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Identification of Novel *TMC1* and *TECTA* Mutations in the Pakistani Population: Insights into the Genetic Basis of Hearing Impairment

Saba Zafar[1] , Rehan Sadiq Shaikh[2]

[1] Department of Biochemistry and Biotechnology, The Women University, Multan, Pakistan
[2] Center for Applied Molecular Biology (CAMB), University of the Punjab, Lahore, Pakistan

Abstract

Hearing impairment is the 4th most prominent reason for disability worldwide, and according to the WHO report of 2018, the highest prevalence of HI is observed in Europe (8.36%), followed by South Asia (7.37%). The occurrence of significant reciprocal hearing impairment is around 1.6 out of 1000 among individuals of the Pakistani population. This study provides insight into the genetic basis of the hearing loss in the Population of Pakistan. identified by linkage mapping or Exome Sequencing (ES). We found novel mutations in two families, NM_138691.3: c.1259G>A [p. (Cys420Tyr)] and NM_005422.4: c.1247_1248delGG [p. (Gly416Aspfs*24)], in *TMC1* and *TECTA* genes, respectively. Pathogenicity analysis for these novel variants was performed using various insilico tools, which established the deleterious impacts of these variants on the encoded proteins. Variants identified in *TECTA, TMC1* were classified as pathogenic or likely pathogenic. The Clustal W alignment online tool showed the high conservation of the altered amino acid residues by aligning sequences from different species. Further, the effects of alteration in protein were predicted by the 3D modeling and it showed the visible change in structures of proteins for both identified variants. This study would help to expand knowledge and understanding of the genetic spectrum of hearing loss genes in the Pakistani population. Advances in molecular genetics will play a crucial role in the diagnosis and genetic counseling of families affected by hearing loss, ultimately paving the way for progress in personalized medicine and gene therapy.

Key Words: *Hearing loss, TMC1, TECTA, Genetic spectrum , Non Syndromic hearing loss*