The genetics of hearing loss

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Hearing impairment is the most common sensory deficit with half of the causes of hearing loss having a genetic basis. There is a range of treatment devices but these do not correct the underlying pathology. Advances in molecular biology have greatly enhanced our understanding of the pathophysiology of genetic hearing loss, including potential treatments.

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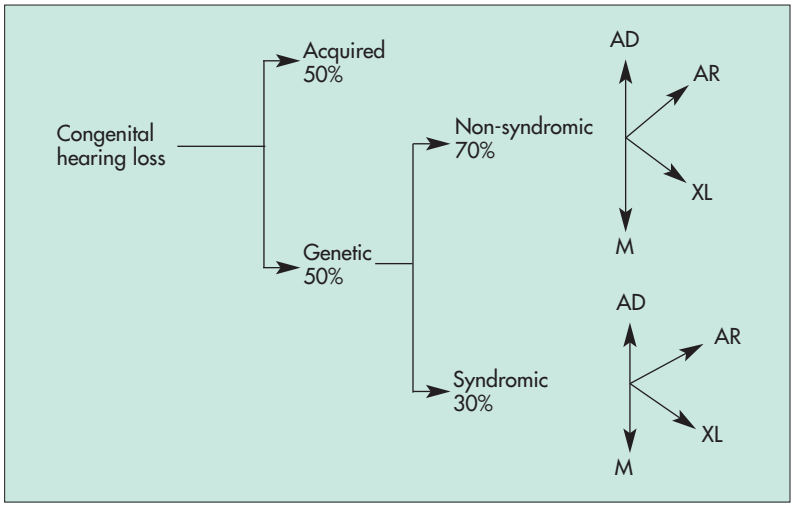
One in 1000 newborn children have profound hearing loss (Parving, 1999) and a further one in 1000 children have hearing loss which is significant enough to affect speech and language development (Fitzgerald et al, 2004). Genetic causes account for over half of all these cases of prelingual hearing loss and the remainder are attributed to environmental factors (Steel, 2000; Hone and Smith, 2003) (*Figure 1*).

The prevalence of hearing loss increases with advancing age, 10% of 65-year-olds and 50% of 80-year-olds suffer sufficient hearing loss to benefit from hearing amplification (Steel, 2000; Hone and Smith, 2003), reflecting the impact of genetic and environmental factors. Over the years there has been a gradual decline in the incidence of environmental causes of hearing loss as a result of improved neonatal care and the implementation of vaccination programmes in an attempt to prevent infection.

Figure 1. Classification of hearing loss. AD = autosomal dominant; AR = autosomal recessive; M = mitochondrial and other; XL = X-linked.



GENETICS

During the last decade several hundred genetic loci implicated in hearing loss have been isolated. The first gene was isolated in 1992 (Bitner-Glindzicz, 2002), and many more genes remain to be identified (Smith et al, 1999). Hereditary hearing loss can be considered clinically as syndromic (SHL) or non-syndromic (NSHL), and genetically according to the mode of inheritance (*Tables 1* and *2*) (Smith et al, 1999; Bitner-Glindzicz, 2002). However, the diversity of genes and genetic loci implicated in hearing loss illustrates how complex the genetic basis of this special sense is. In addition the same gene may be implicated in more than one syndrome or present with a different mode of inheritance.

SHL is present in up to 30% of individuals with hereditary hearing loss and is associated with abnormalities in other organs; the remainder have NSHL where hearing loss and possible middle and inner ear malformations are the only clinical manifestations (Smith et al, 1999; Bitner-Glindzicz, 2002; Hone and Smith, 2003) (*Figure 1*).

Syndromic hearing loss

Over 400 syndromes have been reported which include hearing loss as one of the clinical features (Smith et al, 1999; Hone and Smith, 2003). Genetic loci for at least 100 of these syndromes have now been identified (Phillips, 2003) and more than 50 of these loci have been mapped. For virtually all inherited forms of SHL there is a detailed description of the molecular genetics and the clinical features associated with the syndrome available at the Online Mendelian Inheritance in Man website (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) (Friedman et al, 2003).

It is important to recognize SHL as the observation may alert the clinician to other features

TABLE 1.
Examples of syndromic hearing loss

Syndrome	Mode of inheritance	Gene	Phenotype
Waardenburg's syndrome 1	Autosomal dominant	PAX3	Pigmentation abnormalities of skin, hair, eyes and dystopia canthorum
Waardenburg's syndrome 2	Autosomal dominant	MITF	Pigmentation abnormalities of skin, hair, eyes but no dystopia canthorum
Waardenburg's syndrome 3	Autosomal dominant	PAX3	Pigmentation abnormalities of skin, hair, eyes and upper limb abnormalities
Waardenburg's syndrome 4	Autosomal dominant	EDNRB, EDN3, SOX10	Pigmentation abnormalities of skin, hair, eyes and Hirschsprung's disease
Branchio-otorenal syndrome	Autosomal dominant	EYA1	Branchial cleft cysts/fistulae. External ear malformations and renal abnormalities
Stickler syndrome	Autosomal dominant	STL1, STL2, STL3	Cleft palate, spondyloepiphyseal dysplasia and myopia with STL1 and STL3
NF type 2	Autosomal dominant	NF2 gene	Vestibular schwannomas on chr 22
Usher's type 1	Autosomal recessive	USH1C, MYO7A CDH23	Retinitis pigmentosa. Congenital severe to profound sensorineural hearing loss and vestibular dysfunction
Usher's type 2	Autosomal recessive	USH2A	Retinitis pigmentosa. Congenital mild to severe sensorineural hearing loss and normal vestibular function
Usher's type 3	Autosomal recessive	USH2A	Retinitis pigmentosa, progressive hearing loss and progressive vestibular dysfunction
Pendred's syndrome	Autosomal recessive	SLC26A4	Euthyroid goitre. Mondini dysplasia or dilated vestibular aqueduct. Vestibular dysfunction
Jervell and Lange–Nielsen syndrome	Autosomal recessive	EKG	Prolonged QT interval on electrocardiography
Alport's syndrome	X-linked in 85% of cases	COL4A5/6	Glomerulonephritis, ophthalmological abnormalities
Mohr–Tranebjaerg syndrome	X-linked	TIMM8A	Dystonia, mental retardation, visual abnormalities
MELAS	Mitochondrial	MTRNTI	Neurological symptoms
Diabetes mellitus	Mitochondrial	MTRNTI	Diabetes

MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like-episodes; NF = neurofibromatosis.

associated with the syndrome and the potential for early treatment, hence the importance of carefully examining all children with a hearing loss. Particular attention to detail should be paid to facial features, skin and hair pigmentation (Bitner-Glindzicz, 2002). Although the hearing impairment may be obvious the other associated clinical features may not and advice from a geneticist at this stage is invaluable to arrive at the correct diagnosis.

SHL is typically conductive (external or middle ear impairment) or mixed (conductive and sensorineural) with a prelingual (before acquisition of speech) onset, although it can be characterized by a sensorineural hearing loss too (Phillips, 2003).

The four most common types of SHL are branchio-otorenal syndrome, Pendred's syndrome, Usher's syndrome and Waardenburg's syndrome (Hone and Smith, 2003).

Non-syndromic hearing loss

This form of hearing impairment occurs in 70% of those with hereditary hearing loss (Smith et al, 1999; Bitner-Glindzicz, 2002; Battey, 2003; Rehm, 2003; Hone and Smith, 2003). About 30 genes involved with NSHL have been identified and over 70 different loci mapped (Hone and Smith, 2003; Laer et al, 2003). These genes code for a variety of proteins involved in the pathophysiology of hearing including myosin, cytoskeletal proteins, extracellular matrix components and transcription factors. The function

TABLE 2.
Examples of non-syndromic hearing loss

Gene	Mode of inheritance	Predicted function	Hearing loss phenotype
DFNA1	Autosomal dominant	Cytokinesis and cell polarity	Postlingual low frequency
DFNA3	Autosomal dominant	Gap junction protein	Postlingual and mostly high frequency
DFNB1	Autosomal recessive	Gap junction protein	Prelingual severe to profound hearing loss
DFNB12	Autosomal recessive	Cell adhesion protein	Prelingual profound hearing loss
DFNB29	Autosomal recessive	Tight junction protein	Prelingual profound hearing loss
DFN1 Xq22	X-linked	Mitochondrial import protein	Postlingual rapidly progressive
MTRNR1	Mitochondrial		Aminoglycoside-induced ototoxic hearing loss
OTSC1 OTSC2 OTSC3	Autosomal dominant		Otosclerosis
TIMM9	Others		Menière's disease

of some of these genes, however, remains undetermined (Laer et al, 2003).

Mode of inheritance

Between 75 and 80% of prelingual NSHL shows autosomal recessive inheritance; 20–25% is inherited as an autosomal dominant, 2% as X-linked with mitochondrial inheritance, and the other causes of hearing loss such as that seen in Menière's disease account for the rest. Such data are not available for postlingual NSHL, although the predominant pattern of inheritance in postlingual NSHL is autosomal dominant (Smith et al, 1999; Bitner-Glindzicz, 2002; Laer et al, 2003).

The majority of the recessively inherited NSHL tends to be associated with a profound and prelingual hearing impairment caused almost entirely by cochlear defects (Phillips, 2003). The dominantly inherited forms on the other hand tend to produce a progressive but less severe hearing impairment of postlingual onset (usually before the age of 20 years) which may be difficult to identify clinically. However, there are a few exceptions, for example mutations of genes GJB2 and GJB6, which are implicated in autosomal dominant NSHL and are characterized by a prelingual onset of hearing loss which is non-progressive (Smith et al, 1999).

Most X-linked inherited forms of hearing losses are recessive, so only males are affected. The onset of hearing loss may be before or after the acquisition of speech and language and tends to be characterized by a combination of conductive and sensorineural hearing loss (Smith et al, 1999).

Mitochondrial inherited hearing loss may be SHL or NSHL. These intracellular organelles are responsible for generating energy through oxidative phosphorylation in almost every cell, hence the potential for multiorgan dysfunction with mitochondrial mutations (Bitner-Glindzicz, 2002; Fischel-Ghodsian, 2003; Karkos et al, 2004). Sperm do not carry mitochondria, so the mitochondrial genome is maternally inherited although recently there have been reports of unconventional paternal transmission of mitochondrial DNA (Karkos et al, 2004). Mitochondrial hearing loss is characteristically postlingual in onset (affecting the higher frequencies), bilateral and progressive. The hearing impairment has been associated with the loss of outer hair cell function in the organ of Corti so these individuals may be suitable for cochlear implantation (Bitner-Glindzicz, 2002).

The overall contribution of mitochondrial gene defects to inherited hearing loss is small. However, SHL of mitochondrial origin should be considered where hearing loss presents in an individual with multiple symptoms involving organs with a high energy requirement (e.g. muscle, brain). NSHL associated with mitochondrial inheritance tends to appear where hearing loss is present in all multi-generation families and not associated with male transmission.

Otosclerosis

Otosclerosis is one of the most common causes of hearing impairment. Pathologically otosclerosis only affects the temporal bone. The disease involves abnormal new bone formation around the ossicles (typically the stapes) producing a conductive hearing loss or the otic capsule (bone around the inner ear) resulting in a sensorineural hearing loss. If both the ossicles and otic capsule are involved then a mixed hearing loss is seen.

The genetics of otosclerosis remain unclear but most would agree that it is usually associated with autosomal dominant inheritance with variable expression and a reduced penetrance of less than 50% (Menger and Tange, 2003). Sporadic mutations are possible where neither of the parents are carriers of the gene. It is believed other genetic and environmental factors influence the development of otosclerosis. A more recent hypothesis is that otosclerosis requires a combination of a specific genetic susceptibility with exposure to specific viruses for it to be expressed and hearing loss to occur. The pathogenesis remains unknown. At the time of writing three chromosomal locations important in dominantly inherited otosclerosis have been mapped although the total number of genes involved is still uncertain.

Menière's disease

Menière's disease is a benign condition of the inner ear. While the precise cause is unknown it is postulated that it results from increased pressure within the endolymphatic compartment of the inner ear. The disease is characterized by sudden episodic attacks of vertigo, tinnitus, aural fullness, loss of equilibrium, and progressive loss of hearing (Sugawara et al, 2003). Around 10% of patients with Menière's disease have a family member with the same condition suggesting a genetic component. Previously it has been cited that the disorder shows autosomal dominant inheritance with a penetrance around 60% (Saeed, 1998). Currently no specific gene or locus has been mapped for this disease.

GENETIC SCREENING

Genetic screening enables the comparison of an individual's DNA sequence within a certain region of their genome with the regularly occurring sequence of a normal or mutated gene which has already been established through the Human Genome Project (Rehm, 2003). Genetic screening for hereditary hearing loss is only possible if the gene causing the hearing loss has previously been characterized. Hearing loss is a common symptom, however, the incidence of each individual genetic disorder contributing to hearing loss is very small. Further more, the heterogeneity of the genes implicated in hereditary hearing loss means screening all individuals with hearing loss for all these possible genetic conditions would be impractical (Steel, 2000; Hone and Smith, 2003). Consequently physicians must rely on clinical, audiological, vestibular and radiographical clues that may suggest mutations at a particular gene locus. The genes that are available for genetic screening at present are summarized in *Table 3*.

Mutation of the GJB2 gene that encodes the connexin 26 molecule is responsible for up to half of the cases of autosomal recessive NSHL. This test is available in most institutions and should be considered for all cases of NSHL with unknown aetiology (Steel, 2000; Bitner-Glindzicz, 2002; Hone and Smith, 2003).

Genetic screening may help families and patients understand the cause of the hearing loss and resolve any feelings of guilt. The result can be used to identify other organ abnormalities possibly associated as part of a syndrome as well as predict the risk of giving birth to further children with impaired hearing. The aetiology of the hearing loss may predict the likely prognosis and assess suitability for early cochlear implantation, for example individuals carrying GJB2 mutations may benefit from an implant in early life (Rehm, 2003). It is important to bear in mind that although genetic screening is specific it is not sensitive as the individual may have an unknown genetically determined cause for the hearing loss (Brunger et al, 2001).

Many individuals have misunderstandings about genetic screening. However, with the advent of genetic counselling before and following the genetic tests, the associated fears and misconceptions have largely been overcome. Most people with hearing loss or parents with hearing-impaired children appreciate the advantages of genetic screening and are keen to undertake these tests to ascertain the cause of the hearing loss (Brunger et al, 2001).

TREATMENT OPTIONS

Gene therapy

This procedure aims to replace, manipulate or supplement non-functional or mis-functioning genes with healthy genes by gene transfer. This option offers hope of cure, arrest or reversing the hearing impairment. At present, however, it is a research tool. For gene transfer to be successful, the vector used to incorporate the genetic material must have several inherent attributes. These include being able to incorporate respectable quantities of foreign genetic material, integrate and replicate in non-proliferating, postmitotic cells such as the neuroepithelium and spiral ganglion of the organ of Corti, and not being toxic.

Several viral and non-viral vectors have been tried in cochlear gene therapy but at present there is no single satisfactory vector that meets

TABLE 3.
Genes that can be identified with genetic screening

Genes available for screening on clinical basis	Associated syndrome
GJB2, GJB6	NSHL autosomal recessive
SCL26A4	Pendred's syndrome
MTRNR1	NSHL mitochondrial
PAX3, MITF, EDN3	Waardenburg's syndrome
EYA1	Branchiootorenal syndrome
STL1, STL2, STL3	Stickler syndrome
NF2	Neurofibromatosis type 2
USH2A, USH3A	Usher's type 2 and type 3
DFN3	NSHL X-linked
MTTSI	NSHL mitochondrial
DFNA9	NSHL autosomal dominant

NSHL = non-syndromic hearing loss

the above criteria. A further obstacle is the safe delivery of the vector so that hearing and cochlear architecture are preserved as well as minimizing damage caused by vector dissemination (Lalwani and Mhatre, 2003).

Neurotrophic growth factors and pharmacological agents

The hair cells of the organ of Corti are essential to auditory perception but at the same time are vulnerable to damage with limited capacity of repair. Recent interest has grown in the attempt to use neurotrophic growth factors to regenerate these cells and reverse the hearing loss. A further suggestion has been to trigger the generation of the normal version of the mutated protein involved with hearing using pharmacological agents (Steel, 2000). Both of these are topics of interest but require further research.

CONCLUSIONS

Hearing loss can be distressing, affects all age groups and is often associated with social and financial deprivation. Over the last decade there has been a significant increase in the understanding of the genetic basis of hearing loss. Genetic screening provides a useful diagnostic and prognostic tool and is available in many centres. At present hearing amplification is the main option to improve hearing, however, with the potential breakthroughs of gene therapy, neurotrophic growth factors and pharmacological agents in the future hearing loss may become a problem of the past. HM

KEY POINTS

- Hearing impairment is the most common sensory deficit.
- Genetic causes account for over half of the causes of hearing loss.
- Genetic causes of hearing loss can be classified as syndromic and non-syndromic hearing loss.
- Genetic screening provides a useful diagnostic and prognostic tool.
- Gene therapy may cure hearing loss in the future.

Conflict of interest: none.

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