International Journal of Advanced Biotechnology and Research (IJBR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-8, Issue-3, 2017, pp2401-2410
http://www.bipublication.com

Research Article

Analysis the Molecular Genetics Non-syndromic Hearing Loss (NHL)

Mehdi Alizadeh[1], Abbas Hajizade[2], and Mohammad Halimi[3]

[1]Department of biology, Faculty of Basic Sciences,
Imam Hossein University, Tehran, Iran
[2]Applied Biotechnology Research Centre,
Baqiyatallah University of Medical Sciences, Tehran, Iran
[3]Department of Biology, Babol Branch,
Islamic Azad University, Babol, Iran
*Corresponding Author, E-mail: soheilalizadeh@yahoo.com

ABSTRACT

Autosomal recessive non-syndromic deafness lies or simply NHL is a common inherited disorder of hearing, in Iran, which is inherited in an autosomal recessive hidden (recessive). This means that the disease was transmitted from parent's healthy carriers of the disease to offspring. Our patient is primarily due to the defects (mutations) in genes GJB2 and GJB6. In the world, on average of every 1000 babies, 1 baby is suffering from congenital hearing impairment. More than 60% of the cases are congenital and occur due to genetic factors. In most cases, hearing loss is a multi factorial disorder, which is caused by genetic and environmental factors. Molecular genetics deafness has made significant progress over the past decade. Genes those are responsible for hereditary hearing loss, progressive drawing and copied it. This article focuses on non-syndromic hearing loss, because genes involved in this type of hearing loss, has recently been identified.

Keywords: Deafness, Non-syndromic Deafness, Molecular Genetics

1. INTRODUCTION

Deafness is the most common sensory deficit in human societies, this highly heterogeneous disorder, affects more than 1 in 1,000 people from the general population and nearly half of these cases occur due to genetic factors. In Iran, the figure is much higher than in other countries, and pay special attention to make it more prominent. [2] Approximately 60% of these cases are hereditary etiology, 30% of the cases have been achieved, and 10% are unknown. Non-syndromic types, are responsible for 70% of the etiology and syndromic hereditary provide 30% of them. Among the variety of genetic, auto is the most common type (85% - 75%), with dominant inheritance (13-12%) and (X-linked) or mitochondrial followed, with 3.2% of non syndromic hearing loss.

Autosomal dominant syndrome, may lead to the loss of conductive hearing loss, Sensor neural or both. In contrast, non-syndromic cases of oral asexual losses before the playoffs are almost always Sensor neural.

Anomalies syndrome, for measles, parasitic infection, virus, cytomegalovirus, or may arise smallpox, drug use during pregnancy, lead to hearing loss, which are hereditary, but no genetic basis, like other types of hearing loss syndrome. Many of these syndromes previously described and mapped genes are copied.

Some of the known genes that cause syndromic types are responsible for isolated forms of hearing loss. There does not seem to be a direct correlation between the type of mutation, and cooperation with non-syndromic hearing loss or

syndromic. In addition, analysis of phenotypes, as well as mutations in some families affected by Pendred and Usher, for example, showed that this mutated gene syndromes may also lead to non-syndromic hearing loss. In such cases, there is a high probability that genes are modified factors of cooperation.

The purpose of this study, is described some of the genes to be expressed as mutation, leads to the creation of many different models of non-syndromic hearing loss: Back autosomal dominant, X-linked and mitochondrial. We chose our articles using MEDLINE and investigative mechanisms, using key words such as "Deaf" and "non-syndromic" which is part of the OMIM database. Selected articles were those that were involved in mind-date information about genes and their related proteins, the location provided in the cochlea, and clinical images and acoustics.

2. Autosomal Recessive Non-syndromic hearing loss

Non-syndromic deafness, autosomal recessive, or simply NHL, is one of the most common inherited diseases hearing in Iran, which lies in an autosomal recessive (recessive) is inherited. This means that it is transmitted from parent's carriers of the disease but the disease to healthy children. Our patient is primarily due to the defects (mutations) in genes GJB2 and GJB6. Parents of a sick person, is a carrier of the disease and the incidence of them, in each pregnancy is 25%. They should be done before attempting the next pregnancy, genetic center of their visit, and the first step to do Deaf. In this experiment, they identified gene defect and the possibility of individuation to be determined before birth. Deaf couples who have done the first step, and the possibility of prenatal diagnosis has been possible for them, to refer for prenatal diagnosis of embryo, the pregnancy after the 10th week of pregnancy.

Fortunately, there is the possibility of molecular diagnosis and carrier detection, and prenatal diagnosis of the disease, the Centre of Medical Genetics. If the patient occur in the family, or a family history of the disease exist, it is necessary to first and second degree family members, their counseling before marriage or pregnancy, and if necessary, genetic testing done to them. [1]

Prenatal molecular diagnosis and disease stage:

The first step NHL: Blood samples from patients, and disease-causing mutation detection

Duration of the first step: 3-4 weeks

Second, the applicant's parent or other adult approved by a mutation in tests, which are relative to the patient.

The third stage (detection of fetal status): sampling of the fetus, at 10 weeks gestation. The sampling is performed at 10 weeks gestation, the placental villi (CVS) by a gynecologist, or radiologist.

The second phase of testing time: 2-3 weeks

Connexon, as the building blocks of fractured joints, form channels between cells that cause the release of ions and small molecules and thus communication between neighboring cells. Oligomerization6 forms the subunit Connexon.

3. Literature Review

List of non-syndromic hearing losses

Different chromosome locations, the types of non-syndromic genetic deafness, with the acronym DFN (from deafness English), which is followed by A or B, respectively autosomal dominant transmission means (DFNA), and transition back (DFNA). When used independently of the DFN, is X-linked deafness. After the letters numbers that are indicative of gene discovery.

Physiology of hearing

In order to understand the consequences of mutations, which regulate the hearing process, you need to know about the physiology of normal cochlea. After stimulating sound, the sound move energy in outer hair cells of the cochlea, is converted to an electrical signal (mechanical - electrical transmission). At the top of the hair cells, there are small villi audio epidermis covered with acting and myosin specialized restoration, which varies the sound, which is helping to move the bones, the stapes oval window, which moves fluid around the hair cells. Flagellums curvature adjacent channel audio transfer them open, makes it possible internal loss of potassium from internal lymph both hair cells, leading to cell membrane

depolarization, and activation of calcium channels in the horizontal plane of the membrane, which are sensitive to the settings voltage. There is another inflow of calcium, which leads to the release small bag, containing neurotransmitters in the synaptic end of the eighth cranial nerve. So, after sound stimulation, hair cells, a high concentration of potassium inside cells are highly polarized. Thus, the new thrill is possible, potassium must be removed. This movement of potassium ions, the hair cells in the cochlear supporting cells in the inner lymph returns through internal relations, and created specialized, listed connections or communication gap that exists between supporting cells, fibrocystic of spiral ligament and spiral limbus. [3]

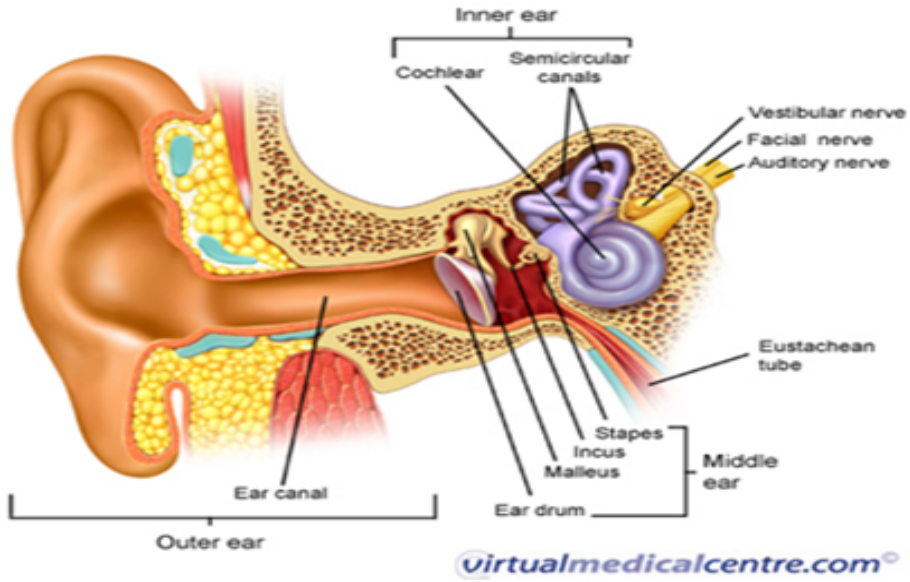

Figure1. A view of the structure of the ear

Molecular genetics non-syndromic hearing loss
CPM-genetic proteins, with cells in the cochlear hair:
1) Unconventional myosin proteins:
Bohemian of myosin proteins forms a family, which is divided into 16 categories, which are found in most cells in non-muscle. They are smaller than muscle myosin, for this reason, they are called mini-myosin. These stimulating proteins create strings which move with the force produced by the decomposition of ATP in acting filaments. They are present in the screw-in cell membrane formation and extension movements, gestures and signs of synaptic vesicle transport inner and outer hair cells. [4]
a) Myosin VIIA: it is expressed in inner ear outer hair cells and in a great variety of epithelial cells that present apical microvilosities, in addition to retina photoreceptor cells. In the cochlea, the protein is present along the stereo cilia, close to the junction between hair cells and supporting cells and present in the synaptic region,Gene MYO7A, located in chromosome 11 (11q13.5) has 49 exons that codify non-conventional myosin protein VIIA (2215 amino acids.
Mutations in the gene cause structural defects of the protein and consequent affections in auditory function, responsible for non-syndromic firms of hearing loss, one of profound recessive autosomal transmissionDFNB2, comprising different grades of vestibulardys function and variable age of onset, and another one that is autosomal dominant – DFNA11, whose onset takes place only after complete speech acquisition and causes progressive hearing loss. When the mutations cause also retina cell abnormalities,phenotypic picture is characterized as Usher syndrome.The chromosomic site for one of the genetic types of Usher syndrome – USH1B was also mapped in the same region of chromosome 11, responsible for 75%of the cases of USH type 1 7. Usher syndrome is the more frequent cause of hearing loss associated with blindness and vestibular pathology since childhood.

Studies on mutation of gene MYO7A that causesDFNB2, DFNB11 and Usher1B were the first ones to show that one single gene could determine both forms of hearing loss, syndromic and non-syndromic.

b) Myosin XV: non-conventional protein (3,530 amino acids) codified by gene MYO15 with at least 50 exons and located on chromosome 17 (17p11.2). In the inner ear, the expression of this gene seems to be restricted to hair cells, on the cuticular plaque. Mutations of this gene determine DFNB3.

c) Myosin VI: gene MYO6 (32 exons), located at chromosome 6 (6q13), codifies non-conventional protein myosin VI (1262 amino acids), concentrated on cuticular plaque of hair cells 1. Mutations determineDFNA22 and DFNB37, characterized by progressive hearing loss, post-lingual, which starts during childhood to 10 years to start symptoms, 6 to 8 years for onset of audiometric affections), progressing to profound level at the age of 50 anos.

d) Myosin III: non-conventional protein recently described in a Jewish family of Mosul, in Iraq, codified by geneMYO3A (10p11.1).10 Mutations determine DFNB30,characterized by bilateral progressive hearing loss that affects primarily high frequencies, starting on the second decade, and at age 50 years, it reaches severe level in high and medium frequencies and moderate level in low frequencies.

2) Harmonin: gene site, if mutant, causes DFNB18, and was mapped at chromosome 11 (11p15.1), at the same gene location as USH1C (Usher Syndrome Type (IC– 11p15.1). Gene USH1C (28 exons) codifies a protein that contains domain PDZ, denominated harmonin. At the cochlea, harmonin is restricted to hair cells, in which it is present in the cellular body and stereo cilia. In patients with pre-lingual and severe DFNB18, mutation of geneUSH1 has been recently detected, located in an alternative exon present in the transcription to the inner ear, but not to the retina transcription 11. Functional characterization of domain corresponding to harmonin protein provides the understanding of the pathogenesis of DFNB18 andUSH1C syndrome.

3) Villin: protein that belongs to the molecule that contains PDZ domain; it acts as an organizer of sub membranous molecular complexes that control and coordinate polymerization of actin for the growth of membrane in stereo cilia of inner and outer hair cells. Gene villin (9q32-q34), with 12 exons, codifies protein of the same name, with 465 amino acids and if mutant they are responsible for pre-lingual profound DFNB31. Protein villin is similar to protein harmonin because it shares 95% of its three PDZ domains. [5]

4) Cadherin-23: it belongs to the family of Tran's membrane proteins, dependent on Ca2+ ions, with over 20 different members, making part of a molecular structure of intercellular adhesion junctions or zones of adhesion (zonnulaad herens).

Chromosome sites for DFNB12 (10q21-q22)13 and Usher syndrome Type I (USH1D-10q) were mapped in chromosome 10. Gene CDH23,with 69 exons codifies protein cadherin-23 (3354 amino acids) expressed in both cochlear hair cells, promoting strong adhesion between each of their types, maintaining polarization of plasma membrane depending on occlusion junctions (claudin-14 protein) and cytoskeleton. Mutations of gene CDH23 were detected in families with DFNB12, which presented pre-lingual profound hearing loss.

Conversely, only deletions or displacements were founding patients with USH1D. Therefore, the type of mutation can have a crucial role in phenotypic expression.

5) Diaphanus-1: it belongs to family of proteins related to forming, involved in cell polarization and cytokinesis. GeneDIAPH1 or HDIA1 (26 exons), located at chromosome (5q31), codifies protein diaphanous-1 (1252 amino acids), homologous to protein diaphanous of Drosophila. At the cochlea, the protein is found in hair cells and external supporting cells, but in small concentrations. Gene mutations affect the cytoskeleton of acting in outer hair cells and cause DFNA1, described in a family in Costa Rica, in which they located the first affected ancestral namedMonge.14 it is characterized by progressive hearing loss that at first affects low frequencies (Konigs mark syndrome, by

identification of three families with hearing loss and this audio logical pattern). At the age of 40 years, approximately, hearing loss reaches severe level in all frequencies.

6) KCNQ4: gene KCNQ4, with 14 exons, mapped in chromosome 1 (1p34), codifies a protein subunit of family

KCNQ of potassium channels, protein KCNQ4 (695 amino acids). In the cochlea, channels KCNQ4 are expressed not only in outer hair cells, but also in inner hair cells, whose main function is to promote the out flow of potassium from the cells to supporting cells. Mutations of this gene were identified in families affected by progressive hearing loss – DFNA2, starting at adolescence or at the age of 20 years, and preferably involving high frequencies, becoming profound within 10 years.

7) Otoferlin: gene OTOF, with 48 exons, codified protein otoferlin (1977 amino acids) located at chromosome 2 (2p22-p23), whose mutation determines DFNB9,characterized by pre-lingual profound hearing loss involving all frequencies.16 Protein otoferlin is expressed in inner hair cells and it is involved in the fusion, triggered by calcium, of synaptic vesicles with the plasma membrane, releasing glutamate neurotransmitter to the afferent innervations system to take the sound message codified by inner hair cells in the form of electrical impulses to the central auditory areas.

8) POU4F3: A deletion of only 8 base pairs was the mutation found in gene POU4F3 (2 exons), located in chromosome (55q31), determining DFNA15, starting between 18 and 30years, progressive, and which reaches moderate to severe level at the age of 50, approximately. Gene POU4F3 codifies transcription factor of the same name (338amino acids), belonging to the family of proteins of domain POU. In both hair cells in the cochlea, gene POU4F3 seems to express the migration of the same layers of supporting cells for the hair cell layer of the lumen in addition to their maturation and survival.

4. Non-muscle

Proteins that were developed genetically expressed in the cells of the cochlea:

1) Connexin: Connexin protein, except for the gap junction intercellular structure, which is responsible for potassium current support cells for fibrocystic spiral ligament and spiral limbus into the lymph inner hair cells after they have been removed.

A) Connexin26: In 1997, gene connexin26 (13q11-12) was discovered, which is to DFNA3 and DFNB1. It is assumed that the gene Cx26 or GJB2, only one exon, formulated the connexin26 protein (226 amino acids), which could be responsible for both types of hearing loss. With pre-speech hearing loss, progressive, intense, with the threshold values at all frequencies described above.

B) Connexin31: if the protein connexin31 (270 amino acids), was present in all links of the inner ear, was still not clear. Cx31 location or GJB3, on chromosome 1 (1p34) KCNQ4 gene is similar in both hairy cell expressed, and if the mutation causes the DFNA2. For this reason, the Cx31 gene mutations lead to hearing loss dominant, but even with the presence of genes in different locations KCNQ4, both a name referred DFNA2.

C) Connexin30: setting gene connexin30 (261 amino acids) is located on chromosome 13, (13q13) and if the mutation, leads to DFNA3 and DFNB1 (also both models are created by Cx26). If not found any mutation in the Cx26 gene in patients heterozygous for 35delG, gene mutations Cx30, with regard (about 76% identical amino acids) and near places to gene Cx26, may consider them responsible for hearing loss, both Cx26 is called. This fact, in addition to proximity, Cx26 and Cx30 by the fact that it is possible to create channels hetro topic connexin explained, and they are dividing like cells in the cochlea. Therefore, path physiological hypotheses associated with hearing loss associated with Cx26 and Cx30 are similar.

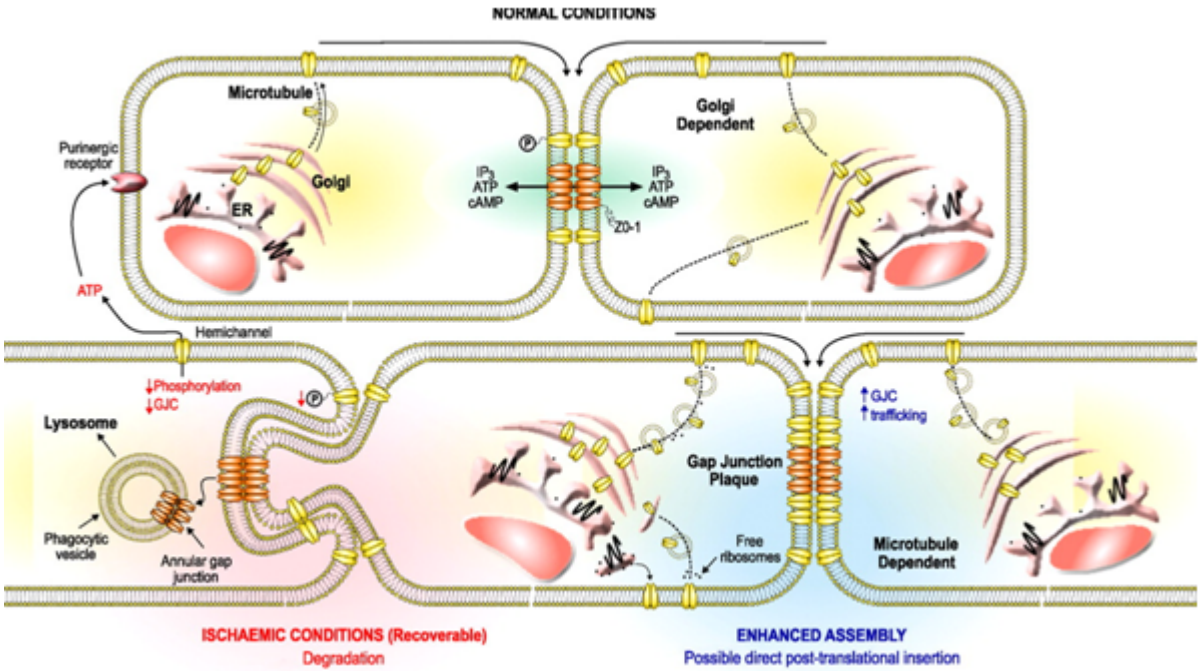

Figure2. Connexin functions in hearing

2) Pendrin: Pendrin protein (780 amino acids) by gene PDS (21 exons) is formulated, is located on chromosome 7. Mutations in the gene responsible for the syndrome Pendrin (7q21-34) and DFNB4 (gene SLC26A4-7q31) are. DFNB4 with progressive hearing loss and vestibular wide channel, without affecting the thyroid described. The adult worm, Pendrin protein, in cells of the dominant spirals and spiral out slots adjacent cells expressed.

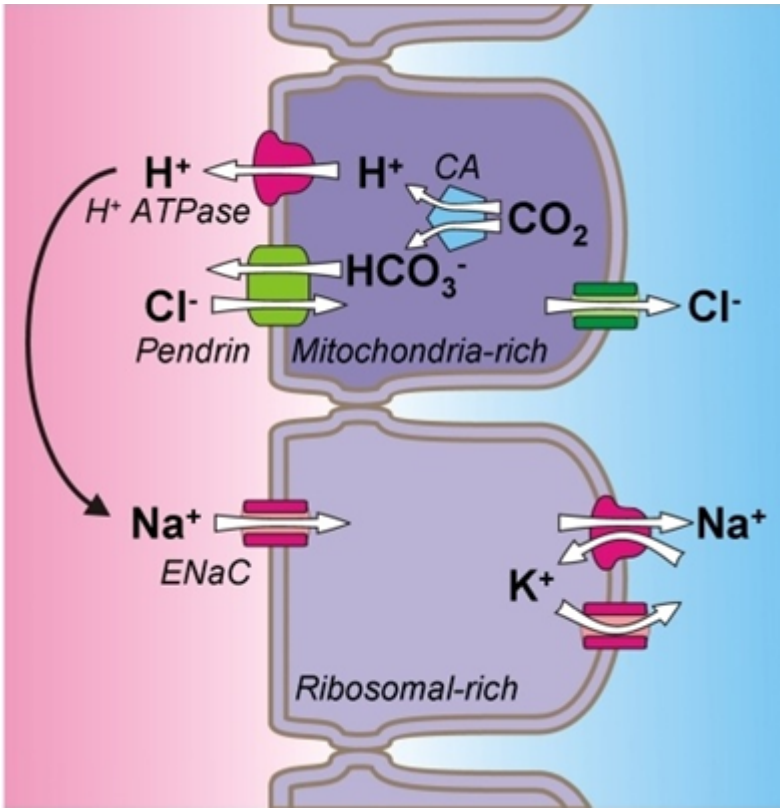

Figure 3 Pendrin hearing

3) Kladyn -14: Gene CLDN14, is located on chromosome 21 (21q22), Kladyn the formulation of the protein (amino acid 239), one of the components of gap junction or hard links. Unknown combination of ions and small molecules that block or link gap through

intercellular space, in addition to maintaining cell polarization and cell components Additional links limits. The cochlea, the gene is expressed in hair cells and support cells. Mutations of this gene are responsible for DFNB29.

4) Coquelin: Coquelin protein (550 amino acids) by COCH (11 exons) is formulated, is located on chromosome 14 (14q12q13). The cochlea, the gene is expressed in spiral ganglion and matrix extracellular especially limbus, spiral ligament and bone spiral blade. Mutations are responsible DFNA9 that, almost, begins between the ages of 20 and 30 years of age. First, in high frequencies with different advance Nakosis at 50-40 years of age is extreme. Atrial the whole conflict, the lack of symptoms associated with hypothyroidism vestibular vertigo and varied. Coch Gene mutation may be one of the genetic factors that are associated with symptoms of Meniere's disease, and this hypothesis should be considered in patients with symptoms of the disease. Histopathology analysis (historical pathology) shows the temporal bone in patients remaining DFNA9 the mucopolysaccharides in cochlear and vestibular nerve channels. These findings suggest that settling or remaining may be used for the destruction of nerve fibers in the inner ear, which lead to hearing loss.

5) EYA4: Gene EYA4 (21 exons), a member of the same family EYA absent eyes (visual progress regulator), chromosome 6 drawn (6q22.3-23.3), the formulation of the protein EYA4 (639 amino acids) to. EYA4 genes are expressed in different tissues in early embryo development, and although EYA gene expression pattern is a, there's a lot in common, which are expressed, EYA1 and EYA4 both visual and derivatives in small bags. The difference with the phenotype caused by mutations in the gene EYA1 (Brachyv-Atv-renal syndrome) occurs, there is no genetic abnormalities in DFNA10, is characterized by progressive hearing loss, which is His starting from second to fifth decade of absence severe goes deep. The average starting frequency loss, and ultimately "are both low and high frequencies.

6) POU3F4: Gene POU3F4 (1 exon), mapped on chromosome X (Xq21.1) and is responsible for transcription regulatory elements. POU3F4 gene expression in the development of the inner ear is limited to Mesenchyma. Transcript begins when, Mesenchyma to create optical capsule and protein POU3F4 (361 amino acids) is dense, remains at the core of Mesenchyma cells. Then they'll the temporal bone cavity, the atrial Scala, swelling of the skin and internal audio channels, cause. Snail adults, the gene are expressed in spiral ligament fibrocystic. Mutations in these genes cause DFN3; the first type of non-syndromic X is connected. Phenotype, because patients affected by conductive hearing loss, probably created due to the consolidation of the stirrup bones, along with a deep progressive hearing loss.

5. Genetically codified proteins with expression

On tectorial membrane:

1) Collagen XI (alpha2 chain): Collagen XI protein, codified by gene COL11A2 (62 exons) located in chromosome 6, is one of the components of tectorial membrane.26 It is an cellular membrane comprising many different types of collagen (II, V, IX, XI), non-collagen proteins and proteoglicans, and it is involved in deflection of ciliary bundle of cochlear outer hair cells, immediately after sound stimulus.5 Mutations of gene COL11A2 cause both DFNA13

(6p21), such as Stickler syndrome Type 2 (STL2 – 6p21.3, progressive myopia, early vitreo-retina and articular degeneration, facial hyperplasia, deafness). DFNA13 is characterized by post-lingual progressive loss starting from the 2nd and 4th decades of life and there are some rare patients with vestibular disorders.

2) Alpha-tectorine: many different types of cells synthesize alpha-tectorine protein during development of the inner ear. Due to sequence of DNA in TECTA gene, it is assumed that tectorine protein is synthesized from a precursor adjacent to plasma membrane, via glycosil-Phosphatidylinositol, released from the membrane by proteolytic cleavage of precursor. Gene TECTA (23 exons), located in chromosome 11, codifies alpha-tectorine protein

(2155amino acids) and it is one of the components of tectorial membrane. Mutations in gene cause two forms of autosomal dominant hearing loss (DFNA8 and DFNA12-q22-24, both pre-lingual and they may be progressive and non-progressive) and an autosomal recessive form) DFNB21 – 11q, pre-lingual, severe to profound).

Phenotypic expression may range depending on the occurrence of impaired alleles, because Swiss family was identified as possibly being a dysgenic penetrance of hearing loss, involving location of DFNA12, in chromosome 11, and location DFNA2 in chromosome 1.

6. DNA affections

28Forms of hearing loss caused by mitochondrial. Diseases related to mitochondrial DNA are transmitted to both genders, only by the mother, and they may be syndromic or non-syndromic. Mitochondrial DNA codifies 13RNA messenger (mRNA), 2 RNA ribosomic (rRNA) and 22RNA-transporters (tRNA). Mutation 1555A->G was detected in mitochondrial gene 12S rRNA in patients with family hearing loss and also in isolated cases of hearing loss induced by the use of amino glycoside antibiotics. This mutation takes susceptible subjects to hearing loss after treatment with amino glycosides in concentrations that would not normally affect hearing. To present, other described non-syndromic mitochondrial mutations that cause hearing loss followed or not by other affections are located in gene RNA-transporter –gene tRNA (UCN): 7445A->G= keratoderm palmoplantar; 7472insC= neurological dysfunction – ataxia,dysarthria and myoclonus; 7510T->C and 7511T->C= only hearing loss. Syndromic mitochondrial mutations can also be located in tRNA, causing hearing loss associated with neuromuscular syndrome or diabetes mellitus. Recent studies suggested that mitochondrial mutations, such as deletions del4977 Pb, del4834 Pb and del3867 Pb may be responsible for family cases of presbyacusis.

7. Otosclerosis

Hearing loss caused by clinical otosclerosis has prevalence of 0.2 to 1% among Caucasian adults. The manager of onset is 3rd decade and 90% of affected patients are below the age of 50 years at the time of diagnosis.

Conductive hearing loss is developed when the focus invades stapedial-vestibular articulation, on the oval window, interfering with free movement of stapes. Profound sensor neural hearing loss, reaching all frequencies, may also be present, characterizing cochlear otosclerosis, in about 10%of affected subjects. Location of OTSC1, OTSC2 and OTSC3, respectively, in chromosomes 15 (15q26.1-qter), (7q34-q36) and 6 (6p21.3-22.3) were identified in families with autosomal dominant transmission for otosclerosis. However, in most cases, etiology remains unknown.

8. DISCUSSION

The fact that one same mutation leads to different clinical presentations may be the indication that the knowledge of molecular genetics has not reached the details of auditory dynamics yet, as well as the myriad of neurological abnormalities involved. However, it seems to move towards that. New mutations are described, new genes are cloned and mapped, and there are about 34 genes already identified to form recessive autosomal non-syndromic forms, 40 genes for dominant autosomal forms, 8 for X-linked forms, and 2genes for mitochondrial heritage.

Despite the significant advances in understanding molecular basis of hearing loss, precise identification of genetic cause still presents some difficulties, owing to phonotypical variation. First we have to rule out non-genetic causes, then syndromic causes, and then look for non-syndromic causes.

Most non-syndromic recessive autosomal forms causepre-lingual loss that is severe to profound and not associated with radiological findings. Exception to this rule is DFNB2 (MYO7A)6, DFNB8/10 (TMPRSS3) and DFNB16 (STRC)in which age at onset may occur in later phases of childhood;DFNB4 (SLC26A4)21 in which there may be dilation of vestibular aqueduct and endo lymphatic sac, and DFNA9 (COCH)23 that may be associated with degeneration of cochlear nerve fibers by deposits of mucopolysaccharidos.

Not very frequent phenotypes in autosomal dominant form soft hearing loss include low frequency hearing loss in DFNA1 (HDIA1) and DFNA6/14/38 (WFS1), medium frequency loss in DFNA8/12 (TECTA) 27 and DFNA13 (COL11A2)26 and vestibular signs and symptoms in DFNA9 (COCH) 23 and sometimes in DFNA11 (MYO7A).6 Owing to the great variety of genes involved, and in view of costs, assessment should be the most specific possible, maybe based on clinical picture. Expectations concerning results and conclusion in relation to them should be very careful.

Otorhinolaryngologists, pediatricians and geneticists should be aware of this phonotypical variety and especially that DFNB1 is the most frequent form of non-syndromic recessive autosomal hearing loss; molecular investigation should be made in such cases, reducing the costs of complementary tests normally requested for the investigation of patients with hearing loss.

Facility and benefits of genetic tracking, especially formulations that cause DFNB1, should make it an important public health issue so that determinations of early diagnosis of hearing loss can be properly established. Molecular tests cannot help all children with hearing loss and it is not reasonable to wait for these tests to replace already existing screening programs.

Whether or not screening programs with acoustic otoemission Audio and brain evoked audio metry should include molecular tests for DFNB1 is another different issue.

Genetic counseling of families whose parents have normal hearing and one single hearing child has been very difficult owing to non existence of genetic tests to identify specific mutations, especially in developing countries. In most cases, considering the important role of environmental causes of pre-lingual hearing loss, it is difficult to recognize whether hearing loss is of genetic origin. It is essential to inform health care professionals, the general population, and the hearing impaired population about genetic advances and to train professionals on genetic counseling.

Genetic tests for hearing loss are a reality because they have changed the assessment pattern of patients with hearing impairment and should be used by physicians for diagnostic purposes. In the next years, there will certainly be an expansion in the role of these tests and counseling will not be limited to reproductive results. Even though tests may be confusing for medical professionals that are not used to them, in daily practice, they are an important part of medical care. New findings and technologies will expand and enhance complexity of these tests and it will be on Otorhinolaryngologists and Pediatricians to get familiar with recent discoveries and include them in their investigation protocols - the genetic tests.

Reaction to sounds is the first sign that a child has his auditory capacity preserved. Owing to delay in speech acquisition, absence of reaction to sounds or other disorders, parents are the first ones to suspect of hearing loss. The delay between suspicion and diagnosis reduces significantly the possibilities of rehabilitation, because if intervention does not take place early, it will cause communication deficits that have significant morbidity, which can be manifested by paucity of social activities and professional opportunity losses. Conversely, it is surprising that some parents and even some professionals hesitate to accept hearing loss, considering it as unimportant, translating lack of knowledge about the importance of auditory function for the development of conceptual processes that support human’s reasoning and speech.

REFERENCES

1. Center of Medical Genetics, non syndromic hearing loss, http://isfahangenetics.com/index.php?option=com_content&view=article&catid=94&id=106&Itemid=445&lang=fa
2. Nejat Mahdiyeh, Bahareh Rabbani, the molecular mechanisms of hearing and deafness genetic types in Iran, Health Technology Development Office, Department of Research and Technology, Ministry of Health, Volume 16 - Special Issue (1): 27-38
3. Libby RT, Steel KP. The roles of unconventional myosins in hearing and deafness. Essays Biochem 2000; 35: 159-74.

4. Mburu P, Mustapha M, Varela A, Weil D, El-Amraoui A, Holme RH, et al. Defects in whirlin, a PDZ domain molecule involved in stereo cilia elongation, cause deafness in the whirler mouse and families with DFNB31. Nat Genet 2013; 34: 421-8.
5. Rabionet R, Gasparini P, Estivill X. Molecular genetics of hearing impairment due to mutations in gap junction genes encoding beta connexins. Hum Mutat. 2000; 16(3): 190-202.
6. Van Den Bogaert K, Govaerts PJ, Schatteman I, Brown MR, Caethoven G, Offeciers FE, et al. A second gene for otosclerosis, OTSC2, maps to chromosome 7q34-36. Am J Hum Genet 2011; 68: 495-500.
7. Yang JJ, Wang WH, Lin YC, Weng HH, Yang JT, Hwang CF, et al. Prospective variants screening of connexin genes in children with hearing impairment: genotype/phenotype Correlation. Hum Genet. 2010; 128(3): 303-13.