2009
2. Morton, N.E., *Genetic Epidemiology of Hearing Impairment.* Annals New York Academy of Sciences: Genetic Epidemiology. P16-31. Accessed March 2015.
3. Lin, J., and Oghalai, J., *Towards an Etiologic Diagnosis: Assessing the Patient with Hearing Loss.* Advanced Otorhinolaryngology. 70: 20-36; 2011
4. Haraksingh, R., Fereshteh, J., et. al., *Exome sequencing and genome-wide copy number variant maping reveal novel associations with sensorineural hereditary hearing loss.* BMC Genomics 15:1155 2014.
5. VanCamp, G., Smith, RHJ., *The Hereditary Hearing Loss Homepage.* Available online. 2010 Accessed April 2015.
6. Hilgert, N., Smith, RHJ., VanCamp, G. *Forty-six genes causing nonsyndromic hearing impairment: which ones should be analyzed in DNA diagnostics?* Mutation research 681(2-3):189-196. 2009.
7. Smith, R., Shearer, A., Hildebrand, M., Van Camp, G., *Deafness and Hereditary Hearing Loss Overview.* Gene Reviews [Internet] Updated January 2014. Accessed March 2015.

ABOUT THE RCPU:

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate intellectual disabilities through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.

Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of intellectual disabilities. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

Acknowledgments:

The RCPU Newsletter is funded by the Raymond C. Philips Research and Education contract with the Department of Health, Children's Medical Services.