ARTICLES

The Molecular Basis of Hereditary Deafness in Palestine

By Moien Kanaan

Childhood genetic diseases are a major health burden in the entire Middle East region, as a result of social preference for consanguineous inbred marriage (marriage within a family) and large family size. Consanguineous marriage increases the chance that both members of a couple will carry same genetic variant (referred to as recessive inheritance) present in the family, and transmission by both parents will result in a homozygous state (same variants from both parents) in their children. If this variant is deleterious, the result is severe recessive disease. New genetic technologies now enable us at the Hereditary Research Lab (HRL), Bethlehem University, to elucidate the molecular basis of many such diseases, including hearing loss, and this genetic information is critical for disease prevention. The general aim of HRL is to develop an on-going, integrated clinical and molecular resource that addresses genetic diseases common in the region's Palestinian population. This resource lab currently provides the basis for scientific discovery of new genes, as well as provision of culturally appropriate genetic services to affected families and communities. Creation of such services is particularly important because of their implications for prevention of diseases that pose considerable human, economic, and logistic challenges that can scarcely be met by limited medical resources in Palestine. Critical components of the appropriate genetic service are 1) education of clinical and laboratory genetic specialists; 2) physician outreach, in order to identify families at risk; and 3) improved genetic/molecular analysis of locally relevant disease, through identification of disease genes and delineation of the local mutational spectrum. Our work specifically aims to develop precisely these crucial clinical and molecular capabilities and to create a comprehensive genetic service for the Palestinian population. The clinical and laboratory expertise to be developed, and the locally relevant data that will be generated, will continue to serve the Palestinian population.

There are two main advantages to studying genetic diseases in the highly inbred Palestinian population, and hearing loss has been no exception. Marriage within a family reveals recessive mutations (variants) and increases the prevalence of recessive disease. In addition, genetic mapping to reveal the underlying variants is much easier in consanguineous families. The underlying assumption is that when a recessive disease arises in a consanguineous family, it must be due to a mutation that is identical in both parents, and affected children are expected to be carrying the same variant inherited from both parents.

Severe or profound deafness occurs in approximately 1 in 1,000 children at birth or during early childhood. In some segments of the Palestinian population, this number is higher and almost triple the rate worldwide due to consanguinity (inbreeding); and hearing loss may affect 10 percent of children. There are many social implications of hearing loss, including problems of isolation and loneliness for those who lose their hearing later in life, and comparatively poor educational achievements, especially for those who lose their hearing early in life.[1] Early detection and intervention is crucial for proper communication skills to be formed in congenitally deaf children.

Hearing impairment can result from a variety of injuries or diseases, and can occur both in association with other

> High-throughput genetic research and technology are changing the face of genetic diagnosis and counselling. While in the past, it would take on average one to five years to identify a mutation that leads to deafness, today the genetic basis for deafness can be determined within months in a child or adult with inherited hearing loss. Obstacles and challenges still remain, but the field is changing at a dramatic rate, making gene discovery a much easier and more efficient task than in the past.

Affymetrix Microarray Mapping Platform utilised in gene mapping of recessive hearing loss at the HRL, Bethlehem University.

Bethlehem University's Hereditary Research Lab facility and infrastructure.

symptoms in the form of syndromic deafness, or as an isolated finding, non-syndromic deafness. Hearing loss can be genetic or acquired. It may occur pre-lingually due to inherited mutation or childhood disease, or post-lingually due to inherited mutation, extreme exposure to noise, or infection. Presbyacusis (age-related hearing loss) is even more common.[ii] Despite its high prevalence, little is known about the molecular events that lead to deafness or the genetic mechanisms that assure normal hearing. An understanding of this process would enable early diagnosis of hearing loss and thus provide a means to treat or cure this problem.

Overall, as many as 100 genetic causes may be involved in regulating the hearing process. To date, over 60 mutations that cause non-syndromic deafness have been identified.[iii] Large families with inherited deafness provide a source for isolating the additional genes that are involved in hearing loss. This has recently been demonstrated by a study in the HRL on the genetic basis of non-syndromic deafness in the Palestinian population. Approximately 39 Palestinian-specfic novel mutations (genetic variants) were found in CDH23, MYO7A, MYO15A, OTOF, PJVK, Pendrin/SLC26A4, TECTA, TMHS, and TMPRSS3, PTPRQ, GPSM2, TRIOPB, and OTOA genes. In an HRL study that involved a large cohort of Palestinian families affected by hearing loss, three novel genes (TRIOPB, PTPRQ, and GPSM2) with damaging changes were identified. Other genes, though less prevalent in hearing loss in the overall population, are also amenable to screening. This reflects the genetic heterogeneity of hearing loss.[iv] What is particularly captivating is the variety of genes and proteins they encode, as well as the types of mutations that lead to hereditary hearing loss.

Knowledge regarding the molecular basis of deafness and the biological function of the proteins involved in auditory transduction is in its infancy. The multitude of advances in only the last two years suggests that this field will continue to accelerate rapidly, with tangible results. Today our options for improving hearing in children are restricted to the use of hearing aids and cochlear implants. Understanding the function of genes in the inner ear will lead toward a new generation of treatments and management of audio-vestibular disorders, including sensory hair-cell regeneration and gene therapy.[v],[vi] As an immediate solution, recent advances in the identification of genes involved in deafness offer genetic counselling to affected Palestinian families.

It should be noted here that the HRL collaborative work currently provides genome-related practical know-how as well as computing-intensive tools for the entire academic community of Palestine. It is supporting new biotechnology enterprises in the areas of diagnostics, agriculture, combating genetic diseases, genetic counselling and training. We have identified the exact components of current genomics technology that can be directly transferred and thus be of practical application to medical and public health research in Palestine, as well as enable students, physicians, public health workers, and researchers to obtain up-to-date training in these disciplines on one hand, and help advance research work in Palestine on the other. The HRL reflects our conviction that the genetics of human populations presents both the greatest challenge and the greatest opportunity for genetics in the future. We also believe that the genetics of a people is most appropriately addressed by scientists who live in the same areas as the populations being studied.

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