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# Genetics of Hearing Loss

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## 1. Introduction

Hearing loss (HL) is the most common sensory defect in human beings, affecting 1.86 in 1000 newborns around the *world* which half of it is due to genetic causes (Morton & Nance, 2006). HL can be syndromic or nonsyndromic. Individuals affected with syndromic form have additional clinical signs whereas nonsyndromic HL is not associated with other clinical signs and symptoms. All Mendelian pattern of inheritance have been observed in nonsyndromic HL (NSHL) including autosomal dominant (AD), autosomal recessive (AR), X-linked inheritance (XL) and mitochondrial inheritance (MT); autosomal recessive is the main form of NSHL, i.e. 75-85 % of NSHL show AR pattern in affected pedigrees.

As known, ear is the organ of hearing and balance. Hearing is dependent on a series of complex events. The ear has three anatomical parts including outer, middle and inner ear. The external ear which is composed of the auricle, ear canal and eardrum membrane collects sound waves and transmits them to the eardrum. Three tiny bones of middle ear (the ossicles) act as levers and conduct the sounds to the oval window, and finally through the cochlea (a snail-shaped organ) which has the auditory receptors (the organ of Corti) in the inner ear [Raphael & Altschuler 2003]. A collagen-based extracellular matrix, called tectorial membrane on top of the hair cells is vibrated by sound waves [Richardson et al., 2008]. Within the organ of Corti, physical vibrations produce a mechanoelectrical transduction which is detected by hair cells and these cells respond by producing electrical impulses. Nerves transmit these impulses to the brain where they are interpreted. Different sound frequencies stimulate the hair cells in different parts of the organ of Corti and lead to perception of different sound frequencies. Sounds are processed in both sides of the brain but the interpretation of the sounds takes place at the left side of brain. Sounds are heard at normal hearing thresholds between 0-20 dB across the 125-8000 Hz range while loss of more than 20 dB, is said to have hearing loss which is confirmed by measuring pure tone average (PTA) (average hearing sensitivity at 500, 1000 and 2000 Hz).

Nearly one hundred and twenty million people suffer from hearing impairment around the world. History of some important events about human hereditary HL is shown in table 1 [Nance & Sweeney, 1975; Wallis et al., 1988; Kimberling et al., 1990; Leon et al., 1992;

Guilford et al., 1994; Kelsell et al., 1997; Lynch et al., 1997; Eudy et al., 1998; Gorlin, 2004; Dror & Avraham 2009].

| Time | Event |
|---|---|
| Sixteenth century | Reports indicating the prevention of the deaf from marrying |
| Seventeenth century | The mode of recessive and dominant HL |
| Nineteenth century | "The most frequent causes of congenital deafness are hereditary.. ." |
| 1968 | One of the genetic forms of deafness was described |
| 1975 | The forms of HL, the need for research and genetic counseling were described |
| 1988 | An X-linked form of deafness was mapped in a large Mauritian family |
| 1990 | The first locus for syndromic HL, *USH2A*, was mapped |
| 1992 | The first locus for ADNSHL*, DFNA1, was mapped in a Costa Rican family |
| 1994 | The first and second loci for ARNSHL▪, DFNB1 and DFNB2, and DFNA2 loci were mapped |
| 1997 | *GJB2* and DIAPH1 genes were discovered for DFNB1 and DFNA1 loci, respectively |

*Autosomal domiant non syndromic hearing loss, ▪Autosomal recessive nonsyndromic hearing loss

Table 1. Chronological events regarding hereditary HL.

One of the main programs of the World Health Organization (WHO) is to encourage countries for the prevention of deafness [Emery, 2003]. Understanding the molecular and genetic mechanisms of HL may lead to development of new therapy and treatment approaches. Here, we review major causes leading to either syndromic or nonsyndromic HL.

## 2. Classification of hearing loss

Approximately two-thirds of the HL affected children show the problem at birth and unfortunately it may not be diagnosed before the age of 3 years. HL has several classification criteria which are important for diagnosis, prognosis and treatment [Mahdieh et al., 2010a]. These criteria are summarized in table 2.

### 2.1 Etiology

Based on the cause of sensorineural deafness, HL is categorized into three major forms as acquired, genetic and unknown. There are many causes for hearing loss:

1. Acquired HL: infectious and pharmaceutical agents known as teratogens would affect the sense of hearing. HL could occur by physiological, biochemical or infectious factors. However, genetic background has an important effect on its occurrence. The risk factors that may affect the hearing process are as follows:

a. factors before birth including congenital infections (e.g. toxoplasmosis, measles, syphilis, smallpox, cytomegalovirus, herpes virus), congenital deformities of aurical and ear duct [Willems, 2004; Shin et al., 2011].
b. factors during birth including prematurity and low birth weight (less than 1500gr) and increased blood bilirubin [Willems, 2004].
c. factors affecting after birth including infections and bacterial meningitis, mumps, otitis media, blood infection and autotxic drugs such as aminoglycosides, head injury or skull fracture which lead to anesthesia [Willems, 2004].

2. Genetic HL: the genetic basis of HL is known for more than 100 years. In the early decade of 1800s, the Irish physician William Wild explained the inheritance of HL. His theory differentiated between dominant and recessive inheritance. He also observed that men showed more X-linked transmission [Willems, 2004].

### 2.2 Severity

Intensity of the sound is calculated in units of decibel (dB), which is logarithm intensity of the sound wave to a reference sound intensity divided by ten [Willems, 2004]. The normal hearing threshold is 15 dB. A regular conversation occurs at level of 45 to 60 dB.

### 2.3 Position of damage

a. Conductive HL: Factors affecting sound transmission including aurical, ear canal, eardrum, outer and middle ear bones to the cochlea cause conductive HL. The most common causes of conductive HL are the external and middle ear congenital abnormalities such as atrophy and dysplasia, duct obstruction, impacted cerumen, otitis, middle ear and Tympanic membrane problems.
b. Sensorineural HL (SNHL): The disorder occurs in the auditory nerve or the cochlea. In other words, the abnormalities occur some place between the hair cells and auditory brain regions. The most common causes of SNHL are:
   b1. congenital causes such as rubella, syphilis, Usher syndrome, Alport Syndrome, Waardenburg syndrome and autosomal dominant and recessive sensorineural deafness [Friedman et al., 2003].
   b2. acquired factors: Infections such as measles, cytomegalovirus, bacterial meningitis, autotoxicity of drug consumption, noise pollution including long-term exposure, presbycusis and sudden idiopathic HL [Willems, 2004].
c. Mixed HL: in this type of hearing loss, conductive and sensorineural problems are observed simultaneously. Infections such as tuberculosis, some syndromes and skull fractures may also cause mixed HL.

### 2.4 Age of onset

On the basis of the age of onset, HL is divided into the following types:

a. Prelingual: Loss of hearing occurs before speech is acquired. If a child has a congenital hearing impairment, he would not be able to speak normally.
b. Postlingual: Loss of hearing occurs after speech is developed.
c. Presbycusis or age-related HL (ARHL): Epidemiologic studies show that nearly 25 % of 60 year olds and more than 50 % of 80 year ages undergo ARHL [Dror & Avraham, 2009; Huang & Tang, 2010].

### 2.5 Signs

HL may be associated with other physical problems which are called syndromic HL. Genetic HLs without any other complications is called non-syndromic genetic hearing loss [Willems, 2004]. HL loci are named with the prefix DFN, followed by the mode of inheritance which is indicated by B, A, X and Y for autosomal recessive (DFNB), autosomal dominant (DFNA), X-linked (DFNX) and Y-linked (DFNY), respectively. The order in which loci have been described is denoted by a number after these letters, e.g. DFNB1 is the first identified locus causing autosomal recessive HL [Guilford et al., 1994].

| Criterion | Class | Definition and example |
|---|---|---|
| Age of onset | Prelingual HL | HL occurs before language acquisition |
| | Postlingual HL | HL occurs after language acquisition |
| | Presbycusis | Age-related HL |
| Etiology | Acquired | Caused by environmental agents such as viral and bacterial infections (prenatal, e.g., CMV, toxoplasmosis, rubella; postnatal, e.g, meningitis), hyperbilirubinemia, head trauma, anoxia, noise exposure and ototoxic drugs |
| | Genetic | Caused by gene mutation |
| | Idiopathic | Unexplained cause |
| Clinical phenotypes | Syndromic | associated with other symptoms |
| | Nonsyndromic | Deafness is the only defect |
| Position of damage | Conductive HL | Caused by a problem transferring sound waves through the external ear, tympanic membrane or middle ear |
| | Sensorineural HL | Caused by damage to the inner ear (vestibulocochlear nerve) |
| | Mixed HL | Caused by a combination of sensorineural and conductive HL |
| Severity | Mild | Difficulty in hearing of 26–40 dB sounds |
| | Moderate | 41–55 dB |
| | Moderately severe | 56–70 dB |
| | Severe | 71–90 dB |
| | Profound | >90 dB |
| Mode of inheritance | Autosomal dominant | DFNA loci (DFNA1-64) |
| | Autosomal recessive | DFNB loci (DFNB1-96) |
| | Sex-linked | DFNX loci (DFN1-8) |
| | Y-linked | DFNY loci (DFNY1) |
| | Mitochondrial | 12SrRNA (MT-RNR1), $tRNA^{Ser(UCN)}$ (MT-TS1) |

Table 2. Various criteria for the classification of hearing loss.

## 3. The frequency of genetic HL

Genetic HL occurs 1 in 2000 to 1 in 650 live births [Morton & Nance, 2006]. About 70% of the cases are nonsyndromic [Tekin et al., 2001]. Studies show that 75% of nonsyndromic HL

are inherited as autosomal recessive [Tekin et al., 2001]. 10-20% of cases are inherited as autosomal dominant and 1-5% are X-linked recessive. Approximately, 1% of human genes, i.e 200 to 250 genes are responsible for hereditary HL [Finsterer & Fellinger, 2005]. So far, more than one hundred loci and 55 genes have identified which are involved in nonsyndromic HL (http://hereditaryhearingloss.org).

## 4. Non-syndromic HL

A high frequency of genetic HL occurs without any abnormality in other organs classified as non-syndromic HL. Different patterns of inheritance have been observed in NSHL.

### 4.1 Different types of NSHL

Variety of protein coding genes such as gap junctions (connexin encoding genes), motor proteins (myosins) cytoskeletal (e.g. actin), ion channels, structural proteins (Tectorin alpha, Otoancorin, Stereocilin, etc), transcription factors (POU3F4, POU4F3 and Eyes absent 4 or EYA4), and additionally microRNA genes are involved in HL [Willems, 2004; Mencia et al., 2009; Mahdieh et al., 2010a]. *GJB2* mutations are seen in 50% of autosomal recessive HL in the Caucasians [Kelsell et al., 1997; Tekin et al., 2001]. Some genes e.g. *GJB2* gene is expressed in a variety of organs of the body while others such as *OTOA*ncorin is only expressed in the inner ear.

#### 4.1.1 Autosomal recessive non-syndromic HL

Autosomal recessive non-syndromic HL (ARNSHL) was first described in 1846. It is the severest form of congenital HL in which there is a defect in cochlea in nearly all cases. Loci of ARNSHL are designated as the DFNB; DF stands for Deafness and B indicates the autosomal recessive pattern of inheritance. Up to date, 46 genes and nearly 100 loci have been identified for HL (Table 3). Regarding different studies, connexin 26 gene mutations differ depending on geographical place and ethnicity [Zelante et al., 1997; Morell et al., 1998; Mahdieh & Rabbani, 2009]. Here, we discuss the most common genes causing ARNSHL.

##### 4.1.1.1 *GJB2* and *GJB6* genes and connexins

The first locus of ARNSHL designated as DFNB1 was identified by Guilford and colleagues in 1994. These researches confirmed linkage to chromosome 13q12-q13 in two consanguineous families [Guilford et al., 1994]. More consanguineous families of different ethnic groups were linked to the DFNB1 locus [Morle et al., 2000]. Phenotypic differences were observed within different families which indicated that allelic heterogeneity may be present in the locus DFNB1.

*GJB2* is a small gene encompassing 5.5 Kb. It has two exons encoding a 4.2Kb mRNA and a protein of 226 amino acids. A six repeat of G is located at position 30 to 35 of coding region of *GJB2* gene from which deletion of one G is known as 35delG or 30delG (Figure 1) [Kelley et al., 1998]. 35delG is the most common mutation in the Caucasians and may cause up to 70% of all *GJB2* gene mutations. Profound HL caused by *GJB2* gene mutations is found in 50% of the cases; 30% are severe, 20% moderate and 1-2% are mild cases [Smith & Hone, 2003]. Other *GJB2* mutations have been reported with higher frequencies in some ethnic

groups [Morell et al., 1998; Mahdieh & Rabbani, 2009]. A large number of studies have been reported about *GJB2* mutations including genotype-phenotype correlations, phenotypic variability, de novo mutations, dominant mutations, ethnic-specific distribution of mutations, digenic inheritance and allelic heterogeneity [del Castillo et al., 2002; Smith & Hone, 2003; Mahdieh et al., 2009; 2010b, 2010c]. Also, a modifier gene has been suggested because of intrafamilial phenotypic variability of the cases [Higert et al., 2009a; Mahdieh et al., 2010b].

*GJB2* and *GJB6* genes are about 35 kb apart from each other. *GJB6* gene encodes a protein called Connexin 30 (MIM 604418) which has 261 amino acids. Connexin 30 is produced in different tissues of the body such as the cochlea, brain and thyroid [Grifa et al., 1999]. The importance of this gene was evident when some families had a mutated allele of *GJB2* and the second mutant allele was in the *GJB6* (digenic inheritance) [del Castillo et al., 2002].

| Locus | Location | Gene | references |
|---|---|---|---|
| X-Linked | | | |
| DFNX1 | Xq22 | *PRPS1* | Liu et al., 2010 |
| DFNX2 | Xq21.1 | *POU3F4* | De Kok et al., 1995 |
| DFNX4 | Xp22 | *SMPX* | del Castillo et al., 1996 |
| Autosomal Dominant | | | |
| DFNA1 | 5q31 | DIAPH1 | Lynch et al., 1997 |
| DFNA2A | 1p34 | *KCNQ4* | Kubisch et al., 1999 |
| DFNA2B | 1p35.1 | GJB3 | Xia et al., 1998 |
| DFNA3A | 13q11-q12 | *GJB2* | Kelsell et al., 1997 |
| DFNA3B | 13q12 | *GJB6* | Grifa et al., 1999 |
| DFNA4 | 19q13 | *MYH14* | Donaudy et al, 2004 |
| DFNA5 | 7p15 | *DFNA5* | Van Laer et al., 1998 |
| DFNA6 | 4p16.3 | *WFS1* | Bespalova et al., 2001 |
| DFNA9 | 14q12-q13 | *COCH* | Robertson et al., 1998 |
| DFNA10 | 6q22-q23 | *EYA4* | Wayne et al., 2001 |
| DFNA11 | 11q12.3-q21 | *MYO7A* | Liu et al., 1997 |
| DFNA12 | 11q22-24 | *TECTA* | Verhoeven et al., 1998 |
| DFNA13 | 6p21 | *COL11A2* | McGuirt et al., 1999 |
| DFNA15 | 5q31 | *POU4F3* | Vahava et al., 1998 |
| DFNA17 | 22q | *MYH9* | Lalwani et al., 2000 |
| DFNA20 | 17q25 | *ACTG1* | Zhu et al., 2003, |
| DFNA22 | 6q13 | *MYO6* | Melchionda et al., |
| DFNA28 | 8q22 | *GRHL2* | Peters et al., 2002 |
| DFNA36 | 9q13-q21 | *TMC1* | Kurima et al., 2002 |
| DFNA39 | 4q21.3 | *DSPP* | Xiao et al., 2001 |
| DFNA44 | 3q28-29 | *CCDC50* | Modamio-Hoybjor et al., 2007 |
| DFNA48 | 12q13-q14 | *MYO1A* | Donaudy et al., 2003 |
| DFNA50 | 7q32.2 | *MIR96* | Mencia et al., 2009 |
| DFNA51 | 9q21 | *TJP2* | Walsh et al., 2010 |
| DFNA64 | 12q24.31-12q24.32 | *SMAC/DIABLO* | Cheng et al., 2011 |

| Locus | Location | Gene | references |
|---|---|---|---|
| Autosomal Recessive | | | |
| DFNB1 | 13q12 | *GJB2* | Kelsell et al., 1997 |
| DFNB2 | 11q13.5 | *MYO7A* | Liu et al., 1997 |
| DFNB3 | 17p11.2 | *MYO15A* | Wang et al., 1998 |
| DFNB4 | 7q31 | *SLC26A4* | Li et al., 1998 |
| DFNB6 | 3p14-p21 | *TMIE* | Naz et al, 2002 |
| DFNB7/11 | 9q13-q21 | *TMC1* | Kurima et al., 2002 |
| DFNB8/10 | 21q22 | *TMPRSS3* | Scott et al., 2001 |
| DFNB9 | 2p22-p23 | *OTOF* | Yasunaga et al., 1999 |
| DFNB12 | 10q21-q22 | *CDH23* | Bork et al., 2001 |
| DFNB15 | 19p13 | *GIPC3* | Charizopoulou et al., 2011 |
| DFNB16 | 15q21-q22 | *STRC* | Verpy et al., 2001 |
| DFNB18 | 11p14-15.1 | *USH1C* | Ouyang et al., 2002 |
| DFNB21 | 11q | *TECTA* | Mustapha et al., 1999 |
| DFNB22 | 16p12.2 | *OTOA* | Zwaenepoel et al ., 2002 |
| DFNB23 | 10p11.2-q21 | *PCDH15* | Ahmed et al, 2003 |
| DFNB24 | 11q23 | *RDX* | Khan et al., 2007 |
| DFNB25 | 4p13 | *GRXCR1* | Schraders et al., 2010 |
| DFNB28 | 22q13 | *TRIOBP* | Riazuddin et al, 2006 |
| DFNB29 | 21q22 | *CLDN14* | Wilcox et al., 2001 |
| DFNB30 | 10p11.1 | *MYO3A* | Walsh et al., 2002 |
| DFNB31 | 9q32-q34 | *WHRN* | Mburu et al., 2003 |
| DFNB32 | 1p13.3-22.1 | *GPSM2* | Walsh et al., 2010 |
| DFNB35 | 14q24.1-24.3 | *ESRRB* | Collin et al., 2008 |
| DFNB36 | 1p36.3 | *ESPN* | Naz et al., 2004 |
| DFNB37 | 6q13 | *MYO6* | Ahmed et al., 2003 |
| DFNB39 | 7q21.1 | *HGF* | Schultz et al., 2009 |
| DFNB42 | 3q13.31-q22.3 | *ILDR1* | Borck et al., 2011 |
| DFNB49 | 5q12.3-q14.1. | *MARVELD2* | Riazuddin et al., 2006 |
| DFNB53 | 6p21.3 | *COL11A2* | Chen et al., 2005 |
| DFNB59 | 2q31.1-q31.3 | *PJVK* | Delmaghani et al., 2006 |
| DFNB61 | 7q22.1 | *SLC26A5* | Liu et al., 2003 |
| DFNB63 | 11q13.2-q13.4 | *LRTOMT/ COMT2* | Ahmed et al., 2008 |
| DFNB66 | 6p21.2-22.3 | *LHFPL5* | Shabbir et al., 2006 |
| DFNB72 | 19p13.3 | *GIPC3* | Rehman et al., 2011 |
| DFNB73 | 1p32.3 | *BSND* | Riazuddin et al., 2009 |
| DFNB74 | 12q14.2-q15 | *MSRB3* | Ahmed et al., 2011 |
| DFNB77 | 18q12-q21 | *LOXHD1* | Grillet et al., 2009 |
| DFNB79 | 9q34.3 | *TPRN* | Rehman et al., 2010 |
| DFNB84 | 12q21.2 | *PTPRQ* | Schraders er al., 2010 |
| DFNB91 | 6p25 | *SERPINB6* | Sirmaci et al., 2010 |
| DFNB95 | 19p13 | *GIPC3* | Charizopoulou et al., 2011 |

Table 3. Non-syndromic genes responsible for HL up to 2011.

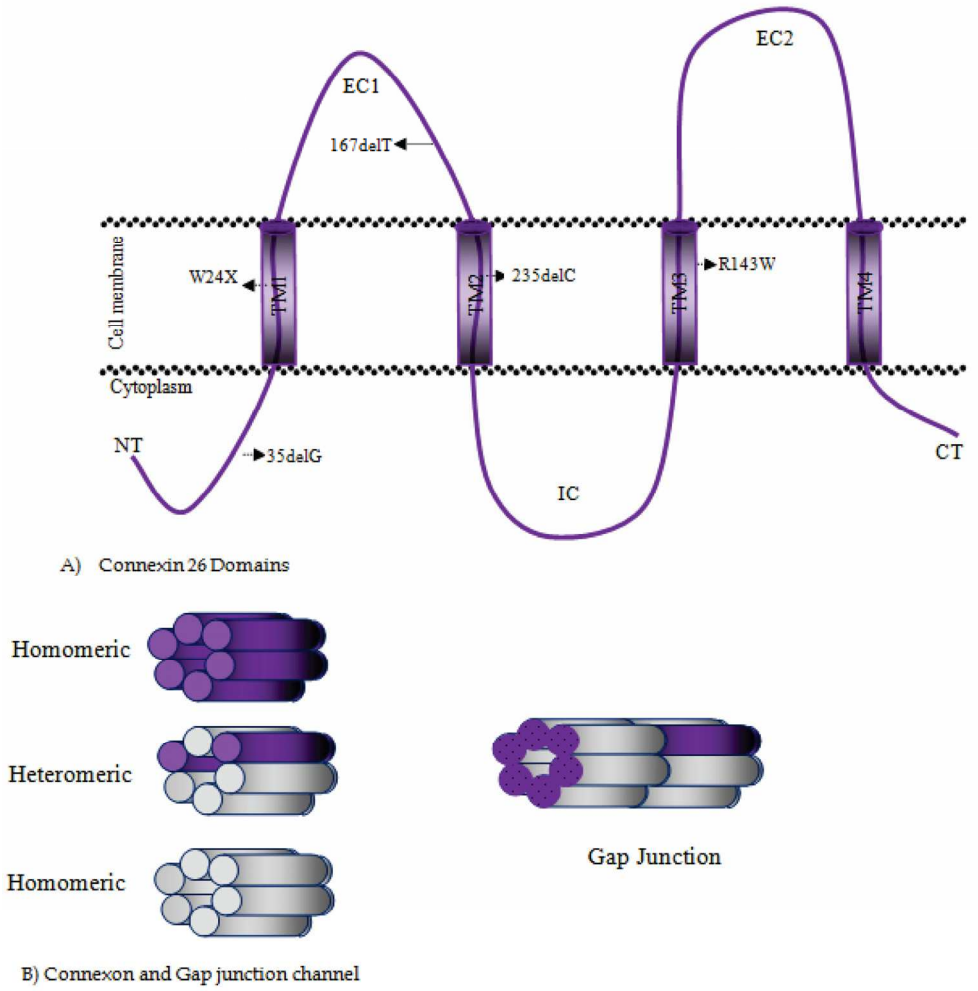


Fig. 1. Schematic structure and domains of Connexin 26 protein, Connexon and Gap Junction channel. A) The most common mutations in specific populations (35delG, 167delT, 235delC, R143W and W24X mutations in the Caucasian, Ashkenazi Jewish, Japanese, Ghanian and Indian populations, respectively) are shown. 35delG, W24X, 167delT, 235delC and R143W located on NT, TM1, EC1, TM2 and TM3 domains, respectively. TM1-TM4 denotes transmembrane domains, EC1-2 denotes extracellular domains, IC denotes cytoplasmic domain, NT denotes amino (NH2) terminus and CT denotes carboxyl (COOH) terminus. B) Six connexins can oligomerize to form hemichannels named connexons. Connexons then pass throughout the membrane to make the gap junction channels. Homomeric and heteromeric channels can be formed as connexins selectively interact with each other.

A few point mutations have also been reported in *GJB6* as the cause of ARNSHL *GJB6* [del Castillo et al., 2005; Pallares-Ruiz et al., 2002]. Later studies determined that *GJB6* mutations in cis state, not in trans, would destroy the *GJB2* expression. Therefore, the digenic hypothesis may not be correct. Four large deletions have been recognized in *GJB6* gene including del(*GJB6*-D13S1830), del(*GJB6*-D13S1854), del(chr13:19,837,344-19, 968,698) and 920 Kb deletion [del Castillo et al., 2002, 2005; Wilch et al., 2010]. The deletions may include more than 10% of DFNB1alleles [Stevenson et al., 2003]. So far, del (*GJB6*-D13S1830) has not been seen in many populations [Mahdieh et al., 2004, 2011]. The del (*GJB6*-D13S1830) and del (*GJB6*-D13S1854) mutations not only truncate the synthesis of *GJB6* gene but also destroy *GJB2* gene expression.

Connexins encoded by GJ genes are members of transmembrane family proteins that have 20 members in humans [Holms & Steel, 1999]. These proteins were classified in three groups of alpha, beta and gamma proteins. Common nomenclature system is based on molecular weight of proteins e.g. Cx26 and Cx32. Despite the differences in the size and primary amino acid composition, connexins have similar topology. These proteins have four transmembrane domains which are connected by two extracellular and one intracellular loop. The carboxyl and amino terminals are located at the cytoplasmic side. Most cells express more than one type of connexin. Gap junctions show different permeability and conductance which may create channels with specific characteristics. Also, in order to compensate for the decrease in the expression of some of the connexins, other connexins may be produced at an enhanced rate [Kumar & Kilula, 1996]. Hemi-channels (connexons) are composed of six connexin subunits and two hemi-channels make the channel forming the gap junctions [Kelley et al., 1998]. The important role of these channels is transportation of potassium ions [Kelley et al., 1998] and glutamate released from hair cells to initiate action potential. Different connexins may be made up of hemi channels with homomer or heteromer subunits.

#### 4.1.1.2 *MYO15A* gene in DFNB3 locus

In 1995, a report showed that 2% of rural individuals in the north coast of Bali, Indonesia were affected with a profound sensorineural non-syndromic HL. Due to high percentage of deaf people in this village a local sign language had been created for communication [Wang et al., 1998].

The locus was mapped on chromosome 17p11.2 by whole genome study. *MYO15A* gene has 66 exons and 71097 bp, encoding a 11863 bp transcript [Liang et al., 1999]. Myosin gene was identified by positional and functional cloning approaches [Wang et al., 1998]. Mutations in the gene are responsible for 5% of severe to profound deafness cases in Pakistan [Friedman et al., 2003]. *MYO15A* gene mutations were reported in families from Turkey, Brazil and India [Kalay et al., 2007; Nal et al., 2007; Lezirovitz et al., 2008]. The role of myosin filaments can be traced in a variety of cellular functions including cell motility, muscle contraction, synaptic transmission, cytokenesis, endocytosis, exocytosis and probably in gene expression as a modulator [Craig & Woodhead, 2006; Loikkanen et al., 2009]. As the organism gets more complex, there may be more myosin isoforms found in the organism [Oliver et al., 1999; Friedman et al., 1999]. The heavy chain of XV myosin has 3531 amino acids. There is a unique proline-rich region at the amino terminal of myosin which weighs 140KDa and has no similarity to any of the known proteins. Next to this domain exists a motor domain and a tail domain [Belyantseva et al., 2003]. In addition to the

sensory cells of cochlear, myosin is expressed in the pituitary gland, neuroendocrine cells, parathyroid and pancreas [Llyod et al., 2001]. It is also found in stereocilia of hair cells [Belyantseva et al., 2003].

#### 4.1.1.3 *SLC26A4* gene in DFNB4 locus

DFNB4 locus, located at chromosome 7q31, was first reported to be linked to recessive non-syndromic deafness in a large Middle-Eastern Druze family. In 1997, the *SLC26A4* (Penderin coding protein) was identified by positional cloning at the pendred syndrome locus (Everett et al. 1997) and was later also shown to be the gene mutated in DFNB4 [Li et al., 1998]. Pendred syndrome was identified in 1896 as neurosensory HL and goiter. HL in Pendred syndrome is the most common cause of deafness due to defect of cochlea such as dilation sac and duct of endolyph and enlarged vestibular duct [Everett et al., 1997].

Mutations of *SLC26A4* gene are the second leading cause of ARNSHL. So far, more than 140 mutations have been reported for Pendred syndrome. Phenotypic spectrum of *SLC26A4* gene mutations varies from Pendred syndrome to nonsyndromic HL. Four mutations are common in northern Europeans i.e L236P, T416P, E384G, IVS8 +1 G> A) [Hilgert et al., 2008]. In a study conducted in Spanish population 27% had homozygous *SLC26A4* mutations [Pera et al., 2008]. Mutations of *SLC26A4* gene have been observed in several ethnic populations [Albert et al., 2006; Hu et al., 2007; Yoon et al., 2008]. The prevalence of *SLC26A4* gene mutation is about 40% in Caucasians of which 24% are bi-allelic [Albert et al., 2006].

*SLC26A4* gene has 21 exons within 57175 bp of DNA sequence. Its transcript is about 5 Kb encoding into a 87KDa protein having 780 amino acids. The gene is expressed in lining cells of endolymph duct as well as non-sensory cells of utricle, saccule, kidney and thyroid. Various models have been reported for the structure of Pendrin protein. New model suggests that pendrin protein is a transmembrane protein traversing fifteen times throughout the membrane [Dossena et al., 2009]. The protein in involved in anion exchange of HCO-, Cl-, I-and OH- ions [Mount & Romero, 2004].

#### 4.1.1.4 *TMC1* gene in DFNB7/11 locus

DFNB7 and DFNB11 were determined as the cause of HL on chromosome 9q13-q21 in two Indian and two inbred Israeli families, respectively [Jian et al., 1995]. In 2002, eight different mutations in *TMC1* gene were linked to one DFNA36 family and eleven DFNB7/11 families [Kurima et al., 2002]. More than twenty different point mutations and two deletions have been identified in different families. It seems that c.100C>T mutation includes appromximately 40% of all *TMC1* mutations in Turkey [Hilgert et al., 2008, 2009b]. In a survey of 51 Turkish families, 5 patients had mutations of *TMC1* gene [Hilgert et al., 2008]. Mutations of *TMC1* are responsible for at least 6% of all cases of ARNSHL in northeast and eastern part of Turkey [Kalay et al., 2005]. Three mutations c.100C> T (R34X), c.77611G> A and g.94615A> C have been reported in Iranian families [Hilgert et al., 2009b].

Based on sequence homology studies, eight TMC genes exist in vertebrates. *TMC1* gene has 24 exons and encodes a 3201 nucleotide RNA. It expresses a complete transmembrane protein with six membrane passing domain which has no similarity to proteins of known function. Mouse ortholog transcript (*TMC1*) is expressed in cochlea and vestibular hair cells [Kurima et al., 2002].

#### 4.1.1.5 *TMPRSS3* gene in DFNB8/10 locus

DFNB8/10 locus was separately mapped on chromosome 21q22.3 in two consanguineous Pakistani (DFNB8) and Palestinian families (DFNB10) [Bonné-Tamir et al., 1996; Veske et al., 1996]. Haplotype analysis and sequencing analysis of the families resulted in detection of mutations in *TMPRSS3* [Scott et al., 2001]. The gene belongs to a subfamily of transmembrane serine proteases type III protein [Szabo et al., 2003] expressed in supporting cells of the organ of Corti [Guipponi et al., 2002]. Although, the specific role of *TMPRSS3* protein in growth, development and survival of auditory apparatus has not been found but it activates the epithelial sodium channel (ENaC) in vitro [Guipponi et al., 2002]. The mutated alleles of the gene may inactivate the serine protease catalytic activitiy. Therefore, *TMPRSS3* proteolytic function may be important during the development of inner ear [Guipponi et al., 2002, 2008].

*TMPRSS3* gene has 13 exons within 24 Kb, encoding a 2468 bp mRNA which encodes a protein with 454 amino acids [Guipponi et al., 2008]. In 2009, 16 mutations in *TMPRSS3* have been reviwed and reported by a study [Hilgert et al., 2009b]. From 25 studied Turkish families, three had mutations of *TMPRSS3* gene [Wattenhofer et al., 2005; Sahin-Calapoglu et al., 2005]. Mutations of *TMPRSS3* gene account for 1% of hearing loss in Caucasian children with non-syndromic HL [Wattenhofer et al., 2005]. Mutations of *TMPRSS3* gene have been reported in 4 of 290 Pakistani families [Ahmed et al., 2004].

#### 4.1.1.6 *OTOF* gene in DFNB9 locus

*OTOF* gene contains 48 exons encoding a 1997 amino acid polypeptide called otoferlin which is member of Ferlin family of proteins [Mirghomizadeh et al., 2002]. Ferlin family of proteins have a domain called C2. These proteins contain a transmembrane C-terminal domain [Yasunaga et al., 1999]. C2 domain is a structural domain in some proteins that are involved in directing proteins to the cell membrane [Davletov & Südhof, 1993].

Otoferlin is expressed in the brain and cochlea. This protein plays an important role in releasing neurotransmitters in the auditory nerve cells [Yasunaga et al., 1999]. Mutations of the gene can lead to auditory neuropathy in which the sound from inner ear is not transferred to the brain. Q829X mutation is very common in the Hispanic which is the third cause of ARNSHL [Migliosi et al., 2002]. Mutations of the gene have been found in families of Lebanese origin [Yasunaga et al., 1999]. Varga *et al*. reported 8 mutations in 65 studied families with ARNSHL [Varga et al., 2006]. OTOF mutations have been found in Pakistani families; gene mutations may account for deafness in 2.3% of this population [Choi et al., 2009].

#### 4.1.1.7 *CDH23* gene in DFNB12 locus

The superfamily of cadherin has about 100 members with a variety of roles in cell adhesion, growth and developmental signaling, maintenance and function of the tissues [Jamora & Fuchs, 2002; Nelson & Nusse, 2004; Gumbiner, 2005; Halbleib & Nelson, 2006]. Cadherin 23 protein has a role in connection of developing stereocilia [Siemens et al., 2004]. In 1996, DFNB12 was mapped to chromosome 10q21-q22 in a consanguineous Syrian family [Chaib et al., 1996]. Usher syndrome type 1 D (USH1D) was also mapped to the same position. Allelic mutations of the *CDH23* gene encoding cadherin 23 cause DFNB12 HL and USH1D [Bolz et al., 2001; Bork et al., 2001]. Missense mutations usually cause DFNB12 HL

but nonsense and premature stop codon mutations cause Usher syndrome type 1D although this relationship is not definite. No single gene mutation is common in this gene [Hilgert 2009b]. In 64 Japanese families, five mutations were found in *CDH23* [Wagatsuma et al., 2007].

#### 4.1.1.8 *TMHS* or LHFPL5 genes in DFNB67 locus

Non syndromic HL in a Pakistani family linked to a new region on chromosome 6p21.1-p22.3 defining a new locus, DFNB67 in 2006; *TMHS* or *LHFPL5* gene was mapped in this region [Shabbir et al., 2006]. *LHFPL5* has 4 exons and encodes a 2162 nucleotide mRNA and translates into a protein of 219 amino acids. The proposed structure of the protein is a four pass transmembrane domain. Mutations of this gene have been reported in patients from Pakistan and Turkey (C161F, Y127C, P83fsX84). *TMHS* is important for the transmission of sound.

### 4.1.2 Autosomal dominant non- syndromic hearing loss

Late onset, mild and progressive forms of HL are the usual phenotypes associated with autosomal dominant form of deafness. About 25 genes and more than 60 loci have been reported for autosomal dominant non- syndromic hearing loss (ADNSHL). There is no frequent gene mutated in ADNSHL but mutations in some genes including *WFS1*, *KCNQ4*, *COCH* and *GJB2* have been suggested to be common (Kelsell et al., 1997; Nie 2008; Higert et al., 2009).

#### 4.1.2.1 *WFS1* gene and its protein

The *WFS1* (Wolfram) gene at DFNA6 locus, located on 4p16, consists of 8 exons and has a length of about 33.4 kb and a 3.6 kb transcript. It codes for a polypeptide of 890 amino acids [Hofmann et al., 2003]. The Wolframin protein is a resident component of the endoplasmic reticulum (ER) and may be involved in membrane trafficking, processing and/or regulation of ER calcium homeostasis [Fonseca et al., 2010]. In the inner ear, however, this protein may be helpful to maintain the appropriate levels of calcium ions and/or other charged particles required for hearing process [Cryns et al., 2003].

Dominant mutations in *WFS1* can cause a characteristic type of HL which affects the low frequencies and less loss in hearing in the high frequencies [Bespalova et al., 2001; Fukuoka et al., 2007]. It has been shown that dominant mutations are usually located in the C-terminal domain. The recessive Wolfram syndrome is caused by numerous mutations distributed along the entire gene. Two mutations c.424_425ins16 and c.1362_1377del16 have a high frequency in some specific populations including Spanish patients and Italians, respectively [Gómez-Zaera et al., 2001; Colosimo et al., 2003]. It is hypothesized that, inactivating mutations may lead to Wolfram syndrome and missense mutations occurring in the C-terminal domain can cause the characteristic low-frequency ADNSHL [Cryns et al., 2003].

#### 4.1.2.2 *KCNQ4* gene and its protein

The *KCNQ4* gene at DFNA2 locus, located on 1p34, consists of 14 exons and codes for a polypeptide of 695 amino acids, a voltage-gated potassium channel. It is a member of the KCNQ voltage-gated K+ channel family [Coucke et al., 1999]. It has an important role in $K^+$

secretion into the endolymph by strial marginal cells. Ten missense mutations, two small deletions and one splice mutation in *KCNQ4* have been reported so far. It is believed that a dominant-negative effect of the missense mutations in this gene lead to interference of the mutant protein with the normal channel subunit, affecting the pore structure of the channels. Therefore, hearing loss with a lower age of onset is observed at all frequencies [Coucke et al., 1999; Akita et al., 2001]. Deletion mutations which have a haploinsufficiency effect lead to a milder HL with an older age of onset at high frequencies [Coucke et al., 1999; Akita et al., 2001].

#### 4.1.2.3 *COCH* gene and its protein

The DFNA9 causative gene, *COCH* located on 14q12-q13, consists of 11exons and encodes a 550 amino acid extracellular matrix protein named cochlin. This protein has several domains including two von Willebrand factor A-like domains (vWFA1 and 2) and a LCCL domain (a region homologous to a domain in factor C of Limulus). To date, eleven missense mutations and one small deletion in *COCH* gene have been reported. Most of the missense mutations are located within exon 4 and 5 which encode the LCCL domain (Figure 2) [Robertson et al., 1998; Collin et al., 2006].

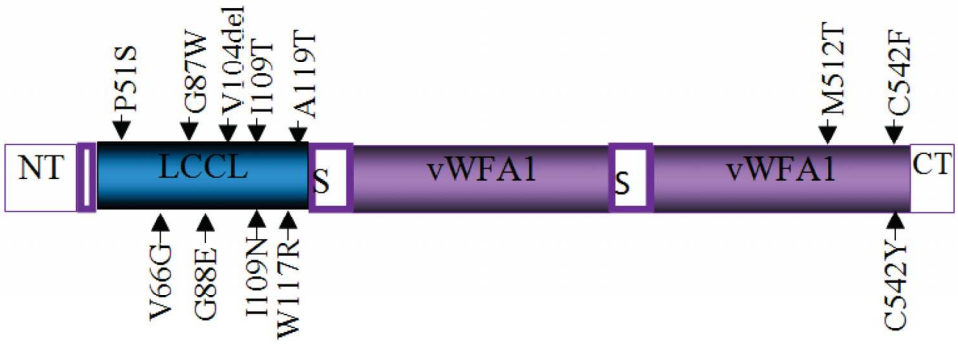


Fig. 2. Schematic structure of cochlin and distribution of the mutations along its domains. The NT signal peptide is followed by a LCCL domain and two vWF domains. S indicates several cysteine residues, NT denotes amino (NH2) terminus and CT denotes carboxyl (COOH) terminus.

### 4.1.3 X and Y linked HL

There are fewer X-linked forms of HL (DFNX) than ARNSHL and ADNSHL. X-linked form of deafness has been reported as prelingual or progressive in different families. Five loci and three genes (POU3F4, *SMPX* and *PRPS1*) have been reported for X-linked HL (http://hereditaryhearingloss.org/).

To date, only one locus has been linked to chromosome Y (DFNY1) that was found in a very large Chinese family (seven generations) [Wang et al., 2004]. They reported that the ages of onset for the patrilineal relatives were from 7 to 27 years. *PCDH11Y*, encoding a protocadherin, was suggested to be the causality [Wang et al., 2004].

### 4.1.4 Mitochondrial HL

In healthy individuals, only one type of mitochondrial DNA genotype (homoplasmy) exists, but in many mitochondrial diseases, mitochondrial genome has mixed genotype (heteroplasmy). Heteroplasmy differs from one tissue to another and can even differ within the cells of a tissue. A few genes contribute to mitochondrial HL [Fischel-Ghodsian, 2003]. Due to the important function of mitochondria in producing chemical energy through oxidative phosphorylation, mitochondrial DNA mutations can cause systemic neuromascular disorders such as HL. mtDNA mutations may be inherited or acquired (Table 4); the inherited mitochondrial mutations can cause many clinical features including myopathy, neuropathy, diabetes mellitus and sensorineural HL [Finsterer & Fellinger, 2005; Guan 2011]. Acquired mitochondrial mutations may be associated with aging and age-related HL or presbycusis [Fischel-Ghodsian, 1999, 2003]. Multiorganic mitochondrial syndromes are often lethal in homoplasmic state. Mitochondrial homoplasmy exists in LHON (Leber Hereditary Optic Neuropathy) and maternal inherited HL [Fischel-Ghodsian, 2003]. Myoclonic epilepsy and ragged red fibers (MERRF), Kearns-Sayre syndrome (KSS) and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes are associated with progressive HL [Zeviani et al., 1998; Goto et al., 1990].

| Gene | Mutation | Phenotype | Reference |
|---|---|---|---|
| *MTRNR1* (12S rRNA) | 1555A->G | NSHL/Aminoglycoside induced/worsened | Estivill et al., 1998 |
| | 1494C->T | NSHL/Aminoglycoside induced/worsened | Zhao et al., 2004 |
| | 961 (mutations) | NSHL/Aminoglycoside induced/worsened | Bacino et al., 1995 |
| | 1095T>C | NSHL/Aminoglycoside induced/ parkinsonism, and neuropathy | Zhao et al., 2004 |
| | 827A>G | NSHL/Aminoglycoside induced | Li et al., 2005 |
| *MTTS1* ($tRNA^{Ser(UCN)}$) | 7444G>A | NSHL/Aminoglycoside induced | Pandya et al., 1999; |
| | 7445A->G | NSHL/Palmoplantar keratoderma | Fischel-Ghodsian, 2003 |
| | 7472insC | NSHL/Neurological dysfunction, including ataxia, dysarthria and myoclonus | Jaksch et al., 1998 |
| | 7510T->C | NSHL/no additional symptoms | Hutchin et al.2000 |
| | 7511T->C | NSHL/no additional symptoms | Friedman et al., 1999 |
| | 7512T>C | HL/Progressive myoclonic epilepsy and ataxia | Jaksch et al., 1998 |
| *MTTL1* ($tRNA^{Leu(UUR)}$) | 3243A>G | maternally inherited diabetes and deafness/MELAS | Goto et al., 1990 |
| $tRNA^{Lys}$ | 8296A>G | maternally inherited diabetes and deafness | Kameoka et al., 1998 |
| | 8332A>G | dystonia, stroke-like episodes and HL | Gal et al., 2010 |
| $tRNA^{Glu}$ | 14709T>C | maternally inherited diabetes and deafness | Rigoli et al., 2001 |

Table 4. Identified mitochondrial DNA mutations in HL.

## 5. Age-related HL

Biological changes accumulate in people during life as individuals age. About one hundred thousand individuals die each day of age-related causes around the world [de Grey, 2007]. Age-related HL (ARHL) or presbycusis is the most frequent sensory defect in the elderly people. It occurs due to accumulation of environmental and genetic changes i.e. gradual deleterious changes in the ear gives rise hearing impairment in older people. Approximately 25 % of 60 year olds and more than 50 % of 80 year ages suffer from ARHL [Dror & Avraham, 2009; Huang & Tang, 2010]. Many heterogeneous factors including family history, exposure to loud noises, ototoxic medication, exposure to chemicals, free radical (reactive oxygen species) chronic medical conditions, malnutrition, mtDNA mutations, alcohol abuse and smoking etc. may cause this type of HL [Van Eyken et al., 2007b; Huang & Tang, 2010].

Some common deletions and acquired mtDNA point mutations due to reactive oxygen spicies (ROS) have also been suggested to cause prebyscusis. Although genetic studies on ARHL are increasing in the recent years, there is a little information about the role of genes to its etiology. Two basic approaches have been used to identify susceptibility genes for ARHL: the linkage study and the association study [Van Eyken et al., 2007b]. Several single nucleotide polymorphisms (SNPs) have been reported to correlate with presbycusis; variants in *GRHL2*, *GRM7*, *KCNQ4* and N-acetyltransferase 2 are involved (Table 5) [Van Eyken et al., 2006, 2007a; Van Laer et al., 2008; Friedman et al., 2009]. Mutations in cadherin 23 coded by *CDH23* gene may also cause ARHL [Johnson et al., 2010]. More recently, a genome-wide association scan was conducted on ARHL in the genetically isolated Finnish Saami population. This study confirmed, and also provided further evidence for the role of the previous reported gene, *GRM7* in ARHL. *IQGAP2* gene was also proposed to be involved in presbycusis [van Laer et al., 2010]. Mechanism of ARHL is not well understood. However, new promising technology and strategies may help to discover the exact role of genetic mutations in presbycusis. Finding of the genetic variants causing ARHL will ultimately lead to discovery of new pharmaceutical interventions and the development of new approaches to identify at risk individuals.

| SNP (RS number) | Gene | Protein or Function | |
|---|---|---|---|
| SNP9 (rs727146)<br>SNP12 (rs2149034)<br>SNP18 (rs12143503) | *KCNQ4* | Potassium channel (voltage-gated) | Van Eyken et al., 2006 |
| NAT2*6A (rs1799930) | N-acetyltransferase 2 | metabolism of cytotoxic, carcinogenic compounds and ROS | Unal et al., 2005 |
| 36738A>G (rs10955255)<br>42731C>T (rs2127034)<br>53110C>T (rs1981361) | *GRHL2* | transcription factor cellular promoter 2-like 3 | Van Laer et al., 2008 |
| 7155702T>A (rs11928865) | *GRM7* | glutamate receptor, metabotropic,7 | Friedman et al., 2009 |
| 75920972A>G (rs457717)<br>75922504C>T (rs1697845) | *IQGAP2* | IQ motif-containing GTPase-activating-like protein | Van Laer et al., 2010 |

Table 5. SNPs associated with ARHL.

## 6. Syndromic genetic deafness

More than 400 syndromes have been described in OMIM. Here, genetic aspects of common syndromes which are associted with HL are briefly explained.

**Usher Syndrome:** Usher syndrome, named after Charles Usher (1914) a British ophthalmologist, is the most prevalent cause of autosomal recessive HL, accounting for nearly 3-5 per 100,000 in the general population and 1-10% among profoundly deaf children [Boughman et al., 1983]. Several clinical subtypes have been distinguished based on its characterized features i. e. severity of the HL and the onset of retinitis pigmentosa [Yan & Liu, 2010]. Type 1 patients have profound HL, vestibular dysfunction and the onset of retinitis pigmentosa in childhood [Hope et al., 1997]. The type 2 patients have normal vestibular response, mild to moderate HL and RP begins in the second decade of life [Hope et al., 1997]. Progressive HL and variable vestibular response characterize type 3 patients and the onset of retinitis pigmentosa is variable as well [Smith et al., 1995]. Usher syndrome has a heterogeneous causality (Table 6); to date, 12 different loci and 10 genes have been reported (http://hereditaryhearingloss.org/). One of these identified genes, *MYO7A*, encoding myosin 7A, is a unique molecular motor for hair cells [Weil et al., 1995]. Cadherin 23, an adhesion molecule, coded by *CDH23* gene may have an important role in crosslinking of stereocilia [Bolz et al., 2001; Bork et al., 2001].

| Locus | Gene | Ref. |
|---|---|---|
| USH1B (11q13.5) | *MYO7A* | Weil et al.,1995 |
| *USH1C* (11p15.1) | *USH1C* | Smith et al., 1992 |
| USH1D (10q22.1) | *CDH23* | Bork et al., 2001 |
| USH1F (10q21-22) | *PCDH15* | Ahmed et al., 2001 |
| USH1G (17q24-25) | *SANS* | Mustapha et al., 2002 |
| *USH2A* (1q41) | *USH2A* | Kimberling et al., 1990 |
| USH2C (5q14.3-q21.3) | *VLGR1* | Weston et al., 2004 |
| USH2D (9q32) | *WHRN* | Ebermann et al., 2007 |
| USH3 (3q21-q25) | *USH3A* | Joensuu et al., 2001 |
| 10q24.31 | *PDZD7* | Ebermann et al., 2010 |

Table 6. Reported genes for Usher syndrome.

**Pendred syndrome:** Pendred syndrome, named after Vaughan Pendred (1896) a British physician, is the most common syndromic form of HL and associated with abnormal iodine metabolism (goiter). It is an autosomal recessive disorder which accounts for 4-10% of deaf cases [Fraser 1965]. The defective organic binding of iodine in the thyroid gland may distinguished by a positive potassium perchlorate discharge test; however the test is not specific and its sensitivity is unclear. HL is usually bilateral, severe to profound and may be present at birth, and sloping in the higher frequencies [Kopp et al., 2008]. The casual gene is *SLC26A4* (PDS) on chromosome 7q31 encoding a protein named pendrin (Figure 3). It regulates transportation of iodine and chloride/ bicarbonate ions in the inner ear, thyroid, and kidney. Mutations of this gene can cause NSHL DFNB4 and enlarged vestibular aqueduct syndrome as well [Everett et al., 1997].

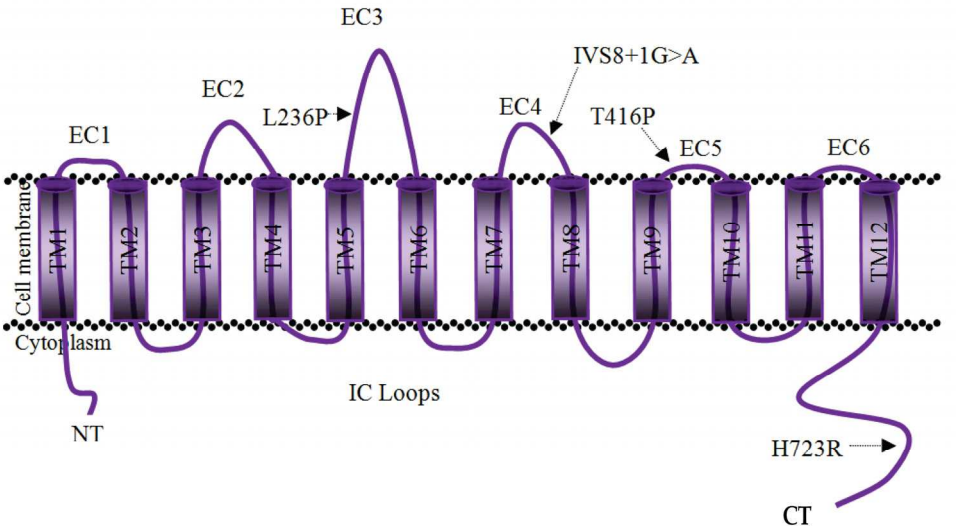


Fig. 3. Hypothetic structure and domains of Pendrin protein. The most common mutations (L236P, IVS8+1G>A, T416P, and H723R) accounting for approximately 60% of the total PS genetic load are shown. TM1-TM12 denotes transmembrane domains, EC1-6 denotes extracellular domains, IC denotes cytoplasmic domain, NT denotes amino (NH2) terminus and CT denotes carboxyl (COOH) terminus.

**Alport syndrome:** Alport syndrome, a hereditary disorder of basement membranes, is characterized by renal abnormalities including glomerulonephritis, hematuria ("red diaper") and renal failure, and ocular problems as well as progressive sensorineural HL [Wester et al., 1995]. Mutations in various genes encoding type 4 collagen (COL4A3, COL4A4 and COL4A5) have been reported to cause Alport syndrome [Lemmink et al., 1994; Hudson et al., 2003]; nearly 85% of the cases are due to COL4A5 mutations [Hudson et al., 2003]. These collagens are components of the basilar membranes, the spiral ligament and stria vascularis. X-linked pattern of inheritance is observed in the majority (80 %); the remaining shows autosomal recessive [Lemmink et al., 1994] and autosomal dominant [van der Loop et al., 2000], inheritance patterns. It is estimated that 10% to 15% of X-linked patients represent de novo mutations in *COL4A5* [Gubler et al., 2007]. Since uremia leads to death in males prior to 30 years of age, it is essential to diagnose it early in men. Symptoms are usually more severe than women. The progressive sensorineural HL usually begins in the adolescent years [Wester et al., 1995]. The mechanism of HL has not been explained exactly yet, although the basement membrane damages are suggested to affect adhesion of the cells of the organ of Corti and basilar membrane leading to HL [Merchant et al., 2004].

**Waardenburg syndrome**: Waardenburg disease, named after Petrus Johannes Waardenburg (1886-1979), accounts for 1-3% of congenital HL [Read & Newton, 1997]. In addition, the disease shows other clinical features. Four types of syndrome can be distinguished on the basis of accompanying abnormalities [Read & Newton, 1997]: In type 1, patients show dystopia canthorum, iris heterochromy, brilliant blue eyes, broad nasal root, premature

graying of hair, white forelock, and vestibular dysfunction. Type 2 patients have similar phenotype but not dystopia canthorum. In type 3 (so called Klein-Waardenburg syndrome) [Klein, 1983], upper extremity abnormalities other Type 1 clinical features and dystopia canthorum and are observed. In type 4 (so called Shah-Waardenburg syndrome) [Shah et al., 1981] patients demonstrate all findings shown in Type 2 with the addition of pigmentation abnormalities and Hirschsprung's disease. Sensorineural hearing loss is observed in 60 % and 90 % of type 1 and type 2 patients, respectively [Newton, 1990].

Types 1 and 3 of Waardenburg syndrome occur due to mutations in the *PAX3* gene encoding a DNA-binding protein essential for determining the fate of neural crest cells [Baldwin et al., 1994]. Type 2 is due to mutations in MITF gene [Tassabehji et al., 1994]. Mutations in three genes, *EDN3*, *SOX10* and *EDNRB* genes, can lead to Type 4 [Edery et al., 1996; Hofstra et al., 1996; Pingault et al., 1998]. *SOX10* mutations, account for approximately half of type 4 patients and are likely responsible for about 15% of Type 2 as well [Bondurand et al., 2007]. *In vitro* studies have shown that *EDN3* plays as a stimulation factor of proliferation and melanogenesis of neural crest cells. *EDNRB* is suggested to have an important role in the development of epidermal melanocytes and enteric neurons. *SOX10* is a DNA-binding transcription factor and involved in promoting cell survival prior to lineage commitment [Kapur, 1999]. There is a wide range of variation in HL phenotype so that some patients may not exhibit HL.

**Branchio-oto-renal syndrome:** Branchio-oto-renal syndrome (BOR) is an autosomal dominant disorder, accounting for 2% of profoundly deaf children and is characterized by branchial derived anomalies, otologic anomalies (Mondini's dysplasia and stapes fixation) and renal malformation. HL may affect 70-93% of the BOR patients but there is a high variability in age of onset and severity [Chen et al., 1995]. HL can be sensorineural, conductive or mixed, stable or progressive and mild or profound. Mutations in *EYA1* gene have been identified to cause BOR syndrome (BOR1) [Abdelhak et al., 1997]. It has been shown that this gene has a role in development of the inner ear and kidney [Abdelhak et al., 1997]. Studies of transgenic mice have indicated that EYA1 homozygous knockouts have not developed ears and kidneys. In addition to *EYA1*, mutations in two genes named SIX1 and SIX5 have been reported to cause BOR3 and BOR2, respectively [Ruf et al., 2004; Hoskins et al., 2007].

**Stickler Syndrome:** Stickler Syndrome (STL), named after Stickler (1965), follows an autosomal dominant pattern of inheritance and is characterized by progressive sensorineural HL, cleft palate, abnormal development of the epiphysis, vertebral abnormalities and osteoarthritis. On the basis of clinical features, four types of STL exist. Type 1 patients have typical features of the disease including progressive myopia leading to retinal detachment, midface hypoplasia, cleft palate, variable sensorineural HL and vitreoretinal degeneration. Mutations in *COL2A1* gene encoding a fibrillar collage type 2 subunitA1 can cause the classic phenotype [Ahmad et al., 1991]. There is no retinal detachment in Type 2 andthe phenotype is caused by *COL11A1* gene mutations [Richards et al., 1996]. Facial abnormalities seen in Type 1 are not observed in Type 3. Mutations of *COL11A2* lead to STL Type 3 [Vikkula et al., 1995]. Recently, mutations in *COL9A1* have been identified to cause an autosomal recessive form of STL, Type 4 [Van Camp et al., 2006].

## 7. Genetic evaluation

The main problem in the diagnosis of disorders such as deafness is its heterogenicity. Genetic study of HL has considerable benefits for patients which are as follows:

a. Identifying the medical and non medical decisions e.g cochlear implant
b. Carrier testing and prenatal diagnosis
c. Prediction for the progressive state of the disease
d. Eliminating unnecessary tests and investigations
e. Providing appropriate genetic counseling before marriage, especially when they have heterogeneous conditions that carry different mutated genes.

Genetic evaluation should be considered for children with newly diagnosed loss of hearing especially if no specific cause is determined. For example, there is no need for genetic evaluation of the family of a child with HL due to meningitis; although, they may need assurance of not transmitting the disease to the next generation. Genetic evaluation includes several steps:

1. Reviewing the complete history of prenatal, neonatal and medical history of growth and development
2. Complete physical examination of patients and other family members
3. Evaluating the genetics, molecular and cellular diagnosis

Based on previous studies, deaf people have positive assortive marriage; it is estimated that 90% of deaf individuals marry deaf. Depending on the pattern of inheritance they might have a deaf child. For example if both parental recessive alleles are similar, there is 100% chance of having a deaf child; and if one of the parents carry a dominant form of HL and the other carry the recessive form of HL the chance would be 50% for the dominant gene.

Early diagnosis of HL is important in gaining speech progression and social skills of the children which would lead to better life of these individuals and would later help them in cochlea implant. Hereditary or genetic understanding of the causes of HL is important. The benefits of this understanding and knowledge, not only allows physicians to help the families of at risk but also may help in treatment and control of HL. Sometimes it is possible to prevent hearing loss from worsening. HL may be one of the clinical signs of a syndrome and if the genetic cause of HL is determined it may help to predict and treat other clinical complications [Extivill et al., 1998].

## 8. Conclusion

HL is the most common sensory defect affecting human beings. It is categorized on the basis of several criteria. Genetic factors can be traced in half of the cases. Nonsyndromic HL can follow any of the Mendelian inheritance patterns, but the majority are ARNSHL. Approximately fifty genes have been reported to be involved in HL, and based on an estimation nearly 200 to 250 genes may cause HL. Genetic understanding of the causes of HL and finding the molecular mechanism of hearing process are valuable for genetic counseling, prevention and development of new therapeutic approaches. Many studies have been published about finding new genes causing prelingual nonsyndromic HL. Presbycusis is very common among eldely people and research on this phenotype needs more attention.

New technology and strategies such as next generation sequencing can help to discover new genes for deafness in future.

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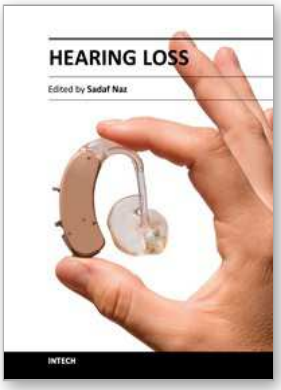


**Hearing Loss**

Edited by Dr. Sadaf Naz

ISBN 978-953-51-0366-0
Hard cover, 406 pages
**Publisher** InTech
**Published online** 28, March, 2012
**Published in print edition** March, 2012

Authored by 17 international researchers and research teams, the book provides up-to-date insights on topics in five different research areas related to normal hearing and deafness. Techniques for assessment of hearing and the appropriateness of the Mongolian gerbil as a model for age-dependent hearing loss in humans are presented. Parental attitudes to childhood deafness and role of early intervention for better treatment of hearing loss are also discussed. Comprehensive details are provided on the role of different environmental insults including injuries in causing deafness. Additionally, many genes involved in hearing loss are reviewed and the genetics of recessively inherited moderate to severe and progressive deafness is covered for the first time. The book also details established and evolving therapies for treatment of deafness.



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