The fundamental and medical impacts of recent progress in research on hereditary hearing loss

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INTRODUCTION

Hereditary hearing loss

The overall impact of hearing impairment is greatly influenced by the severity of the hearing defect and by the age of onset. If the defect is severe and presents in early childhood, it has dramatic effects on speech acquisition and thereby cognitive and psycho-social development. A hearing defect appearing at a later age can also severely compromise the quality of life as it results in the isolation of an affected individual.

Deafness can be due to genetic or environmental causes or a combination of both. The main contributing environmental factors are meningitis, mumps, perinatal complications, maternal-fetal infections (toxoplasma, rubella and cytomegalovirus infections), acoustic trauma and ototoxic drugs. Approximately 1/1000 infants are affected by severe or profound deafness at birth or during early childhood, i.e. the prelingual period. In developed countries, it has been estimated that ~60% of the cases without an obvious environmental origin have a genetic basis (1). Although these figures need to be considered with caution, the proportion of cases with a genetic origin is expected to continuously increase as public health improves. A further 1/1000 children become deaf before adulthood and these forms are usually less severe and progressive. The proportion of such cases with a genetic basis is not well documented. Finally, for the late onset forms, 0.3 and 2.3% of the population manifest a hearing loss >65 decibels hearing level (dB HL) between the ages of 30 and 50 years and between 60 and 70 years, respectively. These forms are generally considered to result from a combination of genetic and environmental causes, thus explaining the lack of epidemiological data available concerning the genetic origin. One particular, and frequent, form of late onset deafness, otosclerosis (see below), deserves to be highlighted, as there is evidence supporting a significant genetic basis.

Structure and function of the ear

The adult mammalian ear is a highly intricate organ. It is made up of three distinct parts, the external, middle and inner ear, which function as one unit (Fig. 1). The external ear is the sound collecting funnel and the middle ear transmits the sound to the inner ear, where it is processed. In addition to sound processing, the inner ear has another function, which is the control of equilibrium. The external ear consists of the auricle and the external auditory canal, which collect the vibrations received by the tympanic membrane and transmit them to the oval window of the inner ear. The inner ear is composed of two fluid-filled labyrinths. The membranous labyrinth is an elaborate system of endolymph-filled, epithelium-lined chambers and canals. The membranous labyrinth lies within the temporal bone in a series of similar shaped cavities constituting the bony labyrinth. The narrow space between the bony and membranous labyrinths is filled with perilymph. The sound processing portion of the membranous labyrinth is the snail-shaped cochlea duct, which comprises 2.5 turns and can process 20 Hz–20 kHz sound in humans and 1.75 turns with a capacity of 1–100 kHz in mice. The remaining portion is collectively referred to as the vestibular apparatus. It is composed of the saccule and utricule, which

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Figure 1. Schematic representation of the mammalian inner ear. The mammalian ear is composed of three compartments: the outer ear made up of the auricle and external auditory canal, the middle ear made up of the ossicles within the tympanic cavity and the inner ear made up of the vestibular apparatus and the cochlea. Modified and reprinted with permission from Petit (17).

Figure 2. The organ of Corti of the cochlear duct (scala media). The organ of Corti is situated on the floor of the endolymph-filled cochlear duct and is made up of an array of sensory (ihe, ohe) and supporting (p, d, h) cells and the overlying tectorial membrane (tm). Each sensory cell is capped by a stereociliary bundle which is deflected by shearing of the tm. The organ of Corti is flanked by the inner sulcus cells on the medial side and the Claudius’ cells (c) on the lateral side. The stria vasculäris (sv) on the lateral wall of the cochlear duct is responsible for the unique ionic composition of the endolymph. The cochlear duct is surrounded above and below by perilymph-filled spaces (scala vestibuli, scala tympani). sg, spiral ganglion; cn, cochlear nerve; sl, spiral limbsus; i, interdental cells; ihc, inner hair cells; p, pillar cells; ohe, outer hair cells; d, Deiter’s cells; h, Hensen’s cells; bm, basilar membrane; sp, spiral prominence; rm, Reissner’s membrane. Reprinted with permission from Cohen-Salmon et al. (20) (© 1997 National Academy of Sciences, USA).

SYNDROMIC HEARING LOSS

It has been estimated that 30% of prelingual deafness cases are syndromic. Several hundred such syndromes, consisting of hearing loss in association with a variety of anomalies (such as eye, musculo-skeletal, renal, nervous and pigmentary disorders) have been described (4). Syndromic hearing loss can have many modes of transmission, including maternal inheritance due to a mitochondrial mutation. The forms may be conductive, sensorineural or mixed defects. Table 1 lists the genes and encoded molecules identified as underlying some of these syndromic forms. Two recently isolated genes deserve to be highlighted, as they underlie frequent forms of hearing loss and encode two newly identified proteins. The first of these two genes underlies Pendred syndrome. The encoded protein, Pendrin, is a putative sulphate transporter (5). The second underlies the less frequent Branchial-Oto-Renal (BOR) syndrome (6). The encoded protein, EYA1, is a transcriptional co-activator (7). There exist numerous examples of syndromic forms of deafness where the causative gene has not yet been cloned, but these forms represent the less prevalent syndromes.
Table 1. Molecules encoded by genes underlying syndromic forms of deafness

<table>
<thead>
<tr>
<th>Category</th>
<th>Gene</th>
<th>Encoded molecule</th>
<th>Syndrome</th>
<th>Localization</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracellular matrix components</td>
<td>COL4A3, -A4</td>
<td>Type IV (α3, α4) collagen</td>
<td>Alport, autosomal recessive</td>
<td>2q35–37</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>COL4A5, -A6</td>
<td>Type IV (α5, α6) collagen</td>
<td>Alport, X-linked</td>
<td>Xq22</td>
<td>24,25</td>
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<td></td>
<td>COL2A1</td>
<td>Type II (α1) collagen</td>
<td>Stickler</td>
<td>12q13.1–13.3</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>KAL</td>
<td>Anosmin-1</td>
<td>X-linked Kallmann’s</td>
<td>Xp22.3</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>NDP</td>
<td>Norrin</td>
<td>Norrie</td>
<td>Xp11.3</td>
<td>28</td>
</tr>
<tr>
<td>Enzymes</td>
<td>IDUA</td>
<td>α-l-iduronidase</td>
<td>Hurler</td>
<td>4q13.3</td>
<td>29</td>
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<tr>
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<td>IDS</td>
<td>Iduronate-2-sulfatase</td>
<td>Hunter</td>
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<td>ERCC3</td>
<td>Helicase</td>
<td>Cockayne’s</td>
<td>2q21</td>
<td>31</td>
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<td>Factors belonging to transcriptional complexes</td>
<td>PAX3</td>
<td>PAX3</td>
<td>Waardenburg type 1/3</td>
<td>2q36</td>
<td>31,33</td>
</tr>
<tr>
<td></td>
<td>MITF</td>
<td>MITF</td>
<td>Waardenburg type 2</td>
<td>3p12.3–14.1</td>
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<td>SOX10</td>
<td>SOX10</td>
<td>Waardenburg-Hirschsprung</td>
<td>22q13</td>
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<td></td>
<td>EYA1</td>
<td>EYA1</td>
<td>Branchio-Oto-Renal</td>
<td>8q13.3</td>
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<td>SALL1</td>
<td>SALL1</td>
<td>Townes-Brocks</td>
<td>16q21.1</td>
<td>36</td>
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<tr>
<td>Cytoskeletal components</td>
<td>NF2</td>
<td>Merlin</td>
<td>Neurofibromatosis type II</td>
<td>22q12</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>MYO7A</td>
<td>Myosin VIIA</td>
<td>Usher type IB</td>
<td>11q13.5</td>
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<td>Membrane components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Two molecules forming a functional ionic channel</td>
<td>KvLQT1</td>
<td>KvLQT1</td>
<td>Jervell and Lange–Nielsen</td>
<td>11p15.5</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>KCNE1/II/K</td>
<td>minK/II/K</td>
<td>Jervell and Lange–Nielsen</td>
<td>4p12</td>
<td>40</td>
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<tr>
<td>Receptors plus their ligands</td>
<td>FGFR2</td>
<td>Fibroblast growth factor receptor 2</td>
<td>Crouzon</td>
<td>10q25–26</td>
<td>41</td>
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<td></td>
<td>EDNRB</td>
<td>Endothelin-B receptor</td>
<td>Waardenburg-Hirschsprung</td>
<td>13q22</td>
<td>42,43</td>
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<tr>
<td></td>
<td>EDN3</td>
<td>Endothelin 3</td>
<td>Waardenburg-Hirschsprung</td>
<td>22q13.2–13.3</td>
<td>44,45</td>
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<tr>
<td>A putative sulphate transporter</td>
<td>PDS</td>
<td>Pendrin</td>
<td>Treacher-Collins</td>
<td>5q32–33.1</td>
<td>46</td>
</tr>
<tr>
<td>A putative nucleolar phosphoprotein</td>
<td>TCOF1</td>
<td>Treacle</td>
<td>Treacher-Collins</td>
<td>5q32–33.1</td>
<td>46</td>
</tr>
<tr>
<td>Mitochondrial genes</td>
<td>tRNA(Val(UUR))</td>
<td>transfer RNA(Val(UUR))</td>
<td>NIDDM+ MELAS+</td>
<td>Mitochondrial</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>tRNA(lys)</td>
<td>transfer RNA(lys)</td>
<td>MERRF, MERRF/MELAS+</td>
<td>Mitochondrial</td>
<td>48,49</td>
</tr>
</tbody>
</table>

Only the causative genes for which the type of encoded molecule has been identified are presented here.

*NIDDM, non-insulin-dependent (type II) diabetes; MERRF, myoclonus epilepsy with ragged-red fibres; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes. NIDDM, MERRF and MERRF/MELAS are all associated with sensorineural deafness.

NON-SYNDROMIC HEARING LOSS

The non-syndromic forms of hearing loss are collectively referred to as DFN for the X-linked forms, DFNA for the autosomal dominant forms and DFNB for the autosomal recessive forms. Among the prelingual forms, DFNB account for ~85% of the cases, DFNA for 15% and DFN for 1–3%. Maturally inherited hearing loss due to a mitochondrial mutation, with or without an autosomal recessive mutation, have also been described (7–10). The autosomal recessive forms of hearing loss are often the most severe and account for the vast majority of cases of congenital profound deafness. These forms are almost exclusively sensorineural, due to cochlear defects. The mode of inheritance of postlingual forms of non-syndromic hearing loss manifesting before adulthood has not been extensively studied. However, as more pedigrees are described, the postlingual forms seem to be either autosomal dominant or maternally inherited due to mitochondrial mutations. The autosomal recessive forms are rare. Postlingual forms also seem to be mainly sensorineural defects and are often progressive. Among the late onset forms, which appear in young adulthood, otosclerosis is the most common cause of hearing impairment (0.2–1% of the adult population). This disorder has an autosomal dominant mode of transmission with incomplete penetrance. It is characterized, histologically, by isolated endochondral bone sclerosis of the bony labyrinth. Otosclerotic foci invade the oval window, interfering with free motion of the stapes and resulting in conductive hearing loss. A sensorineural component has also been documented, which may be due to the otosclerotic foci spreading inwards towards the cochlea.

To date, 20 DFNB, 14 DFNA and 4 DFN loci have been mapped. However, on occasion, more than one locus has been assigned to the same chromosomal region, indicating that the same gene could underlie both disorders. This has already been shown to be the case for the forms DFNB2 (11,12) and DFNA11 (13), as well as for DFNB1 (14) and DFNA3 (15). To date, taking into account that two deafness loci mapping to the same region could be due to a single gene defect, the minimum number of non-syndromic deafness loci identified is 36. However, these known loci do not account for all of the families studied to date, indicating that there still remain a significant number of unidentified loci underlying isolated forms of hearing loss. Finally, although the late onset disorder otosclerosis is thought to be genetically heterogeneous, the first locus to be linked to the defect was recently mapped to 15q25–q26 (16).
Table 2. Molecules encoded by genes underlying non-syndromic forms of deafness

<table>
<thead>
<tr>
<th>Category</th>
<th>Gene</th>
<th>Encoded molecule</th>
<th>Form</th>
<th>Type of defect</th>
<th>Localization</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracellular matrix components</td>
<td>TECTA</td>
<td>α-Tectorin</td>
<td>DFNA8/12</td>
<td>Prelingual; sensorineural</td>
<td>11q22–24</td>
<td>22</td>
</tr>
<tr>
<td>Transcription factors</td>
<td>POU3F4</td>
<td>POU3F4</td>
<td>DFN3</td>
<td>Prelingual; progressive; mixed</td>
<td>Xq21.1</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>POU4F3</td>
<td>POU4F3</td>
<td>DFNA15</td>
<td>Postlingual; progressive; sensorineural</td>
<td>5q31</td>
<td>51</td>
</tr>
<tr>
<td>Cytoskeletal components</td>
<td>MYO7A</td>
<td>Myosin VIIA</td>
<td>DFNB2</td>
<td>Prelingual; sensorineural</td>
<td>11q13.5</td>
<td>11,12</td>
</tr>
<tr>
<td></td>
<td>MYO15</td>
<td>Myosin XV</td>
<td>DFNB3</td>
<td>Prelingual; sensorineural</td>
<td>17p11.2</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>diaphanous</td>
<td>Diaphanous 1</td>
<td>DFNA1</td>
<td>Postlingual; progressive; sensorineural</td>
<td>5q31</td>
<td>53</td>
</tr>
<tr>
<td>Membrane components</td>
<td>PDS</td>
<td>Pendrin</td>
<td>DFNB4</td>
<td>Prelingual; sensorineural</td>
<td>7q31</td>
<td>54</td>
</tr>
<tr>
<td>Mitochondrial genes</td>
<td>12s rRNA</td>
<td>12S rRNA</td>
<td>MINSD a</td>
<td>Postlingual; progressive; sensorineural</td>
<td>Mitochondrial</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>tRNAser(UCN)</td>
<td>tRNAser(UCN)</td>
<td>MINSD a</td>
<td>Postlingual; progressive; sensorineural</td>
<td>Mitochondrial</td>
<td>9</td>
</tr>
</tbody>
</table>

*MINSD, maternally inherited non-syndromic deafness.

The difficulties encountered in linkage analysis and cloning of the genes responsible for non-syndromic hearing loss have been extensively discussed elsewhere (17). A large number of these difficulties have now been circumvented by linkage analysis of carefully selected families (18). The particular requirements of linkage studies are such that, in most instances, they result in the definition of a large and unmanageable candidate gene interval. In such cases, the candidate gene approach is the most appropriate cloning strategy. However, this approach itself presents many difficulties, due to the paucity of molecular data concerning the development of the inner ear and auditory function. Such a situation exists due to the great variety of cochlear cells and because each of these groups of cells is present in small numbers. Amongst the putative candidate genes, those which are preferentially (19) or specifically (20) expressed in the inner ear can now be effectively isolated by PCR-based cDNA subtraction techniques. The power of this approach has been largely demonstrated by its application to the isolation of genes responsible for retinal deficiencies (21) and has recently found its first application in isolated forms of deafness. The gene encoding α-tectorin, a major component of the tectorial membrane and the first cochlear specific-component to be identified (using a biochemical approach), has been demonstrated to underlie an autosomal dominant form of deafness (DFNA8/12) (22). Today, a total of 10 genes have been cloned and shown to underlie non-syndromic hearing loss (see Table 2). The first gene to be identified was the mitochondrial gene 12S rRNA (8). Interestingly, it has only been in the last 2 years that the remaining genes were cloned, illustrating the recent boom in interest and progress in this subject.

INSIGHTS INTO THE DEVELOPMENT AND PHYSIOLOGY OF THE EAR

Studies of the molecular basis of hearing loss bring to light the genes encoding proteins for which no functional redundancy exists in the ear. As shown in Tables 1 and 2, the genes underlying syndromic and non-syndromic forms of deafness encode a large diversity of molecules, including extracellular matrix components, enzymes, factors belonging to transcriptional complexes, cytoskeletal components and membrane components, as well as four different mitochondrial encoded proteins, three tRNA molecules and one rRNA molecule. In most instances, in itself, the identification of a deafness gene provides limited information. It allows an entry point into the corresponding developmental or physiological processes, beyond which, however, there still remains a world of understanding. Specific difficulties are encountered in understanding the role of each of these molecules. The ease with which these difficulties can be addressed depends...
on the amount of information already available concerning related molecules and the developmental/differentiation processes in which the molecule is involved, as well as the availability of an animal model, usually a mouse model. Below we will discuss the major progress achieved during the last years in understanding the pathogenesis of syndromic and non-syndromic deafness. This concerns the auditory–pigmentary diseases, Jervell and Lange-Nielsen syndrome and, to a lesser extent, the isolated forms of deafness DFNB1/DFNA3 and BOR syndrome, as well as Usher 1B syndrome (and the isolated forms of deafness DFNB2/DFNA11).

Most of the melanocytes of the body are derived from neural crest cells which migrate out of the neural tube, through the mesenchyme of the developing embryo to specific target sites, including skin, hair follicles and inner ear, where they differentiate and begin to synthesize melanin. Mutations in the genes encoding proteins involved in the development, differentiation or survival of neural crest cells and their melanoblast derivatives and in the melanogenesis process can result in a hypopigmentary disorder (for a review see ref. 55). A fraction of the numerous pigmented diseases described are associated with deafness. The mutations so far identified in genes involved in formation of melanosomes or in synthesis of melanin do not lead to deafness, which is consistent with the normal hearing of albino animals. In contrast, mutations in certain genes involved in the earlier stages of neural crest cell development to the maturation of melanocytes do lead to deafness. Indeed, vestibular dark cells and cells of the cochlear stria vascularis (marginal and/or intermediate) are derived from the neural crest. It is accepted that the vestibular dark cells and the marginal cells of the stria vasculare are involved in secretion of potassium into the endolymph. When these cells are defective it leads to an abnormal endocochlear potential and thus hearing impairment. Included in the category of genes underlying auditory–pigmentary diseases are PAX3 (Waardenburg type 1 and 3), MITF (Waardenburg type 2), SOX10, EDNRB and EDN3 (Waardenburg–Hirschsprung disease, also called Waardenburg–Shah (WS4) syndrome). Another two genes belonging to this category, encoding the receptor c-kit and its ligand steel, have been shown to be responsible for an auditory–pigmentary disease in mice, but have not been associated with an auditory defect in humans.

PAX3 is a transcription factor with two putative DNA binding domains (a paired box domain and a homeobox domain), an octapeptide domain and a putative transcription activation site (56). MITF belongs to the basic helix–loop–helix zipper family of transcription factors (57). In mice, MITF has been shown to bind to the melanocyte-specific enhancer element M box in the regulatory regions of two genes involved in melanin production, tyrosinase and TRP-1 (tyrosinase-related protein 1) (58). Moreover, it has recently been shown that PAX3 directly transactivates the MITF promoter (59). This is the first characterization of a cascade of transcription factors involved in the development/differentiation of melanocyte precursors migrating from the neural tube to the developing ear. In the mouse, Pax3 has been shown to be expressed in the cephalic neural crest cells (56) and Mitf at the 25–26 somite stage in cells located between the otic vesicle and the neuroepithelium of the hindbrain (60). These cells are likely to represent migrating neural crest-derived melanocyte precursors that will eventually colonize the presumptive stria vascularis.

Taken together, the above results suggest that Pax3 and Mitf play roles in the early development of neural crest-derived melano-
binds to a transcriptional co-activator, dachsund (81), and to the MYO7A of deafness DFNB2 (11, 12) and DFNA11 (13) are also caused by dimerization of the tail of this protein (12). In the inner ear, exerting a dominant negative effect as a result of the homo-
copies which appear before puberty. This autosomal recessive disorder is
classified with vestibular dysfunction and retinitis pigmentosa
syndrome, which is characterized by congenital deafness asso-
cerved in the branchial arches (which give rise to the outer and
inner ear anomalies indicative of an early developmental defect. Mutations
in a human homologue (EYA1) of the Drosophila developmental
gene eyes absent have been shown to underlie the syndrome (6).
Two other human homologues of EYA1 have been identified,
providing evidence for a novel gene family, which has also been
characterized in the mouse (6, 79, 80). The EYA family members
are composed of a highly conserved C-terminal region and a
divergent N-terminal region (6). In mice, the N-terminal region
has been shown to be a transactivator domain (7). Recent studies in
Drosophila have shown that the conserved C-terminal region
binds to a transcriptional co-activator, dachsund (81), and to the
transcription factor sine oculis (82). Taken together, these results
indicate that EYA1 is a transcriptional co-activator. The Drosop-
phila eyes absent gene has been shown to direct eye specification
and differentiation of photoreceptor cells (81, 82). EYA1 is
expressed in the branched arches (which give rise to the outer and
middle ear) and differentiating otic vesicle (the inner ear precursor),
consistent with the outer, middle and inner ear anomalies of the syndrome (V. Kalatzis, manuscript in prepara-
tion). The proteins interacting with EYA1 during ear development
and the particular role of EYA1 in inner ear developmental
and differentiation pathways remain to be determined.

Usher IB syndrome is the most frequent form of Usher I
syndrome, which is characterized by congenital deafness asso-
ciated with vestibular dysfunction and retinitis pigmentosa
appearing before puberty. This autosomal recessive disorder is
caused by mutations in the MYO7A gene encoding an unconven-
tional myosin, myosin VIIA (38). Moreover, the isolated forms
of deafness DFNB2 (11, 12) and DFNA11 (13) are also caused by
mutations in MYO7A. DFNA11 is likely to be due to mutations
exerting a dominant negative effect as a result of the homo-
dimerization of the tail of this protein (12). In the inner ear,
MYO7A is expressed as early as E10 (83) and its expression is
subsequently restricted to the sensory cells (84, 85). Myosin VIIA
is localized in the growing and mature stereocilia of hair cells
(84, 85). It is particularly concentrated around the cuticular plate
in which the roots of the stereocilia are anchored (86), although
not exclusively localized to this region. The existence of a variety
of mouse mutants carrying mutations in Myo7A, the shaker-1
mutants (87, 88), has already proved to be a useful start for our
understanding of inner ear physiological processes which are
impaired as a result of defects in this gene. Studies of some of
these mice have shown that myosin VIIA is involved in the
organization of the hair cell stereociliary bundles (89). Moreover,
this protein is also involved in hair cell trafficking of aminoglyco-
sides, which are known to induce ototoxicity (90). However,
the precise role that myosin VIIA plays in each of these processes still
remains to be determined.

Figure 3. Localization of connexin26 in the adult mouse inner ear. Immuno-
histofluorescence using a polyclonal antibody to connexin26 results in a strong
signal in the inner sulcus and Claudius’ cells on either side of the organ of Corti
and in the fibrocytes of the spiral limbus (sl) and of the spiral ligament (SL). rm,
Ressner’s membrane; sg, spiral ganglion; sv, stria vascularis. Courtesy of A.
El-Amraoui (Institut Pasteur, France).

required which, to date, does not exist, given that the knock-out
of this gene is lethal in mice due to placental anomalies (78).
BOR syndrome is an autosomal dominant disorder character-
ized by varying combinations of branchial, otic and renal
anomalies indicative of an early developmental defect. Mutations
in a human homologue (EYA1) of the Drosophila developmental
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mutations in MYO7A. DFNA11 is likely to be due to mutations
exerting a dominant negative effect as a result of the homo-
dimerization of the tail of this protein (12). In the inner ear,
MYO7A is expressed as early as E10 (83) and its expression is
subsequently restricted to the sensory cells (84, 85). Myosin VIIA
is localized in the growing and mature stereocilia of hair cells
(84, 85). It is particularly concentrated around the cuticular plate
in which the roots of the stereocilia are anchored (86), although
not exclusively localized to this region. The existence of a variety
of mouse mutants carrying mutations in Myo7A, the shaker-1
mutants (87, 88), has already proved to be a useful start for our
understanding of inner ear physiological processes which are
impaired as a result of defects in this gene. Studies of some of
these mice have shown that myosin VIIA is involved in the
organization of the hair cell stereociliary bundles (89). Moreover,
this protein is also involved in hair cell trafficking of aminoglyco-
sides, which are known to induce ototoxicity (90). However,
the precise role that myosin VIIA plays in each of these processes still
remains to be determined.

MEDICAL IMPACT OF DEAFNESS RESEARCH

The recognition of various isolated forms of deafness by their
genetic basis should lead to their clinical characterization. This in
turn should allow division of the vast collection of these sensorineural defects into several nosological entities. Included in
such a characterization should be information on the age of onset,
the degree of severity, the shape of the audiometric curves, the
progressiveness of the disorder and the putative inter- and
intra-familial phenotypic variations. In addition, information
concerning the possible association of vestibular dysfunction as
well as the presence/absence of cochlear anomalies, detectable by
computerized tomography, should also be available. Finally, for
the autosomal recessive forms, evidence of a putative a
minima hearing defect in carrier individuals should be included.

To date, the bulk of the clinical information available concerns
the autosomal dominant forms of hearing loss, as most of the
studied families live in developed countries. In contrast, few data
have accumulated concerning the autosomal recessive forms, as
the highly consanguineous families studied mainly live in
underdeveloped countries. In the most favourable situations,
a detailed clinical description of a few families selected for linkage
analysis is provided. However, this description remains fairly
limited and a larger number of families needs to be analysed in
order to obtain a reliable clinical description. The paucity of such
data is regrettable, as a detailed clinical description is a
prerequisite for guiding the future search for mutations in the
corresponding gene and for subsequently providing accurate
genealogical counselling. Along the same lines, current epidemiologi-
ical data concerning hereditary forms of deafness are scarce.

Nevertheless, major advances in the medical field have recently
surfaced which allow the rapid determination of the genetic origin
of deafness in a large number of cases. This stems from the
identification of two genes which frequently underlie non-
syndromic forms of deafness, despite the extreme genetic hetero-
genety of these forms. Firstly, the Cx26 gene, which contains a
single coding exon, thus making the search for mutations facile, was
shown to account for up to 50% of all cases of prelingual, autosomal
recessive hereditary hearing loss (91, 92). Moreover, one particular
Cx26 mutation (which may be related to a mutation hot-spot), called
either 30delG (91) or 35delG (92), represents ~70% of all Cx26
mutations. These data are derived from studies performed mainly on
populations from France, Spain, Italy, the UK, New Zealand and
Tunisia (91 – 93); there is a noticeable absence of data from the
Americas, Africa and Asia. Due to the high prevalence of Cx26

Figure 3. Localization of connexin26 in the adult mouse inner ear. Immuno-
histofluorescence using a polyclonal antibody to connexin26 results in a strong
signal in the inner sulcus and Claudius’ cells on either side of the organ of Corti
and in the fibrocytes of the spiral limbus (sl) and of the spiral ligament (SL). rm,
Ressner’s membrane; sg, spiral ganglion; sv, stria vascularis. Courtesy of A.
El-Amraoui (Institut Pasteur, France).
mutations, genetic counselling of the deaf is perhaps the most beneficial outcome of deafness research. In contrast to other sensory defects, such as retinal deficiencies, environmental causes frequently underlie forms of deafness and are thought to be overlooked in numerous situations. Thus, when confronted with a single case of isolated deafness within a family asking for the risk of recurrence of the defect, only molecular diagnosis could afford a genetic origin. The discovery that mutations in Cx26 underlie a huge proportion of isolated forms of deafness is a considerable aid in genetic counselling, as a genetic origin can now be quickly established in families with a single affected child. Medical geneticists now need to be prepared to respond to possible requests for prenatal diagnosis. The ensuing ethical discussion should take into consideration, on the one hand, the quality of life that deaf children can have with adequate education and hearing aids or cochlear implants (see below) and, on the other hand, the severity of the hearing defect. Unfortunately, though, the inner ear defects arising from Cx26 mutations have not yet been characterized fully.

Secondly, a mutation in the mitochondrial tRNA gene, A1555G, was shown to underlie both an isolated form of sensorineural deafness (9,10) and deafness induced by aminoglycoside treatment (94,95), and to occur rather frequently. Again, the bulk of the data available concerning A1555G has been derived from a European population, namely Spanish (95). Assuming that this mutation is also frequent in other populations, the discovery that A1555G predisposes one to deafness arising from aminoglycoside treatment should find immediate medical application in the prevention of future use of these antibiotics. This work emphasizes the importance of a thorough investigation of the clinical history of all family members of a child who is a candidate for aminoglycoside treatment. The particularly simple search for this mutation should be generally performed and, moreover, systematically employed when there is the slightest suspicion of hearing impairment within a family or, a fortiori, in the child in question.

So far, this research has yet to result in the development of new treatments. The treatments available, to date, are the amplification of sound (using hearing aids) or stimulation of the cochlear nerve or nucleus via cochlear or auditory brainstem implants respectively. We now know, from isolation of some of the causative deafness genes, that diverse developmental, physiological and cellular anomalies are at the origin of hereditary hearing loss. Consequently, the development of new treatments will only be possible when a minimum amount of knowledge concerning each of these defective processes has been accumulated. Parallel efforts to induce regeneration of inner ear sensory cells (96,97) and to introduce replacement genes via viral vectors (98) will soon become the most exciting avenues leading to possible treatment of hearing impairment, regardless of whether the origin of the defect is genetic or environmental.

REFERENCES


