Genetics and Gene based Therapies: Emerging Horizons in the Management of Hereditary Hearing Disorders in India

Ramakrishnan V[1]

1. Senior Consultant ENT Surgeon, Aster MIMS Kannur, Kerala*

Published on 30th June 2026

Corresponding Author: Dr. Ramakrishnan V
Senior Consultant ENT Surgeon, Aster MIMS Kannur, Kerala.
Email: joshrama@yahoo.com

*See End Note for complete author details

Cite this article as: Ramakrishnan V. Genetics and Gene based Therapies: Emerging Horizons in the Management of Hereditary Hearing Disorders in India. Kerala Journal of ENT and Head & Neck Surgery. 2026 Jun 30;5(1):1–3.

Hearing loss remains a major public health concern in India, with congenital and early onset hearing impairment contributing significantly to long term disability, educational disadvantage and socio-economic burden. A substantial proportion of these cases are hereditary, yet clinical management has traditionally focussed on rehabilitation rather than etiological treatment. Rapid advancement in human genetics and gene based therapies are now poised to transform this landscape, offering Indian otolaryngologists an opportunity to move forward precision driven and potentially curative interventions.[1]

GENETIC BURDEN OF HEREDITARY HEARING LOSS

India's genetic diversity, high population density and prevalence of consanguinity in certain regions contribute to a distinct spectrum of hereditary hearing disorders. The first non-syndromic deafness gene was discovered in 1993 was the Gap Junctions Beta 2 gene (GJB2), the gene for non-syndromic hearing loss.[2] Mutations in GJB2 account for 30%-50% of all cases with non-syndromic hearing loss making it the most frequent cause of hearing loss in infants. GJB2 encodes the gap junction protein, Connexin 26, found in the supporting cells, connective tissue and other cells of cochlea.[8] They help form intercellular gap junction or channels between cells and may play a role in the recycling of potassium ions from the hair cells to stria vascularis. A mutation in the gene GJB2 on one chromosome inherited along with a second mutation, usually a large deletion in the gene GDB6, located on chromosome (13q) will cause hearing loss.[6] Non syndromic autosomal disorders predominates with mutations in genes such as GJB2, OTOF, SLC26A4 and MY015A frequently reported in Indian cohorts.[4] The genetic architecture in familial meniere's include FAM136, DTNA, PRKCB, SEMA3D, DPT, TECTA, OTOG and in sporadic meniere's like GJD3, MY018A, PTPN22, NFKB1, TCR2, CXCL10, NTN4, NOX3, ESRRBCLDN14 has also been extensively studied in detail. Allelic mutations in some genes can cause recessive and dominant hearing loss, mutations in the same gene may cause syndromic or non-syndromic hearing loss, and recessive hearing loss may be caused by a combination of two mutations in different genes for the same functional group.

Syndromic deafness is charaterised by additional manifestations such as retinitis pigmentosa (eg Usher's syndrome), euthyroid goiter and inner ear malformations (pendred syndrome), craniofacial dysmorphia (Treacher collin's syndrome), marfanoid body habitus (stickler syndrome), renal abnormalities

(Alport's syndrome), or the presence of long QT interval (Jervall and Lange-Nielsen syndrome). Pendred syndrome accounts for 3% of all congenital hearing loss and mutations in SLC26A4 including cases of non-syndromic congenital hearing loss.[7] SLC 26A4 encodes a chloride-iodide transporter and is critical for maintaining endolymphatic ion homeostasis which is essential for inner ear function.

Genetic studies have demonstrated the presence of six loci (OTSC1.OTSC2, OTSC3, OTSC4, OTSC5 and OTSC7) located on chromosomes 15q,7q,16q,3q and 6q in otoslcerosis patients. Otitis media has been linked to several regions on chromosomes 3p25,10q22,10q26,17q12 and 19q13.

Autosomal dominant sensorineural hearing loss is often post lingual and progressive, whereas recessive sensorineural hearing loss is pre lingual as a rule. Inspite of this, genetic evaluation is still underutilised in routine ENT practice due to limited access, cost constraints and limited awareness.[3]

The increasing availability of next generation sequencing platforms in india, coupled with cost effectiveness has made genetic diagnosis more feasible than ever before. Integration of genetic testing into early hearing detection and intervention programmes can enable accurate diagnosis, prognosis and family counselling thereby reducing diagnostic uncertainty and inappropriate interventions.[5]

Gene based therapeutic strategies: Clinical relevance in India

Gene based therapies aim to address hearing loss at its molecular origin. Several approaches are particularly relevant to the Indian clinical setting:

Gene replacement therapy – using viral vectors to deliver functional gene copies to cochlear cells, has demonstrated promising early clinical results, particularly in OTOF-related auditory neuropathy spectrum disorder. Such conditions are not uncommon in Indian practice and are often misdiagnosed or detected late. Successful translation of this therapy could significantly alter outcomes in affected children, especially when combined with early newborn hearing screening.

Genome editing technologies including CRISPR -based systems, offer future potential for correcting pathogenic mutations at the DNA level. Although currently in the experimental phase, these approaches may be particularly relevant for dominant and complex genetic mutations encountered in Indian families with multi-generational hearing loss.

RNA based therapies provide additional options by modulating gene expression without permanent genmomic alteration. Examination of stem cell viability and plasticity in the inner ear has provided us with the vehicle for cochlear cell replacement and repair. These strategies may offer safer and more adaptable interventions suitable for broader clinical applications in the future.

Challenges in translations to clinical practice

While scientific progress is rapid several challenges must be addressed before gene based therapies can be widely adopted in India. These include the need for infrastructure for safe inner ear drug delivery, trained multidisciplinary delivery teams, long term safety monitoring and robust ethical frameworks, particularly in pediatric populations.

Cost and accessibility remain major concerns in a resource limited healthcare system. However, India's growing biotechnology sector, expanding genomic laboratories and experience with large scale public health programmes present a unique opportunity to develop cost-effective and indigenous solutions.

Role of the Indian Otolaryngologist

The emergence of gene base therapies necessitates a shift in the role of the otolaryngologist -from a rehabilitation specialist to a genetically informed clinician. Familiarity with indications for genetic testing, interpretation of results, and timely referral for emerging therapies will become essential components of ENT training and practice. Collaboration with geneticists, pediatricians, audiologists and public health professionals will be critical to ensure optimal patient outcomes.

Future directions

For India, the greatest impact of genetic and gene based therapies lies in early identification and intervention. Strengthening newborn hearing screening programmes, integrating genetic counselling into ENT services and establishing national registries for hereditary hearing

loss can pave the way for future clinical trials and targerted therapies.

In conclusion, personalized genomic medicine, genetic testing and gene based therapies are redefining the management of hereditary hearing disorders. While widespread clinical application may still be evolving, the trajectory is unmistakable. For Indian otolaryngology, embracing this paradigm shift is not merely an academic exercise but a public health imperative-one that holds the promise of transforming the lives of millions affected by hereditary hearing loss.

END NOTE

Author information

Dr Ramakrishnan V, Senior Consultant,
ENT Surgeon, Aster MIMS Kannur, Kerala.

Financial Support: Nil

Conflict of Interest: None declared.

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