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Spectrum of MYO15A mutations and report of a novel splicing mutation in an iranian family with sensorineural hearing loss

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Introduction: Non-syndromic sensorineural hearing loss (SNHL) is the most common sensorineural disorder accounts for ~70% of hereditary hearing loss which 80% of cases have an autosomal recessive mode of inheritance (ARNSHL).To date, Over 60 genes and more than 100 genetic loci have been identified for ARNSHL (Hereditary Hearing Loss Homepage, http://hereditaryhearingloss.org). The genes GJB2, SLC26A4, MYO15A, OTOF, and CDH23 are most commonly implicated in ARNSHL. MYO15A Mutations (NM_016239) have been reported to cause sensorineural hearing loss in human [autosomal recessive 3 (DFNB3)]. The DFNB3 locus (OMIM-600316) was first identified in an isolated village in Indonesia where 2% of their population had affected by hearing loss Then, another study identified a causative role for MYO15A gene mutation in DFNB3.MYO15A have 66 exons spanning 71 kb of DNA on chromosome 17p11.2]. The MYO15A mRNA transcript encodes a 3530 amino acid protein (myosin XVa),which has MyTh4 (Myosin-Tail like Homology region 4) domains, FERM (4.1 protein, Ezrin, Radixin, and Moesin) motifs, a SH3 (Src Homology 3) domain, and the PDZ domain. Myosin-XVa is a critical protein for tip localization of whirlin and differential elongation of hair-cell stereocilia and organization of actin within the hair cells of cochlea so Myosin-XVa is an important element in normal auditory function. There are several linkage analysis studies about mutations of MYO15A causing ARNSHL in consanguineous families from specific countries, such as Pakistan, Turkey, and Iran. Mutations of MYO15A at the DFNB3 locus are the second cause of autosomal recessive non syndromic deafness in Iranian population. In present study, we reported a novel MYO15A mutation identified by clinical exome sequencing in a consanguineous Iranian family with ARNSHL. To the best of our knowledge, this mutation has not been reported in any data base.

Materials and Methods: A 22 years old female with hearing loss was referred to Medical Genetic Department, Urmia Medical University, for detection of any possible hereditary hearing loss mutation. Parents were consanguineous with F=1/16 (first cousin) and clinical examination exclude dysmorphic features. Audiometric records were compatible with sensorineural hearing loss, so non-syndromic sensorineural hearing loss was confirmed. Molecular analysis was performed after obtaining informed consent. Sanger sequencing for the common deafness genes, that is, GJB2 and GJB6, was negative. Clinical exome sequencing was performed on a single proband case. After preliminary detection of mutation by Clinical exome sequencing, PCR amplification and Sanger sequencing were performed to verify that the identified mutation co-segregate with the phenotype in the studied family.

Results: A novel homozygous mutation c.9611_9612+8del (p.Leu3204Cysfs*17) found at exon 58 of MYO15A in a consanguineous Iranian family with a case of non-syndromic sensorineural hearing loss. The new reading frame ends in a stop codon 16 positions downstream. The deletion is in close proximity to the highly conserved donor splice site of exon 58. This mutation has been confirmed by Sanger sequencing. It is classified as likely pathogenic (class2) according to the recommendations of ACMG. This novel mutation is predicted to disrupt the function of the myosin XVa protein, which is integral to the mechanosensory and neurosensory activity of hair cells in the inner ear. The alignment of MYO15A from different species of human, chimpanzee, monkey and cattle was analyzed. The result proved that this region was conservative among multiple species which highly suggesting that these residues are important for the proper protein function.

Biography

Isa Abdi Rad received his M.D. degree from Tehran University of Medical Sciences in 1991 and his Ph.D. degree in Medical Genetics and also Fellowship in Neurogenetics from University of Nottingham, England in 2002. Prof. Isa Abdi Rad is the member of British Clinical Genetics Society, American Society of Human Genetics, and Iranian Neurogenetics Society. Currently, he is Professor of Neurogenetics and head of Medical Genetics Department of Motahari Teaching Hospital, Urmia University of Medical Sciences, Iran. His primary research interests are in the field of neurogenetics and dysmorphic disorders.

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