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The molecular genetics of inherited deafness – current knowledge and recent advances

RACHEL E. HARDISTY, PH.D., JANE FLEMING, PH.D., KAREN P. STEEL, PH.D.

Current knowledge

Hereditary deafness affects around 1 in 2000 births. One third of these cases are syndromal (deafness associated with other clinical features) and the other two-thirds are non-syndromal. In the non-syndromal cases, approximately 85 per cent are autosomal recessive, 15 per cent are autosomal dominant, one to three per cent are X-linked and a few have been described that are due to mitochondrial effects.

The majority of deafness genes discovered to date are those associated with syndromal disease. It is easier to study syndromal deafness as additional clinical features help to distinguish families that have a mutation in the same gene or gene pathway. Gene defects commonly associated with inherited deafness include craniofacial and skeletal defects, eye defects and pigmentation anomalies. Around 60 human syndromal deafness genes have been mapped and approximately 30 of these have been identified (e.g. Steel and Brown, 1994; Hughes, 1997; Van-Camp *et al.*, 1997; Fischel-Ghodsian, 1998).

The majority of cases of hereditary deafness are non-syndromal and the majority of these are due to an autosomal-recessive gene defect. It has been estimated that 30–100 genes are involved in non-syndromal autosomal-recessive deafness and these are mostly associated with anomalies in the inner ear (Morton, 1991). To date 15 dominant (DFNA1-15) and 17 recessive (DFNB1-17) genes involved in causing non-syndromal hearing loss have been mapped to a particular chromosomal location, and a few of these genes have been identified by finding mutations in the DNA from affected individuals (see later).

The mouse as a model

The mouse has proved to be a useful model for the study of genetic deafness because of the availability of many hearing-impaired mouse mutants with similarities in pathology to human genetic deafness. The mouse has an advantage over humans for the finding of its genes by positional cloning (that is, identifying a gene on the basis of its position on the chromosome). A very large number of offspring can be generated, all carrying the same mutant gene. The large number of meioses that can be studied gives greater detailed information about the location of each gene by linkage analysis (Stopps and MacDonald, 1998). Once a gene has been identified in this manner in the mouse it is relatively easy to find the human homologue and to look for mutations in the DNA of deaf people. Some of the genes involved in causing hearing impairment in the mouse have been identified, others are known because mutations have been described at distinct loci but the genes have not yet been identified, and yet others remain to be discovered.

Our knowledge of how these genes work is limited and grouping mutants according to the type of pathology is a useful first step to unravelling the mechanisms by which a mutation leads to deafness. Hereditary deafness can be caused by middle-ear defects, peripheral neural defects, central auditory system defects and inner ear defects. Inner ear defects are the most common causes of hearing impairment in the human population, so we shall summarize our knowledge of the genetics and pathology in this group only. Other recent reviews can be consulted for further information (e.g. Steel and Brown, 1994; Steel, 1995; Petit, 1996; Hughes, 1997; Van Camp *et al.*, 1997; Fischel-Ghodsian, 1998).

Inner ear pathology

Inner ear pathology is generally divided into categories devised by Steel and Bock (1983). These are morphogenetic, neuroepithelial, and cochleosaccular defects. Outlines of these types of pathologies are shown in Table I and Figure 1.

Malformations

Morphogenetic defects occur when the early events in the formation of the labyrinth are inter-

From the MRC Institute of Hearing Research, University Park, Nottingham, UK.

TABLE I
CLASSIFICATION SYSTEM FOR INNER EAR PATHOLOGY

Defect	Pathology
Morphogenetic	Early disruption of the development of the membranous and bony labyrinth leading to gross inner ear malformation
Neuroepithelial	Primary abnormality in the organ of Corti
Cochleosaccular	Primary abnormality in the stria vascularis often associated with pigmentation defects

rupted in some way, leading to a malformed inner ear. The neural tube is believed to contribute inductive signals important for the correct development of the inner ear (Deol, 1966). In mutants such as *kreisler* and *dreher*, structural abnormalities and abnormal gene expression in the neural tube, whilst the inner ear is developing, are associated with malformation of the inner ear (Deol, 1964a; Deol, 1964b; Frohman *et al.*, 1993; McKay *et al.*, 1994). The causal link between neural tube abnormalities and inner ear malformation has recently been supported with the identification of the *kr* gene, which is expressed only in the neural tube, but results in the mouse having a severely malformed inner ear (Cordes and Barsh, 1994). This expression pattern is not seen in all mutants with a malformation of the inner ear, as some mutations have been shown to affect genes expressed in the ear. Inner ear defects in this group are often asymmetric, with more severe abnormalities on one side than the other. Asymmetry is a feature occasionally seen in humans with malformations of the inner ear, too.

Several genes with mutations leading to morphogenetic defects have been identified. Most of these are transcription factor genes, containing sequences with homology to DNA-binding domain sequences, suggesting that they control expression of other genes.

The *Splotch (Sp)* locus encodes a paired box transcription factor, *Pax3*, that is expressed in the dorsal neural tube (Goulding *et al.*, 1991). Mice

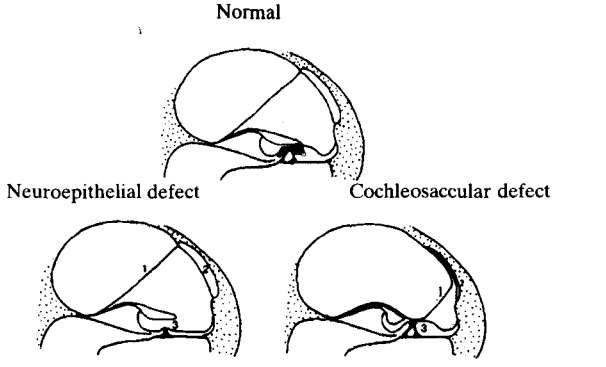

FIG. 1

The main features of neuroepithelial and cochleosaccular pathology. Adapted from Steel and Bock, 1983. Arch. Otolaryngol. 109, 22–29. Copyright 1983, American Medical Association.

homozygous for *Sp* mutations show morphogenetic inner ear defects (Deol, 1966). One human known to be homozygous for a *PAX3* mutation was reported as deaf (Zlotogora *et al.*, 1995), suggesting similar mechanisms may lead to inner ear defects in both humans and mouse.

Another mouse mutation that causes morphogenetic inner ear defects is *his*. This is not a transcription factor, but instead a mutation in the *his* gene leads to a reduction in activity in the enzyme histidase (Taylor *et al.*, 1993). The resulting raised histidine levels cause inner ear defects in the offspring of mutant mothers.

A basic domain-leucine zipper (bZIP) transcription factor encoded by the *kr* locus was one of the earliest genes involved in deafness to be identified, by positional cloning (Cordes and Barsh, 1994). As mentioned above, the action of the gene is mediated by the hindbrain as this was found to be the site of expression and not the developing ear. The developed ear when studied by Deol (1964b) was grossly malformed.

The mutations mentioned above were identified by starting with an abnormal mouse, localizing the mutation to a specific location on a chromosome, then identifying the mutated gene by examining all the genes in the critical chromosomal region for evidence of pathological mutations. However, another way of investigating the function of particular genes and assessing their roles in inner ear development is to produce a mouse mutant with the gene of interest targeted and 'knocked out'. This approach has been used by several laboratories to study gene function. One such gene that has been targeted in his manner is the homeobox-containing gene *Hoxa1*. The phenotype of the knockout mouse has some similarities with that in the *kreisler* mutant. The membranous labyrinth is considerably dilated and the divisions into utricle, saccule and cochlea cannot be identified. This mutant, like *kreisler*, displays structural defects of the neural tube and the gene is expressed in the neural tube not the developing ear itself (Lufkin *et al.*, 1991; Chisaka *et al.*, 1992; Mark *et al.*, 1993).

The *Fgf3* fibroblast growth factor has been found to be necessary for inner ear development and targeted inactivation of this gene results in mice with an inner ear defect. This mutant fails to develop an endolymphatic duct and shows cystic expansion of the inner ear cavities (Mansour *et al.*, 1988).

Recently, Hadrys *et al.* (1998) knocked out another homeobox gene called *Nkx5.1*, which shows specific domains of expression in the developing vestibular system of the inner ear. This resulted in a mouse with impaired development of the semicircular canals but normal cochlear function (Hadrys *et al.*, 1998). This indicates that specific signals are required for development of different components of the inner ear and that positional specificity is set up early in development.

It is likely that up to 15 per cent of deaf children may have malformed inner ears, but in very few cases do we know the molecular basis for the

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abnormal development, indicating the value of the investigation of mutations causing malformations in the mouse in the first instance.

However, recently the gene involved in an inner ear malformation in humans has been identified directly in humans. The gene responsible for Pendred's syndrome encodes Pendrin, a putative sulphate transporter (Everett *et al.*, 1997). This syndrome is characterized by congenital deafness caused by minor specific malformation of the inner ear and goitre.

Neuroepithelial defects

Neuroepithelial defects involve primary abnormalities of the sensory epithelia, the organ of Corti in the cochlea, the maculae of the sacculus and utriculus and the cristae of the semicircular canals. Unlike the morphogenetic mutants mentioned above, the gross structure of the inner ear develops normally. Mutations causing this type of pathology are often recessive in inheritance and uniformly penetrant in individuals homozygous for the mutation. From the limited temporal bone studies that have been carried out, it appears that neuroepithelial defects are the most common form of cochlear pathology in humans. Until 1995, no genes involved in this type of pathology had been identified. The first gene to be identified as causing neuroepithelial defects was the myosin VIIA gene which was found to be mutated in the *shaker-1* mouse (Gibson *et al.*, 1995). *Shaker-1* mice have a profound hearing impairment, a disorganization of stereocilia on the hair cells of the cochlea and demonstrate hyperactive and circling behaviour (Self *et al.*, 1998). The gene was mapped to mouse chromosome 7, which is homologous to a region of human chromosome 11 (11q13). *USH1B*, a type of Usher syndrome type 1, maps to this region of human chromosome 11. Once this gene was identified in the mouse the human version was rapidly screened for mutations in patients with *USH1B*. It was confirmed that the same gene was responsible for the mouse mutation and the human syndrome (Weil *et al.*, 1995). Deafness and vestibular dysfunction is seen in both man and mouse but retinitis pigmentosa is only seen in humans (unpublished observations). Recently mutations in myosin VIIa have been identified in families with non-syndromic hereditary deafness (Liu *et al.*, 1997a,b). The second gene to be identified as involved in neuroepithelial deafness was the gene encoding myosin VI, which was found to be responsible for the Snell's waltzer mouse mutant (Avraham *et al.*, 1995). Currently there is no known human deafness caused by myosin VI mutations, but it is likely that some cases will eventually be found. It also seems likely that there will be more members of the superfamily of unconventional myosins, such as myosin VIIA and myosin VI, that will be found to be involved in the development of hair cells and play a role in hereditary deafness.

More recently, other genes have been found to be involved in neuroepithelial defects. For example, a mouse knockout of the gene *Fgfr3* was generated and has a unique organ of Corti development: the failure of pillar cells to differentiate, causing cochlear dysfunction (Colvin *et al.*, 1996).

Cochleosaccular defects

The primary abnormality in this defect lies in the stria vascularis which is responsible for generating the high resting potential, the endocochlear potential, in the endolymph of the cochlea. Melanocytes (pigment cells) are involved in this process. This type of inner ear pathology is often associated with pigmentation defects visible as white patches on the hair or skin, and when these patches devoid of melanocytes extend to the stria vascularis, it cannot function properly in generating the endocochlear potential and sensory hair cell function is impaired. Waardenburg syndrome is one example of a human syndrome showing the association between deafness and pigmentation anomalies. *PAX3* was identified some time ago as the gene mutated in human Waardenburg syndrome type 1 and type 3 (Baldwin *et al.*, 1992; Tassabehji *et al.*, 1992). More recently, three other genes have been identified in humans causing deafness associated with pigmentation defects. The *microphthalmia (mi)* locus was first identified in the mouse, and encodes Mitf, a transcription factor (Hodgkinson *et al.*, 1993; Hughes *et al.*, 1993). Mutations were later found in *MITF*, the human version of the gene, in individuals with Waardenburg's syndrome type 2 (Tassabehji *et al.*, 1994). Mutations in other genes can also cause Waardenburg syndrome, such as *EDN3* and *EDNRB* (Attie *et al.*, 1995; Edery *et al.*, 1996), and in the past month the *SOX10* gene has been implicated in one form of Waardenburg syndrome (Pingault *et al.*, 1998). In all three cases, the mouse mutations were described before the human mutations.

However, not all forms of cochleosaccular pathology result from pigment cell defects in the stria. Two genes involved in Jervell and Lange-Nielsen syndrome have been identified as *KVLQT1* and *KCNE1* (Neyroud *et al.*, 1997; Schulze-Bahr *et al.*, 1997; Tyson *et al.*, 1997). These genes are involved in forming ion channels in the stria vascularis, and in the case of *KCNE1* (otherwise known as *Isk*), the precise physiological defect has been described in stria vascularis cells from the knockout mouse (Vetter *et al.*, 1996). These ion channel defects are also responsible for the cardiac anomalies that lead to a long QT interval, the second defining feature of Jervell and Lange-Nielsen syndrome.

Variable expression of phenotype

One interesting feature that has become evident as we learn more about the molecular basis of hearing impairment is the extent of variability of expression of mutations in the same gene. In some cases, there is a consistent pattern of expression, and all affected members of a family carrying the same gene mutation will have the same pattern of hearing impairment, while for other genes, this is not the

case. There are three main classes of variable expression.

Firstly, variability in gene expression has been seen within a single family, which is presumed to carry the same mutation of the same gene. For example, in Waardenburg syndrome type I varying degrees of sensorineural hearing loss are observed from normal hearing to profound deafness, and the impairment is often unilateral (Morell *et al.*, 1997).

Secondly, mutations within the same gene can be associated with different expression in different families, either because the mutation itself is different and has a different effect on the protein produced by the gene, or because the genetic background is different and affects the expression of the gene. One example of this is the myosin VIIA gene. Many mutations in this gene are associated with Usher syndrome type 1B (profound deafness and vestibular dysfunction with progressive retinitis pigmentosa), while other mutations lead to non-syndromic deafness, either recessive and congenital or dominant and progressive (Weil *et al.*, 1995; Adato *et al.*, 1997; Liu *et al.*, 1997a,b; Weil *et al.*, 1997). Another example is the Pendrin gene, which has now been shown to be involved in both Pendred syndrome and non-syndromic deafness (Li *et al.*, 1998).

Thirdly, mutations in the same gene in different species can lead to different phenotypes. For example, the myosin VIIA mutations seen in *shaker-1* mutant mice lead to deafness and vestibular dysfunction alone, while in humans the myosin VIIA mutations were originally described in Usher syndrome. This information about a difference in expression was useful to us, as it led us to search for mutations in this same gene in humans with non-syndromic deafness, which were indeed found (Liu *et al.*, 1997a,b; Weil *et al.*, 1997). *Pax3* mutations when heterozygous (i.e. only one copy of mutant gene present) in humans cause deafness and pigmentation defects, while the pigmentation defects alone are seen in the mouse homologue, *Splotch* (Tassabehji *et al.*, 1992; Steel and Smith, 1992). Interestingly, there was an unconfirmed report that when the *Splotch* mutation was placed onto a different genetic background, hearing impairment was seen in the resulting mice (T. Friedman, personal communication). Recently, it has been demonstrated that there is an 8bp deletion in the POU-domain of the human homologue of the murine *Pou4f3* in a family whose deafness has been mapped to 5q31 (the DFNA 15 locus) (Vahava *et al.*, 1998). This disorder is a progressive non-syndromic hearing loss and is dominant in its inheritance. A mutation in the murine homologue of this transcription factor results in complete deafness and has a recessive mode of inheritance (Erkman *et al.*, 1996).

Recent advances

It will be obvious from the frequent use of the word 'recent' that research in the area of genetic deafness is a very fast moving field at the moment. Up-to-date references and information concerning the recent advances in this field can be found on the Hereditary Hearing Loss Home Page,[1] but we shall include a brief description of some of the most recent reports of identified genes responsible for deafness.

Syndromic deafness

In 1996 the gene for Treacher Collins syndrome was positionally cloned (Dixon *et al.*, 1996). This gene was named *Treacle* and currently is of unknown function. The clinical features of Treacher Collins syndrome include abnormalities of the external ears, atresia of external auditory canals, and malformation of the middle ear ossicles which result in bilateral conductive hearing loss. Within the last year the gene for branchio-oto-renal syndrome has been identified. This gene is *EYA1* (Abdelhak *et al.*, 1997). As mentioned above, the genes for Jervell and Lange-Nielsen syndrome have been identified as *KVLQT1* and *KCNE1* (Neyroud *et al.*, 1997; Schulze-Bahr *et al.*, 1997; Tyson *et al.*, 1997).

Non-syndromic deafness

As well as the deafness genes that have been identified through first identifying the mouse homologue, several non-syndromic deafness disorders have now been identified through the study of large human families. In May of 1997, mutations were reported in the gap-junction gene connexin 26 (*Cx26,* or *GJB2*) in recessive deafness. This mutation segregates with the profound deafness in the families (Kelsell *et al.*, 1997). A particularly exciting recent finding is that this gene may be responsible for a large proportion of non-syndromic deafness in a number of human populations (Denoyelle *et al.*, 1997; Zelante *et al.*, 1997). The gene is small, facilitating easy screening, so the possibility of screening for mutations in this gene in isolated cases of childhood deafness to provide greatly-improved genetic counselling is soon to become a reality. One of the most recent papers to come out of the field, a paper by Lynch *et al.* (1997) reported a gene, which when mutated, results in the nonsyndromic disorder DFNA1 and is homologous to the *Drosophila diaphanous* gene. The role of this gene is thought to be regulation of actin polymerization in cells. Finally, Vahava *et al.* (1998) have just described the *POU4F3* mutation in a family with dominant progressive non-syndromic hearing loss, DFNA15. This transcription factor gene appears to be essential for maintenance of cochlear function.

It is clear that the field of the molecular genetics of deafness is moving so fast that any review will be out of date before it is printed, but we hope that we have presented some of the important concepts and key recent results in the field that will give a flavour of the progress. The next few years should see progress to the next stage of the research: understanding what these genes are doing in the normal cochlea, and moving towards strategies to intervene to prevent abnormal development or further progression of hearing impairment.

[1]The web address is: http://dnalab-www.uia.ac.be/dnalab/hhh

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Address for correspondence:
Professor Karen P. Steel,
MRC Institute of Hearing Research,
University Park,
Nottingham NG7 2RD.

e-mail: karen@ihr.mrc.ac.uk