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Identification of a novel splice site variant of *OTOF* in the Korean nonsyndromic hearing loss population with low prevalence of the *OTOF* mutations

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ABSTRACT

Purpose: (1) To describe the frequency of the *OTOF* mutations among Korean ARNSHL (autosomal recessive nonsyndromic hearing loss) populations; (2) to report the vertical transmission of DFNB9 in a family, where two related DFNB9 patients in the family manifested a different audiological phenotype.
Method: We analyzed the prevalence of *OTOF* mutations among 71 Korean sporadic or possible ARNSHL pediatric patients, as well as among AN/AD (auditory neuropathy/auditory dys-synchrony) patients by direct PCR (polymerase chain reaction) sequencing or targeted resequencing of known deafness genes.
Results: The AN/AD phenotype which was characterized by preservation of OAE (otoacoustic emission) was present in 5 (7%) of 71 probands, and the prevalence of *OTOF* mutations was calculated to be 20% (1/5) and 1.4% (1/71) among AN/AD patients and total sporadic/ARNSHL patients, respectively. *PJVK* mutations did not account for Non-DFNB9 AN/AD patients. To our interest, the only proband (SB4-11) with two *OTOF* mutant alleles in our cohort had deaf parents, who also turned out to be DFNB9. We identified a novel splice site variant of OTOF from the mother (SB4-13) of SB4-11. This was the first observation of vertical transmission of DFNB9 phenotype from parents to son in this population where the prevalence of *OTOF* is very low and consanguineous marriage is not allowed. Another DFNB9 patient (SB4-12), the father of SB4-11, carried a homozygous p.Y374X mutation that affected only the long isoform of *OTOF* and did not manifest AN/AD.
Conclusion: The *OTOF* mutations do not contribute significantly to Korean ARNSHL and AN/AD unlike in Japan and Taiwan. This low prevalence mandates a search for other etiologies. Our observation of the discordant audiologic phenotype within the same DFNB9 family is more likely due to the loss of OAE over time rather than a genotype–phenotype correlation.

1. Introduction

Auditory neuropathy/dys-synchrony (AN/AD) is a sensorineural hearing disorder characterized by the presence of otoacoustic emissions (OAE) and severe abnormality of auditory pathways in audiologic tests, which reveal dysfunctional neural conduction of auditory pathway despite intact outer hair cell function [1,2]. The etiology of AN/AD can be classified into genetic, infectious, and neonatal/prenatal risk factors [3–6]. Pre-lingual genetic nonsyndromic AN/AD has been associated with mutations in the *OTOF*, *PJVK*, *DIAPH3*, and *GJB2* genes [7–10].

OTOF (OMIM: 603681), initially known as a causative gene for DFNB9 [7], was the first reported gene responsible for pre-lingual nonsyndromic genetic AN/AD [11,12]. Unlike unpredictable results after cochlear implantation for some AN/AD patients, *OTOF*-related AN/AD has been successfully rehabilitated by cochlear implantation [13], underlining the importance of molecular genetic diagnosis of these AN/AD patients.

The prevalence of *OTOF* mutations in AN/AD and autosomal recessive nonsyndromic recessive hearing loss (ARNSRHL) patients significantly varies depending upon ethnicities. The

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OTOF mutations are responsible for 2–3% nonsyndromic hearing losses in Western and some Middle Eastern populations [14–16]. As for East Asian populations, epidemiological studies with only preferential or exclusive recruitment of AN/AD patients have been conducted. These studies reported a prevalence of 5.2% and 5.5% of *OTOF* mutations in Korean and Chinese AN/AD populations, respectively, without any predominant founder *OTOF* mutations [17,18]. In contrast, prevalence of 23% and 56.5% of *OTOF* mutations was reported in Taiwanese and Japanese AN/AD populations, respectively, with their own predominant founder mutant alleles for *OTOF*, p.E1700Q and p.R1939Q [19,20]. However, not all DFNB9 patients express AN/AD phenotypes [12,21]. DFNB9 patients without AN/AD phenotype are likely to exhibit a loss of OAE at an early stage as previously described [12]. Alternatively, the mutations in certain residues or isoforms of *OTOF* might have a different or weak capability of preserving OAE, and as a result of a genotype-phenotype correlation, it is manifested as ARNSHL. There are 'long' and 'short' isoforms of *OTOF* formed because of different transcription start sites [22]. To date, among those carrying bi-allelic mutations specific to the long isoform of *OTOF*, all except one patient was reported to exhibit ARNSHL, without AN/AD [20]. Therefore, it may be worthwhile to check ARNSHL patients, especially in populations with currently very low prevalence of *OTOF* from definite AN/AD patients. However, there has been no estimate of DFNB9 deafness prevalence among ARNSHL patients in East Asian populations.

With this background, we tried to evaluate the prevalence of *OTOF* mutations among sporadic/autosomal recessive nonsyndromic hearing loss patients, as well as AN/AD patients in a Korean population. During this study, we also observed a vertical transmission of DFNB9 deafness from father to son due to recessive mutations of *OTOF*.

2. Materials and methods

2.1. Ethical considerations

The Institutional Review Boards (IRBs) at the Seoul National University Hospital (SNUH) (IRBY-H-0905-041-281) and Seoul National University Bundang Hospital (SNUBH) (IRB-B-1007-105-402) have approved this study. A written informed consent from all the participants was obtained in this study. In the case of minors, the written informed consent was obtained from their parents or guardians.

2.2. Study participants

Clinical phenotype evaluations included medical and developmental history interviews, physical examinations, pure tone audiometry and imaging studies (temporal bone computed tomography and/or magnetic resonance imaging), whenever possible as previously described [23]. An initial cohort of 151 pediatric patients (under 15 years of age) with varying degrees of hearing loss was studied at the otolaryngology clinics of two institutes, SNUH and SNUBH, from May 2010 through May 2012. Thirty-one probands with syndromic features were excluded from this study. Among the remaining 118 probands, forty probands showed a definite autosomal dominant inheritance pattern and 7 other probands were associated with either X-linked inheritance or mitochondrial mutations (Fig. 1), leaving only 71 probands. The 71 patients exhibited deafness either sporadically or in autosomal recessive inheritance pattern, or in a combined pattern where a recessive inheritance cannot be excluded. *OTOF* was screened in these 71 patients either by Sanger sequencing or by Panel sequencing.

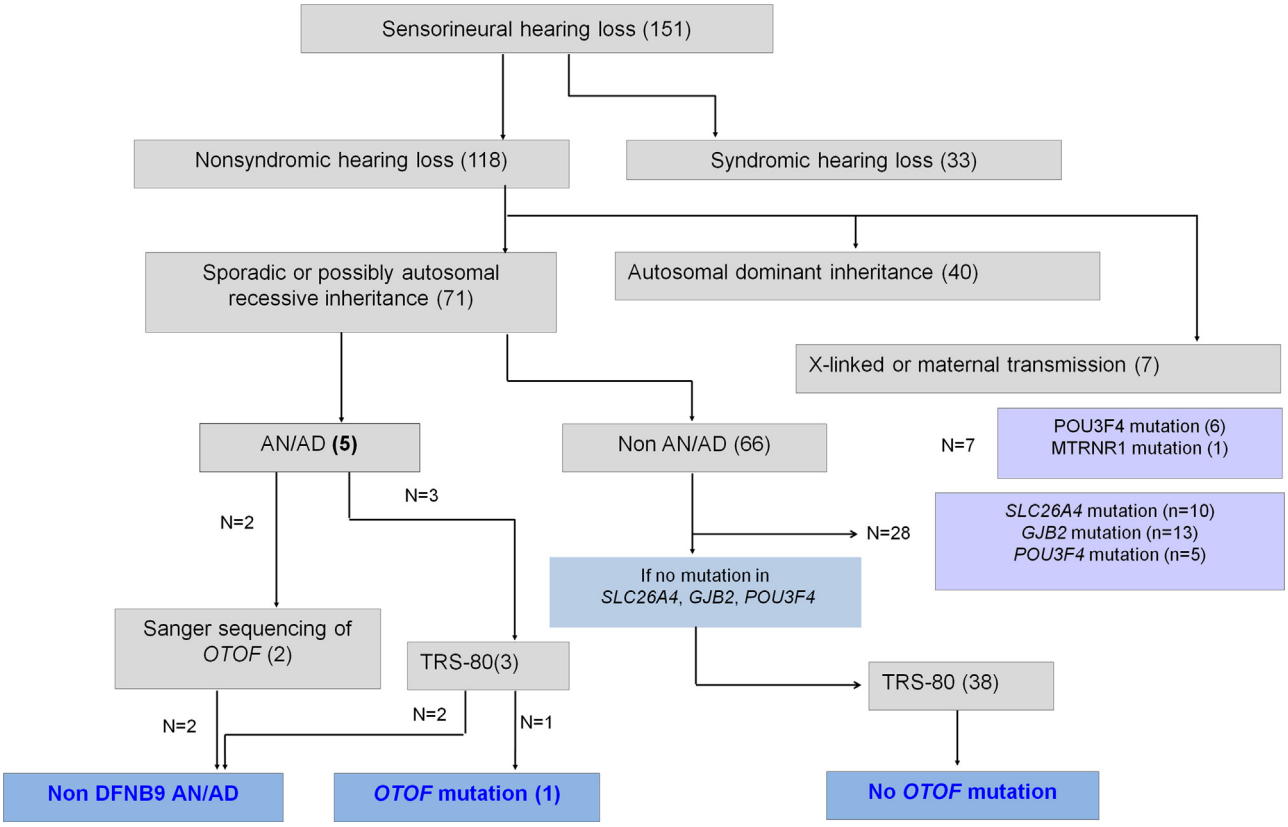

Fig. 1. Flow of analysis for probands with sensorineural hearing loss. Among 151 probands, 71 patients segregate deafness either in sporadically or in autosomal recessive inheritance pattern, and were screened to detect a mutation in the *OTOF* gene by Sanger sequencing or Panel sequencing. Among the 5 probands with AN/AD, 1 patient is confirmed to have mutation in *OTOF* gene. AN/AD indicates auditory neuropathy/auditory dys-synchrony.