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Review Article

Non-syndromic Autosomal Recessive Deafness in Pakistani Population: Epidemiology and Genetics

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Abstract.- Hearing loss is quite common in Pakistani population leading to communication disabilities. Hearing loss is influenced by environmental and genetic factors. High ratio of cousin marriages, infection, trauma and various diseases are major contributors to hearing impairment among Pakistani individuals. Pakistani population provides a valuable genetic resource for identifying various loci and genes involved in deafness phenotypes. A number of genes causing pre-lingual, severe to profound or profound hearing impairment have been identified using single consanguineous family. The identification and functional analysis of deafness loci/genes play an important role in our understanding of processes of the auditory function.

Key words: Auditory sensing, cochlea, nonsyndromic, deafness, autosomal recessive, hearing impairment.

INTRODUCTION

The partial or complete inability to perceive sounds is a common disorder in humans. Approximately one in thousand newborn is affected by severe to profound hearing loss (HL) either at birth or during early childhood (Birkenhager *et al*., 2007). Genetic causes account for half of cases of childhood deafness and the remainder are attributed to environmental factors (Veske *et al*., 1996). Hearing loss is expected to increase to 25% by 2020 along with increased life expectancy (Rosenhall *et al*., 1999). Hearing impairment is the world's third leading chronic disease (Van Camp and Smith, 2006). Hearing loss prevalence in isolated ccommunities is almost 15% in newborns (Friedman *et al*., 2007).

Of the more than 4000 infants born deaf each year, more than half have a hereditary disorder (Steel, 1998). Hearing impairment affects 1/2000 (0.05%) or in some populations its ratio is 1/1000 (0.1%) newborns (Morton and Nance, 2006; Parving and Newton, 1995). Hearing loss is the most common sensorineural disorder in developed countries with congenital origin (Keat *et al*., 2002). Almost 60% of hearing impairment is due to genetic factors (Piatto *et al*., 2005; Smith *et al*., 2005).

Bilateral permanent sensorineural hearing loss which appears by adolescence affects 3.5 per 1000 individuals (Morton and Nance, 2006). According to Tranebjaerg (2008), the worldwide prevalence of profound, congenital genetic deafness is 11 per 10,000 children.

Hereditary hearing loss is not always by birth, some children inherit the tendency to develop hearing loss later in life (Van Camp *et al*., 1997). Most inherited forms of deafness segregate as monogenic traits but digenic inheritance has also been reported (Zheng *et al*., 2005). In monogenic cases, hearing loss can segregate as an autosomal

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dominant, autosomal recessive, X-linked, Y-linked or with a mitochondrial mode of inheritance. The phenotypic spectrum of deafness includes both syndromic (characterized by hearing loss in combination with other abnormalities) and non-syndromic forms (with only hearing loss) (Van Camp and Smith, 2006). Most forms of non-syndromic autosomal recessive deafness are pre-lingual and are usually due to cochlear defects (sensorineural deafness). The degree of severity of the hearing loss may vary from mild, moderate, severe to profound and also by the site of defect. In contrast, syndromic forms may be conductive, sensorineural or both (mixed loss) and account for 30% of genetic deafness (Van Camp and Smith, 2007). More than 400 distinct syndromes have been identified that are associated with deafness. It is estimated that approximately 75% of all non-syndromic deafness cases are autosomal recessive (*DFNB*), 12-24% are autosomal dominant (*DFNA*), 1-3% cases are X-linked (*DFN*), while less than 1% of deafness is mitochondrial and Y-linked (*DFNY*) (Wajid *et al*., 2003).

Identification of deafness genes and functional analysis of the proteins they encode is playing a very important role in our understanding of the process of the auditory functions (Kalay *et al*., 2007). Recessive inherited deafness in Pakistan in high due to high rate of consanguineous marriages. Pakistani population is one of the richest genetic resources to study hereditary deafness. Almost 35 autosomal recessive non-syndromic loci have been mapped by using Pakistani genetic resources (Hereditary Hearing Loss Home Page URL: http://hereditaryhearingloss.org/ Accessed May, 2012). The present review focuses on the genetics and epidemiology of autosomal recessive non-syndromic deafness in Pakistani population.

MOLECULAR BASIS OF HEARING LOSS

A particular disorder might be referred as "running in a family" if more than one person in the family has the condition. Genetic disorders due to mutated genes that are passed to next generation are called hereditary (Genetics Home http:// ghr.nlm.nih.gov). These types of mutations persist throughout a person's life (Starr *et al*., 1996), and can prevent one or more of proteins from proper functioning (Willems, 2000). The vertebrate ear, a marvel of nature has an intricate structure. The development and functioning of this highly sophisticated organ is under the genetic control (Moller, 1994). Mutations in genes that regulate the hearing process, results in hearing pathophysiology (Petit, 2006).

The minute size, delicacy and cellular diversity of the inner ear tissues has posed exceptional challenges to proteomics studies (Thalmann *et al*., 2003). The cochlea is a closed space, and cochlear function is sensitive to small changes in fluid volume (Hardisty *et al*., 1999). The conventional biochemical and physiological methods are not as convenient and successful to understand the mechanism of auditory system. Forward genetic approach is a powerful technique to identify the essential component of the auditory transduction, but the mapping of deafness genes through forward genetics is delimited by problems arising from phenotypic and genotypic heterogeneity, as many different genetic forms of hearing loss can produce similar clinical phenotypes. Frequent assortative mating among nuclear families segregating recessive deafness leads to coexistence of several defective genes in a single pedigree and making them inappropriate for linkage studies (Van Camp *et al*., 1997). Mapping strategies have circumvented some of these drawbacks by using large, extended multi-generation consanguineous families, and populations isolates (ethnic group), in which there is greater likelihood of genetic homogeneity (Yan and Liu, 2008).

Recent progress in characterizing the genetic deafness in humans has paralleled the enrollment of families segregating hearing deficit with the availability of clinical data, genetic markers, genetic maps, physical maps, full genome sequence of human and transcription data bases. Animal models, which can mimic the human genetic deafness are also helpful. A genetic approach to study the molecular basis of inner ear function is promising to characterize unknown molecules involved in the process of auditory dysfunction.

SYNDROMIC/NON-SYNDROMIC HEARING IMPAIRMENT: A BRIEF HISTORY

Hereditary hearing loss is categorized as non syndromic where hearing loss is the only symptom and syndromic where deafness co-segregates with some other clinical manifestations (Bitner-Glindzicz, 2002). A disruption of different classes of proteins involved may cause hearing impairment with or without associated syndromic features. Initially the genes involved in syndromic deafness were identified, as individuals with syndromic mode of deafness share other clinical problems in addition to hearing loss that helps in recognition of a distinct entity. In contrast, non-syndromic hearing loss requires linkage analysis in single large families.

The genetic dissection of hearing loss started with the localization of the first locus for autosomal dominant form of post-lingual hearing loss; *DFNA1*, in an extended pedigree from Cost Rica (Leon *et al*., 1992). In next two years, the first autosomal recessive non-syndromic locus, *DFNB1* was mapped in a Tunisian family (Guilford *et al*., 1994). During the past decade, remarkable progress has been made in the localization of loci/genes for non-syndromic hereditary deafness. Approximately 154 different chromosomal loci associated with non-syndromic deafness have been mapped/reserved that include 59 autosomal dominant loci, 88 autosomal recessive loci, 6 X linked loci and one Y-linked locus. Of these, 25 genes have been identified for autosomal dominant (*DFNA*), 39 for autosomal recessive (*DFNB*) and 3 for X-linked (*DFN*) deafness (Hereditary Hearing Loss Home Page, URL: http://hereditaryhearingloss.org/ Accessed May, 2012).

NON-SYNDROMIC DEAFNESS

The loci responsible for autosomal recessive hearing impairment have been designated as DFNB1, DFNB2 an and so on in the same order in which they were reserved or reported. Non-syndromic autosomal recessive deafness is clinically heterogeneous, non-progressive in nature and exhibits a high degree of genetic heterogeneity

Non-syndromic autosomal recessive deafness is usually clinically heterogeneous, non-progressive in nature, and exhibits a high degree of genetic heterogeneity (Ansar 2003a). Non-syndromic hearing loss (NSHL) with autosomal recessive mode of inheritance is responsible for 70% of congenital deafness (Bayazit *et al*., 2003).

Given this structural complexity of cochlea it could be suggested that hereditary deafness is remarkable feature for its genetic heterogeneity (Keats and Berlin, 1999). The great degree of genetic heterogeneity reflects different types of molecules needed in the inner ear and indicate large number of genes orchestrating the hearing process (Van Camp and Smith, 2006). Almost 120 genes have been identified, having a role in hearing phenomena (Yildrim and Yilmaz, 2006).

Different mutations in the same gene can also lead to different hearing loss phenotypes (Chen *et al*., 1997). Two different genes can also interact in causing deafness in one family due to marriages involving two hearing impaired individuals, making the carriers of both more severely affected (Balciuniene *et al*., 1998). As the environmental as well as genetic factors independently or in combination, results in hearing impairment it further complicates the story (Nance, 2003). Molecular and genetic information regarding non-syndromic hearing loss clearly reveals that there are still many loci and genes to be identified.

NON-SYNDROMIC AUTOSOMAL RECESSIVE DEAFNESS IN PAKISTANI POPULATION

Recessively inherited deafness in the Pakistani population is higher 1.6 per 1000 individuals than world average 1 per 1000 individuals due to high consanguinity (Hussain and Bittles, 1998).

Hearing loss in Pakistani population is genetically heterogeneous and various recessively inherited hearing loss loci differ in prevalence as compared to other populations. A high incidence of hearing loss has been seen in children living in developing countries, where the prevalence of consanguinity is high, with both genetic and acquired forms of hearing loss (Mukherjee *et al*., 2003). Marriages within the family increase the risk of hearing impairment with and without other

diseases (Hussain and Bittles, 1998).

Pakistani population is one of the richest genetic sources to study hereditary diseases due to its unique socio-cultural trends where out of every ten marriages, six are consanguineous, and among those four are between first cousins (Hussain and Bittles, 1998). Hussain (1999), reports about two-thirds of marriages in Pakistan are consanguineous and according to another report, approximately 80% are first cousin marriages in Pakistani population (Hussain and Bittles, 1998). These marriages increase the chance that both members of a couple carry any recessive variant that is being transmitted in their family, and that this will manifest in the homozygous state in their children, with the high risk of birth prevalence of infants with serious recessive disorders (Modell and Darr, 2002). The prevalence of hearing impairment in Pakistan is 1.6 per 1,000 live births, (Elahi *et al*., 1998) which is higher than world average of 1 per 1000 live births (Atar and Avraham, 2005). A number of genes causing pre-lingual, severe to profound or profound hearing impairment have been identified using single consanguineous Pakistani families (Riazuddin *et al*., 2000).

The occurrence of many deafness loci indicates the diverse genetic repertoire as well as extreme heterogeneity in Pakistani population. A number of non syndromic autosomal recessive loci have been first mapped using genetic resources of Pakistani population including *DFNB8* (Veske *et al*., 1996), *DFNB16* (Campbell *et al*., 1997), *DFNB20* (Monihan *et al*., 1999), *DFNB26* (Riazuddin *et al*., 2000), *DFNB29* (Wilcox *et al*., 2001), *DFNB35* (Ansar *et al*., 2003a), *DFNB36* (Naz *et al*., 2004), *DFNB37* (Ahmed *et al*., 2003a), *DFNB38* (Ansar *et al*., 2003b), *DFNB39* (Wajid *et al*., 2003), *DFNB42* (Aslam *et al*., 2005), *DFNB44* (Ansar *et al*., 2004), *DFNB46* (Mir *et al*., 2005), *DFNB47* (Hassan *et al*., 2006), *DFNB48* (Ahmed *et al*., 2005), *DFNB49* (Ramzan *et al*., 2005), *DFNB51* (Shaikh *et al*., 2005), *DFNB55* (Irshad *et al*., 2005), *DFNB62* (Ali *et al*., 2006), *DFNB63* (Tariq *et al*., 2006), *DFNB65* (Khan *et al*., 2007), *DFNB67* (Shabbir *et al*., 2006), *DFNB68* (Santos *et al*., 2006), *DFNB72* (Ain *et al*., 2007), *DFNB73* (Riazuddin *et al*., 2009), *DFNB74* (Waryah *et al*., 2009), *DFNB79* (Rehman *et al*., 2010), *DFNB81* (Rehman *et al*., 2011) and *DFNB86* (Ali *et al*., 2012).

PREVALENCE OF COMMON NON-SYNDROMIC AUTOSOMAL RECESSIVE DEAFNESS LOCI IN PAKISTANI POPULATION

Almost 35 autosomal recessive non syndromic deafness loci or genes have been identified by using Pakistani genetic resources. Large cohort consanguineous families with hereditary deafness show *DFNB4/PDS* locus as the predominant cause followed by *DFNB1*, *DFNB2/USH1B*, *DFNB3* and *DFNB12/USH1D*, *DFNB8/10* and *DFNB7/11* in Pakistani population. Prevalence of different recessive loci is markedly different from that in other populations. Genetic analysis of hereditary hearing loss in various populations show *DFNB1* as leading cause approximately 30-50%, but *DFNB1* mutation is not a major contributor in Pakistani deaf individuals (Santos *et al*., 2005; Gasparini *et al*., 1997).

Genetic analysis of genetic resource place *DFNB4/ PDS* as most prevalent deafness locus with contribution in both syndromic and nonsyndromic hearing loss in Pakistani population (Anwar *et al*., 2009). *DFNB4/PDS* account for 10% of hearing impairment in rest of the world (Coyle *et al*., 1998; Cremers *et al*., 1998; Reardon *et al*., 1997). *DFNB2/USH1B* is also a prevalent locus among Pakistani individuals segregating neurosensory deafness (Ahmed *et al*., 2003a).

Recessive mutations of *MYO15* causes profound hearing impairment *DFNB3* is responsible for 5% of recessive deafness in Pakistani population (Friedman *et al*., 2002). Autosomal recessive non syndromic *DFNB12* is responsible for 5% isolated hearing impairment and 10% of *USH1D* is also prevalent in Pakistani deaf families (Astuto *et al*., 2002). Identification of these deafness loci is paving the way towards our understanding of molecular basis of hereditary deafness.

CONCLUSIONS

Inter family marriages are a common practice in Pakistani culture. In order to reduce the ratio of

hereditary deafness in Pakistani population, identification of molecular carriers is a fundamental step. To date 35 autosomal recessive non-syndromic deafness loci have been identified in Pakistani population. Pakistani population provides a rich genetic resource for mapping deafness loci and identifying the genes orchestrating hearing pathways. Application of molecular genetics approach has significantly contributed to our knowledge of genetic deafness. The role of modifier genes involved in rescuing or causing different type of hearing impairment has been demonstrated.

REFERENCES

AHMED, J., KHAN, S. N., KHAN, S. Y., RAMZAN, K., RIAZUDDIN, S., AHMED, Z. M., WILCOX, E. R., FRIEDMAN, T. B. AND RIAZUDDIN, S., 2005. *DFNB48* a new nonsyndromic recessive deafness locus maps to chromosome 15q23-q251. *Hum. Genet.*, **116**: 407-12.

AHMED, Z. M., MORELL, R. J., RIAZUDDIN, S., GROPMAN, A., SHAUKAT, S., AHMAD, M. M., MOHIDDIN, S. A., FANANAPAZIR, L., CARUSO, R. C., HUSNAIN, T., KHAN, S. N., RIAZUDDIN, S., GRIFFTH, A. J., FRIEDMAN, T. B. AND WILCOX, E. R., 2003a. Mutation of *MYO6* are associated with recessive deafness *DFNB37*. *Am. J. Hum. Genet*., **72**: 1315-1322.

AIN, Q., NAZLI, S., RIAUDDIN, S., JALEEL, A. U., RIAZUDDIN, S. A., ZAFAR, A. U., KHAN, S. N., HUSNAIN, T., GRIFFTH, A. J., AHMED, Z. M., FRIEDMAN, T. B. AND RIAZUDDIN, S., 2007. The autosomal recessive nonsyndromic deafness locus *DFNB72* is located on chromosome 19p133. *Hum. Genet*., **122**: 445-50.

ALI, R. A., REHMAN, A. U., KHAN, S. N., HUSNAIN, T., RIAZUDDIN, S., FRIEDMAN, T. B., AHMED, Z. M. AND RIAZUDDIN, S., 2012. *DFNB86*, a novel autosomal recessive non-syndromic deafness locus on chromosome 16p13.3. *Clin. Genet*., **81**: 498-500.

ALI, G., SANTOS, R. L., JOHN, P., WAMBANGCO, M. A., LEE, K., AHMAD, W. AND LEAL, S., 2006. The mapping of *DFNB62* a new locus for autosomal recessive non-syndromic hearing impairment to chromosome 12p132-q1123. *Clin. Genet*., **69**: 429-33.

ANSAR, M., AMIN UD DIN, M., ARSHAD, M., SOHAIL, M., FAIYAZ-UL-HAQUE, M., HAQUE, S., AHMAD, W. AND LEAL, M. A., 2003a. Novel autosomal recessive non-syndromic deafness locus (*DFNB35*) maps to 14q241-14q243 in large consanguineous kindred from Pakistan. *Eur. J. Hum. Genet*., **11**: 77-80.

ANSAR, A., RAMZAN, M., PHAM, T. L., YAN, K., JAMAL, S. M., HAQUE, S., AHMAD, W. AND LEAL, S. M., 2003b. Localization of a novel autosomal recessive nonsyndromic hearing impairment locus (*DFNB38*) to 6q26-27 in a consanguineous kindred from Pakistan. *Hum. Hered*., **55**: 71-74.

ANSAR, M., CHAHROUR, M. H., AMIN UD DIN, M., ARSHAD, M., HAQUE, S., PHAM, T. L., YAN, K., AHMAD, W. AND LEAL, S. M., 2004. *DFNB44* a novel autosomal recessive non-syndromic hearing impairment locus maps to chromosome 7p141-q1122. *Hum. Hered*. **57**: 195-9.

ANWAR, S., RIAZUDDIN, S., AHMED, Z. M., TASNEEM, S., ATEEQ-UL-JALEEL, KHAN, S. Y., GRIFFTH, A. J., FRIEDMAN, T. B. AND RIAZUDDIN, S., 2009. SLC26A4 mutation spectrum associated with *DFNB4* deafness and Pendred's syndrome in Pakistanis. *J. Hum. Genet*., **54**:266-70.

ASLAM, M., WAJID, M., CHAHROUR, M. H., ANSAR, M., HAQUE, S., PHAM, T. L., SANTOS, R. P., YAN, K., AHMAD, W. AND LEAL, S. M., 2005. A novel autosomal recessive nonsyndromic hearing impairment locus (*DFNB42*) maps to chromosome 3q1331-q223. *Am. J. med. Genet.*, **133**: 18-22.

ASTUTO, L. M., KELLEY, P. M., ASKEW, J. W., WESTON, M. D., SMITH, R. J., ALSWAID, A. F., AL-RAKAF, M. AND KIMBERLING, W. J., 2002. Searching for evidence of *DFNB2*. *Am. J. med. Genet.*, **109**: 291-297.

ATAR, O. AND AVRAHAM, K. B., 2005. Therapeutics of hearing loss expectations vs reality. *Drug Discov. Today*, **10**: 1324-1230.

BALCIUNIENE, J., DAHL, N., BORGE, E., SAMUELSSON, E., KOISTI, M. J., PETTERSSON, U. AND JAZIN, E. E., 1998. Evidence for digenic inheritance of nonsyndromic hereditary hearing loss in a Swedish family. *Am. J. Hum. Genet.*, **63**: 786-93.

BAYAZIT, Y. A., CABLE, B. B., CATALOLUK, O., KARA, C., CHAMBERLIN, P., SMITH, R. J., KANLIKAMA, M., OZER, E., CAKMAK, E. A., MUMBUC, S. AND ARSLAN, A., 2003. *GJB2* gene mutations causing familial hereditary deafness in Turkey. *Int. J. Pediatr. Otorhinolaryngol.*, **67**: 1331-1335.

BIRKENHAGER, R., ASCHENDORFF, A. J., SCHIPPER, J. AND LASZIG, R., 2007. Non-syndromic Hereditary Hearing Impairment. *Laryngo Rhino. Otol*., **86**: 299-313.

BITNER-GLINDZICZ, M., 2002. Hereditary deafness and phenotyping in humans. *Br. med. Bull*. **63**: 73-94.

CAMPBELL, D. A., MCHALE, D. P., BROWN, K. A., MOYNIHAN, L. M., HOUSEMAN, M., KARBANI, G., PARRY, G., JANJUA, A. H., NEWTON, V., AL-GAZALI, L., MARKHAM, A. F., LENCH, N. J. AND MUELLER, R. F., 1997. A new locus for non-syndromal, autosomal recessive, sensorineural hearing loss (*DFNB16*) maps to human chromosome 15q21-q22. *Med. Genet.*, **34**: 1015–1017.

CHEN, A., WAYNE, S., BELL, A., RAMESH, A.,

SRISAILAPATHY, C. R. S., SCOTT, D. A., SHEFFIELD, V. C., VAN HAUWE, P., ROSS, I. S., ZBAR, R. I. S., ASHLEY, J., LOVETT, M., VAN CAMP, V. AND SMITH, R. J. H., 1997. New gene for autosomal recessive non-syndromic hearing loss maps to either chromosome 3q or 19p. *Am. J. med. Genet*., **71**: 467-471.

COYLE, B., REARDON, W., HERBRICK, J. A., TSUI, L. C., GAUSDEN, E., LEE, J., COFFEY, R., GRUETERS, A., GROSSMAN, A., PHELPS, P. D., LUXON, L., KENDALL-TAYLOR, P., SCHERER, S. W. AND TREMBATH, R. C., 1998. Molecular analysis of the *PDS* gene in Pendred syndrome. *Hum. mol. Genet*., **7**: 1105-12.

CREMERS, W. R., BOLDER, C., ADMIRAAL, R. J., EVERETT, L. A., JOOSTEN, F. B., VAN HAUWE, P., GREEN, E. D. AND OTTEN, B. J., 1998. Progressive sensorineural hearing loss and a widened vestibular aqueduct in Pendred syndrome. *Arch Otolaryngol. Head Neck Surg*., **124**: 501-5.

DENOYELLE, F., MARLIN, S., WEIL, D., MOATTI, L., CHAUVIN, P., GARABEDIAN, E. N. AND PETIT, C., 1999. Clinical features of the prevalent form of childhood deafness *DFNB1* due to a connexin-26 gene defect implication for genetic conselling. *Lancet*, **353**: 1298-303.

ELAHI, M. M., ELAHI, F., ELAHI, A. AND ELAHI, S. B., 1998. Pedriatics hearing loss in rural Pakistan. *J. Otolaryngol*., **27**: 348-53.

FRIEDMAN, L. M., DROR, A. A. AND AVRAHAM, K. B., 2007. Mouse models to study inner ear development and hereditary hearing loss. *Int. J. Dev. Biol.*, **51**: 609-631.

FRIEDMAN, T. B. AND GRIFFITH, A. J., 2003. Human Nonsyndromic sensorineural deafness. *Ann. Rev. Genomics Hum. Genet*., **4**: 341-402.

FRIEDMAN, T. B., HINNANT, J. T., GHOSH, M., BOGER, E. T., RIAZUDDIN, S., LUPSKI, J. R., POTOCKI, L. AND WILCOX, E. R., 2002. DFNB3, spectrum of MYO15A recessive mutant alleles and an emerging genotype-phenotype correlation. *Adv. Otorhinolaryngol.*, **61**:124-30.

GASPARINI, P., ESTIVILL, X., VOLPINI, V., TOTARO, A., CASTELLVI-BEL, S., GOVEA, N., MILA, M., DELLA-MONICA, M., VENTRUTO, V., DE BENEDETTO, M., STANZIALE, P., ZELANTE, L., MANSFIELD, E. S., SANDKUIJL, L., SURREY, S. AND FORTINA, P., 1997. Linkage of *DFNB1* to nonsyndromic neurosensory autosomal recessive deafness in Mediterraneon families. *Eur. J. Hum. Genet*., **5**: 83-88.

GUILFORD, P., ARAB, S.B., BALANCHARD, S., LEVILLIERS, J., WEISSENBACH, J., BELKAHIA, A. AND PETIT, C. A., 1994. Nonsyndromic form of neurosensory recessive deafness maps to the pericentromeric region of chromosome 13q. *Nat. Genet.*, **6**: 24-8.

HARDISTY, R. E., MBURU, P. AND BROWN, S. D., 1999. ENU mutagenesis and search for deafness genesis. *Br. J. Audiol*., **33**: 279-283.

HASSAN, M. J., SANTOS, R. L., RAFIQ, M. A., CHAHROUR, M. H., PHAM, T. L., WAJID, M., HIJAB, N., WAMBANGCO, M., LEE, K., ANSAR, M., YAN, K., AHMAD, W. AND LEAL, S. M., 2006. A novel autosomal recessive non-syndromic hearing impairment locus (*DFNB47*) maps to chromosome 2p25.1-p24.3. *Hum. Genet.*, **118**: 605-610.

HUSSAIN, R., 1999. Community perceptions of reasons for preference for consanguineous marriages in Pakistan. *J. Biosoc. Sci.*, **31**: 449-461.

HUSSAIN, R. AND BITTLES, A. H., 1998. The prevalence and demographic characteristics of consanguineous marriages in Pakistan. *J. Biosoc. Sci.*, **30**: 261-275.

IRSHAD, S. M., SANTOS, R. I., MUHAMMAD, D., LEE, K., MCARTHUR, N., HAQUE, S., AHMAD, W. AND LEAL, S. M., 2005. Localization of a novel autosomal recessive non-syndromic hearing impairment locus *DFNB55* to chromosome 4q12-q132. *Clin. Genet*., **68**: 262-267.

KALAY, E., CAYLAN, R., KIROGLU, A. F., YASAR, T., COLLIN, R. W., HEISTER, J. G., OOSTRIK, J., CREMERS, C. W., BRUNNER, H. G., KARAGUZEL, A. AND KREMER, H. A., 2007. A new locus for autosomal recessive nonsyndromic hearing impairment *DFNB63* maps to chromosome 11q132-q134. *J. mol. Med*., **85**: 397-404.

KEATS, B.J.B. AND BERLIN, C.I., 1999. Genomics and Hearing Impairment. *Genome Res*., **9**: 7-16.

KEATS, B.J.B., POPPER, A.N. AND FAY, R.R., 2002. *Genetics and auditory disorders*. Springer, New York, pp. 1-322.

KHAN, S. Y., AHMED, Z. M., SHABBIR, M. I., KITAJIRI, S., KALSOOM, S., TASNEEM, S., SHAYIQ, S., RAMESH, A., SRISAILAPATHY, S., KHAN, S. N., SMITH, R. J. H., RIAZUDDIN, S., FRIEDMAN, T. B. AND RIAZUDDIN, S., 2007. Mutations of RDX gene cause nonsyndromic hearing loss at the *DFNB24* locus. *Hum. Mutat.*, **28**: 417-423.

LEON, P.E., RAVENTOS, H., LYNCH, E., MORROW, J. AND KING, M. C., 1992. The gene for an inherited form of deafness maps to chromosome 5q31. *Proc. nat. Acad. Sci. USA*, **89**: 5181-5184.

MIR, A., ANSAR, M., CHAHROUR, M. H., PHAM, T. L., WAJID, M., HAQUE, S., YAN, K., AHMAD, W. AND LEAL, S. M., 2005. Mapping of a novel autosomal recessive nonsyndromic deafness locus (*DFNB46*) to chromosome 18p1132-p1131. *Am. J. med. Genet*., **133A**: 23-26.

MODELL, B. AND DARR, A., 2002. Genetic counselling and customary consanguineous marriage. *Nature*, **3**: 225.

MOLLER, A. R., 1994. Auditory neurophysiology. *J. Clin.*

Neurophysiol. **11**: 319-342.

MOYNIHAN, L., HOUSEMAN, M., NEWTON, V., MUELLER, R. AND LENCH, N., 1999. *DFNB20*: a novel locus for autosomal recessive, non-syndromal sensorineural hearing loss maps to chromosome 11q25-qter. *Eur. J. Hum. Genet*., **7**: 243-6.

MORTON, C. C. AND NANCE, W. E., 2006. New born hearing screening- a silent revolution. *New Engl. J. Med.,* **18**: 2151-2164.

MUKHERJEE, M., PHADKE, S. R. AND MITTAL, B., 2003. Connexin 26 and autosomal recessive non-syndromic hearing loss. *Ind. J. Hum. Genet*., **9**: 40-50.

NANCE, W. E., 2003. The Genetics of deafness. *J. Mental Retard. Develop Disab*., **9**: 109-119.

NAZ, S., GRIFFTH, A. J., RIAZUDDIN, S., HAMPTON, L. L., JR BATTERY, J. F., KHAN, S. N., RIAZUDDIN, S., WILCOX, E. R. AND FRIEDMAN, T. B., 2004. Mutations of *ESPN* cause autosomal recessive deafness and vestibular dysfunctionl. *J. Med. Genet.,* **41**: 591-595.

PARVING, A. AND NEWTON, V., 1995. Guidelines for description of inherited hearing loss. *J. Audiol. Med*., **4**: 2-5.

PETIT, C., 2006. From deafness genes to hearing mechanisms harmony and counterpoint. *Trends mol. Med*., **12**: 57-64.

PIATTO, V.B., NASCIMENTO, E.C.T., ALEXANDRINO, F., OLIVEIRA, C.A., LOPES, A.C.P., SARTORATO, E.L. AND MANIGLIA, J.V., 2005. Molecular genetics of nonsyndromic deafness. *Rev. Bras. Otorrinolaringol*., **71**: 216-223.

RAMZAN, K., SHAIKH, R. S., AHMED, J., KHAN, S. N., RIAZUDDIN, S., AHMED, Z. M., FRIEDMAN, T. B., WILCOX, E. R. AND RIAZUDDIN, S., 2005. A new locus for nonsyndromic deafness *DFNB49* maps to chromosome 5q123-q141. *Hum. Genet*., **116**: 17-22.

REARDON, W., COFFEY, R., PHELPS, P. D., LUXON, L. M., STEPHENS, D., KENDALL-TAYLOR, P., BRITTON, K. E., GROSSMAN, A. AND TREMBATH, R., 1997. Pendred syndrome -- 100 years of underascertainment? *QJM Int. J. Med.*, **90**: 443-7.

REHMAN, A. U., GUL, K., MORELL, R. J., LEE, K., AHMED, Z. M., RIAZUDDIN, S., SHAHZAD, M., JALEEL, A. U., ANDRADE, P. B., KHAN, S. N., BREWER, C. C., AHMAD, W., LEAL, S. M., RIAZUDDIN, S. AND FRIEDMAN, T. B., 2011. Mutations of GIPC3 cause nonsyndromic hearing loss *DFNB72* but not *DFNB81* that also maps to chromosome 19p. *Hum. Genet*., **130**: 759-65.

REHMAN, A. U., MORELL, R. J., BELYANSTEVA, I. A., KHAN, S. Y., BOGER, E. T., SHAHZAD, M., AHMAD, Z. M., RIAZUDDIN, S., KHAN, S. N., RIAZUDDIN, S. AND FRIEDMAN, T. B., 2010. Targeted capture and next-generation sequencing identifies *C9orf75* encoding taperin as the mutated gene in nonsyndromic deafness *DFNB79*. *Am. J. Hum. Genet*., **86**: 378-88.

RIAZUDDIN, S., ANWAR, S., FISCHER, M., AHMED, Z. M., KHAN, S. Y., JANSSEN, A. G., ZAFAR, A. U., SCHOLL, U., HUSNAIN, T., BELYANSTEVA, I. A., FRIEDMAN, P. L., RIAZUDDIN, S., FRIEDMAN, T. B. AND FAHLKE, C., 2009. Molecular basis of *DFNB73* mutations of *BSND* can cause nonsyndromic deafness or Bartter syndrome. *Am. J. Hum. Genet.*, **85**: 273-80.

RIAZUDDIN, S., CASTELEIN, C. M., AHMED, Z. M., LALWANI, A. K., MASTROIANNI, M. A., NAZ, S., SMITH, T. N., LIBURD, N. A., FRIEDMAN, T. B., GRIFFITH, A. J., RIAZUDDIN, S. AND WILCOX, E. R., 2000. Dominant modifier *DFNM1* suppresses recessive deafness *DFNB26*. *Nat. Genet*., **26**: 431-33.

ROSENHALL, U., JONSSON, R. AND SODERLIND, O., 1999. Self-assessed hearing problems in Sweden a demographic study. *J. Audiol*., **38**: 328-334.

SANTOS, R. L., HASSAN, M. J., SIKANDAR, S., LEE, K., ALI, G., MARTIN, P. E., WAMBANGCO, M. A., AHMED, W. AND LEAL, S. M., 2006. *DFNB68* a novel autosomal recessive non-syndromic hearing impairment locus at chromosomal region 19p132. *J. Hum. Genet*., **120**: 85-92.

SANTOS, R.L., WAJID, M., PHARM, T.L., HUSSAIN, J., ALI. G., AHMAD, W. AND LEAL, S.M., 2005. Low prevalence of Connexin 26 (*GJB2*) variants in Pakistani families with autosomal recessive non syndromic hearing impairment. *Clin. Genet*., **67**: 61-68.

SHABBIR, M.I., AHMED, Z.M., KHAN, S.Y., RIAZUDDIN, S., WARYAH, A.M., KHAN, S. N., CAMPS, R.D., GHOSH, M., KABRA, M., BELYANTSEVA, I.A., FRIEDMAN, T.B. AND RIAZUDDIN, S., 2006. Mutations of human *TMHS* cause recessively inherited non-syndromic hearing loss. *J. med .Genet.,* **43**: 634-640.

SHAIKH, R. S., RAMZAN, K., NAZLI, S., SATTAR, S., KHAN, S. N., RIAZUDDIN, S., AHMED, Z. M., FRIEDMAN, T. B. AND RIAZUDDIN, S., 2005. A new locus for nonsyndromic deafness *DFNB51* maps to chromosome 11p13-p12. *Am. J. med. Genet. A*, **138**: 392-5.

SMITH, R. J., BALE, J. F. AND WHITE, K. R., 2005. Sensorineural hearing loss in children. *Lancet*, **365**: 2085-6.

STARR, A., PICTON, T. W., SININGER, Y. V., HOOD, L. J. AND BERLIN, C. I., 1996. Auditory neuropathy. *J. Brain Res.*, **119**: 741-753.

STEEL, K. P., 1998. A new era in the genetics of deafness. *New Engl. J. Med.*, **339**: 1545–1547.

TARIQ, A., SANTOS, R. L., KHAN, M. N., LEE, K., HASSAN, M. J., AHMED, W. AND LEAL, S. M., 2006. Localization of a novel *DFNB65* to chromosome 20q132-1332. *J. mol. Med.*, **84**: 484-90.

THALMANN, R., HENZL, M. T., KILLICK, R., IGNATOVA, E. G. AND THALMANN, I., 2003. Toward an understanding of cochlear homeostasis the impact of location and the role of OCP1 and OCP2. *Acta Otolaryngol*., **123**: 203-208.

TRANEBJAERG, L., 2008. Genetics of congenital hearing impairment: A clinical approach. *Intl. J. Audiol.*, **47**: 535-545.

VAN CAMP, G., WILLEMS, P. J. AND SMITH, R. J. H., 1997. Nonsyndromic hearing impairment unparalleled heterogeneity. *Am. J. Hum. Genet.*, **60**: 758-764.

VAN CAMP, G. AND SMITH, R. J. H., 2006. *Hereditary hearing loss*. Homepage. http//webhostuaacbe/hhh/

VAN CAMP, G. AND SMITH, R. J. H., 2007. *Hereditary hearing loss*. Homepage. http//webhostuaacbe/hhh/

VESKE, A., OCHLINANN, R., YOUNAS, F., MOHYUDDIN, A., MULLER-MYHSOK, B., MEHDI, S. Q. AND GAL, A., 1996. Autosomal recessive non-syndromic deafness locus (*DFNB8*) maps on chromosome 21q22 in a large consanguineous kindred from Pakistan. *Hum. mol. Genet*., **5**: 165-168.

WAJID, M., ABBASI, A. A., ANSAR, M., PHAM, T. L., YAN, K., HAQUE, S., AHMAD, W. AND LEAL, S. M., 2003. DFNB39 a recessive form of sensorineural hearing impairment maps to chromosome 7q1122-q2112. *Eur. J. Hum. Genet.*, **11**: 812-815.

WARYAH, A. M., REHMAN, A., AHMED, Z. M., BASHIR, Z. H., KHAN, A. Y., ZAFAR, A. U., RIAZUDDIN, S., FRIEDMAN, T. B. AND RIAZUDDIN, S., 2009. *DFNB74* a novel autosomal recessive nonsyndromic hearing impairment locus on chromosome 12q142-q15. *Clin. Genet.*, **76**: 270-5.

WILCOX, E.R., BURTON, Q.L., NAZ, S., RIAZUDDIN, S., SMITH, T. N. M., PLOPLIS, B., BELYANSTEVA, I., BEN-YOUSAF, T., LIBURD, N. A., MORELL, R.J., KACHAR, B., WU, D.K., GRIFFTH, A.J., RIAZUDDIN, S. AND FRIEDMAN, T.B., 2001. Mutations in the gene encoding tight junction Claudin-14 cause autosomal recessive deafness *DFNB29*. *Cell*, **104**: 165-172.

WILLEMS, P. J., 2000. Mechanisms of disease Genetic causes of hearing loss. *New Engl. J. Med.*, **342**: 1101-1109.

YAN, D. AND LIU, X. Z., 2008. Cochlear molecules and hereditary deafness. *Frontiers Biosci.*, **13**: 4972-4983.

YILDIRIM, A. AND YILMAZ, B. M., 2006. An overview of hereditary hearing loss. *J. Oto-Rhino-Laryngol.*, **68**: 57–63.

ZHENG, Q.Y., YAN, D., OUYANG, X.M., DU, L.L., YU, H., CHANG, B., JOHNSON, K.R. AND LIU, X.Z., 2005. Digenic inheritance of deafness caused by mutations in genes encoding cadherin 23 and protocadherin 15 in mice and humans. *Hum. mol. Genet*., **14**: 103–111.

Web resources

(Genetics Home (http//ghrnlmnihgov/).

Hereditary Hearing Loss Home Page (http//hereditaryhearinglossorg).

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