Mid-frequency DFNA8/12 hearing loss caused by a synonymous TECTA mutation that affects an exonic splice enhancer.

Abstract:

Autosomal dominant hearing loss is highly heterogeneous. Hearing impairment mainly involves the mid-frequencies (500-2000 Hz) in only a low percentage of the cases. In a Dutch family with autosomal dominant mid-frequency/flat hearing loss, genome-wide SNP analysis combined with fine mapping using microsatellite markers mapped the defect to the DFNA8/12 locus, with a maximum two-point LOD score of 3.52. All exons and intron-exon boundaries of the TECTA gene, of which mutations are causative for DFNA8/12, were sequenced. Only one heterozygous synonymous change in exon 16 (c.5331G>A; p.L1777L) was found to segregate with the hearing loss. This change was predicted to cause the loss of an exonic splice enhancer (ESE). RT-PCR using primers flanking exon 16 revealed, besides the expected PCR product from the wild-type allele, a smaller fragment only in the affected individual, representing part of an aberrant TECTA transcript lacking exon 16. The aberrant splicing is predicted to result in a deletion of 37 amino acids (p.S1758Y/G1759_N1795del) in alpha-tectorin. Subsequently, the same mutation was detected in two out of 36 individuals with a comparable phenotype. Owing to the position of the protein deletion just N-terminal of the zona pellucida (ZP) domain of alpha-tectorin, it is likely
that the deletion of 37 amino acids may affect the proteolytic processing, structure and/or function of this domain, which results in a clinical phenotype comparable to that of missense mutations in the ZP domain. In addition, this is the first report of a synonymous mutation that affects an ESE and causes hereditary hearing loss.