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Development and Maintenance of Ear Innervation and Function: Lessons from Mutations in Mouse and Man

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The inner ear contains two important sensory modalities, the vestibular system for orientation in space and the auditory system for hearing. Progress in recent years has been dramatic regarding the molecular governance of ear development (Torres and Giraldez 1998), the pathways of innervation in this organ (Fritzsch et al. 1997*a*), and the genetics of hearing-related disorders (Cremers 1998). The ability to create targeted mutations has been key in many of these advances. Here we focus on mouse mutations that cause developmental ear defects and those that affect either the formation or the maintenance of sensory neurons in the hearing or vestibular systems.

Although the lessons from these studies are likely to be general, human mutations in most of these genes are unavailable, probably because they have pleiotropic effects and lead to embryonic or perinatal death, as, indeed, many of them do in the mouse. Several genes implicated in ear innervation seem to act in other aspects of sensory neurogenesis, and they (or related genes) may underlie human conditions in which the senses of taste and touch are compromised. We also argue that the ear is a system with unique advantages for the study of developing sensory systems, and we conclude with a discussion of several human genes that illustrate the molecular analysis of hearing disorders.

The Molecular Basis of Ear Development in the Mouse

The ear is induced by an interplay of the hindbrain and mesoderm surrounding the ear region (Fritzsch et al. 1998). This interaction leads to the formation of a placode that invaginates to form a hollow sphere, the otocyst. Many genes expressed in or adjacent to the otocyst, such as *Pax2, Gata3, Dlx3, bone morphogenetic factor 4* (*Bmp4*), and *lunatic fringe* (Morsli et al. 1998), are known or suspected to play a role in further maturation and compartmentalization. These genes may be expressed in the brain or the ear exclusively or may be found in both organs.

Kreisler encodes a zinc-finger protein that is expressed not in the inner ear but in the adjacent hindbrain, a pattern that is also seen with the homeobox genes, *Hoxb1* and *Hoxa1*. Null mutations of *Kreisler* result in cystic differentiation of the ear, with little formation of sensory structures. It has been suggested that Kreisler acts primarily by regulating *Hoxb3* expression (Manzanares et al. 1997). Interestingly, *Hoxa1*-null mutants show variable phenotypes, having lost the cochlea and some or all parts of the vestibular system. When combined with *Hoxb1*-null mutations, the *Hoxa1/Hoxb1* double-mutant phenotype always shows a hypomorphic development of the entire ear (Gavalas et al. 1998). Thus, these genes seem to act synergistically through unknown intermediates, on the morphogenesis of the ear.

Fgf3 is expressed in both the ear and the brain. The mutant has an arrested development of the endolymphatic duct and a partially penetrant developmental arrest of the ear (Torres and Giraldez 1998). The primary effect of the *Fgf3*-null mutation may be related to the expression in the brain rather than to that in the ear. However, differential regulation of expression in either the ear or the hindbrain is needed to distinguish between effects related to both expressions. Other genes, such as *Pax2* or *Otx1*, are also expressed in both the brain and the ear. The expression of the latter genes in the brain is remote from the ear and may not contribute to the phenotype in these mutants. *Pax2*-null mutants lack a cochlea (fig. 1) but form a normal vestibular system (Torres and Giraldez 1998). *Otx1* mutants lack the horizontal semicircular canal (fig. 1) but have no defect in the cochlea. The horizontal semicircular canal, including its sensory epithelium, is also missing in the *Hmx3*-null mutation (Torres and Giraldez 1998).

Other genes that are more or less exclusively expressed

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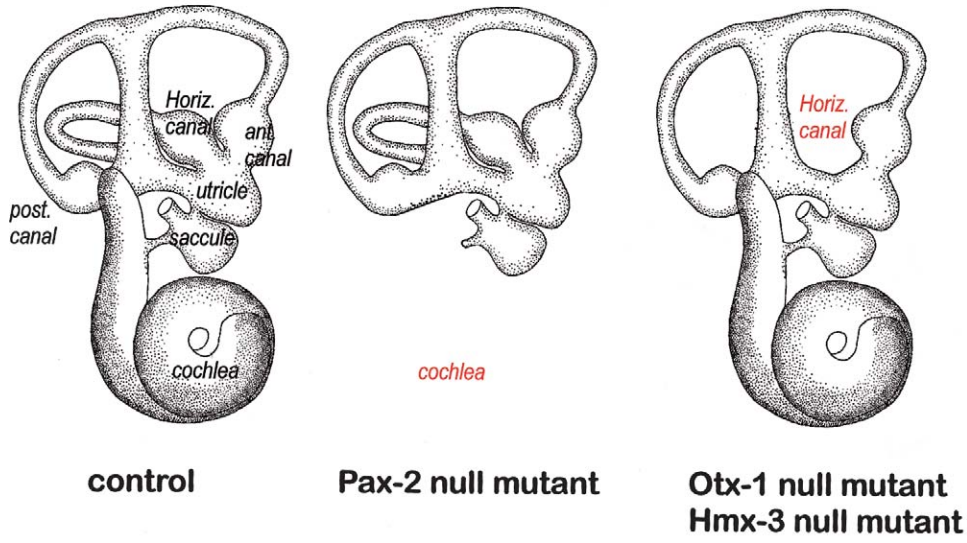

Figure 1 Effects on ear morphology, arising from different gene deletions. The *Pax2* mutation appears to be specific for the formation of the cochlea, since this part of the ear never develops in mutant animals. In contrast, *Otx1* and *Hmx3* mutations affect the formation of the horizontal canal and, possibly, also the sensory epithelium. Other mutations, like those in *Hoxa1* or *Kreisler,* also affect ear morphogenesis, as a result of global defects in pattern formation of the otocyst.

in the ear are related to specific aspects of ear development. *Pou4f3* (also known as "*Brn3c*," or "*Brn3.1*") is expressed in postmitotic hair cells. In *Pou4f3*-null mutants, hair cells form initially but fail to differentiate (Xiang et al. 1997), and all innervation degenerates. A corresponding human deafness gene (called "*POU4F3*"), which is located at the DFNA15 locus, may act somewhat differently from the mouse gene, in that *POU4F3* mutations appear to be dominant in humans, and heterozygotes display a late hearing loss (at 18–30 years of age). Therefore, in humans *POU4F3* most likely affects long-term survival but not initial differentiation of hair cells.

Molecules That Form and Maintain the Innervation of the Ear and the Taste Buds

Auditory and vestibular impairment are found in more than one-third of the population $\geqslant$65 years of age, making ear-related disorders one of the most frequent ailments of old age. Much of age-related impairment involves the loss of sensory hair cells, which are essential for the mechanoelectric transduction to perceive acoustic or gravistatic stimuli. As a consequence of hair-cell loss, the sensory neurons, which conduct the electric signals from the ear to the brain, eventually die. Communication can be restored to these hearing-impaired or deaf people by cochlear implants, electromagnetic devices that directly stimulate the sensory neurons, thus bypassing the lost mechanoelectric transducers, the hair cells. These devices require the presence of sensory neurons to conduct the electric signals to the brain, so the genes that establish and maintain inner-ear innervation are crucial, if imperfectly understood, factors in the success of this therapy. Interestingly, the same molecules that play a role in the development of ear innervation are also important in the development of taste-bud innervation (Fritzsch et al. 1997*b*). In contrast to the situation with the ear, problems with taste innervation and maintenance of taste buds may relate to known clinical disorders such as familial dysautonomias (including Riley-Day syndrome), which are characterized by the absence of fungiform papillae.

All inner-ear sensory neurons form from an anteroventral patch that displays an overlapping expression of several genes (Morsli et al. 1998), including the basic helix-loop-helix transcription factor *neurogenin-1* (*Ngn1*). Null mutants of *Ngn1* fail to develop afferent innervation of the ear. Thus, a single gene is required for the initial formation of all sensory neurons of the ear (Ma et al. 1998). In contrast, the papillae on the tongue—and, most likely, the taste buds as well—seem to form autonomously through local interactions in the tongue epidermis. Much less is known about the molecular interaction that leads to the induction of epibranchial placodes, the source of all taste-bud sensory neurons. Recent data (Ma et al. 1998) suggest that epibranchial placodes are also critically dependent on

a basic helix-loop-helix factor, *neurogenin-2* (*Ngn2*). However, the neural crest seems to restore some of the sensory neurons after their initial formation is blocked in *Ngn2* mutants.

Maintenance of these sensory connections requires four genes, belonging to two gene families that appear to function rather generally in sensory neurons: (1) the neurotrophins, a family with six known members, and (2) the Trk's, a family of at least five high-affinity neurotrophin receptors. It has recently been shown that one of the Trk genes (*NTRK1*) is mutated in patients with congenital insensitivity to pain with anhidrosis (also known as "familial dysautonomia type II"; Indo et al. 1996). In targeted mutations of the mouse *NTRK1* homologue (*Ntrk1*, formerly known as "*TrkA*"), most sympathetic neurons die in neonates, and there is a lack of pain sensation, most likely as the result of the loss of the small dorsal root ganglia responsible for pain sensation. Neither *Ntrk1* nor its ligand *NGF* seems to play a major role in the innervation of the ear.

In situ hybridization has revealed that, of the four mammalian neurotrophins, only two, brain-derived neurotrophic factor (*BDNF*) and neurotrophin-3 (*NT-3*), are expressed in the sensory epithelia of the ear at the time when the sensory neurons grow toward and establish their connections with sensory cells. Whereas *BDNF* is expressed in all sensory hair cells throughout the ear, the expression of *NT-3* is more restricted and shows a greater variation in temporal and spatial distribution. Some sensory epithelia of the vestibular system (the semicircular canals) express only *BDNF* (for review, see Fritzsch et al. 1997*a*). Inner-ear sensory neurons express specific receptors for *BDNF* (*Ntrk2*) and *NT-3* (*Ntrk3*) during the period when they extend their processes into the ear, suggesting a crucial role for these two neurotrophins in the survival of sensory neurons. Although other neurotrophins and their receptors also have been investigated, there is no evidence that they participate in sensory-neuron maintenance.

In contrast to the ear, taste sensory neurons seem to require only a single neurotrophin, *BDNF,* which is expressed early in the developing taste buds (for review, see Fritzsch et al. 1997*b*). A second ligand for *Ntrk2, NT4/5,* also play a role in this process. Sensory neurons in this tissue simultaneously express the high-affinity receptor *Ntrk2* and its ligand, *BDNF.* Thus, in the taste sensory neurons, ligand and receptor form an autocrine loop that is maintained into adulthood, which may explain the ability of these cells to regenerate after their peripheral processes are transected. Such an autocrine loop does not exist in the inner-ear sensory neurons of mammals, which thus lack the regenerative capacity of taste sensory neurons.

Data generated in mice with a targeted disruption of the genes coding for these neurotrophins agree well with the suggestions derived from neurotrophin- and receptor-expression studies. For example, double mutants that lack neurotrophins *BDNF* and *NT-3* (now known as "*Ntf3*") show a rapid loss of all sensory neurons of the inner ear, and no sensory neurons to the ear persist in newborn double mutants. Likewise, data on double *Ntrk2* and *Ntrk3* mutations suggest an additive effect over single Trk mutations. No surviving sensory neurons were found in newborn double *Ntrk2/Ntrk3* mutants. The data on both double-ligand and double-receptor mutants show that only two neurotrophins and their two receptors are required to maintain the afferent innervation of the ear (Silos-Santiago et al. 1997).

Single-ligand and receptor mutants show that each combination plays a slightly different role in maintaining specific components of the inner-ear innervation. Both *BDNF* and *Ntrk2* mutants show a complete loss of all innervation to parts of the vestibular system, the semicircular canals (fig. 2). In contrast, the innervation to the gravistatic receptors in the utricle and saccule of the ear is reduced but is not completely lost. Overall, there is a loss of 85% of vestibular neurons in *Ntrk2* mutants (Silos-Santiago et al. 1997). The remaining innervation of sensory neurons to the utricle and saccule is likely supported by the second neurotrophin expressed in the gravistatic sensory epithelia. In the cochlea of mutant mice, only ~10% (in animals lacking *BDNF*) or 20% (in *Ntrk2* mutants; Silos-Santiago et al. 1997), of sensory neurons are missing, and in both cases, only a portion of the cochlea shows reduced density of innervation (Fritzsch et al. 1997*a*). This mild effect contrasts with findings in the tongue, where sensory neurons are reduced by 50% in *BDNF*-deficient animals and are almost completely lost (95%; Fritzsch et al. 1997*b*) in *Ntrk2* mutants. The difference between *BDNF* and *Ntrk2* phenotypes may be explained by the presence, in the tongue, of another ligand for *Ntrk2,* NT4/5. This protein, which is absent from the ear, is known to support the survival and outgrowth of sensory neurons derived from epibranchial placodes, and it may also play a role in geniculate-ganglion survival. *Ntrk2* mutants show an initial formation of papillae and taste buds, even in the complete absence of a specific innervation (Fritzsch et al. 1997*b*). However, in neonates, taste buds become disorganized, shrink in size, and may even disappear. This pathology is reminiscent of the loss of taste buds in familial dysautonomia types I and II, but further tests are needed to clarify this similarity.

Unlike innervation in the vestibular system and in the taste sensory neurons, cochlear innervation in mice is critically dependent on *NT-3*. In mutants lacking *NT-3,* 85% of all sensory neurons in this structure are lost. Although it has been proposed that this loss specifically affects the sensory neurons that innervate the inner hair cells, recent data show that the effect of the mutation is

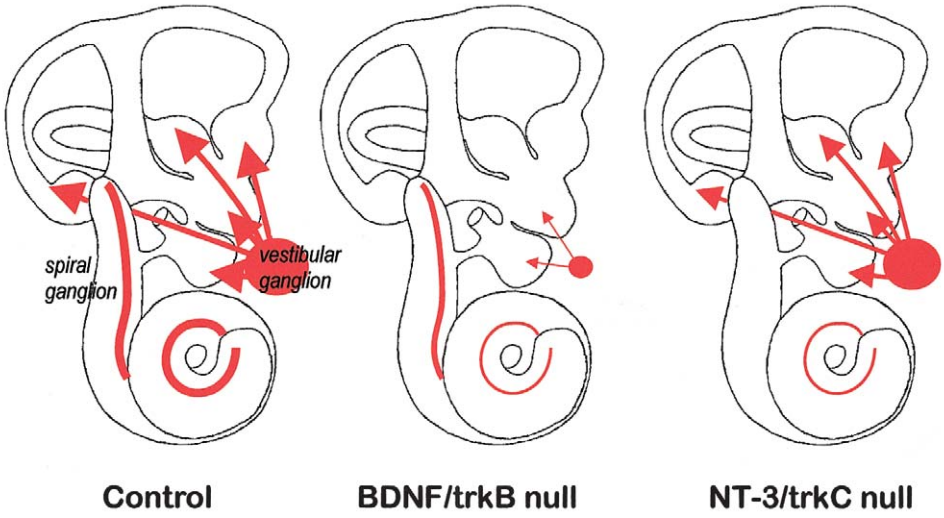

Figure 2 Pattern of innervation in various single neurotrophin and neurotrophin receptor (trk) mutants. Note that, in both *BDNF* and *Ntrk2* mutants (trkB), there is a complete loss of innervation to the semicircular canals, a severe reduction of the vestibular ganglion, and a reduction of the apical innervation density in the cochlea. In contrast, in *Ntf3* (NT-3), and *Ntrk3* (trkC) mutations, there is only a small reduction in the vestibular ganglion but a severe reduction in the cochlear innervation, with a complete or almost complete loss of the sensory neurons in the basal turn.

more complex (Fritzsch et al. 1997*a*). It appears that all sensory neurons in certain areas of the developing cochlea are lost in *Ntf3* mutations (fig. 2), and there is a dramatic reorganization of the remaining innervation. Moreover, electron-microscopic investigations have shown innervation of the inner hair cells in both *Ntf3* and *Ntrk3* mutants (Fritzsch et al. 1997*a*).

Double Mutations in Trk-Family Genes: A Simple System with Complex Effects on the Cochlea

Topologically restricted losses of cochlear sensory neurons recently were used to test the effects of gene dosage in various backgrounds. We bred mice heterozygous for *Ntrk2* and *Ntrk3* null mutations and obtained all combinations of homo- and heterozygosity in these two receptor genes. Some combinations, we found, simply aggravate the phenotype of a single receptor mutation. Thus, *Ntrk2* heterozygosity on an *Ntrk3* homozygous mutant background exaggerates the *Ntrk3* phenotype so that it mimics the more severe *Ntf3* mutant phenotype. However, certain other combinations of mutations lead to novel phenotypes that are not found in any of the single mutants. *Ntrk3* heterozygosity, if expressed in an *Ntrk2* homozygotic mutant background, leads to a retention of precisely those cochlear sensory neurons that are lost in an *Ntrk3*-null animal (Fritzsch et al. 1997*a*). It appears likely that some of these effects arise through cross-talk between ligands and receptors—that is, that the specificity of a given neurotrophin for a given receptor breaks down under these circumstances. It is also notable that interplay between only two genes can generate a dramatic variability in the pattern of innervation. Such issues would be all the more difficult to study in other areas of the brain, where all three receptors are expressed and perform overlapping functions (Silos-Santiago et al. 1997). Comparable effects are expected in various neurotrophin combinations, but these have not yet been studied.

The role of neurotrophins in stabilizing the pattern of innervation of the ear raises the question of gene-dosage effects. Once all genotypic combinations are available for the two receptor and two ligand genes that participate in this process, it should be possible to untangle the full level of genetic complexity in this well-defined system. Such a comprehensive approach would be quite daunting in other systems, such as the dorsal root ganglion, where there are three or more receptors and ligands to take into account.

The Molecular Basis of Deafness: Some Essential Components of the Cochlea

The cochlea is a mechanoelectric transducing device that transforms sound into electrical activity, which is conducted by sensory neurons to the brain, for interpretation. Major players in acoustic transduction include the hair cells, the tectorial membrane that covers them, and the K^+ ion–rich endolymphatic fluid in which they are bathed. Sound induces movement of the organ of

Corti, which pushes hair cells against the tectorial membrane, thus deflecting the stereocilia bundles of the hair cells (fig. 3). This deflection of the bundles causes ion channels in the stereocilia to open, allowing K^+ to flow into the hair cells and alter their membrane potential (fig. 3). K^+ concentration is maintained in the endolymph by lateral diffusion of K^+ ions through gap junctions to the stria vascularis, where the ions are secreted back into the endolymph (Pickles 1995).

Mutations in any of these functionally important components will affect mechanoelectric transduction and, thus, hearing. Hereditary hearing loss and balance impairment exhibit extensive heterogeneity and are associated with a large number of genes; $\geqslant$20 of these syndromic and $\geqslant$35 nonsyndromic loci have been identified (see the Heredritary Hearing Loss home page). Prelingual hereditary hearing loss is predominately nonsyndromic and constitutes 70% of the hereditary forms of deafness. Autosomal recessive (DFNB) forms constitute ~85% of these cases, with autosomal dominant (DFNA) and X-linked (DFN) loci representing 12%–15% and 1%–3%, respectively (Cremers 1998). It has been suggested that as many as 100 genes are involved in hearing impairment, and this number reflects the complex cytoarchitectural, neurosensory, and neural requirements for detection of acoustic and gravistatic/ movement signals. We focus on four different disorders that demonstrate the wide variety of genes that affect the structural and/or physiological integrity of the inner ear.

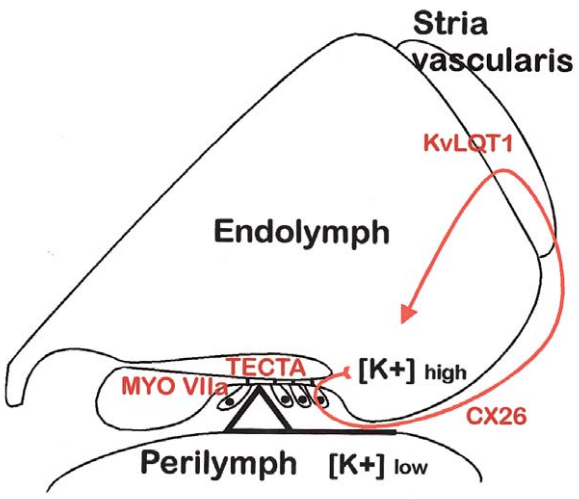

Figure 3 Organ of Corti, shown with inner hair cells and three rows of outer hair cells. During sound stimulation, the organ of Corti moves against the tectorial membrane, which requires Tecta protein to develop a necessary degree of stiffness. This movement induces a shearing force on the stereocilia, whose flexibility depends on the normal expression of myosin VII. As a result of shearing, K^+ flows through the hair cells, causing a change in membrane potential that is proportional to the intensity of acoustic stimulation. K^+ ions flow through an array of gap junctions (composed of the connexin protein Cx26) into the stria vascularis, from which the ions are secreted back into the endolymph through the KvLQT1 and IsK channels. Mutations that affect any step in the flow of K^+ ions may result in deafness.

Tectorin and the Mechanical Properties of the Organ of Corti

Tectorin is expressed in association with both the tectorial membrane of the cochlea and the otolithic membranes of the vestibular sensory epithelia (Legan et al. 1997). The tectorial membrane is a sheet of extracellular-matrix components, of which the noncollagenous glycoproteins, including tectorin, contribute as much as 50% of the total protein mass. The α–tectorin protein is processed into three cross-linked polypeptides, of ~45, ~60, and ~173 kD, whereas β–tectorin is an ~43-kD peptide (Legan et al. 1997). Single-copy genes in mice and humans, *Tecta/TECTA* and *Tectb/TECTB,* encode the α- and β-tectorin proteins.

TECTA is an autosomal dominant, nonsyndromic hearing loss (DFNA) gene whose expression is exclusively associated with the inner ear (Legan et al. 1997; Verhoeven et al. 1998). *TECTA* has been mapped to human chromosome 11q23; the mouse homologue is at the 25.5 cM position of chromosome 9, in a region of conserved synteny (Hughes et al. 1998). The chromosomal location and genomic organization of *Tectb* has yet to be identified. Recently, Verhoeven et al. (1998) identified the intron-exon structure of *TECTA,* and subsequent mutational analysis of two families, one with DFNA8 and the other with DFNA12, identified missense mutations. These mutations replaced conserved amino acid residues in the zona pellucida domain of α–tectorin; it has been proposed that this domain contributes to the filamentous architecture of the tectorial membrane by interacting with zonadhesin-like domains on other tectorin molecules. Clearly, a loss of structure in the tectorial membrane could compromise its function as a resonator—and so lead to deafness (fig. 3). One mutation in the *TECTA* zona pellucida domain, Thr101Cys, may have a dominant-negative phenotype (Verhoeven et al. 1998), although this same missense mutation has also been associated with a recessive form of deafness.

Myosin Genes and the Interconnection of Stereocilia

A number of unconventional myosins are expressed in the inner ear, including myosin IB, VI, VIIa, and XV. Subcellular localization in vestibular and cochlear hair cells shows expression throughout the stereocilia that form linkages with cross-linked adjacent stereocilia, in the pericuticular necklace, and in the cell bodies. Myosin VIIa is found in photoreceptor cells, nasal cilia cells, sperm, kidney distal tubules, and hair cells but not else-

where in the inner ear (Hasson et al. 1997). Two major transcript variants have been identified, along with a number of alternative spliced variants (Chen et al. 1996). The resulting products are 138 and 250 kD, with the larger variant being the predominant form. Both of these proteins have a common motor or head domain, but their tail regions are distinct from those in other myosin isoforms.

The locus for *MYO7A* occurs on human chromosome 11q13.5 and the 48.1 cM position of mouse chromosome 7 (for review, see Cremers 1998), and its genomic organization is known. Mutations in mouse *Myo6,* human and mouse *MYO7A,* and human and mouse *MYO15* result in hearing loss (Avraham et al. 1995; Wang et al. 1998). Both syndromic (Usher syndrome 1b [USH1B]) and nonsyndromic (DFNB2 and DFNA11) forms of hereditary deafness are associated with mutations in *MYO7A*. Mutational analyses demonstrate that a wide variety of defective alleles exist (for review, see Cremers 1998). With >30 deafness alleles (including missense, premature stop codon, deletions, and splicing mutations), no single mutation appears to predominate, and most of the mutations are population specific. Both homozygotes and compound heterozygotes are observed. Cytoskeletal abnormalities in Usher syndrome patients are indicated by abnormal organization of microtubules in the axoneme of photoreceptor cells, nasal cilia cells, and sperm, as well as the by degeneration of the organ of Corti. Variations in clinical manifestation observed in defective *MYO7A* are also reflected in the mouse equivalent, the *shaker-1* mouse, in that allelic difference in electrophysiological responses, hair-cell development, and stereocilia malformation correlate with the severity of the *Myo7a* mutation (Self et al. 1998). Similarly, a missense mutation in *Myo15* causes stereociliary bundles to be malformed and unable to perform electromechanical transduction.

Ion Homeostasis in the Ear: Roles of Gap Junctions and K^+ Channels

Gap junctions are plasma-membrane hemichannels formed by six connexin subunits; interactions between the gap junctions on adjacent cells create channels that permit the exchange of small cytoplasmic molecules. *CX26* encodes a widely expressed gap-junction peptide of 26 kD. Within the cochlea, it is found in the nonsensory epithelium that extends from the organ of Corti to the stria vascularis. The gap-junction network within this epithelium is believed to recirculate extracellular K^+ ions back into the endolymph that bathes the apex of the hair cells (fig. 3). *CX26* is located on human chromosome 13q12 and at the 19.5 cM position of mouse chromosome 14. This gene, also referred to as "*gap junction protein 2*" (*GJB2*), represents a nonsyndromic-hearing-loss locus with dominant (DFNA3) and recessive (DFNB1) forms. DFNB1 underlies half of the cases of recessive nonsyndromic deafness (for review, see Cremers 1998).

Although a *Cx26*-null mutant mouse has been produced (Gabriel et al. 1998), homozygous defective mice die in utero at approximately embryonic day 11 and therefore do not provide a model for this form of human nonsyndromic hearing loss. The most common mutation associated with DFNB1 is a G deletion, converting GGGGGG to GGGGG (termed "30delG" or "35delG"). The majority of other DFNB1 genetic defects involve frameshifts (deletions or insertions) and nonsense mutations. Missense mutations are observed and are primarily represented by residue changes in membrane-spanning domains (for review, see Cremers 1998). In DFNA3, a G→C transversion results in a Trp44Cys mutation and produces a dominant-negative effect, which most likely causes a structural malformation of the inner-ear connexin system. Recently, White et al. (1998) have demonstrated that another putative dominant mutation (Met34Thr) exerts a dominant-negative effect on the wild-type CX26 protein when coexpressed in vitro.

Restoration of extracellular K^+ concentration after the transduction of an acoustic signal requires that this ion be secreted back into the endolymph by the cells of the stria vascularis (fig. 3). Two voltage-gated K^+ channel proteins, KvLQT1 (encoded by the human gene *KCNQ1*) and IsK (encoded by *KCNE1*) are expressed in the marginal cells of the stria vascularis and in the dark cells, which serve as the counterpart of this structure in the vestibular system (Neyroud et al. 1997). The KvLQT1/IsK channels mediate this aspect of ion homeostasis in the inner ear, and they are also expressed extensively elsewhere in the body. Both genes are alternatively spliced. A wide variety of *KCNE1* transcripts are produced by different transcription-initiation sites, alternative RNA splicing, and multiple polyadenylation sites, but all of these share a common open reading frame, so any diversity of the 15-kD IsK protein probably occurs posttranslationally. Two KvLQT1 polypeptide isoforms (61 and 75 kD) that differ by 131 amino acid residues at their N-terminus and S1 transmembrane region (Demolombe et al. 1998) have distinct electrophysiological properties. The long isoform "1" of the KvLQT1 protein can produce a fast-activating current, whereas the truncated isoform "2" is inactive as a K^+ conduit and reduces the amplitude of the current that is carried by isoform 1. Interestingly, IsK forms a channel with a slow-activating current and reduces the inhibitory effects of KvLQT1 isoform 2 on isoform 1 function (Demolombe et al. 1998).

The human *KCNQ1* and mouse *KCNQ1* chromosomal locations are 11p15 and at the 62.0 cM position of chromosome 7, respectively, and the chromosomal

locations for *KCNE1* are 21q22.1-q22.2 and at the 64.4 cM position of chromosome 16, respectively (for review, see Splawski et al. 1998). Jervell Lange-Nielsen syndrome (JLNS) is a variation of the congenital long-QT syndrome (LQTS), also know as "Romano-Ward syndrome," and constitutes prelingual sensorineural hearing loss associated with syncopal episodes and sudden death (reviewed by Vincent 1998). At least two loci, *KCNQ1* and *KCNE1,* are associated with JLNS (Neyroud et al. 1997; Tyson et al. 1997). Recently, the genomic organizations were determined for both of these human genes (Splawski et al. 1998). Mutations in either of these genes can cause LQTS and generally result in dominantly inherited loss of channel function (for review, see Li et al. 1998). JLNS is inherited as a codominant disorder, with a mild form of LQTS generally observed in heterozygotes. Curiously, some mutations in these genes can lead either to JLNS or to dominantly inherited LQTS; evidently, additional factor(s) determine whether deafness in these individuals is accompanied by cardiac arrhythmias.

The precise mechanism for development of deafness is still unknown, although electrophysiological examination of mutants suggest that there is a loss or reduction of channel function (Chouabe et al. 1997). Mutant mouse lines lacking *KCNE1* exhibit the classic shaker/waltzer phenotype (a reflection of vestibular malfunction), as well as aberrant cardiac rhythms (for review, see Drici et al. 1998), and they may provide a useful model for the molecular basis of these conditions.

Conclusions

These examples show how the detailed analysis of targeted and spontaneous genetic disturbances in the development of the inner ear and in the functioning of the adult auditory and vestibular systems can provide insights into their corresponding genetic controls. Because the inner ear is relatively isolated from the rest of the body and has unique physiological functions, the genes responsible for its development and function also reflect this specialization. In no other system could the quantitative effect that various neurotrophin/neurotrophin-receptor mutations have on the pattern of innervation be analyzed at the level of detail that is possible in the developing ear of the mouse.

Likewise, the genes may show either syndromic or ear-specific effects, the latter indicating differential phenotypic expression of a mutation or of gene-dosage effects in different tissues; these effects may be unmasked only in the ear, because of its unique environment. As demonstrated by *MYO7A* mutations, both syndromic and nonsyndromic forms of deafness, as well as recessive and dominant patterns of inheritance, can be associated with a single gene. This variability in outcome certainly reflects differences between the ear and other organs, in sensitivity to the effects of altered proteins. Similarly, mutations in *CX26* and in the *KCNQ1* and *KCNE1* genes demonstrate the diverse physiological phenotypes that can arise from perturbed-ion homeostasis. Epistatic effects, which may be seen when similar mutations lead to distinct clinical outcomes or patterns of inheritance, provide productive areas for future investigations. Thus, although the ear may offer a set of unique problems, it also appears to offer unique opportunities to study genetic effects on development and function in an environment with a unique set of constraints.

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Electronic-Database Information

URLs for data in this article as follows:

Hereditary Hearing Loss home page http://dnalab-www.uia.ac.be/dnalab/hhh/

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Constraints on the overall length of this article prevented us from citing many relevant references; they are included in a Supplemental Reading List, which appears, in the electronic version of the article, as a hypertext link, immediately after the References.

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