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 communities 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
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 (DFX), 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 Costa 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 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 a 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 (Yildirim 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), DFNB53 (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 AUTOSOMATIC 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.

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(Received 21 May 2012, revised 25 August 2012)