

GENETICS OF DEAFNESS: RECENT ADVANCES AND CLINICAL IMPLICATIONS

Abraham Goldfarb^{1,2} and Karen B. Avraham²

*¹Department of Otolaryngology/Head and Neck Surgery,
Hadassah University Hospital, Jerusalem and*

*²Department of Human Genetics and Molecular Medicine,
Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

ABSTRACT

Genetic research into the causes of deafness has advanced considerably in the last years. Progress has been made in both discovering loci and cloning genes associated with syndromic and non-syndromic hearing loss. To date, close to 75 loci have been identified and 29 genes have been cloned for non-syndromic deafness. The proteins these genes encode range from transcription factors to molecular motors to ion channels. We review the recent discoveries and discuss the impact of this research.

KEY WORDS

deafness, hearing loss, genes, loci, genetic research

INTRODUCTION

Otolaryngologists encounter hearing impaired patients on a daily basis. In fact, hearing loss and deafness are the most common sensory impairment. It is estimated that a severe to profoundly deaf child is born once in every 1,000 births (reviewed in /1/). The implications for the family and the child involve every aspect of life. The public

Reprint requests to: Karen B. Avraham, Department of Human Genetics and Molecular Medicine, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. e-mail: karena@post.tau.ac.il

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expenditure is also considerable. However, the tools of intervention available to the medical profession are crude compared with the intricate anatomy and physiology of the auditory system. Cochlear implantation, which is considered the state of the art treatment for the profoundly deaf, essentially involves the destruction of the cochlea to allow the introduction of electrodes to stimulate the nerve. Furthermore, much has yet to be learned about the molecular structure and function of the auditory system. Since the introduction of molecular medicine and genetics to the field of ear research, many advances have been achieved in elucidating the genetic nature of both syndromic and non-syndromic deafness. A better understanding of the structure and function of the ear and of the pathologic processes that cause deafness is at hand, affording us tools of early diagnosis and counseling. Ultimately, it is the hope that intervention strategies will be developed at the molecular level.

Genetic research of deafness is a young and growing field of research. Until 1995, no genes for non-syndromic deafness had been cloned, but since then 29 genes have been cloned and close to 75 loci have been discovered /2/ (Table 1). It is estimated that more than 100 genes may be involved in causing hearing loss. As more genes are cloned, the mechanism by which a genetic disorder causes a disruption of normal hearing is being elucidated. The work of discovering genes for deafness is nonetheless complicated, at times by (1) the relatively small size of families, which makes linkage analysis more difficult, (2) the large variety of genes that can be affected, (3) the lack of characteristic phenotypes for non-syndromic deafness, and (4) the difficulty of isolating genetic material and protein products from human cochleas. Finding appropriate mouse models for human deafness is instrumental for rapid advancement in this field (reviewed in /3/). As our understanding grows, it is expected that many conditions of progressive hearing loss now classified as idiopathic, as well as some cases of presbycusis (age-related hearing loss), will prove to be genetic in nature.

In this review we concentrate on non-syndromic hearing loss and the new advances made in gene discovery that enhance our understanding of the pathological processes in the ear.

TABLE 1
Genes discovered in non-syndromic hearing loss

Category	Locus	Gene
Autosomal recessive genes	DFNB1	<i>GJA1, GJB2, GJB6</i>
	DFNB2	<i>MYO7A</i> ¹
	DFNB3	<i>MYO15A</i>
	DFNB4	<i>SLC26A4</i> ¹
	DFNB6	<i>TMIE</i>
	DFNB7/B11	<i>TMCI</i>
	DFNB8/B10	<i>TMPRSS3</i>
	DFNB9	<i>OTOF</i>
	DFNB12	<i>CDH23</i>
	DFNB16	<i>STRC</i>
	DFNB18	<i>USH1C</i> ¹
	DFNB21	<i>TECTA</i>
	DFNB22	<i>OTOA</i>
	DFNB29	<i>CLDN14</i>
	DFNB30	<i>MYO3A</i>
Autosomal dominant genes	DFNA1	<i>DIAPH1</i>
	DFNA2	<i>GJB3</i> <i>KCNQ4</i>
	DFNA3	<i>GJB2</i> <i>GJB6</i>
	DFNA5	<i>DFNA5</i>
	DFNA6/A14/A38	<i>WFS1</i> ¹
	DFNA8/A12	<i>TECTA</i>
	DFNA9	<i>COCH</i>
	DFNA10	<i>EYA4</i>
	DFNA11	<i>MYO7A</i> ¹
	DFNA13	<i>COL11A2</i>
	DFNA15	<i>POU4F3</i>
	DFNA17	<i>MYH9</i>
	DFNA22	<i>MYO6</i>
DFNA36	<i>TMCI</i>	
X-linked genes	DFN3	<i>POU3F4</i>

¹ Mutations in gene associated with syndromic hearing loss as well.

ANATOMY AND PHYSIOLOGY OF THE NORMAL EAR

The auricle and external ear canal concentrate the sound waves on the tympanic membrane /4/. The membrane moves in response and displaces the auditory ossicles, ending with movement of the stapes footplate in the oval window. The human cochlea is embedded in the tympanic portion of the temporal bone and is organized into three compartments, the scala vestibuli, scala tympani, and the scala media. The scala vestibuli and scala tympani meet at the helicotrema. The fluid within the scala vestibuli and tympani resembles the extracellular fluid, whereas the scala media has an ionic concentration similar to that of intracellular fluid. In humans, the entire structure is coiled into two and a half turns. The vibration of the stapes footplate causes hydrostatic pressure differences across the basilar membrane, thus moving the basilar membrane. The resulting shearing force causes movement of the stereocilia of the outer and inner hair cells. It is thought that this bending of the stereocilia opens ionic channels that result in depolarization of the hair cells. This in turn is followed by an influx of ions which triggers the release of neurotransmitters that activate the nerve. After this action, the endocochlear potential must be restored. The potassium ions are recycled, and this is largely achieved by the action of the sodium/potassium pumps in the stria vascularis cells. The integrity of the hearing mechanism depends on the proper structure and function of all the elements described above.

THE GENES OF DEAFNESS

Genetic deafness is classified either as autosomal dominant (DFNA), autosomal recessive (DFNB) or X-linked (DFN). Mitochondrial mutations also contribute to a small proportion of non-syndromic hearing loss. Modifier genes (DFNM) are genes that modify the expression of other genes in the auditory system. A full list of the genes and loci associated with hearing loss is published and updated regularly at the Hereditary Hearing Loss Homepage, <http://dnalab-www.uia.ac.be/dnalab/hhh/index.html>.

Autosomal recessive genes

Eighteen genes have been cloned for autosomal recessive deafness (Table 1). The most significant is the *GJB2* gene encoding the gap junction protein connexin 26 (Cx26), since mutations in this gene are responsible for 30-50% of recessive non-syndromic deafness in many parts of the world /5-9/. No other gene is known to be associated with such a large proportion of hearing loss. Connexins are a component of the gap junction that connects two cells, allowing for exchange of ions, secondary messengers and small molecules /10/. Six connexins form a half-channel or connexon, which joins its complement to form the intercellular channel. Different connexins can bind together to form mixed gap junction channels. It has been suggested that the mutations in the *GJB2* gene cause a problem in recycling of potassium ions, from their entry into the hair cells until their return to the endolymph, through the active pumping that occurs in the stria vascularis cells. Mouse mutants with targeted deletion of Cx26 in the epithelial network of their inner ears have hearing impairment but no vestibular dysfunction /11/. The inner ears in these mice develop normally, but soon after the onset of hearing, death of supporting and eventually sensory cells occurs, leading to deformity of the organ of Corti. This model suggests that the connexins are important in preventing apoptosis of cells, and targets future research on possible solutions aimed at preventing cell death in the inner ear.

Other genes of the connexin family that are involved in DFNB1 recessive deafness include the *GJB6* (Cx30) and the *GJAI* (Cx43) genes /12/. A *GJB6* deletion of approximately 340 kilobases in length is found in either the homozygous or heterozygous form; in the latter case, a *GJB2* heterozygous mutation is often found as well /13, 14/. This pattern suggests that either a digenic pattern of inheritance exists for *GJB2* and *GJB6*, in which both genes are inactivated since their protein products can interact to form a channel, or the *GJB6* deletion may encompass a *GJB2* regulatory element necessary for its expression, that together with a *GJB2* mutation will lead to deafness.

Another family of genes associated with hearing loss is that encoding myosins, which are believed to be involved in anchoring of stereocilia and vesicle movement in hair cells. Splicing and missense mutations in myosin VIIA (*MYO7A*) and myosin XVA (*MYO15A*) lead to recessive deafness DFNB2 and DFNB3, respectively /15, 16/.

In mice, *Myo7a* mutations result in disorganization of the stereocilia /17/ and *Myo15a* mutations result in shortened stereocilia /18/. These morphological defects presumably change the ability of hair cells to depolarize, because the deformed hair cell cannot effectively open ion channels in response to the shearing force of the traveling wave. *MYO7A* mutations are also found in patients with Usher syndrome type 1b, causing a combination of deafness, retinitis pigmentosa and vestibular dysfunction /19/. A mouse model for the human recessive myosin VIIA mutation is the shaker-1 mutant, characterized by circling and head tossing coupled with cochlear dysfunction /20/.

DFNB4 deafness is due to mutations in *SLC26A4*, which encodes pendrin, a large hydrophobic protein that contains the signature for the sulfate transporter. Mutations in this gene are responsible for almost 80% of mutations in Pendred syndrome /21/. Two mutations in the gene were described in a family with autosomal recessive deafness /22/. *TECTA* encodes the protein alpha-tectorin that interacts with beta-tectorin to form the non-collagenous matrix of the tectorial membrane. DFNB21 was described in a Lebanese family with profound prelingual non-syndromic deafness, and linkage analysis demonstrated that this locus maps to chromosome 11q23-25, where the *TECTA* gene is located /23/. Further analysis of this gene demonstrated a splice site mutation that results in a truncated protein. Other genes that are associated with recessive deafness include *OTOF*, which encodes otoferlin, a cytosolic protein that may be involved in trafficking of membrane vesicles /24/; *TMCI*, a transmembrane cochlear-expressed gene /25/; and *OTOA*, which encodes otoancorin, an inner ear specific glycosylphosphatidylinositol-anchored protein /26/. Most recently, three myosin IIIA (*MYO3A*) mutations were found in one large Iraqi kindred living in Israel /27/. Most interestingly, this is the first family with late-onset progressive hearing loss to have multiple mutations inherited in a recessive mode. Additional genes are listed in Table 1.

Autosomal dominant genes

Autosomal dominant genes are somewhat harder to isolate because they tend to be present in families with late-onset and progressive deafness. Most individuals with progressive hearing loss fail to reach genetic counseling, and therefore are not referred to laboratories

which identify deafness genes. Nonetheless, progress has been made in this field as well, and 15 genes have been cloned for autosomal dominant deafness (Table 1). The first dominant gene to be cloned was the *DIAPH1* gene encoding diaphanous /28/. The *DIAPH1* mutation is a splice mutation that leads to a protein truncation. Diaphanous belongs to the formin protein family, which share Rho-binding domains and are involved in establishment of cell polarity and cytokinesis. In hair cells, diaphanous may be involved in cytoskeletal maintenance via actin polymerization.

A mutation in the *POU4F3* gene, encoding an inner ear-specific transcription factor, was identified in DFNA15 progressive hearing loss, mapped to chromosome 5q31 /29/. *POU4F3* is a member of the POU family of transcription factors that are involved in neural and inner ear development. Deletion of this gene in mice leads to deafness and vestibular dysfunction /30, 31/. In the family in which the *POU4F3* mutation is described, an 8 base pair deletion forms a premature stop codon. The resulting protein is truncated and thus its function in binding to DNA and activating the transcription of genes important for hair cell function is impaired. The discovery of DFNA15 is a good example of how a mouse model was instrumental in the isolation of a human mutation.

The DFNA2 gene *KCNQ4* encodes a potassium channel /32/. This channel is expressed in the outer hair cells of the organ of Corti and therefore has been suggested to play a role in potassium recycling. Mutations in this gene were reported in four families with DFNA2. Mutations in *GJB3* (Cx31) are also responsible for DFNA2 deafness /33/, since both *KCNQ4* and *GJB3* map to the same region on human chromosome 1p34-35.

The DFNA9 *COCH* gene was isolated from a human fetal cDNA library /34/. This tool is invaluable because of the impossibility of obtaining gene and protein products from the cochlea of living deaf patients. The *COCH* gene is highly expressed in the cochlear and vestibular labyrinths. DFNA9 is the only non-syndromic deafness gene which is manifested by vertigo that shares some symptoms of Meniere's disease /35/. The protein product of the *COCH* gene contains von Willebrand Factor A domains, which are associated with proteins that play a role in extracellular matrix organization, hemostasis and complement system activity. Mutations in the gene have

been described in American families and in the Netherlands and Belgium /34, 36/.

Other autosomal dominant genes include the *DFNA5* gene, which shows no specific homology to any known gene /37/. Despite the fact that this gene was cloned in 1998, its function in the ear is still not known, demonstrating the obstacles to research in this area. More dominant genes include *WFS1* that encodes a transmembrane domain protein wolframin, involved in DFNA6/A14/A38 /38, 39/; *EYA4*, a transcription factor, in DFNA10 /40/; and *MYH9*, nonmuscle-myosin heavy-chain gene, in DFNA17 /41/. Additional genes are listed in Table 1.

It is important to note that mutations in several deafness genes lead to deafness inherited in an autosomal dominant or autosomal recessive mode (Table 1). Examples include DFNA3 and DFNB1, which involves *GJB2* and *GJB6* mutations; DFNA8/A12 and DFNB21 for *TECTA*; DFNA11 and DFNB2 for *MYO7A*; and DFNA36 and DFNB7/B11 for *TMCI*.

X-linked genes, mitochondrial genes, and modifier genes

The X-linked DFN3 phenotype is variable and is characterized by profound sensorineural hearing loss and conductive hearing loss with stapes fixation. This locus was initially described as a syndrome, since it is often associated with stapes fixation that may lead to a perilymphatic gusher upon surgery (gusher-deafness syndrome). DFN3 is the only X-linked gene cloned to date, and encodes the transcription factor POU3F4 /42/.

Several mitochondrial genes, inherited maternally, harbor mutations leading to non-syndromic hearing loss and contribute to approximately 1% of deafness. The A1555 G mutation in the 12S rRNA gene is associated with aminoglycoside-induced deafness /43/. Therefore identification of this mutation can help prevent hearing loss.

To date, only one modifier locus is known, although the gene has not yet been cloned /44/. DFNM1 was discovered in a large Pakistani family with DFNB26 recessively inherited profound deafness. Several members of the family with a DFNB26 haplotype have normal hearing due to suppression of the deafness by the DFNM1 locus.

DISCUSSION

We have described the impressive accumulation of knowledge on the genetic basis of deafness in the last 7 years. However, the clinical professionals in the fields of otolaryngology and audiology remain largely unaware of these findings for a variety of reasons. First, most publications of breakthroughs in genetic research are quite naturally published in the genetic literature. Unfortunately, most clinicians do not read these publications. Second, some clinicians feel that this research is theoretical and lacks practical application to daily work with the hearing impaired. Third, most clinicians are not trained in the tools and language of genetics.

The importance of genetic knowledge for understanding the basis of deafness cannot be underestimated. The advances in research of the genetic causes of deafness are bringing us closer to the day when gene therapy will be a reality. Today, when bilateral cochlear implantation is becoming a more accepted practice, there is a danger that we will obliterate cochleas of patients amenable to genetic therapy. In addition, the knowledge gained about the physiology of hearing through genetic research is important in understanding normal hearing and how environmental factors influence hearing. The ability to predict onset and/or severity of hearing loss through genetic testing may aid in habilitation of the hearing impaired.

Audiologists and otolaryngologists are an important source for patients and subjects for genetic research of deafness because they are likely to be the first ones to encounter these individuals. Cooperation between clinicians in the fields of otolaryngology and medical genetics and genetic researchers will undoubtedly advance research in this area. It is true that the results of genetic research have limited influence on the course of treatment today. However, genetic counseling is already possible for a large number of patients /45/. The future will bring the fruits of many recent technological advances - sequencing of the human and mouse genomes (National Center for Biotechnology Information, <http://www.ncbi.nlm.nih.gov/>), global analysis of inner ear expression involving microarrays /46/, and inner ear-specific cDNA libraries /47, 48/ - which will provide us with a better understanding of the intricate mechanisms of the inner ear.

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Karen B. Avraham
Department of Human Genetics and Molecular Medicine
Sackler School of Medicine
Tel Aviv University
Tel Aviv, Israel
Tel: 972-3-640-7030
Fax: 972-3-640-9360
e-mail: karena@post.tau.ac.il