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Review Article

Genetics of non syndromic hearing loss

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ABSTRACT

Non Syndromic Hearing Loss is an important cause for hearing loss. One in 1000 newborns have some hearing impairment. Over 400 genetic syndromes have been described. Non Syndromic Hearing Loss (NSHL) can be inherited in an Autosomal Dominant, Autosomal Recessive or a Sex Linked fashion. There are several reasons why genetic testing should be done in cases of NSHL, the main reasons being for genetic screening and for planning treatment. This review describes the genes involved in NSHL and the genetic mechanisms involved in the pathogenesis of the disease.

Introduction

Hearing impairment is one of the most common sensory defects. It affects approximately 1 in 1000 newborns worldwide and about 4% of people less than 45 years of age have some form of hearing loss.[1] By the age of 80 years, the prevalence of hearing loss increases to about 50%.[2] There are two main reasons for hearing loss, conductive hearing loss and sensorineural hearing loss (SNHL). There is an increase in both these forms of hearing loss with increasing age. Hereditary hearing loss can be classified into syndromic and non syndromic hearing loss.[3] Syndromic hearing loss includes more than 400 syndromes in which hearing loss occurs in addition to other signs and symptoms.[4] Non syndromic hearing loss (NSHL) can be inherited in an autosomal recessive manner (75–80%), autosomal dominant pattern (20–25%) or in rare instances as an X linked or mitochondrial pattern of inheritance (1–2%). After ageing, the prevalence of autosomal dominant inheritance and mitochondrial inheritance increases while that of autosomal recessive inheritance decreases.[5] There is a considerable genetic heterogeneity involved in NSHL and more than sixty genes and a corresponding number of proteins have been implicated in the pathogenesis of Non Syndromic Hearing Loss.[6]

Why do we need to understand the genetics of non syndromic hearing loss?

There are several reasons why both doctors and patients need to understand the genetics related to NSHL.

Firstly, the aetiology of the NSHL can be explained to the patient. The patient then is aware of the cause for the hearing

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loss. Hereditary causes of hearing loss are distinguished from non genetic causes of hearing loss by family history, audiologic testing, temporal bone imaging, routine urine and haematological investigations, thyroid function studies and an ECG in relevant cases. However, even with this testing workup, a clear distinction between heritable and environmental causes of hearing loss and NSHL or syndromic hearing loss could be difficult. This is where genetic testing becomes important since in several cases, genetic testing can provide a clue for the basis of the hearing loss.

The causes of hearing loss can be broadly classified as conductive, sensorineural and mixed hearing loss. In most cases, a genetic cause is established early, there is no need to investigate the child for conductive hearing loss. The exception is in DFNX3 mutations which is characterized by a mixed conductive-sensorineural hearing loss.[7] In cases with a strong genetic history, the patients can be screened for mutations before the age of six months. Rehabilitation can then be started immediately since it has been seen that early rehabilitation (i.e. before the age of six months) aids in significantly better language development with early intervention.[8]

Secondly, the identification of the specific mutations can be used for both diagnosis and prognostication. Specific mutations are associated with specific auditory features and so identification of these mutations can be used for prognostication. Identification of specific mutations can predict auditory features such as the audiogram in infants with hearing loss. It is difficult to perform subjective tests in children; however tests like Tone Burst ABR (Auditory Brainstem Response) and ASSR (Auditory Steady-State Response) are available and are essential for the workup. However, genetic testing may also be used as an adjunctive test in predicting the auditory features and can therefore provide valuable information to the doctor in planning the fitment of hearing aids and follow up.[9]

Thirdly, specific drugs or specific activities need to be avoided in genetically susceptible patients. In patients with the A1555G mitochondrial mutation, aminoglycosides can induce or aggravate SHNL.[10] However, it has also been shown that there is a very high prevalence of SNHL in patients with the A1555G mutation even in the absence of aminoglycoside exposure.[11] The fact remains that certain drugs should be avoided in patients with specific mutations.

Fourthly, identification of causative mutations in patients with syndromic hearing loss may raise the suspicion of associated diseases in the patient. In patients who harbour the A3243G mitochondrial DNA mutation, diabetes mellitus is also present in addition to SNHL. Patients who have the SLC26A4 mutation have goitres in addition to the SNHL.[5] In such cases, the clinician can expect associated diseases and screen the infant for the same.

Fifthly, genetic testing may also help in prognostication after surgery. Although cochlear implant surgery is routinely offered to all patients, patients with mitochondrial mutations do significantly better after surgery. Although mitochondrial mutations leading to SNHL are very rare, it has been seen that cochlear implant surgery has been highly beneficial in these cases suggesting that the mutations in mitochondrial DNA primarily affect the cochlea.[12]

Finally, identification of a genetic cause for hearing loss can help the doctor to provide adequate genetic counselling. For syndromic SNHL which is associated with severe symptoms other than SNHL, prenatal diagnosis may be considered.

Mechanisms of SNHL

Several proteins are required for functioning of the inner ear. The inner ear is a complex structure made up of the cochlea (responsible for hearing), the saccule, utricle and the three semicircular canals which controls balance and spatial orientation. The development, differentiation and maintenance of this machinery require a large number of genes. Mutations in these genes lead to sensorineural hearing loss.

As mentioned earlier, the mutations can be Autosomal Dominant, Autosomal Recessive, X Linked or Mitochondrial mutations. The loci in inherited NSHL are called DFN loci where DFN stands for DeaFNess. The 'A' signifies that the inheritance pattern is Autosomal Dominant, 'B' means that the pattern of inheritance is Autosomal Recessive and 'X' means that the mode of inheritance is X linked. Three genes are responsible for over one third of patients with congenital hearing loss. These genes are the GJB2, GJB6 and the SLC26A4 genes. Mutations in GJB2 account for 50% of patients with autosomal recessive hearing loss, i.e. 20% of all congenital hearing loss.[1,13] Each one of these mutations will be dealt with briefly.

Autosomal Dominant causes for NSHL

The loci are numbered in the order in which they were discovered. For example, the gene present on the DFNA1 locus is the *DIAPH1* gene which is a homolog of the Drosophila diaphanous gene. Common Autosomal Dominant mutations are those which occur in the WFS1, MYO7A and COCH genes. Several of these genes are also implicated in syndromic HL. These three genes are described in detail. A brief description of the remaining genes is given in Table 1.

WFS1

The protein product is wolframin. Wolframin is a transmembrane protein with nine helical transmembrane segments. Its function in the inner ear is currently unknown, but it is believed to play a role in K^+ and Ca^{2+} homeostasis.[13] The protein is expressed during all the stages of development and therefore it is believed to play a role in inner ear development or in the maintenance of auditory function.[14] *WFS1* mutations cause both ADNSHL and Wolfram syndrome [Autosomal Recessive Hearing Loss, diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD syndrome)].[15] WFS 1 mutations cause a very characteristic pattern of hearing loss. The hearing loss affects the high frequencies and the hearing is normal in the low frequencies.[16] However, as age increases, there is a hearing loss in the lower frequencies as well and the audio profile flattens.[17]

MYO7A

The MYO7A gene encodes for an unconventional myosin called myosin VIIA. Mutations in the MYO7A gene can cause both non syndromic hearing loss (DFNB2) or syndromic hearing loss