

Genetic deafness in Pakistani population

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The consanguineous marriage pattern has significant implication for increased rate of recessive genetic disorders.¹ High rate of consanguinity in any population along with other factors such as religion, ethnicity, language and geography, usually lead to create genetically isolated groups in which typically confined, well-documented, extended and multigenerational pedigrees with several cases of rare diseases are expected.² The extended pedigrees were readily used by geneticists for their linkage studies and for mapping many monogenic autosomal recessive disorders. In this regard, various isolated populations such as the Pakistani population and certain other communities have played prominent role in identifying the novel mutations in these autosomal recessive genetic disorders.

In Pakistan, there is a strong cultural preference for consanguineous marriage and an associated relatively high prevalence of recessively inherited disorders. There are number of factors that significantly increase the prevalence of genetic disorders in the Indian subcontinent. The huge population of Indian sub-continent including Pakistan, India and Bangladesh also provides an opportunity for studies of genetic disorders like deafness. The study of consanguineous families has led to the identification of many new genes.³ But the population of Pakistan is the goldmine for these studies due to its unique geography and history. In addition, it is a mixture of diverse ethnicities with unique familial and social characteristics.⁴

Deafness (or hearing impairment) is the loss of ability to hear normally, whether permanent loss or fluctuating. Deafness is clinically and genetically heterogeneous and can be caused by environmental as well as genetic factors. It is estimated that the prevalence of profound bilateral hearing loss is 1.6 per 1000 in Pakistan and 70% of hearing loss arises in consanguineous-families.⁵

The genetically determined deafness or hearing impairment can be divided into two categories; syndromic and non-syndromic forms. The syndromic forms include several hundred deafness syndromes, with the underlying genetic defect being found in about 30 of them.⁶ In non-syndromic genetic deafness of pre-lingual onset, autosomal recessive inheritance predominates (80%), but autosomal dominant (20%), X-linked (1%), and mitochondrial (<1%) forms have also been described. In post-lingual, non-syndromic deafness, autosomal recessive inheritance is very rare. The autosomal recessive forms are usually more severe than the other forms and are almost exclusively due to cochlear defects.⁶

Syndromic hearing impairment may account for up to 30% of prelingual deafness, which in most cases is of conductive and mixed type but its relative contribution to all deafness is much smaller, reflecting the occurrence and diagnosis of post lingual hearing loss. Over 400 genetic syndromes that include hearing loss have been described.⁶ Syndromic hearing loss is categorized according to the mode of inheritance. Syndromic hearing loss can have many modes of transmission, including maternal inheritance due to a mitochondrial mutation.

Non-syndromic deafness is a paradigm of genetic heterogeneity. It is estimated that more than 70% of hereditary hearing loss is non-syndromic.⁶ The different gene loci for non-syndromic deafness are designated DFN (for DeaFNess). Loci for genes inherited in autosomal dominant forms are referred to as DFNA, and for genes inherited in an autosomal recessive forms as DFNB, and those for genes inherited in an X-linked forms as DFN.

Our previously reported Pakistani study population is a powerful resource for recessive hearing loss studies because their large, consanguineous family structures

support statistically significant linkage scores. They have already estimated the contributions of several other DFNB genes to recessive, severe-to-profound, congenital or prelingual-onset deafness in Pakistani population.^{7,8} Mutations of RDX (0.3%), MYO6 (1.2%), TRIOBP (1.6%), OTOF (2.3%), MYO15A (3.3%), TMC1 (3.4%), SLC26A4 (4.7%) and GJB2 (6.1%) each account for 0.3-6.1% or recessive deafness (DFNB1, DFNB4, DFNB7/11, DFNB3, DFNB9, DFNB37 and DFNB24) respectively in this Pakistani population.^{7,8} These results reflect the extensive genetic heterogeneity and large genetic load of deafness that is still unaccounted for in this and other populations.

Approximately 129 different gene loci associated with non-syndromic hearing impairment have been identified to date.⁹ Presently 57 gene loci associated with autosomal dominant mode of inheritance, 72 with autosomal recessive mode of inheritance, 7 are X-chromosome linked and 4 mitochondrial have been identified. In total 21 genes have been characterized for autosomal dominant (DFNA), 27 for autosomal recessive (DFNB), and 2 for X-linked (DFN) disorders (Hereditary Hearing Loss Homepage; <http://www.dnlab-ua.ac.be/dnlab/hhh>). These genes encode proteins of diverse functions, including transcription factors, cytoskeletal and extracellular matrix components, and ion channels.

In societies in which most couples are unrelated, genes for recessive disorders usually run in families for many generations without manifesting themselves through the birth of an affected child. By contrast, in communities with a cultural preference for consanguineous marriage, as in Pakistan, when a gene for a recessive disorder is present in kindred, there is likely to be an affected child in at least one branch of the extended family. In turn, the diagnosis of disease in a child serves as a marker of an extended family that is at increased genetic risk. Therefore, in such communities, studies of extended families beginning with the first child with a diagnosis may offer an alternative to population screening for identifying present and future couples at risk for producing affected children.¹⁰

It is estimated that about 10 percent of congenital and genetic disorders worldwide are associated with

customary consanguineous marriage; in most of the Middle East, the proportion is 30 percent, and in Pakistan, it is 40 percent.^{10,11} According to WHO estimates, 278 million people worldwide have a disabling hearing impairment. This could increase to 700 million by 2015 and 900 million by 2025.

Screening to identify carriers, genetic counseling, and prenatal diagnosis can greatly reduce the rate of birth of affected infants and improve the prognosis of affected patients. In Pakistan, first-trimester prenatal diagnosis (by PCR) is not objected to on religious grounds and is acceptable and affordable to most families who are at risk. When the foetus is affected, 89 percent of couples choose to terminate the pregnancy. However, the weak health care infrastructure make it impossible to provide population screening.

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