

REVIEW ARTICLE

GENETICS OF HUMAN HEREDITARY HEARING IMPAIRMENT

Rahat Meena, Muhammad Ayub

Human Molecular Genetic Laboratory, Institute of Biochemistry, University of Baluchistan, Quetta-Pakistan

Hereditary hearing impairment is heterogeneous type of disorder which can be caused due to environmental as well as genetical factors. Two distinct types of hereditary hearing loss are syndromic or non-syndromic. Non-syndromic hearing loss is further categorized as autosomal recessive, autosomal dominant, X-linked and mitochondrial deafness. Autosomal recessive occurs more frequently as compared to autosomal dominant. Mutations in various genes are responsible for hereditary hearing impairment. To date, about 99 autosomal recessives and 67 autosomal dominant genes for deafness have been discovered. Some of important genes include GJB2, GJB6, GJB3 which encodes gap junction proteins, MYO7A, MYO15A encodes myosine proteins, OTOF encodes otoferlin, and SLC26A4 encodes anion exchanger protein. Up till now, the mutation in GJB2 gene occurs more frequently in different population of the world and cause autosomal recessive hearing impairment. The purpose of this review article was to explore the mutation and function of those muted genes which encode different type of protein and responsible either for autosomal recessive or autosomal dominant hearing impairment.

Keywords: Recessive deafness, Dominant deafness, Mutation, Encoded proteins, Genetics

J Ayub Med Coll Abbottabad 2017;29(4):671-6

INTRODUCTION

Hearing loss is one of the major problems in the present world. One in thousand offspring is generally affected due to hearing impairment worldwide. It is genetically and phenotypically heterogeneous and almost 300 million individuals suffered from it in the present world.¹⁻³ It is common at all ages. In developed countries about 6-8% people are suffered from genetic hearing impairment and it is considered as the most serious health concern by birth.⁴

It can be due to environmental causes or genetic factors. Almost 50% of hearing impairment is due to genetic factors⁵ that may be non-syndromic or syndromic⁶. The non-syndromic hearing impairment is further categorized as autosomal recessive, autosomal dominant, X-linked and mitochondrial hearing impairment and it is not associated with any other defect in the body only concern with hearing impairment. Almost 75-80% cases of hereditary hearing impairment are of autosomal recessive non-syndromic, 15-25% cases are autosomal dominant non-syndromic, 1-2% cases are mitochondrial or X-linked. Commonly, autosomal recessive hearing impairment indicates pre-lingual or post-lingual deafness which ranges from serious to intense deafness. In autosomal dominant hearing impairment, the phenotype is usually less serious which shows post-lingual deafness and ranges from average to serious.⁷ The syndromic hearing impairment is concerned with defects of other body parts and cause diseases like, i.e., diabetes mellitus, Retinitis Pigmentosa etc and about 30% of hereditary hearing impairment is syndromic and it includes different

syndromes like usher syndrome, warden burg, stickler, Alport etc.⁸

Autosomal recessive deafness is mostly found in the people of Middle East because of consanguineous marriages where the families are large and more affected people and children are found. In Pakistan, the hereditary deafness is congenital and severe and covers 70% of cases while autosomal recessive hearing impairment is the frequent type because in Pakistan most of the marriages are consanguineous which are estimated about 60% and first cousin's marriages are estimated about 80%.^{9,10} It has been estimated that about 40% pathogenic mutation in genes and almost 130 loci have been identified in isolated form. In Pakistan, these loci were identified first in affected individuals.¹¹ According to recent survey, the marriages between first and second cousins results to give birth to offspring with hearing impairment in developed countries.¹²

Up till 2015, 99 autosomal recessive¹³, 67 autosomal dominant¹⁴, six X-linked recessive loci¹⁵ have been identified. The genes responsible for autosomal recessive non-syndromic hearing loss include (*GJB2*, MIM # 121011) encodes gap junction protein beta 2, (*MYO15A*, MIM# 602666) encodes myosin XVA, (*TMCI*, MIM# 606706) encodes transmembrane channel-like 1, (*SLC26A4*, MIM# 605646) encodes solute carrier family 26 (anion exchanger) member 4, (*OTOF*, MIM# 603681) encodes otoferlin and (*CDH23*, MIM# 605516) encodes cadherin-related 23. Each of these has at least more than 20 various mutations and most of these are found in consanguineous families.¹⁶

The aim of this review was to highlight the function and contribution of those muted genes which were responsible for hereditary hearing loss and encode different group of proteins. There are about 25 different proteins encoded by various non-syndromic deafness genes. The important proteins and their relative genes are discussed in this review paper.

The search engines used for this review paper were original research papers, Google Scholar (<https://www.google.com.pk>), OMIM Entry (<https://www.omim.org/entry/121011>), PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>), <http://hereditaryhearingloss.org/>.

Gap Junctions

Gap junctions are intercellular channels and play a vital role in the connection of cytoplasm of nearby cell. Two hemi channels form these gap junctions, each of which consists of six subunits.^{17,18} All the Connexin are named as gap junction because these are involved in the formation of gap junctions. These are helpful in cell to cell communication via plasma membrane of various cells. The transfer of intercellular small molecules in the tiny environment of the tissues is brought by the help of gap junction and participates in intercellular communication.¹⁹ The mutations in Connexin may create serious type of hearing impairment and about 50% of deafness cases are due to these mutations.²⁰⁻²⁴ Various genes encode different types of gap junction proteins. Those genes include GJB2 encodes Connexin 26, GJB3 encodes Connexin 31 and GJB6 encodes Connexin 30.

GJB2 (DFNB1) (gap junction protein beta 2) is a gene located on chromosome 17p11.2, it is a region which is similar to that of mouse model²⁵ and involved in the cochlear homeostasis. GJB2 gene encodes Connexin - 26 proteins, consists of 2 exons and about 23 domains in Homo sapiens. About 189 different types of GJB2 genes have been discovered in different organisms. Connexin 26 is a gap junction protein. The GJB2 gene is responsible for autosomal recessive non-syndromic hearing impairment and was first discovered in 1996 in the consanguineous families of Pakistan.²⁶ In European countries about 50% of autosomal recessive non-syndromic hereditary hearing impairment is due to mutation in GJB2 gene.²⁷ Most of the non-syndromic hearing impairment (~50%) in children is caused due to mutation in GJB2 gene.²⁸ The GJB2 gene mutation with 35delG is mostly responsible for hearing impairment.^{21,29} At least 100 various kinds of mutations are recognized in GJB2 gene in the patients with autosomal recessive non-syndromic hearing impairment in different populations. GJB2 gene mutation is the basic cause of hereditary deafness responsible for DFNB1 and DFNA3.³⁰

GJB3 (DFNA2B) gene encodes connexin-31 protein, therefore also known as gap junction protein beta-3 gene (DFNA2B).^{31,32} GJB3 gene is located at chromosome 1p34.3 and composed of 2 exons in human. It encodes connexin-31 protein (Cx31). At least 157 GJB3 genes have been discovered in various organisms. It is generally involved in autosomal dominant and autosomal recessive hearing impairment. Non-syndromic hearing impairment or erythrokeratoderma is caused due to mutation in GJB-3 gene.³² Erythrokeratoderma variabilis (EKV, MIM ID #133200) is a type of skin disorder but it is a rare autosomal dominant disorder.³³ The GJB3 gene mutation was first identified in Chinese family having autosomal dominant hearing impairment.³⁴

GJB6 gene is located at chromosome 13q12 and consisting of 7 exons. GJB6 gene (MIM 604418) encodes connexin-30 (Cx30), which is part of gap junction proteins in the cochlea of inner ear.³⁵ Cx30 consists of 261 amino acids. About 162 GJB6 genes are identified in variety of organisms. Autosomal recessive non-syndromic hearing impairment is mostly caused by the mutation in GJB6 gene²⁷ but this type of mutation is also responsible for autosomal dominant hearing impairment in various populations. The gap junctions Cx26 and Cx30 are strongly expressed in the cochlea of inner ear and play a vital role in the maintenance of potassium ion homeostasis in the cochlea.³⁶ Important mutations were detected³⁷, in GJB6 gene that screened 23 dominant families and 64 and 30 families of America and Japan with autosomal recessive non-syndromic hearing impairment respectively.³⁷ A 342-kb deletion is considered the most frequent type of mutation in GJB6, if it is homozygous or present in Trans position with recessive GJB2 mutation then causes non-syndromic hearing loss. About 20 various pathogenic type of mutations in GJB6 with Del (*GJB6*-D13S1830) and Del (*GJB6*-D13S1854) are identified proceeding to sensorineural hearing impairment.³⁸

Tight Junction

Tight junctions are very important in the formation of intercellular barrier between the epithelial cells. These intercellular barriers are necessary for the separation of tissue spaces and regulation of solutes through epithelium. Almost 40 various proteins have been recognized as tight junction.³⁹ The most important gene which encodes tight junction is CLDN14 (DFNB29) and mutation in this gene cause autosomal recessive non-syndromic hearing impairment.

CLDN14 (DFNB29) is a gene which encodes claudin-14 protein present in human beings.⁴⁰ This gene is located at chromosome 21q22.3 and consists of 7 exons in Homo sapiens.

There are about 180 different types of CLDN14 genes present in various organisms. Claudin-14 protein belongs to tight junctions normally shows cell to cell adhesion in endothelial and epithelial cell sheets and forms regular seals around the cell and serves as strong physical barrier to stop various solutes and water from entering directly through cellular space. CLDN14 (DFNB29) gene mutation cause autosomal recessive non-syndromic hearing impairment.⁴¹ This type of mutation was identified in about six families of Pakistan suffered from autosomal recessive non-syndromic hearing impairment. CLDN14 is mostly expressed in the cells of cochlea, liver and kidney where it helps in the formation of tight junctions. To date, 6 various pathogenic variants of human *CLDN14* are identified in families having severe to profound deafness, but having no permanent vestibular phenotype.⁴²

Myosins

Myosins belong to huge family of actin-dependent molecular motors which are useful for the creation of a strong force that helps the actin filament in movement and this force is generated with the help of ATP which is bounded and hydrolysed by actin-dependent molecular motors and shows function in the cellular environment.^{43, 44} Some myosins are conventional and some are non-conventional.⁴⁵ MYO7A and MYO15A are two important muted genes responsible for deafness and encode the myosin protein.

MYO7A (DFNB2) is a gene located at chromosome 11q13.5 and consisting of 55 exons.⁴⁶ It encodes for unconventional myosin proteins (VIIA) consisting of 2,215-amino acid. About 236 MYO7A genes have been discovered in different organisms. Myosin VIIA is generally expressed in epithelial tissues of retina and inner ear. The hair cells and stereocilia of inner ear mainly contain Myosin VIIA protein. Any variation in the MYO7A gene is responsible for about 50% of different types of usher syndromes i.e. USH1, USH1B.^{47,48} Mutation in the MYO7A gene is also concerned with autosomal recessive non-syndromic hearing impairment mostly in humans. Different compound heterozygous or homozygous mutations related to MYO7A gene have been reported in variety of affected families of Pakistan, Palestine, Turkey and Iran.

MYO15A gene (DFNB3) is found on chromosome 17p11.2 in humans which is identical to that of mouse model and consisting of 66 exons with 71,097 bp.²⁵ MYO15A gene encodes XVA myosin protein having 3530 amino acids with 39.5 KDa. About 183 MYO15A genes have been recognized in different organisms and mutation of which lead to hereditary hearing loss. MYO15A gene plays a vital role in elongation and development of stereocilia and

actin filament. Cohesion of stereocilia is also brought by the interaction of whirlin and MYO15A gene.⁴⁹ In Homo sapiens, the mutation in the MYO7A gene was first isolated in the families of Indonesia where about 2% of people were suffered from hearing impairment.⁵⁰ At least 43 MYO15 gene mutations have been reported occurring in the motor domain. This type of mutation is generally responsible for autosomal recessive hearing impairment.

Transmembrane Proteins

Transmembrane proteins are important class of membranous proteins which act as a gateway that allow specific molecules to pass through the biological membrane. Various genes encode transmembrane proteins and cause hereditary hearing impairment. Those genes include SLC26A4 (DFNB4), TMC1 (DFNB12), and TMIE (DFNB6).

SLC26A4 (DFNB4) is a gene located at chromosome 7q31 having 23 exons in humans. About 188 various types of SLC26A4 Genes have been discovered in various organisms. SLC26A4 encodes a transmembrane protein.i.e. Pendrin and its fundamental function is the transport of anion (Cl^- , Γ^- and HCO_3^-) in the cell membranes.^{51,52} Pendrin is mostly expressed in the inner ear, thyroid and kidney. SLC26A4 gene mutation is responsible for autosomal recessive non-syndromic hearing impairment but this type of mutation is also concern with enlarged vestibular aqueduct (EVA) and pendred syndrome which is a sensorineural autosomal recessive hearing impairment related to cochlear abnormalities caused by biallelic SLC26A4 gene mutation. Malfunction of pendrin proceeds to Pendred syndrome (PS) and non-syndromic (DFNB4) hearing impairment and EVA.⁵³ Up till now, about 174 *SLC26A4* gene mutations have been identified. The SLC26A4 gene consists of 2 mutant alleles in the patients suffered from Pendred syndrome and responsible for autosomal recessive hearing impairment while one or no muted allele is found in the patients suffered from EVA or non-syndromic deafness.⁵⁴

TMC1 (DFNB12) is a gene located at chromosome 9q21.12 in humans. It encodes transmembrane channel-like 1 (TMC1), and having 25 exons and is about 300kb. About 192 TMC1 genes have been discovered in different organisms. TMC1 is mostly expressed in the hair cells of cochlea and play important role in the function of hair cell.⁵⁵ Up till now, 35 homozygous mutations in TMC1 gene have been identified in 60 different families of the world suffered from autosomal recessive non-syndromic hearing impairment and having identical phenotype which is characterized by pre-lingual serious to extreme hearing impairment.⁵⁶ The frequent type of p.R34X nonsense mutation is the basic cause of autosomal recessive mutation in

TMC1 gene at DFNB7/11 locus mostly found in the population of North Africa and Asia.⁵⁷ TMC1 gene mutation is also concerned with autosomal dominant hearing loss at the DFNA36 locus, but such cases are still less.¹⁶

TMIE (DFNB6) (MIM # 607237) is a transmembrane inner ear gene.⁵⁸ It is found on chromosome 3p21 and has 4 exons. It encodes transmembrane protein, i.e., 154 amino acid peptides and has only one transmembrane domain.⁵⁹ There are about 263 different types of TMIE gene found in different organisms. Mutation in TMIE gene is responsible for hearing impairment in humans as well as mice.⁶⁰ Variants of the TMIE gene responsible for autosomal recessive non-syndromic hearing impairment were frequently found in Pakistani population. There were evaluated 5 types of various recessive homozygous mutations in TMIE gene in patients of consanguineous families having serious to extreme pre-lingual hearing impairment.⁵⁸ Mutation in the TMIE gene cause defect in the sensory cells of the inner ear and create problem in the auditory nerves.

Otoferlin Protein

Otoferlin is engaged in the vesicle fusion with the cell membrane, and in vesicle impletion. The function of otoferlin in vesicle impletion may be involved in the binding as well as intercommunication with endocytic proteins, e.g. adaptor protein 2 (AP2) which approves fast consent of exo-cytosed particles from the vesicular discharge site.

OTOF (DFNB9) is a gene located on chromosome 2p23.1 consisting of 48 coding exons and is 90 Kb. About 175 OTOF genes have been discovered in different organisms. OTOF gene encodes otoferlin protein and its expression is generally found in the hair cells of cochlea and brain.⁶¹ A novel gene OTOF was identified in *Homo sapiens* and mutation in this gene was responsible for homozygous type of autosomal recessive non-syndromic hearing impairment.⁶² OTOF muted gene was also recognized in the consanguineous family of Lebanon with autosomal recessive hearing impairment which might be serious to extreme.⁶³ ARNHL was caused by missense mutation p.Glu1700Gln, in *OTOF* gene.⁶⁴ Up till now, at least 93 various mutations are identified in OTOF gene.

CONCLUSION

In this review, we have described different muted genes responsible for hereditary hearing impairment. The study shows that GJB2, GJB6, MYO7A, MYO5A and SLC26A4 are the most common muted genes responsible for autosomal recessive or autosomal dominant hearing impairment. This review

also highlighted the function and importance of those proteins which are encoded by muted genes. It was also mentioned here that mutation in GJB2, MYO5A and SLC26A4 cause deafness in most of consanguineous families of different population. So genetic counselling may be helpful in investigation of hereditary hearing impairment and complete clinical confession about the impact of mutations in particular genes is essential in consummating the complete potential.

REFERENCES

1. Friedman TB, Griffith AJ. Human nonsyndromic Sensorineural Deafness. *Annu Rev Genomics Hum Genet* 2003;4(1):341–402.
2. Morton CC, Nance WE. Newborn hearing screening—a silent revolution. *N Engl J Med* 2006;354(20):2151–64.
3. Raviv D, Dror AA, Avraham KB. Hearing loss: a common disorder caused by many rare alleles. *Ann N Y Acad Sci* 2010;1214(1):168–79.
4. Petit C, Leveilliers J, Hardelin JP. Molecular genetics of hearing loss. *Annu Rev Genet* 2001;35(1):589–645.
5. Smith RJ, Bale JF Jr, White KR. Sensorineural hearing loss in children. *Lancet* 2005;365(9462):879–90.
6. Mustapha M, Salem N, Delague V, Chouery E, Ghassibeh M, Rai M, *et al.* Autosomal recessive non-syndromic hearing loss in the Lebanese population: prevalence of the 30delG mutation and report of two novel mutations in the connexin 26 (GJB2) gene. *J Med Genet* 2001;38(10):E36.
7. Van Camp G, Willems PJ, Smith RJ. Nonsyndromic hearing impairment: unparalleled heterogeneity. *Am J Hum Genet* 1997;60(4):758–64.
8. Smith RJ, Shearer AE, Hildebrand MS, Van Camp G. Deafness and Hereditary Hearing Loss Overview. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJ, *et al.* editors. *GeneReviews*(®) [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2016 May 31]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1434/>
9. Hussain R, Bittles AH. The prevalence and demographic characteristics of consanguineous marriages in Pakistan. *J Biosoc Sci* 1998;30(2):261–75.
10. Elahi MM, Elahi F, Elahi A, Elahi SB. Paediatric hearing loss in rural Pakistan. *J Otolaryngol* 1998;27(6):348–53.
11. Brown KA, Janjua AH, Karbani G, Parry G, Noble A, Crockford G, *et al.* Linkage studies of non-syndromic recessive deafness (NSRD) in a family originating from the Mirpur region of Pakistan maps DFNB1 centromeric to D13S175. *Hum Mol Genet* 1996;5(1):169–73.
12. Zakzouk S. Consanguinity and hearing impairment in developing countries: a custom to be discouraged. *J Laryngol Otol* 2002;116(10):811–6.
13. Li J, Zhao X, Xin Q, Shan S, Jiang B, Jin Y, *et al.* Whole-Exome Sequencing Identifies a Variant in TMEM132E Causing Autosomal-Recessive Nonsyndromic Hearing Loss DFNB99. *Hum Mutat* 2015;36(1):98–105.
14. Thoenes M, Zimmermann U, Ebermann I, Ptok M, Lewis MA, Thiele H, *et al.* OSBPL2 encodes a protein of inner and outer hair cell stereocilia and is mutated in autosomal dominant hearing loss (DFNA67). *Orphanet J Rare Dis* 2015;10:15.
15. Rost S, Bach E, Neuner C, Nanda I, Dysek S, Bittner RE, *et al.* Novel form of X-linked nonsyndromic hearing loss with cochlear malformation caused by a mutation in the type IV collagen gene COL4A6. *Eur J Hum Genet* 2014;22(2):208–15.

16. Hilgert N, Smith RJ, Van Camp G. Forty-six genes causing nonsyndromic hearing impairment: which ones should be analyzed in DNA diagnostics? *Mutat Res* 2009;681(2-3):189–96.
17. de Waal Malefyt R, Abrams J, Bennett B, Figdor CG, De Vries JE. Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. *J Exp Med* 1991;174(5):1209–20.
18. Harris AL. Emerging issues of connexin channels: biophysics fills the gap. *Q Rev Biophys* 2001;34(3):325–472.
19. Kumar NM, Gilula NB. The gap junction communication channel. *Cell* 1996;84(3):381–8.
20. Kelsell DP, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G, *et al.* Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. *Nature* 1997;387(6628):80–3.
21. Zelante L, Gasparini P, Estivill X, Melchionda S, D'Agruma L, Govea N, *et al.* Connexin26 mutations associated with the most common form of non-syndromic neurosensory autosomal recessive deafness (DFNB1) in Mediterraneans. *Hum Mol Genet* 1997;6(9):1605–9.
22. Denoyelle F, Lina-Granade G, Plauchu H, Bruzzone R, Chaïb H, Lévi-Acobas F, *et al.* Connexin 26 gene linked to a dominant deafness. *Nature* 1998;393(6683):319–20.
23. Estivill X, Fortina P, Surrey S, Rabionet R, Melchionda S, D'Agruma L, *et al.* Connexin-26 mutations in sporadic and inherited sensorineural deafness. *Lancet* 1998;351(9100):394–8.
24. Kelley PM, Harris DJ, Comer BC, Askew JW, Fowler T, Smith SD, *et al.* Novel mutations in the connexin 26 gene (GJB2) that cause autosomal recessive (DFNB1) hearing loss. *Am J Hum Genet* 1998;62(4):792–9.
25. Wang A, Liang Y, Fridell RA, Probst FJ, Wilcox ER, Touchman JW, *et al.* Association of unconventional myosin MYO15 mutations with human nonsyndromic deafness DFNB3. *Science* 1998;280(5368):1447–51.
26. Kenneson A, Van Naarden Braun K, Boyle C. GJB2 (connexin 26) variants and nonsyndromic sensorineural hearing loss: a HuGE review. *Genet Med* 2002;4(4):258–74.
27. Rabionet R, Zelante L, López-Bigas N, D'Agruma L, Melchionda S, Restagno G, *et al.* Molecular basis of childhood deafness resulting from mutations in the GJB2 (connexin 26) gene. *Hum Genet* 2000;106(1):40–4.
28. Denoyelle F, Weil D, Maw MA, Wilcox SA, Lench NJ, Allen-Powell DR, *et al.* Prelingual deafness: high prevalence of a 30delG mutation in the connexin 26 gene. *Hum Mol Genet* 1997;6(12):2173–7.
29. Fuse Y, Doi K, Hasegawa T, Sugii A, Hibino H, Kubo T. Three novel connexin26 gene mutations in autosomal recessive nonsyndromic deafness. *Neuroreport* 1999;10(9):1853–7.
30. Xia JH, Liu CY, Tang BS, Pan Q, Huang L, Dai HP, *et al.* Mutations in the gene encoding gap junction protein β -3 associated with autosomal dominant hearing impairment. *Nat Genet* 1998;20(4):370–3.
31. Wenzel K, Manthey D, Willecke K, Grzeschik KH, Traub O. Human gap junction protein connexin31: molecular cloning and expression analysis. *Biochem Biophys Res Commun* 1998;248(3):910–5.
32. Macari F, Landau M, Cousin P, Mevorah B, Brenner S, Panizzon R, *et al.* Mutation in the gene for connexin 30.3 in a family with erythrokeratoderma variabilis. *Am J Hum Genet* 2000;67(5):1296–301.
33. Xia JH, Liu CY, Tang BS, Pan Q, Huang L, Dai HP, *et al.* Mutations in the gene encoding gap junction protein beta-3 associated with autosomal dominant hearing impairment. *Nat Genet* 1998;20(4):370–3.
34. Lerer I, Sagi M, Ben-Neriah Z, Wang T, Levi H, Abeliovich D. A deletion mutation in GJB6 cooperating with a GJB2 mutation in trans in non-syndromic deafness: a novel founder mutation in Ashkenazi Jews. *Hum Mutat* 2001;18(5):460.
35. Kikuchi T, Kimura RS, Paul DL, Takasaka T, Adams JC. Gap junction systems in the mammalian cochlea. *Brain Res Rev* 2000;32(1):163–6.
36. Kelley PM, Abe S, Askew JW, Smith SD, Usami SI, Kimberling WJ. Human connexin 30 (GJB6), a candidate gene for nonsyndromic hearing loss: molecular cloning, tissue-specific expression, and assignment to chromosome 13q12. *Genomics* 1999;62(2):172–6.
37. Stenson PD, Mort M, Ball EV, Shaw K, Phillips AD, Cooper DN. The Human Gene Mutation Database: building a comprehensive mutation repository for clinical and molecular genetics, diagnostic testing and personalized genomic medicine. *Hum Genet* 2014;133(1):1–9.
38. Yamazaki Y, Okawa K, Yano T, Tsukita S, Tsukita S. Optimized Proteomic Analysis on Gels of Cell-Cell Adhering Junctional Membrane Proteins. *Biochemistry* 2008;47(19):5378–86.
39. Kniessel U, Wolburg H. Tight junctions of the blood-brain barrier. *Cell Mol Neurobiol* 2000;20(1):57–76.
40. Wilcox ER, Burton QL, Naz S, Riazuddin S, Smith TN, Ploplis B, *et al.* Mutations in the gene encoding tight junction claudin-14 cause autosomal recessive deafness DFNB29. *Cell* 2001;104(1):165–72.
41. Lee K, Ansar M, Andrade PB, Khan B, Santos-Cortez RL, Ahmad W, *et al.* Novel CLDN14 mutations in Pakistani families with autosomal recessive non-syndromic hearing loss. *Am J Med Genet A* 2012;158A(2):315–21.
42. Mooseker MS, Cheney RE. Unconventional myosins. *Annu Rev Cell Dev Biol* 1995;11(1):633–75.
43. Krendel M, Mooseker MS. Myosins: tails (and heads) of functional diversity. *Physiology (Bethesda)* 2005;20(4):239–51.
44. Friedman TB, Sellers JR, Avraham KB. Unconventional myosins and the genetics of hearing loss. *Am J Med Genet* 1999;89(3):147–57.
45. Guilford P, Arab SB, Blanchard S, Levilliers J, Weissenbach J, Belkahlia A, *et al.* A non-syndromic form of neurosensory, recessive deafness maps to the pericentromeric region of chromosome 13q. *Nat Genet* 1994;6(1):24–8.
46. Liu XZ, Walsh J, Mburu P, Kendrick-Jones J, Cope MJ, Steel KP, *et al.* Mutations in the myosin VIIA gene cause non-syndromic recessive deafness. *Nat Genet* 1997;16(2):188–90.
47. Adato A, Weil D, Kalinski H, Pel-Or Y, Ayadi H, Petit C, *et al.* Mutation profile of all 49 exons of the human myosin VIIA gene, and haplotype analysis in Usher 1B families from diverse origins. *Am J Hum Genet* 1997;61(4):813–21.
48. Friedman TB, Liang Y, Weber JL, Hinnant JT, Barber TD, Winata S, *et al.* A gene for congenital, recessive deafness DFNB3 maps to the pericentromeric region of chromosome 17. *Nat Genet* 1995;9(1):86–91.
49. Babanejad M, Fattahi Z, Bazazzadegan N, Nishimura C, Meyer N, Nikzat N, *et al.* A comprehensive study to determine heterogeneity of autosomal recessive nonsyndromic hearing loss in Iran. *Am J Med Genet A* 2012;158A(10):2485–92.
50. Scott DA, Wang R, Kreman TM, Sheffield VC, Karniski LP. The Pendred syndrome gene encodes a chloride-iodide transport protein. *Nat Genet* 1999;21(4):440–3.
51. Soleimani M, Greeley T, Petrovic S, Wang Z, Amlal H, Kopp P, *et al.* Pendrin: an apical Cl⁻/OH⁻/HCO₃⁻ exchanger in the kidney cortex. *Am J Physiol Renal Physiol* 2001;280(2):F356–64.
52. Campbell C, Cucci RA, Prasad S, Green GE, Edeal JB, Galer CE, *et al.* Pendred syndrome, DFNB4, and PDS/SLC26A4 identification of eight novel mutations and possible genotype-phenotype correlations. *Hum Mutat* 2001;17(5):403–11.

53. Pryor SP, Madeo AC, Reynolds JC, Sarlis NJ, Arnos KS, Nance WE, *et al.* SLC26A4/PDS genotype-phenotype correlation in hearing loss with enlargement of the vestibular aqueduct (EVA): evidence that Pendred syndrome and non-syndromic EVA are distinct clinical and genetic entities. *J Med Genet* 2005;42(2):159–65.
54. Marcotti W, Erven A, Johnson SL, Steel KP, Kros CJ. Tmc1 is necessary for normal functional maturation and survival of inner and outer hair cells in the mouse cochlea. *J Physiol* 2006;574(Pt 3):677–98.
55. Nakanishi H, Kurima K, Kawashima Y, Griffith AJ. Mutations of TMC1 cause deafness by disrupting mechano-electrical transduction. *Auris Nasus Larynx* 2014;41(5):399–408.
56. Ben said M, Hmani-Aifa M, Amar I, Baig SM, Mustapha M, Delmaghani S, *et al.* High frequency of the p. R34X mutation in the TMC1 gene associated with nonsyndromic hearing loss is due to founder effects. *Genet Test Mol Biomark* 2010;14(3):307–11.
57. Naz S, Giguere CM, Kohrman DC, Mitchem KL, Riazuddin S, Morell RJ, *et al.* Mutations in a novel gene, TMIE, are associated with hearing loss linked to the DFNB6 locus. *Am J Hum Genet* 2002;71(3):632–6.
58. Mitchem KL, Hibbard E, Beyer LA, Bosom K, Dootz GA, Dolan DF, *et al.* Mutation of the novel gene Tmie results in sensory cell defects in the inner ear of spinner, a mouse model of human hearing loss DFNB6. *Hum Mol Genet* 2002;11(16):1887–98.
59. Yang JJ, Su MC, Chien KH, Hsin CH, Li SY. Identification of novel variants in the TMIE gene of patients with nonsyndromic hearing loss. *Int J Pediatr Otorhinolaryngol* 2010;74(5):489–93.
60. Yasunaga SI, Petit C. Physical map of the region surrounding the OTOFERLIN locus on chromosome 2p22–p23. *Genomics* 2000;66(1):110–2.
61. Yasunaga SI, Grati M, Cohen-Salmon M, El-Amraoui A, Mustapha M, Salem N, *et al.* A mutation in OTOF, encoding otoferlin, a FER-1-like protein, causes DFNB9, a nonsyndromic form of deafness. *Nat Genet* 1999;21(4):363–9.
62. Chiu YH, Wu CC, Lu YC, Chen PJ, Lee WY, Liu AY, *et al.* Mutations in the OTOF gene in Taiwanese patients with auditory neuropathy. *Audiol Neurotol* 2010;15(6):364–74.

Received: 22 August, 2016

Revised: 24 February, 2017

Accepted: 23 April, 2017

Address for Correspondence:

Muhammad Ayub, Human Molecular Genetic Laboratory, Institute of Biochemistry, University of Baluchistan, Quetta-Pakistan

Cell: +92 331 527 7232

Email: ayub_2004@hotmail.com