

Opinion

## Focusing on the genetics of hearing: you ain't heard nothin' yet

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### Abstract

The complexity of genetic pathways for hearing is beginning to be amenable to unraveling by systematic functional genomic analysis. Genome-wide mutagenesis studies in the mouse are beginning to shed further light on the structure and regulation of the machinery of hearing.

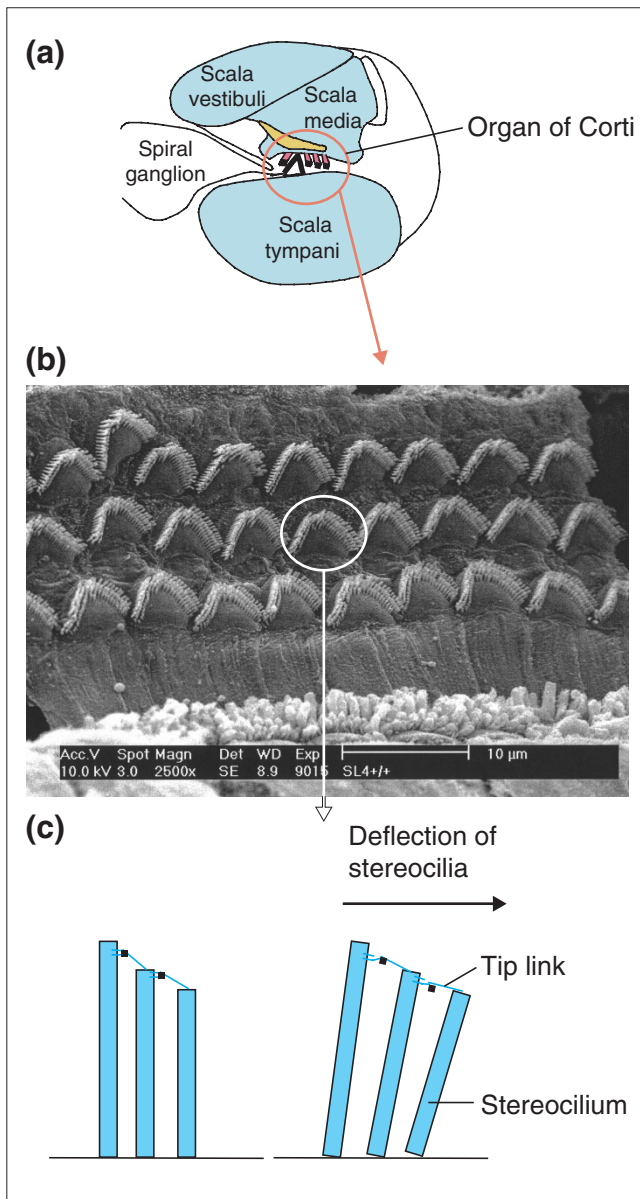
### The genetic complexity of hearing

The process of auditory transduction, whereby sound impulses reaching the inner ear are converted into neural impulses to the brain, is enormously complex. The mammalian ear responds to sounds with a speed, a sensitivity and a frequency resolution that make it the doyen of signaling systems [1]. The exquisite responsiveness of the auditory process is reflected in the structural complexity of the cochlea in the inner ear, which is the pivotal site at which the process of auditory transduction takes place (Figure 1). The snail-like turns of the cochlea house the organ of Corti, a neuroepithelial structure that runs the length of the cochlea. Auditory transduction is critically dependent upon the function of hair cells that constitute one of the most important cell types within the organ of Corti [1]: the organ of Corti is composed of a single row of inner hair cells and three rows of outer hair cells (Figure 1). Hair cells are so called because each projects a remarkable array of actin-filled stereocilia from its apical surface. The apical surfaces of hair cells are bathed by the potassium-rich endolymph of the scala media. Deflection of the stereocilia bundle in response to sound waves traveling down the cochlea results in the opening of ion channels in the stereocilia, cation influx from the endolymph, hair-cell depolarization, neurotransmitter release, and signaling to the spiral ganglion and ultimately the brain. The complexity of the auditory process is not only reflected in the elaborate organ of Corti: the cochlea includes myriad other cell types, many of which are known to be vital for hearing.

Given the complexity and diversity of cochlear structures, it would be expected that a large number of genes would be

involved in hearing. The corollary is that genetic deafness would be expected to be remarkably heterogeneous, and this seems indeed to be the case. A large number of dominant, recessive and sex-linked loci for non-syndromic deafness (deafness with no other symptoms) have been mapped in the human population [2]. In total, to date over 70 loci have been mapped and a number have been cloned. This diversity at the genetic level has touched the ongoing debate over the nature of genetic variation contributing to disease in the human population. At one extreme, it is hypothesized that there are relatively few loci involved in common diseases, with each locus contributing a relatively major effect - the common disease/common variant hypothesis [3,4]. In contrast it has been proposed that a relatively large number of loci may impact on any particular disease, but with each locus having a relatively small contribution to the overall phenotype - the common disease/rare allele hypothesis [5]. The large number of deafness loci has been cited [6] as providing some support for the latter hypothesis, but in fact the genetic complexity of deafness seems more likely to reflect the underlying intricacy of the structure and processes involved in hearing. Indeed, many of the deafness loci mapped to date carry mutations that are of high expressivity and penetrance irrespective of population background, so they do not fit the common disease/rare allele criterion of making a relatively small contribution to the phenotype, although there are many of them.

Similarly, in the mouse a large number of deafness and/or vestibular mutations have been identified that affect hearing or balance and result from disturbances to inner



**Figure 1**

The complexity of the mammalian auditory system and the process of mechanotransduction reflects the underlying genetic complexity of hearing. **(a)** A cross-section through a mammalian cochlea, illustrating the fluid-filled scalae that transmit sound impulses to the organ of Corti, the neuroepithelium where the process of mechanotransduction takes place and sound is converted into neural signals. The organ of Corti consists of one row of inner hair cells and three rows of outer hair cells (illustrated in pink) that are overlaid by the tectorial membrane (yellow). **(b)** A scanning electron micrograph (courtesy of Charlotte Rhodes) illustrating the regular arrays of stereocilia that project from the surface of outer and inner hair cells in the organ of Corti. **(c)** As sound impulses travel down the cochlea, movement of the organ of Corti causes deflection of the stereocilia. Tip links connect adjacent stereocilia and are believed to link ion channels in one stereocilium to the tip of the adjacent stereocilium. Movement of the stereocilia results in an increase in tension on the tip-links and the gating of the ion channels, leading to cation influx from the endolymph of the scala media, hair-cell depolarization, and the transmission of a neural impulse to the brain via the spiral ganglion - the process of mechanotransduction.

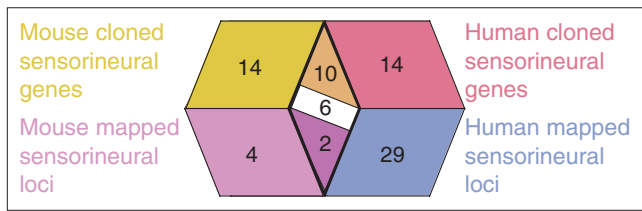
ear function. Figure 2 shows the number of human and mouse deafness loci mapped to date, as well as those loci that appear to be common to mouse and human, on the basis of either the identification of orthologous genes or conserved map position. The observed overlap between the two sets allows us to calculate a very conservative estimate of the total size of the mammalian gene set that may cause non-syndromic hearing loss (see Figure 2 legend): it is clear that at least 126 genes, and probably many more, may be involved in the development and function of structures involved in auditory processing.

### New molecules and new components

The identification of deafness genes has progressed rapidly since the first genes involved in genetic deafness in mice and humans were identified in the mid-1990s (see [7]). To date, over 30 non-syndromic deafness loci have been cloned from mouse or human [2]. They fall into a number of discrete classes, reflecting both the intrinsic molecular properties of the molecules themselves and their likely function in the inner ear (see Table 1).

A number of genes whose products are involved in cytoskeletal structure or dynamics are implicated in deafness. Several genes for unconventional myosins - *Myo7A*, *Myo6* and *Myo15* - have been implicated in hearing impairment, as well as a non-muscle myosin heavy chain gene, *Myh9*. Myosins may play a role in interactions between the apical surface of the hair cell and the underlying actin cytoskeleton, which maintain appropriate membrane tension and stereocilium structures and are possibly mediated by cadherins, a number of genes for which are also deafness loci (*Cdh23*, *Pcdh23* and *Pcdh15*). Espin, an actin cross linking molecule of stereocilia, and Diaphanous-1, a member of the formin-homology family that probably serves as a scaffold for GTPases of the Rho family during assembly of the actin cytoskeleton, also underlie deafness loci.

Mutations in the genes for a variety of gap junction proteins, the connexins, emphasize the importance of the gap-junction network and potassium recycling (which occurs via gap junctions) to the proper functioning of the cochlea. During mechanotransduction (see Figure 1), potassium ions that enter hair cells must be recycled back to the endolymph via supporting cells and other cochlear cell types. Connexin 26 (*Cx26*, encoded by *GJB2*) mutations are responsible for the bulk of non-syndromic recessive deafness in many human populations. *GJB2* is widely expressed throughout the cochlea, indicating that it plays an important role in cation recycling. Other connexins (*Cx30*, *GJB6*; *Cx31*, *GJB3*; and *Cx43*, *GJA1*) have also been shown to be involved in genetic deafness. In addition, mutations in a number of ion channel genes (*KCNQ4*, *KVLQT1*, *KCNE1* and *Slc12a2*) also cause deafness and appear to identify some of the channel components involved in potassium recycling. Mutations in three



**Figure 2**  
The array of mouse and human deafness loci and genes. An analysis of the distribution of identified mouse and human non-syndromic sensorineural genes or loci and their overlap, on the basis of the identification of conserved orthologous genes or conserved map positions (in the case of loci for which the underlying gene has not been identified). A large number of human sensorineural genes (14) or mapped sensorineural loci (29) have been identified for which there is no mouse counterpart (right side of the figure). A corresponding situation exists for the mouse (left side of the figure). There are 18 loci in three classes, however, for which common genes or loci have been identified in mouse and human: 10 mutant loci for which genes have been identified in both mouse and human; 6 mouse mutant loci for which the gene has been identified and for which there appear to be homologous human loci, on the basis of conserved map position); and 2 mapped mouse mutant loci for which the gene has not been identified but there appear to be homologous human loci (based on conserved map position). Given the number of loci identified in these overlapping classes, we can make a determination of the total number of loci in mammals that might lead to non-syndromic hearing loss.  $N$ , the total number of genes in the mammalian set, is given by:  $N = M \times H / C$ , where  $M$  is the total number of mouse loci assayed,  $H$  the total number of human loci assayed and  $C$  the total number of loci held in common. Thus, with current data,  $N = 36 \times 63 / 18 = 126$ . This estimate is very conservative and is likely to be an underestimate for two reasons. Firstly, identifying orthologous loci on the basis of conserved map position is relatively crude and leads to a potential inflation in the number of overlapping loci. Secondly, mutant loci for which genes have been identified in both mouse and human are not ascertained on a random basis. Rather, once a gene has been cloned in one species, significant effort is expended to identify orthologous genes and mutations in the other species.

other ion transporters also cause deafness: *ATP6B1*, the product of which may be responsible for maintaining the  $H^+$  concentration in the endolymph, the Pendred syndrome gene product, *PDS (SLC26A4)*, which is also involved in non-syndromic deafness and encodes an ion transporter of unknown function, and the calcium pump encoded by *ATP2B2*.

A number of extracellular matrix components are critical for auditory function (see Table 1), such as the collagens and tectorins that make up the tectorial membrane overlying the hair cell stereocilia (Figure 1). It might be expected that extracellular matrix components that overlie the organ of Corti could play an important role in signaling pathways that govern the proper development of hair cells and stereocilia, and indeed mice deficient in the  $\alpha_8\beta_1$  integrin (*Itga8*) show stereocilium degeneration. Finally, and not unsurprisingly, transcription factors have also been implicated in genetic deafness (Table 1). It is apparent that, despite the relatively small number of loci cloned, the complexity of the auditory process is also revealed in the range and variety of molecular components that are implicated.

But the story does not end there. Several papers published over the last couple of years underline the notion that we may as yet be only scratching the surface in attempting to define the molecular pathways of hearing. A novel protein - harmonin, which has a PDZ domain, a domain known to be involved in targeting signaling proteins to the cell membrane - was shown to underlie the Usher 1c locus [8,9], one of several loci responsible for the deaf-blind syndrome Usher type 1. Harmonin is expressed in the sensory hair cells in the inner ear. More recently, the gene product underlying the deafness locus *DFNB16* has been identified as a novel protein, stereocilin, that appears to be highly expressed in hair cells and localizes to the stereocilia [10]. Stereocilin and harmonin join a growing list of proteins (including otoferlin and the *DFNA5* product) whose function in the cochlea can only be guessed. This is partly because these genes were implicated on the basis of mutations in human families and we know nothing about the underlying ultrastructural, physiological or molecular defects in the cochlea of affected individuals. The identification of a protein with a PDZ domain makes considerable sense, given that PDZ domains are involved in targeting signaling molecules to sub-membranous sites [11], so they could easily play a key role in events at the apical hair-cell surface; a fuller picture must await the generation or identification of mutations at homologous loci in mice. The recent identification of a transmembrane protein *TMC1*, which underlies the human *DFNA36* and *DFNB7/11* deafness loci as well as the deafness (*dn*) and Beethoven (*Bth*) mouse mutants [12,13] illustrates the value of mouse mutations in understanding human deafness. It is unclear whether *TMC1* acts as, for example, a transporter or an ion channel, but both mouse mutants show hair-cell degeneration, and in the case of the dominant *Bth* mutation hearing loss of a progressive nature, suggesting that further examination of *TMC1* may throw light on the factors required for long-term survival of hair cells.

If we aim to comprehensively relate genes to phenotype within auditory pathways and to build a complete molecular picture of the auditory process, then we will need to exploit mouse mutants. This involves not only making use of the existing deafness mutant resource but, inevitably, generating new mutants, given that, as discussed above, it is likely that in both mouse and human we have not yet identified the full gamut of loci involved in hearing.

### Systematic approaches to developing new mouse deafness models

Over the last year or so, there have been several reports (from groups including our own) describing new large-scale mouse mutagenesis screens [14-16]. The purpose of these mutagenesis programs has been to enhance the mouse mutant resource by providing a new fund of mutant phenotypes for future functional genomics studies. The screens described so far have taken a phenotype-driven approach to

**Table 1****Genes involved in deafness**

Class of protein	Specific proteins and genes
Myosins	Myosin VI ( <i>MYO6</i> ), myosin VIIA ( <i>MYO7A</i> ), myosin XV ( <i>MYO15</i> ), and non-muscle myosin heavy chain gene 9 ( <i>MYH9</i> )
Non-myosin cytoskeletal	Diaphanous-1 ( <i>HDIA1</i> ), Espin ( <i>Espn</i> )
Extracellular matrix	$\alpha$ -tectorin ( <i>TECTA</i> ), novel protein ( <i>COCH</i> ), type XI collagen ( <i>COL11A2</i> ), and otogelin ( <i>OTOG</i> )
Gap junctions/tight junctions	Connexin 26 ( <i>GJB2</i> ), connexin 30 ( <i>GJB6</i> ), connexin 31 ( <i>GJB3</i> ), connexin 43 ( <i>GJA1</i> ), and claudin-14 ( <i>CLDN14</i> )
Ion channels/transporters	K <sup>+</sup> channel ( <i>KCNQ4</i> ), K <sup>+</sup> channel components ( <i>KVLQT1</i> and <i>KCNE1</i> ), Na <sup>+</sup> -K <sup>+</sup> -Cl <sup>-</sup> co-transporter ( <i>Slc12a2</i> ), H <sup>+</sup> -ATPase B1 subunit ( <i>ATP6B1</i> ), pendrin ( <i>PDS</i> , <i>SLC26A4</i> ), and Ca <sup>2+</sup> pump ( <i>ATP2B2</i> )
Signaling molecules	Integrin $\alpha_6\beta_1$ ( <i>Itga8</i> )
Transcription factors	Pou domain transcription factors ( <i>POU4F3</i> and <i>POU3F4</i> ), and Eyes absent homolog 4 ( <i>EYA4</i> )
Others	Transmembrane serine protease ( <i>TMPRSS3</i> ) and Wolfram syndrome gene 1 ( <i>WFS1</i> )
Unknown function	Otoferlin ( <i>OTOF</i> ), novel protein ( <i>DFNA5</i> ), stereocilin, harmonin, and transmembrane cochlear-expressed gene 1 ( <i>TMCI</i> )

This table does not provide a complete listing of all genes involved with deafness, but rather focuses on those involved with non-syndromic deafness in human and mouse, with a few exceptions. For a comprehensive and up-to-date listing, see [2].

mutagenesis, by using the chemical mutagen ethylnitrosourea (ENU) to generate mice carrying random mutations which are then screened for phenotypes of interest. ENU efficiently introduces point mutations with a specific locus mutation rate of  $10^{-3}$  or greater. In the simplest strategy, when a genome-wide screen for dominant mutations is undertaken, male mice are treated with ENU, bred to females and the offspring introduced into phenotype screens. The value of the phenotype-driven approach is that no assumptions are made *a priori* about genes involved in any pathway, and ENU mutagenesis can be expected to be an effective tool for revealing novel gene function and novel pathways involved in the auditory process.

A key question remains, however. Is this an efficient route for generating new mutants affecting the inner ear? There are two large-scale ENU mutagenesis programs in Europe - at the UK Medical Research Council (MRC) Mammalian Genetics Unit at Harwell [17], and at the German National Research Center for Environment and Health (GSF) Institute of Mammalian Genetics in Munich [18]. Both have incorporated screens for deafness and vestibular function into the main screening program (for details of the screens, see [17,18]). Both screens successfully recovered a range of deafness and vestibular phenotypes. Focusing on our MRC Harwell program, in total 54 phenotypes showing balance or circling phenotypes were uncovered, while 28 mice showing hearing impairment were identified (unpublished observations). The rate of recovery of phenotypes in both classes was 0.19% of the total number of mice screened. A number of the putative mutants recovered were bred to confirm inheritance; 80% of the phenotypes tested were inherited, demonstrating that the screens employed were relatively robust. Overall, we can calculate that the UK mutagenesis program generated 64 new deafness and vestibular mutants.

### What have we learned so far from systematic mutagenesis?

Research on many of the classical mouse deafness mutants has already offered us some deep insights into the function of the key molecular pathways of auditory transduction. For example, the cloning of the *shaker1* mutation identified one of the first molecules involved in neuroepithelial deafness in people [19-22], and subsequent studies have elaborated its role in stereocilia organization [23] and, more recently, the phenomenon of adaptation [24]. Will the systematic generation of new mouse models with hearing impairment or balance defects open up new paradigms of gene function in the inner ear, or at the very least allow us to elaborate some of the existing pathways? We would argue that it will.

Many mutants from the two European ENU mutagenesis programs remain to be characterized in detail. A number of mutants have been mapped [14], however, and some of them localize to chromosomal regions where deafness or vestibular phenotypes have not previously been observed. For example, *Jeff*, a deaf mutant, maps to distal chromosome 17, to a region where no deafness mutations have been described [14]. *Spin cycle*, a vestibular mutation, maps to chromosome 15, again in a region where no loci affecting vestibular function have been observed [14]. *Junbo*, a late-onset deafness phenotype, maps to a region on mouse chromosome 3 where no deafness mutants have been characterized (N.P., H Tsai, R Hardisty and S.B., unpublished observations). Overall, the data indicate that some of the identified phenotypes represent new mutations at novel loci in the mouse. Thus, the ENU screens have potentially produced a rich new resource of mutations for the characterization of genes involved in inner ear function in hearing and balance.

In some cases, not unexpectedly, new alleles of known mutations have been recovered. For example, the UK mutagenesis

program identified seven new alleles of the *wheels* locus [25]. Mutations of *wheels* lead to vestibular dysfunction that is caused by defects in the development of the semi-circular canals, and the provision of multiple alleles of *wheels* should aid the cloning of the gene. For some of the mutations, the progress that is being made in identifying the underlying genes is providing useful insights into gene function in the auditory system. The *Bth* mutation described above was identified from the German mutagenesis program [13]. Two dominant vestibular mutations, *slalom* and *headturner*, identified in the UK and German mutagenesis programs, respectively, showed very similar phenotypes [26,27]. Both mutants show normal hearing but are characterized by truncation of the posterior and anterior semi-circular canals as well as a striking patterning anomaly in the organ of Corti. There are reduced numbers of outer hair cells, and in some regions the organ of Corti completely lacks one row of outer hair cells. In addition, occasional supernumerary and atypical hair cells with outer hair cell morphology are seen within the inner hair cell row. Both *slalom* and *headturner* mutants were mapped to mouse chromosome 2 and have been shown to result from mutations in the *Jagged1* gene, and in particular in the second EGF-like repeat of the encoded protein. Identification and characterization of these mutants implicated a new ligand, Jagged1, in the signaling processes that pattern the inner ear neuroepithelium and determine the extraordinarily regular organization of hair cells and neighboring supporting cells. It is interesting to note that although a *Jagged1* knock-out mouse had already been created and its homozygous embryonic lethal phenotype well characterized, the subtle dominant effects in the heterozygote on the vestibular apparatus and neuroepithelial patterning had been missed.

Despite these new mutant resources, the existing catalogue of mouse mutants will still play an important role in dissecting the genetics of auditory function. Indeed, the recent cloning of the *waltzer* [28] and *ames waltzer* [29] genes, both encoding cadherin molecules, has underlined the importance of this class of molecule in the maintenance of the stereocilia on the surface of hair cells.

In conclusion, we have only begun to unravel the genetics of the auditory system. Although the dissection of the genetic complexity of the human auditory system presents formidable challenges, with the aid of mouse functional genomic approaches we can look forward to an increasingly deep insight into the multiple pathways that are required for hearing. There are many surprises still ahead of us.

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