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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

Table 1 – Gene and protein alteration of known genes causing autosomal dominant nonsyndromic hearing impairment.

Locus name	Gene	Protein altered
DFNA1	*DIAPH1*	The polymerisation of actin is altered. Actin is an important component of the cytoskeleton of the hair cells of the inner ear.
DFNA2	*KCNQ4*	The protein is a potassium channel which plays a role in neuronal excitability. The protein is present in the cochlear sensory cells
DFNA2B	*GJB3*	The protein is a component of the gap junctions. These gap junctions are important in providing a route for the diffusion of low molecular weight molecules between cells. The gene is a member of the connexion gene family
DFNA4	*MYH14*	The protein is a part of the gene encodes a member of the myosin superfamily. Myosins are proteins which act independently of actins. Their functions include regulation of cytokinesis, cell motility, and cell polarity.
DFNA5	*DFNA5*	The protein encoded by this gene is expressed in the foetal cochlea. Function of protein unknown.
DFNA6/14/38	*WFS1*	Protein encoded is Wolframin. This is a transmembrane protein. Wolframin is a cation-selective ion channel.
DFNA8/12	*TECTA*	The protein encoded is α Tectorin. This is a major noncollagenous components of the tectorial membrane
DFNA9	*COCH*	Encodes Cochlin which is present in the cochlea and the vestibular system as a part of the extracellular matrix. It provides structural support to the cochlea and also interacts with other molecules in the extracellular matrix.
DFNA13	*COL11A2*	Encodes for Type XI collagen which is a part of the inner ear
DFNA15	*POU4F3*	Encodes for a POU-domain family of transcription factors. Inactivation of this gene causes deafness in mice
DFNA17	*MYH9*	A myosin heavy-chain 9 protein is encoded by this gene. The protein is present in the spiral ligament, the spiral limbus and in the cuticular plate of sensory hair cells. The specific function of the protein is not known.
DFNA20/26	*ACTG1*	Actin Gamma 1 is an isomer of Actin which is a component of the cytoplasm found in non muscle cells. Exact role in NSHL is unknown
DFNA22	*MYO6*	Encodes Myosin VI which interacts with Actins. Myosin VI is important in the development and maintenance of stereocilia of the middle ear. These stereocilia are essential for normal hearing.
DFNA23	*SIX1*	The *SIX1* gene is part of a group of similar genes known as the SIX gene family. The function of the encoded protein is to bind DNA and control the activity of genes involved in ear development.
DFNA25	*SLC17A8*	The protein encoded is a vesicular glutamate transporter. The protein transports the neurotransmitter glutamate into synaptic vesicles before it is released into the synaptic cleft
DFNA28	*GRHL2*	The Grainy Head Like 2 gene encodes a transcription factor. The protein can combine with either GRHL1 or GRHL3. The exact role of the protein is not known.
DFNA36	*TMC1*	The gene encodes transmembrane proteins. The proteins are believed to play a role in the normal function of cochlear hair cells.
DFNA39	*DSPP*	The protein produced is called sialophosphoprotein. Its exact function is not known, however, it is known to be expressed in the middle ear.
DFNA41	*P2RX2*	The protein encoded by this gene belongs to a family of purionoreceptors for ATP. This receptor functions as a ligand-gated ion channel
DFNA44	*CCDC50*	The protein encoded by this gene is a soluble, cytoplasmic, tyrosine-phosphorylated protein. In mouse models, it has been shown to be expressed in the inner ear during development and postnatal maturation.
DFNA48	*MYO1A*	The gene encodes a member of the myosin superfamily. The protein helps in organelle translocation, ion-channel gating, and cytoskeleton reorganization
DFNA50	*MIR96*	The miR-96is a part of the microRNA family. The protein is essential for differentiation and function of the vertebrate inner ear

[Ushers Syndrome]. Allelic heterogeneity can explain these variable manifestations. Alternatively, the expression of modifier genes can also explain this heterogeneity.[18] The hearing loss is first noticed in the first decade of life in most patients with a MYO7A mutation. This hearing loss is seen after complete speech acquisition and the subsequent hearing loss is gradual and progressive. Between the ages of 20 and 60 years, the patients usually have a moderate hearing loss.[19]

COCH

There have been several identified mutations in the COCH gene in families with DFNA9. The onset of the hearing loss occurs between 20 and 30 years. The hearing loss is initially more profound at high frequencies. The progression of the hearing loss is variable and complete deafness occurs by the age of 40–50 years. The clinical spectrum may range from the lack of symptoms to vertigo and deafness.[20]

Autosomal recessive causes for NSHL

The most common genes in cases of autosomal recessive hearing loss in order of frequency are the GJB2, SLC26A4, MYO15A, OTOF, CDH23, and TMC1 genes (Table 2).

GJB2

In cases of non syndromic hearing loss, the most common mutation occurs in the Gap Junction Beta 2 gene (GJB2) which can account for up to 50% of autosomal recessive hearing loss and thus 20% of all congenital hearing loss.[1,13] The GJB2 gene encodes connexin 26 which is a gap junction protein. This protein allows passage of potassium ions in the inner ear. More than 110 different mutations have been identified out of which the 35delG mutation is the most frequent in the majority of people and accounts for 70% of all GJB2 mutations.[21] Indian data supports these findings.[22] The other gene which is closely linked with the GJB2 gene is the GJB6 gene. This gene encodes

Table 2 – Gene and protein alteration of known genes causing autosomal recessive nonsyndromic hearing impairment.

Locus name	Gene	Protein altered
DFNB1	*GJB2* *GJB6*	See text
DFNB2	*MYO7A*	See ADNSHL above
DFNB3	*MYO15A*	The gene encodes an unconventional myosin with a long N-terminal extension. In mouse models, the protein is necessary for actin organisation of the hair cells of the cochlea.
DFNB4	*SLC26A4*	See text
DFNB6	*TMIE*	The protein product is called the Trans Membrane Inner Ear protein. In mouse models, the protein is required for the postnatal maturation of sensory hair cells in the cochlea. The protein is also required for the development of stereocilia bundles.
DFNB7/11	*TMC1*	See DFNA36
DFNB8/10	*TMPRSS3*	The gene encodes a protein of the serine protease family. The protein is believed to be involved in the development and maintenance of the inner ear. It is also responsible for the maintenance of the endolymph and perilymph contents.
DFNB9	*OTOF*	The protein encoded by this gene is called Otoferlin. The protein is believed to play a role in vesicle membrane fusion.
DFNB12	*CDH23*	The protein encoded is a calcium dependant cell to cell adhesion glycoprotein. This protein is believed to play a role in stereocilia organisation and formation of hair bundles.
DFNB16	*STRC*	The protein encoded by this gene is called Stereocilin. It plays a roel in the function of the hair bundles of the sensory hair cells of the inner ear.
DFNB18	*USH1C*	The scaffold protein encoded by this gene plays a role in the normal development and maintenance of cochlear hair cell bundles
DFNB21	*TECTA*	See DFNA8/12
DFNB22	*OTOA*	The Otoancorin protein is present in the inner ear. The precise location is at the interface between the apical surface of the inner ear epithelium and the overlying acellular gels. It attaches the gels to the epithelium.
DFNB23	*PCDH15*	The protein protocadherin 15 helps the cells stick together in the inner ear. The protein also plays a role in the development and maintenance of stereocilia.
DFNB24	*RDX*	The protein Radixin acts as a cross linker between integral membrane proteins and actin filaments of the cytoskeleton.
DFNB25	*GRXCR1*	The protein product of this gene contains GRX-like domains; these domains play a role in the S-glutathionylation of proteins. The protein may play a role in the organisation of actin filaments in the middle ear.
DFNB28	*TRIOBP*	The TRIO and F Actin binding proteins control the organisation of the actin cytoskeleton, cell motility and cell growth. The protein also stabilises F actin structures.
DFNB29	*CLDN14*	The protein encoded is called Claudin 14. This protein is an integral membrane protein and a component of tight junctions which helps in cell – cell adhesion.
DFNB30	*MYO3A*	The gene encodes a protein which belongs to the myosin superfamily. The gene is expressed only in a few organs. The strongest expression is in the retinal and the cochlea.
DFNB31	*CHRN*	The protein is called Whirlin. It helps in the organisation and stabilisation of stereocilia elongation and actin cytoskeletal assembly.
DFNB32/82	*GPSM2*	The encoded proteins modulae the activation of G proteins and act as second messengers. They may also have a role to play in neuroblast division and development of normal hearing.
DFNB35	*ESRRB*	The protein product is similar to the oestrogen receptor. On mouse models, a similar protein is important in placental development.

Table 2 (*Continued*)

Locus name	Gene	Protein altered
DFNB36	*ESPN*	This gene encodes a multifunctional actin-bundling protein. The protein helps in the transduction of sensory signals from mechanosensory and chemosensory cells.
DFNB37	*MYO6*	See DFNA22
DFNB39	*HGF*	Both over expression and under expression of HGF may cause deafness. An over expression of HGF causes a progressive degeneration of outer hair cells in the cochlea. Under expression of HGF is associated with more general dysplasia
DFNB49	*MARVELD2*	There are two genes in the MARVEL domain. The protein encoded is a membrane protein which is present at tight junctions between epithelial cells. These protein help in the development of epithelial barriers in the Organs of Corti.
DFNB53	*COL11A2*	The gene encodes one of the two alpha chains of type XI collagen. When the type XI chain is processed proteolytically, PARP Poly (ADP-ribose) polymerase is produced which is involved in DNA repair and apoptosis
DFNB59	*DFNB59*	Pejvakin is the protein produced. The protein is present in the nerves leading from the inner ear to the brain. The protein is probably essential for normal hearing.
DFNB61	*SLC26A5*	The gene is *SLC26A5* (solute carrier anion transporter family 26, member 5). The protein encoded is called Prestin. The protein is present in the outer hair cells in the cochlea. It is therefore essential for auditory processing.
DFNB63	*LRTOMT*	The LRTOMT gene codes for the LRTOMT protein (Leucine rich transmembrane and O-methyltransferase domain). The protein is essential for auditory and vestibular function
DFNB67	*LHFPL5*	The gene codes for the Lipoma HMGIC fusion partner-like protein 5. The protein LHFP-like protein 5 is responsible for the conversion of sound waves to nerve impulses which are transmitted to the brain.
DFNB73	*BSND*	The protein encoded by the Barttin CLCNK-type chloride channel accessory beta subunit gene product is Barttin. The protein is present in the inner ear and it is essential for the normal placement of ion channels in the cell membrane.
DFNB76	*SYNE4*	Spectrin Repeat containing, nuclear envelope family member 4 gene codes for a protein of the same name. It is a component of the LINC (Linker of Nucleoskeleton and Cytoskeleton) complex, involved in the connection between the nuclear lamina and the cytoskeleton. The protein plays an important role in the transmission of mechanical forces across the nuclear envelope and in nuclear movement and positioning.
DFNB77	*LOXHD1*	The LOXHD1 gene codes for a protein called Lipoxygenase homology domains 1.ns that is encoded In mice, the protein is present in the mechanosensory hair cells in the inner ear. The protein is essential for normal hair cell function
DFNB79	*TPRN*	TPRN (taperin) codes for a protein called Taperin. The protein is a sensory epithelial protein.
DFNB84	*PTPRQ*	The gene encodes a member of the type III receptor-like protein-tyrosine phosphatase family. The protein plays a role in cellular proliferation and differentiation.

Table 3 – Gene and protein alteration of known genes causing X-linked nonsyndromic hearing impairment.

Locus name	Gene	Protein altered
DFNX1 (DFN2)	*PRPS1*	The phosphoribosyl pyrophosphate synthetase 1 gene codes for an enzyme by the same name (PRPP synthetase 1). This enzyme helps produce a molecule called phosphoribosyl pyrophosphate (PRPP). PRPP is important in making purine and pyramidine nucleotides. The exact mechanism by which bit is involved in causing deafness is not known.
DFNX2 (DFN3)	*POU3F4*	The POU3F4 gene encodes a protein called POU domain, class 3, transcription factor 4 whose function is unknown.
DFNX4 (DFN6)	*SMPX*	SMPX is the Small Muscle Protein, X linked is coded for by the gene. Its role in causing deafness is not clear.

for connexion 30. These two genes may be inherited together. 8% of deaf patients with a mutation in GJB2 show a second mutation in GJB6.[23] Phenotypic variations in patients with the GJB2 mutation can be considerable. The degree of hearing loss also varies and it can be mild to severe. Patients with a GJB2 mutation show an excellent outcome with cochlear implants, thus reiterating the importance of genetic testing in cases of hearing loss.[24]

SLC26A4

Mutations in SLC26A4 are the second most frequent cause of autosomal recessive non syndromic hearing loss. Hearing loss may be syndromic as in the case of Pendred's syndrome or non syndromic as in the case of DFNB4. Together, DFNB4 and Pendred's syndrome are estimated to account for 1%–8% of congenital hearing loss. The phenotypic differences between Pendred's syndrome and DFNB4 mutations may be due to the degree of residual function of the encoded protein, pendrin.

Sex linked causes for NSHL

These are rare causes of hearing loss and their inclusion is merely to complete the causes of NSHL (Table 3).

Conclusion

In conclusion, it must be concluded that genetic testing in cases of NSHL remains a very important investigation in the evaluation of patients with Non Syndromic Hearing Loss. The main importance of genetic evaluation of patients lies in genetic counselling, Children with congenital hearing loss need to be screened early so that if one child shows genetic mutation, the foetus can be screened by amniotic fluid analysis. In addition, congenitally deaf children should be rehabilitated as early as possible so that they develop their language skills. Even severe hearing loss can be restored very effectively by hearing aids or cochlear implants coupled with early rehabilitative training in patients with hereditary hearing loss.[25] Screening programs for newborns can evaluate the genetic causes for NSHL and appropriate treatment can be offered.

Conflicts of interest

The authors have none to declare.

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