



Autosomal Recessive Deafness 9

Alternative Names

DFNB9
Neurosensory Nonsyndromic Recessive
Deafness 9
NSRD9
Auditory Neuropathy, Autosomal Recessive 1
AUNB1
Auditory Neuropathy, Nonsyndromic Recessive
NSRAN

WHO International Classification of Diseases

Diseases of the ear and mastoid process

OMIM Number

601071

Mode of Inheritance

Autosomal recessive

Gene Map Locus

2p23-p22

Description

Deafness is the most predominant hereditary sensorineural disease in humans. One in 1000 newborn children is affected by deafness. Seventy percent of the cases of congenital deafness are nonsyndromic. The fraction of hereditary forms of nonsyndromic prelingual deafness is estimated to be ~60% in developed countries. This proportion is expected to be lower in developing countries due to the higher frequency of environmental causes, bacterial and viral infections or ototoxic drugs.

Non-syndromal sensorineural hearing impairment in humans is genetically heterogeneous showing autosomal recessive, autosomal dominant, X-linked or mitochondrial modes of transmission. Autosomal recessive inheritance accounts for the majority (about 80%) of cases especially in countries in which populations are characterized by a high level of consanguinity. These recessive forms are essentially monogenic sensorineural diseases

and are estimated to involve several dozen genes. They are generally more severe than the autosomal dominant forms.

Molecular Genetics

DFNB forms have been predicted to be monogenic diseases that are genetically highly heterogeneous. Recessive nonsyndromic deafness type 9 (DFNB9) is caused by mutations in the otoferlin (OTOF) gene.

Epidemiology in the Arab World

Lebanon

Chaib et al. (1996) reported a Sunnite consanguineous family living in an isolated village of Northern Lebanon with autosomal recessive sensorineural nonsyndromic hearing loss. For affected children, their parents noted deafness at birth or before the age of 2 years. None of the children had balance problems, and there was no evidence for an acquired risk factor predisposing to hearing loss. Audiometry showed no response at 100 dB for frequencies superior to 1000 Hz in all affected subjects. In affected children, no auditory brainstem response was observed up to 100 dB. In the parents, who were obligate carrier heterozygotes, audiometric tests were normal. Chaib et al. (1996) demonstrated linkage of an autosomal form of neurosensory deafness to markers on 2p23-p22. A maximum lod score of 8.03 was detected with a new polymorphic marker, D2S2144. Observed recombinants and homozygosity mapping defined a maximum interval of 2 cM for this gene, which lies between D2S2303 and D2S174. In 1999, Yasunaga et al. used a candidate gene approach to identify the otoferlin (OTOF) human gene as responsible for the autosomal recessive nonsyndromic prelingual deafness (DFNB9) in the family of Chaib et al. (1996). The 10 affected members of the family, as well as the 11 affected members of the three other families,



suffered from a prelingual severe to profound form of sensorineural deafness. The results of the segregation analysis performed in another affected Lebanese family, combined with mapping data previously obtained in family of Chaib et al. (1996), permitted the refinement of the DFNB9 to a ~1cM interval between D2S158 and D2S174. Yasunaga et al. (1999) assigned two genes belonging to different transcription units to this interval. However, these two genes were not considered as candidate genes for deafness due to the putative functions of their encoded proteins. ESTs in the candidate DNA interval were submitted to rounds of 5' RACE-PCR and the deduced amino acids were compared with clones isolated from 2 subtracted mouse cochlear cDNA libraries. In all affected members of the four unrelated Lebanese families they analyzed, Yasunaga et al. (1999) identified a homozygous T-A transversion at position 2416 in exon 18 of the OTOF gene, causing a tyr-to-stop substitution at

codon 730. The mutation was not identified in 106 unrelated, unaffected individuals living in Lebanon.

References

- Chaib H, Place C, Salem N, Chardenoux S, Vincent C, Weissenbach J, El-Zir E, Loiselet J, Petit C. A gene responsible for a sensorineural nonsyndromic recessive deafness maps to chromosome 2p22-23. *Hum Mol Genet.* 1996; 5(1):155-8.
- Yasunaga S, Grati M, Cohen-Salmon M, El-Amraoui A, Mustapha M, Salem N, El-Zir E, Loiselet J, Petit C. A mutation in OTOF, encoding otoferlin, a FER-1-like protein, causes DFNB9, a nonsyndromic form of deafness. *Nat Genet.* 1999; 21(4):363-9.

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