A Novel Mutation in GPR98 gene detected by Next Generation Sequencing Causes Hearing Loss in a Palestinian Family

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Abstract

Inherited hearing loss is a genetically heterogeneous disease. Screening patients to detect genes and mutations represents a major challenge. Next generation sequencing is used to overcome this challenge. The primary purpose of this study is to determine the causative gene and mutation in a Palestinian family with congenital recessively inherited hearing loss in three siblings.

The proband was screened for all know mutations causing hearing loss among Palestinian populations. Then, her DNA was subjected to massively parallel sequencing of targeted genomic capture of all suspected hearing loss genes and loci. The data were filtered and analyzed and the mutation was validated via Sanger sequencing and we fully checked its co-segregation with the disease in the affected family. The mutation was further confirmed by testing 100 normal and 263 hearing loss Palestinian controls and functionally validated to determine the effect of the mutation on mRNA level.

We identified a novel exonic splicing mutation in GPR98 gene. It causes the transition of the last nucleotide of exon 49 from G (Guanine) to A (Alanine) at chr5: 90024750. The novel mutation is private to the tested family and it was not detected in tested controls. This mutation leads to abnormal splicing of exon 49. We predicted that it would lead to translation of truncated GPR98 message with a deletion of highly conserved EPTP domain in addition to partial deletion of EAR (3, 4, and 5) repeats.

GPR98 gene is involved in Usher syndrome type 2. Therefore, it is possible that congenital hearing loss in our family is due to Usher syndrome and may develop Retinitis Pigmentosa later in their life. However, symptoms of Retinitis Pigmentosa are still absent in the two elder adolescent sisters and it is likely that this is nonsyndromic condition.

Keywords: Hearing loss, next generation sequencing, heterogeneous, consanguineous, Usher syndrome type 2, Gpr98 gene.