DEAFNESS GENES AND THE MECHANISM OF HEARING

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RESUME

Durant les dernières années, plusieurs gènes impliqués dans la surdité ont été identifiés. L'exploration de leurs fonctions a permis de réaliser d'énormes progrès dans la compréhension des mécanismes physiologiques de l'audition. Le clonage des gènes de surdité ne constitue, en fait, que la première étape suivie de l'étude de la protéine et de son profil d'expression.
Mots clés: *Surdité, hétérogénéité génétique, fonction de l'audition*

ABSTRACT

Over the past few years, significant progress has been made in the understanding of the hearing mechanism. The identification of genes involved in deafness has begun and is now progressing rapidly. To date, at least 36 genes are known and exploration of their functions has already begun. Indeed, cloning deafness genes is only the first step towards the understanding of the hearing process.
Keywords: *Deafness, genetic heterogeneity, auditory function.*

INTRODUCTION

Deafness is a sensorineural defect which can be due to genetic or environmental causes or a combination of both. It is the most common sensory deficit in humans. In developed countries, it has been estimated that ~60% of severe to profound infantile deafness have a genetic basis with mainly autosomal recessive inheritance [1, 2]. In Tunisia, this estimation is reduced to 23.5% [3] and 47% now (unpublished result). Approximately 1/2000 children are born, or will be, affected by genetic hearing impairment [4, 5]. The criterion for the classification of hearing impairment is whether associated with other symptoms (syndromic) or is the sole defect (non-syndromic or isolated). Hundreds of syndromes associating to hearing loss other symptoms have been reported but a relatively small number of corresponding genes have been characterised. Each of these causative genes has a pleiotropic actions on several tissues demonstrating its likely implication in the development, structure and function of various organs including the cochlea. Many modes of transmission of syndromic hearing loss have been reported including maternal inheritance due to a mitochondrial mutation [6]. They may be conductive, i.e. resulting in an outer of middle ear defect, sensorieneural (mostly due to cochlear defect) or mixed. About 70% of genetic deafness are non-syndromic where only the inner ear is affected [2]. These non- syndromic forms are referred to as DFN for the X-linked forms, DFNA for the autosomal recessive forms and DFNB for the autosomal recessive forms. Among the prelingual deafness, the autosomal recessive forms are often the most severe and account for about 85% of cases of congenital profound non syndromic deafness [7]. According to our results, we have found that all the 102 studied families showed autosomal recessive deafness (Unpublished result). They are almost sensorineural resulting in cochlear defects.

THE STRUCTURE AND FUNCTION OF THE EAR

The human ear is made up of three distinct parts: the outer, the middle and the inner ear (figure1A):

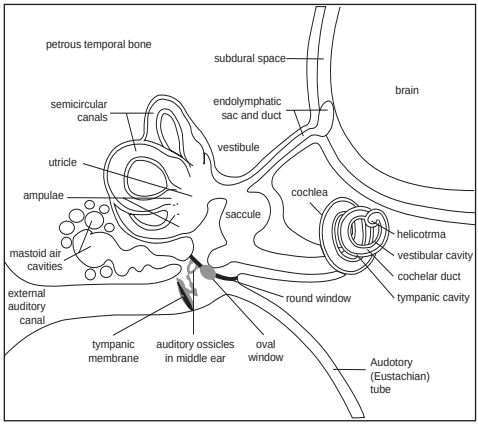

Figure 1*: Schematic representation of the human inner ear. The mammalian ear is made up of three distinct parts: the outer which is closed by the tympanic membrane and consists of the auricle and the external auditory canal; the middle ear comprises an air cavity containing a chain of three ossicles, and the inner ear which is a cmplex membranous labyrinth containing the endolymph immersed in an other liquid, the perilymph. The inner ear is made up of six sensory organs, namely the five vestibular end organs (saccule, utricule and three semi-circular canals) and the cochlea (A. Stevens & J. S. Lowe 1997).*

(i) The outer ear is closed by the tympanic membrane and consists of the auricle and the external auditory canal; (ii) The middle ear comprises an air cavity containing a chain of three ossicles, (iii) The inner ear is a complex membranous labyrinth containing the endolymph immersed in an other liquid, the perilymph.
The outer ear is the sound collecting funnel which transfers the sound to the tympanic membrane. The middle ear collects the vibrations received by the tympanic membrane and transmits them to the oval window of the inner ear. The inner ear comprises six mechano sensory organs, namely the snail shaped cochlea, which is the auditory sense organ and the five vestibular organs responsible for balance. The human cochlear duct comprises, 2, 5 turns and can process sound frequencies between 20 Hz – 20KHz.
The vestibule complex is composed by the saccule, the utricule and the three semi circular canals. It controls equilibrium by detecting head position and movement. The inner ear is composed of sensory hair cells (figure 1B) and various types of supporting cells.

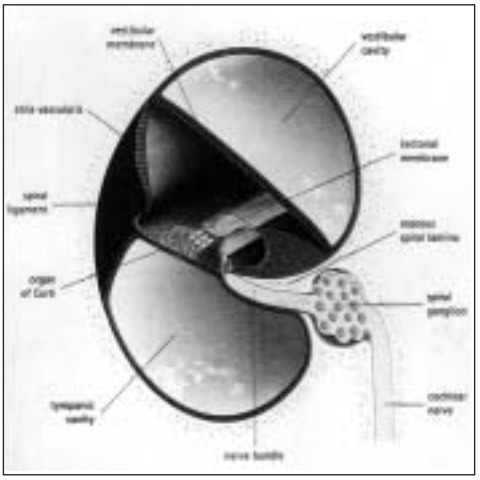

Figure 2: *Transversal section through the cochlear duct. The membranous labyrinth of the cochlea divides the bony labyrinth in three canals, namely the scala vestibuli, the scala tympani and the scala media. The organ of Corti, which is the auditory transduction apparatus, protrudes in the inner ear and is made up of an array of sensory cells and various types of supporting cells. The sensory cells are composed of a single row of inner hair cells and three rows of outer hair cells (A. Stevens & J. S. Lowe 1997).*

The organ of Corti, which is the auditory transduction apparatus, protrudes in the inner ear and is made up of an array of sensory cells and various types of supporting cells. The sensory cells are composed of a single row of inner hair cells (ihc) and three rows of outer hair cells (ohc) and they carry a distinct bundle of actin filled stiff microvilli, called stereocilia, on their apical surface. The organ of Corti is covered by an acellular gel, the tectorial membrane. Sound transfer or head movements result in a relative displacement of the sensory epithelium with regard to the overlaying acellular membrane.
This will provoke the deflection of the sensory hair cell bundles, which, in turn, open the mechanotransduction channels. The influx of the endolymphatic potassium perturbs the ionic balance altering the membrane potentiel and resulting in a depolarisation of the hair cell's membrane. In response, these stimulated cells will release a synaptic transmitter. Upon neurotransmitter release, a pattern of action potentials, specific to the stimulus, is transmitted from the afferent nerve fibre located at the base of the hair cell to the brain [8].

GENETIC OF HEARING LOSS

Specific difficulties are encountered in identification of genes involved in deafness. In fact, epidemiological studies on deafness genes showed an important genetic heterogeneity with an estimation of 100 genes that might be responsible for syndromic and non-syndromic hearing loss [9]. This genetic heterogeneity is explained by the complexity of the inner ear's stucture and function. Mutations in any gene involved in just one of inner ear's crucial functions may disturb a delicate balance and result in hearing loss. This genetic defect may affect the cell membrane depolarisation, the mechanicoelectrical transduction, the transmitter release or the ion transport.
In addition to the extreme genetic heterogeneity, the absence of clinical criteria specific to each different gene, as well as marriages between deaf individuals may increase the difficulties of the localisation and the identification of the deafness causing genes. The latter problem has been circumvented by genetic analysis using large affected consanguineous families living in isolated regions for several generations [10, 11]. In such isolated families, the probability of implication of more than one gene is minimised but not null [12]. Despite these difficulties, Over the past few years, the research on human genetic deafness has remarkably progressed and a great number of genes have been localised on human chromosomes and for some of them, identified. Advances in gene identification are, in principal, due to the utilisation of mouse, the ideal model for studying genes involved in human genetic deafness [13]. The finding of the gene responsible for a defect in a mutant mouse strain lead to the mapping and the identification of the human orthologous gene generally via synteny regions between human and mouse chromosomes. Alternatively, the isolation of human cDNA and, then, its mapping to the human chromosomes were also used. In addition, the intense efforts in the human

genome sequencing as well as the construction of inner ear cDNA libraries are now providing easyly accessible and exploitable data, so much facilitating the identification of new deaf genes. On the other hand, the understanding of the function and the elucidation of interactions between the identified proteins may provide more candidates causing deafness such as ligands. Indeed, numerous loci associated with deafness have been described. Today, 75 loci, for the isolated forms have been identified, 36 loci for the DFNA forms, 29 for the DFNB forms, 8 for the DFN forms and 2 linked to the mitochondrial genome (Homepage). In addition, over 100 syndromes including hearing loss have been reported. A theme becoming remarkable from the cloning of deafness genes, is that mutations in one gene can result in tow or three different types of hearing loss, syndromic and nonsyndromic, autosomal dominant and recessive. For example, several mutations in *MYO7A* can cause either the syndromic USH1B [14], the nonsyndromic autosomal recessive DFNB2 [15] or the aurosomal dominat DFNA11 [15]. Mutations in *PDS* can be responsible for, either Pendred syndrome [16] or the nonsyndromic deafness DFNB4 [16]. In addition, mutations in *GJB2* can cause the nonsyndromic autosomal dominant deafness DFNA3 [17] as well as the autosomal recessif deafness DFNB1 [18].

MUTATIONS AFFECTING DIFFERENT GENES

Over the past two years, rapid progress has been made in the identification of genes at these loci. To date, mutations in at least (20) genes are known to cause different forms of deafness (Homepage). It has been demonstrated that these genes are involved in crucial functions in the ear. Some of them are involved in the early inner ear development. Indeed, the two human deafness genes, SALL1 and EYA1 encode transcription factors which are expressed in the otic epithelium giving rise, later, to the coiled cochlea [21]. These two genes cause Townes-brocks and branchio-oto-renal (BOR) syndromes [22, 23]. Their expression patterns suggest their likely involvement in the specification and differenciation of the sensory organs [5].

Alternatively, mutations may affect genes expressed in the sensory hair cells of the organ of corti, causing alteration of their function and then, leading to deafness. Hair cell function is crucially dependent on its structure. So that, hearing impairment can be caused by mutations in genes involved in actin cytoskeletal organisation. Myosins are likely the major important proteins needed to organise the actin structures of hair cells. Three members of the myosin superfamily, have been demonstrated to be the causative genes of different forms of deafness: myosin VI, myosin VIIA and recently myosin XV which are responsible, for deafness in mice with Snell's Waltzer syndrom [24], Usher 1B syndrome, DFNB2 and DFNA11 [12, 13, 25] and DFNB3 [26] respectively.

Other genes are likely involved in the regulation and the maintenance of the actin cytoskelete of hair cells: such as the human homologue of Drosophila Diaphanous, Diaphanous, causing DFNA1 [27], the transcription factor *POU4F3* causing DFNA15 [28] …

Mutations can also affecting the endolymph homeostasis and the ionic balance. Indeed, in the inner ear, sensory hair cells are bathed in potassium-rich endolymph. Upon mechanical stimulation, depolarisation and repolarisation depend on ion movements through channels. The potassium channel (*KCNQ4*) was shown to cause deafness in DFNA2 patients [29]. In 2addition, mutations in *GJB2* and *GJB3*, encoding gap junctional proteins connexin 26 and connexin 31, respectively, also cause sensorineural deafness [20, 30] Another gene involved in ion transport is *PDS* encoding a sulfate transporter, pendrin [16]. Mutations in PDS cause Pendred syndrome [31] a disorder associating congenital deafness with variable thyroid goiter findings.

Mutations in genes controlling melanocyte development can cause deafness [32]. Waardenburg syndromes with its four types, is caused by anomalies in melanocyte development resulting in hypopigmentation and hearing loss. It can be caused by mutations in *PAX3* [33] *SOX10* [34] and *MITF* [35]…

CONCLUSION

Over the past two years, a great number of genes are identified. For some of them, the function is established, for the others, it is still unknown. Despite detailed studies of physiological process of the inner ear and the function of some involved genes, much remains to be known about the other gene's functions and molecular mechanisms implicated in the hearing and the balance.

Intense efforts are made to study the proteins encoded by these genes and their expression pattern. Indeed, elucidation of the genes functions will be crucial to understand the molecular basis of hearing loss as well as the development of the normal auditory function.

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