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Despite a lack of otoacoustic emission, word recognition is not seriously influenced in a TECTA DFNA8/12 family☆

Reinhard Ramsebner [a], Martin Koenighofer [a], Thomas Parzefall [a], Trevor Lucas [b], Christian Schoefer [b], Klemens Frei [a,*]

[a] Department of Otorhinolaryngology, Medical University of Vienna, Vienna, Austria
[b] Center of Anatomy and Cell Biology, Medical University of Vienna, Vienna, Austria

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ABSTRACT

Objectives: Similar to other zona pellucida mutations in the alpha-tectorin (*TECTA*) gene, the p.Y1870C alteration in DFNA8/12 causes prelingual, nonsyndromic, autosomal dominant hearing loss. Here we investigated the effect of p.Y1870C on reverse transduction by audiometric studies in the family.
Methods: Pure tone audiometry, brainstem evoked response audiometry, the Freiburger test for speech understanding and transient evoked and distortion product otoacoustic emissions were assessed in three available affected members bearing p.Y1870C.
Results: Pure tone audiometry showed U-shaped curves with moderate to severe degrees of hearing impairment confirmed by brainstem evoked response audiometry. Transient evoked and distortion product otoacoustic emissions were completely absent in all affected family members whereas word recognition scores were up to 95%.
Conclusions: Although the missense p.Y1870C *TECTA* mutation leads to complete failure of the cochlear amplifier in humans, very high speech perception scores can be achieved with appropriate therapy.

1. Introduction

In the cochlea, the organ of *Corti* is the essential anatomical structure responsible for hearing. This auditory sensory epithelium positioned on the basilar membrane and covered by the tectorial membrane, is an assembly of connecting reticular lamina, supporting cells and stimulatory hair cells [1]. The predominantly afferent innervated inner hair cells (IHC) take the role of a sensory receptor whereas predominantly efferent innervated outer hair cells (OHC) play an important role in the cochlear amplifier [2]. The longest row of stereocilia from the OHC is embedded in the underside of the tectorial membrane [3]. OHC's influence the excitability of IHC by modifying the interaction between the tectorial membrane and the reticular lamina system [4]. Depending on the frequency and sound pressure level, this highly organized sensory structure is able to amplify optimal incoming mechanical waves by up to 40 decibells in a process known as reverse transduction [5]. A functioning cochlear amplifier is detected clinically by the presence of distortion product (DP) otoacoustic emissions (OAE).

In mammals the tectorial membrane is an extracellular matrix structure composed of various types of collagen and the glycoproteins alpha-tectorin (*TECTA*), beta-tectorin and otogelin [1]. The *TECTA* gene, encoding the glycoprotein alpha-tectorin, is transcribed from 23 exons and contains a c-terminal zona pellucida (ZP) domain responsible for intraprotein interactions [6]. *TECTA* mutations in DFNA8/12 families have been described with prelingual and postlingual hearing impairment [7,8]. Phenotype hearing impairment levels [9] are from mild to severe (mild, 20–40 decibell [dB]; moderate, 41–70 dB; severe, 71–95 dB; profound, >95 dB) in different frequency ranges [6,10].

A number of mutations in the *TECTA* ZP domain have been identified worldwide that cause mid-frequency hearing loss that may be pre or postlingual and have variable progression (stable or progressive) [8,10–14]. Alterations occur in exons 16, 17, 18 and 20, have different genetic origins [13–16] and cause mild to profound hearing impairment (21–100 dB) at different frequency ranges. All these published data suggest a variable relationship between genotype and phenotype of ZP mutations.

A dominant *TECTA* ZP mutation p.Y1870C causing autosomal dominant, prelingual, non-syndromic hearing loss (NSHL) in an

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* Corresponding author at: Department of Otorhinolaryngology, Medical University of Vienna, AKH-8J, Währinger Gürtel 18-20, 1090 Vienna, Austria. Tel.: +43 1 40400-3361; fax: +43 1 40400 6452.
E-mail address: klemens.frei@meduniwien.ac.at (K. Frei).

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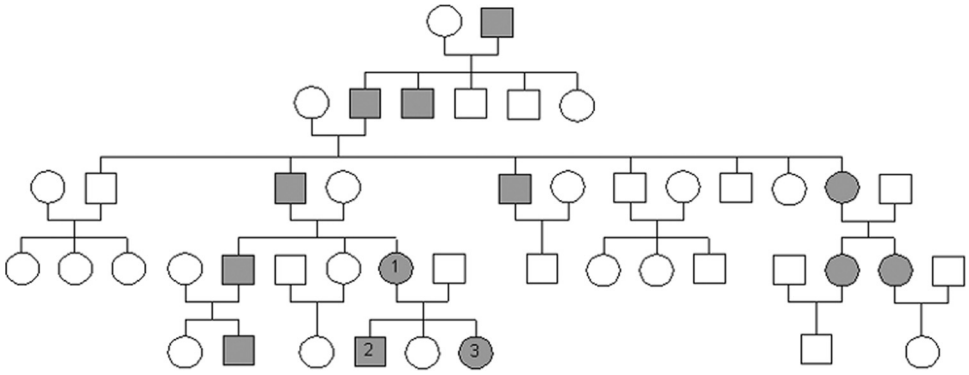

Fig. 1. Pedigree of the Austrian family bearing the autosomal dominant p.Y1870C *TECTA* alteration showing individuals with U-shaped hearing impairment (shaded). The 47-year old mother, 25-year old son and 21-year old daughter (numbered 1–3) were examined in the study.

Austrian Caucasian family with impaired mid-frequency thresholds, has been extensively studied [14]. p.Y1870C is the only *TECTA* mutation that has been identified in the Austrian hearing impaired population, whereas gene alterations as a cause for hearing impairment are as common in Austria as in other European countries. p.Y1870C mutated *TECTA* is not secreted but retained in cytoplasmic vesicles [17]. Transgenic $TECTA^{Y1870C/+}$ mice have normal hair bundle structure and normal mechanotransduction in OHC, but a disrupted tectorial membrane matrix structure, mild loss in hearing sensitivity measured by DP-OAE and a moderate effect on mechanical tuning [18].

Recently, some members of a Spanish family carrying a p.C1837G *TECTA* ZP mutation were identified that show reduced OAE thresholds [11]. In this study we report for the first time, a complete loss of DP-OAE in all affected members of a family bearing the p.Y1870C mutation. These data indicate that p.Y1870C

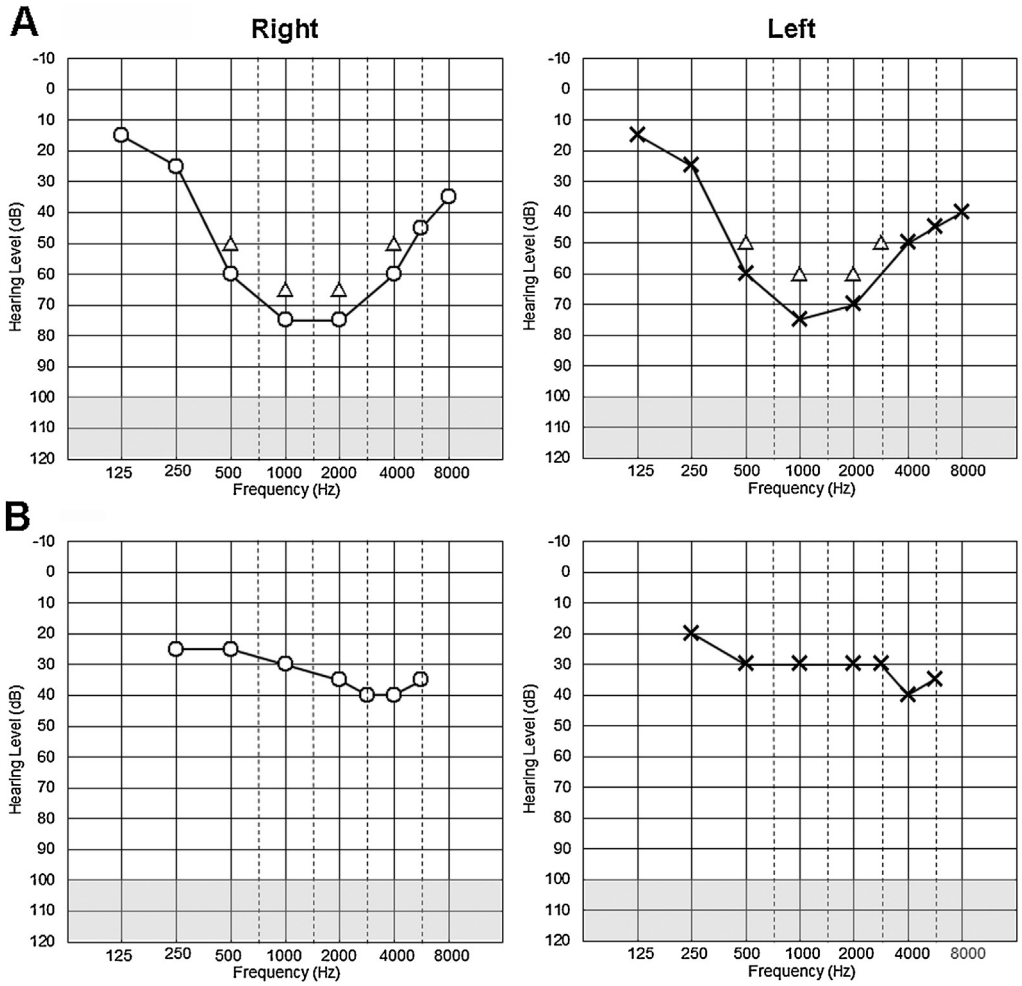

Fig. 2. Unaided, masked pure tone audiograms in dB hearing loss with air conduction, right (○) and left (×) sides and bone conduction (Δ) on each ear separately shown (A) from the mother with mid frequency severe hearing impairment corrected to a mild form (B) with the use of hearing aids.