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Abstract Title:- Comprehensive gene screening among individuals with non-syndromic hearing loss from Odisha population

Presenting author name :- Ruchika Raghuvanshi

Presenting author institute:- Institute of Life Sciences, Bhubaneswar; Regional Centre for Biotechnology, Faridabad, India

Co-authors name:- PV Ramchander, Khirod Chandra Panda

Co-authors institute:-Institute of Life Sciences, Bhubaneswar, India, ENT Unit, Capital Hospital, Bhubaneswar; Present address - SCB Medical College & Hospital, Cuttack, India

Aims:-Hereditary non-syndromic hearing loss (NSHL) is characterized by extreme genetic heterogeneity, ethnic variability and multiple inheritance patterns. Our aim was to investigate genetic variants causing NSHL in Odisha population.

Methods:- We employed candidate gene sequencing approach followed by next generation sequencing (NGS) analysis in NSHL cases. Owing to the importance of gap and tight junctions in inner ear fluid homoeostasis, protein coding regions of GJB2, GJB3, GJB4, CLDN9 and CLDN14 were screened for disease causing variants in cases (n=200) and ethnically-matched control individuals (n=200) using Sanger sequencing. Next, six unrelated probands of unsolved etiology and positive family history were further selected for targeted or whole exome sequencing analysis including affected and unaffected family members (n=17). Potential pathogenic variants were checked for their co-segregation with hearing loss in the respective families by PCR-RFLP and Sanger sequencing methods.

Results:- We found that GJB2 pathogenic variations specifically, stop-gained variants c.71G>A (p.W24X) and c.231G>A (p.W77X) are predominant in this cohort. Novel missense rare variants were identified in the other gene candidates (GJB3/GJB4/CLDN14) and were mostly heterozygotes occurring alone or with GJB2 biallelic variants in the cases. Family studies showed autosomal recessive inheritance and the prominent compound heterozygosity in this cohort. The cause in around 88% of the cases was still obscure. Subsequent NGS analysis in unsolved familial cases revealed 04 novel pathogenic variants in 3 genes - MYO6, MYO7A and MARVELD2. These genetic variants when screened in our case-control cohort of 400 individuals revealed their rare nature in the population attributing to genetic heterogeneity of hearing loss in this population.

Conclusions:- Overall, this study expands the spectrum of NSHL variants in Indian population. The MYO6 variant marks the first association of MYO6 gene with hearing loss in an Indian population. The study also emphasizes on the significance of NGS screening in families affected with hearing loss in delineating the genetic factors involved in Indian population. The findings might aid in pre-natal diagnosis and genetic counselling in the affected families.

Keywords:- Hearing loss, candidate gene, exome sequencing, novel variant