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Genetic Research in Otosclerosis: A New Frontier in Otology

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Editorial

Otosclerosis is a progressive disease of the otic capsule with adult-onset hearing loss noted commonly in the 2nd to 4th decade of life. Rigid bone of the labyrinth is replaced here by abnormal spongiotic bone with remodelling causing stapes fixation [1]. This results in conductive hearing loss in early stages which can progress onto mixed loss in advanced stages. Hearing loss has a high prevalence and disease burden to our youth society, as it has significant impact on social life. Candidates with far advanced otosclerosis end up with profound hearing loss beyond the range of support offered by conventional hearing amplification devices. The only option left for them then is a cochlear implant [1].

The prevalence of otosclerosis shows ethnic disparities due to environmental and lifestyle factors. It is reported in 1% of Caucasian population, 0.5% of Japanese, South American and in African American population [2]. The Indian subcontinent has no clear estimates of otosclerosis, but it is well known to be much more common in the current clinical scenario with Indian otologists well versed with the art of stapedotomy. Especially in the South Indian population, the incidence is higher due to familial predisposition [2]. Till date the specific genetic constitution which leads to such a higher rate of otosclerosis in South Indians is unknown [2,3]. This has initiated keen interest among experts today, to investigate the genetic basis of Otosclerosis in this ethnically susceptible population.

Otosclerosis is reported to be inherited in autosomal dominant traits with variable penetrance estimated at 80-90% exhibiting a complex disease pattern. Familial history is found to be positive in 50% of such affected individuals [4]. Extensive research has implicated the role of environmental and genetic factors in the development of this disease. The evidence for the association of the genes involved in molecular pathways such as immunological, endocrine, inflammation pathways in bone metabolism has been extensively studied for its role in the disease pathology [2,4].

Traditional effective methods such as linkage analysis and association studies have been used to uncover the genetic aetiology of complex diseases. Linkage analysis uses large families with several affected individuals across generations showing Mendelian segregation of autosomal dominant inheritance to identify chromosome loci [3]. Such analysis has currently helped decipher the enigma of otosclerosis. Till date eight loci OTSC1 OTSC2, OTSC3, OTSC4, OTSC5, OTSC7, OTSC8 and OTSC10 located on chromosome 7q, 6p, 16q, 3q, 6q, 9q, and 1q have been genetically mapped in monogenic forms in different populations, but none of the genes from these 8 loci have been identified till date. The other two known loci OTSC6 and OTSC9 are registered with HUGO, but their chromosomal locations are not yet known [3,4].

Half of the affected individuals with otosclerosis, are found to be sporadic despite the strong genetic role involved. Several association studies have been carried out to determine the genetic contributions to these sporadic forms of otosclerosis [2,5]. Single nucleotide polymorphisms (SNPs) have been genotyped and statistically analysed in the large sets of these cases and controls to determine the susceptibility factors that influence the development of this disease. The SNPs in the TGFb1, RELN, NOG, COL1A1, COL1A2, BMP2 and, BMP4 were extensively studied in the populations of Dutch, Belgium, Tunisia, Germany, British, Campania, Hungarians, UK and now also in India [3]. If a strong genetic association is found in one population, replicating the association in other population is important to measure its significance. But none of these variants is reported to be associated in all the populations, adding complexity to the disease pathology [3].

The high-throughput DNA sequencing technology known as Next-generation sequencing (NGS) permits 'massively parallel' sequencing of entire human genome within a few hours. It has made a tremendous impact on basic and clinical research, in identifying mutations in monogenic disorders, rare diseases and also complex disorders. A recent study on otosclerosis, using NGS technology on European ancestry identified mutations in the gene serpin peptidase inhibitor, clade F (SERPINF1) in four unrelated families [5]. Out of six rare mutations identified, three missense and three 5'UTR variants were present in seven affected individuals in the familial cohort. The SERPINF1 is suggested to play a functional role in bone matrix remodelling. Studies also report mutations in Matrix extracellular phosphoglycoprotein (MEPE) associated with otosclerosis in unrelated individuals. This gene encoder plays a keyrole in the inhibition of bone mineralization, resorption, renal calcification suppression and in serum phosphate regulation [5].

Such exciting results have catapulted "Otogenetics" into becoming a hot-topic for research in premium centres across the world. Recent studies utilizing Next-generation sequencing identified mutations in SERPINF1 and MEPE genes in otosclerosis, shows the potential power of advanced sequencing techniques in identifying mutations in complex disease with variable penetrance and heterogeneity [6]. The onus is now on identifying the causative genes for familial counselling and to devise the best possible hearing preservation methods in the earlier stages of the disease [4-6]. Future horizons open up exciting venues for genetic engineering to overcome this defect. If successful this may pave the way forward to induce modification in the gene causing otosclerosis and thereby prevent this hereditary disease.

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