What’s new in genetic testing for hearing impairment?

BY ALI A DANESH

Often the first question following the diagnosis of a hearing loss is ‘why?’ In this article Ali Danesh explores the advances made in uncovering ‘why’ from a genetics perspective. Ali describes the panel of genetic tests now commercially available to clinicians to help patients and families understand the underlying genetics of hearing loss.

Auditory clinicians have daily encounters with a routine question from their patients: “Why do I have hearing loss?” For many, the response is a straightforward answer which includes factors such as advanced age, noise exposure, or active ear diseases. However, for a large number of patients the underlying reason for their hearing loss is not entirely clear and this is where the question of genetic factors arises. It has been known that genetic factors contribute to almost 50% of hearing losses. Out of almost 22,000 genes that humans carry in their cells, around 10% of them contribute to human communication and there is at least one gene causing hearing loss on each chromosome that we humans have (including the Y chromosome in males). Therefore, having proper knowledge about the available genetic tests for hearing loss is crucial for both clinicians and their patients.

Why is genetic testing important for hearing loss?

The application of genetic hearing tests has many advantages. It provides a better understanding of individual case management, it helps in the identification of potentially co-existing conditions with delayed onset, and it assists in decisions for family planning. Genetic hearing losses can be syndromic (i.e. associated with additional phenotypic features) or non-syndromic. Genetic hearing losses are inherited through a variety of genetic transmission modes. A great majority of genetic hearing losses are inherited through recessive and dominant modes of inheritance. Some less common modes of inheritance include X-linked, Y-linked and mitochondrial DNA inheritance. Sloan Heggen et al. (2016) employed comprehensive genetic tests on 1,119 cases with hearing loss [1]. They were able to identify 440 patients (39%) with genetic hearing loss. Bilateral hearing loss was detected in almost all of their cases except for one unilateral case with a variant gene for a family with branchio-oto-renal (BOR) disorder.

What kind of genes can be evaluated?

Genetic testing centres for hearing loss can test for a variety of syndromic and non-syndromic aetiologies. These tests employ next-generation sequencing technology and tests for mutations of connexin disorders (e.g. GJB2, GJB6), and disease specific analyses for conditions such as Usher’s syndrome, branchio-oto-renal abnormalities and Pendred syndrome. Recently, the American College of Medical Genetics and Genomics (ACMG) provided guidelines for the use of next-generation sequencing (NGS) for the genetic testing of hearing loss [2]. These guidelines emphasise in-depth otologic and audiologic evaluations prior to genetic testing. In cases where there are suspicions for hearing loss, the guidelines further recommend use of single gene tests, genomic sequencing and chromosomal studies. The advantage of NGS is that in contrast to older techniques where only sequencing of a single DNA fragment was employed, the NGS provides this process across millions of DNA fragments. This capability provides low error probability and the highest accuracy for gene sequencing. The ACMG guidelines describe the NGS technologies and emphasise their role in “disease-targeted exon capture, whole-exome sequencing (WES), or whole-genome sequencing (WGS) strategies”. The authors of the genetic testing guidelines applaud these genetic tests as they address the issue of genetic heterogeneity and their ability in identifying phenotypic features that may not be easily distinguished clinically [2].

Where do the samples for genetic tests for hearing loss come from?

Samples of DNA can be extracted from peripheral blood or in some cases from the umbilical vein. Samples can also be extracted from saliva. Some of the genetic tests include mutation screening using Sanger sequencing, targeted exon sequencing, Invader assay and TaqMan genotyping assay for common deafness genes [3]. Other scientists have recommended the use of targeted next generation sequencing panel (Illumina TruSightTM Exome) which can cover abnormalities of more than 2700 genes [4, 5]. Some of the common genes for hearing loss include the following:
- GJB2 (35 delG, 176del16, 235del1C, 299del1AT)
- GJB3 (C538T)
- SLC26A4 (IVS7-2A>G, A2168G)
- Mitochondrial 12S rRNA (A1555G, C1494T)

In summary, genetic testing for hearing loss provides multiple benefits. It can reveal the underlying aetiology of hearing loss and reduce the need for further testing. It provides guidance to genetic counsellors and provides a roadmap for management of hearing loss. Several commercially available genetic tests such as OtoSeq, OтоGenome, and OtoSCOPE are available (see below for a list of genes that can be tested by these genetic tests). The average cost is US$3,800, and most insurance companies in the USA cover genetic testing for hearing loss. There are also less expensive genetic screening tests such as SoundGene which test for only very common genes and cost around US $200. Patients and families should consult their otologist or audiologists for appropriate referrals to geneticists and genetic counsellors.
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The following is a list of some of the genes for hearing loss that can be tested with commercially available genetic panels:

- ACTG1
- ATP6V1B1
- BSND
- CACNA1D
- CDH23
- CEACAM16
- CIB2
- CLDN14
- CLPP
- CLRN1
- COCH
- COL11A2
- DIABLO
- DFNA5
- DFNB3-1
- DFNB95
- DIAPH1
- EDN3
- EDNRB
- EDN1
- EYA1
- EYA4
- GIPC3
- GJB2
- GJB6
- GPR98
- GPSM2
- GRHL2
- GRXCR1
- HARS2
- HGF
- ILDR1
- KARS
- KCNQ1
- KCNQ4
- LARS2
- LHFP5
- L2OX1D1
- LRTOMT
- MARVELD2
- MIR156
- MIF
- MSRB3
- MTRNR1 (12S rRNA)
- TMFS (6 rRNA)
- TMC1
- TIP39L
- USH1C
- USH1D
- WFS1

(Aepted from http://personalizedmedicine.partners.org/Laboratory-For-Molecular-Medicine/Ordering/Hearing-Loss/OtoGenome-Test.aspx)

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References

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