Discrete vestibular phenotypes in DFNA9 families with *COCH* variants

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ABSTRACT

Mutations of *COCH* can cause hearing loss and less frequently vestibular symptoms. However, vestibular phenotypes, especially in terms of the location of specific variants are not well documented yet. In this study, a retrospective and prospective cohort survey was performed in two tertiary referral hospitals to demonstrate vestibular phenotypes of DFNA9 subjects with a focus on the relationship with the location of *COCH* mutations. Two DFNA9 subjects were recruited from the previously collected cohort, each segregating p.G38D and p.C162Y of the *COCH* gene. Another two DFNA9 families were newly detected by targeted resequencing of known 129 deafness genes (TRS-129). These two families segregated the p.G38D variant of the *COCH* gene as the causative mutation, making p.G38D the most frequent *COCH* mutation in Koreans. Regarding the detailed clinical phenotype of the four DFNA9 families with documented vestibular phenotypes, we were able to classify them into two groups: one (p.C162Y variant) with a Meniere's disease (MD)-like phenotype and the other three (p.G38D variant) with significant bilateral vestibular loss without any definite MD symptoms. Discrete vestibular phenotypes depending on the location of *COCH* mutations were demonstrated, and this study correlates a genotype of p.G38D in *COCH* to the phenotype of bilateral total vestibular loss, therefore expanding the vestibular phenotypic spectrum of DFNA9 to range from bilateral vestibular loss without episodic vertigo to MD-like features with devastating episodic vertigo. In addition, the p.G38D variant of the *COCH* gene is suggested to be a frequent cause of progressive audiovestibular dysfunction in Koreans.

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INTRODUCTION

- Sensorineural hearing loss (SNHL) is the most common congenital sensorineural disorder, affecting 1 of 500 live births, and at least half of congenital hearing loss can be explained by genetic origin.
- Alterations in the *COCH* gene cause autosomal dominant-type hearing loss (DFNA9) and often also vestibular symptoms.
- Recently, a genotype-phenotype correlation was proposed in DFNA9; i.e., that individuals with von Willebrand factor A (vWFA) domain mutations predominantly exhibit hearing loss, while individuals with Limulus factor C, cochlin, and late gestation lung protein, Lgl1 (LCCL) domain mutations have hearing loss accompanied by vestibular dysfunction.
- In this study, we aimed to address the vestibular phenotypes of DFNA9 subjects with a focus on the relationship between the location of *COCH* mutations and the vestibular phenotype.

METHODS AND MATERIALS

Human Subjects

- We reviewed the vestibular phenotype of our DFNA9 cohort recruited from two tertiary referral centers. Molecular genetic diagnosis of two DFNA9 families (SH-14 and SB-82) was performed previously. The family SH-14 segregated p.G38D of the *COCH* gene and the other family, SB-82, harbored a known pathogenic mutation of p.C162Y.
- To recruit further DFNA9 families, we applied targeted resequencing of 129 known deafness genes (TRS-129) to 22 multiplex Korean families who were segregating bilateral sensorineural hearing loss (SNHL) with varying degrees of hearing loss in an autosomal dominant fashion, and filtered the variants as described previously.

Molecular Genetic Testing

TRS-129 with the extracted gDNA samples of patients was performed by Otogenetics (Norcross, GA, USA). Through the bioinformatic analysis, each raw data was mapped onto the UCSC hg19 reference genome. To identify causative variants from these data, we selected rare single nucleotide variations (SNV) or indels following five steps of filtering:

(1) basic filtering step excluding synonymous SNVs and selecting SNVs whose quality score were more than 30 and read depth were more than 40,
(2) compatibility with autosomal dominant inheritance pattern,
(3) confirmation of presence of mutations by Sanger sequencing,
(4) control study against unrelated 160 Korean control alleles,
(5) compatibility with clinical features.

Analysis of audio-vestibular features of *COCH* mutations

History-taking, audiometric data, and caloric and rotary chair test data for the evaluation of vestibular function.

RESULTS

Targeted resequencing data analysis and the frequency of DFNA9 among autosomal dominant hearing loss

- Among the 22 newly recruited multiplex families segregating hearing loss in an autosomal dominant fashion,
- We identified two DFNA9 families (SH140-294 and SB200-388) carrying a *COCH* mutation.
- The overall frequency of DFNA9 among such cases was calculated to be 5/39 (12.8 %) in Koreans, including the three other DFNA9 families among 17 autosomal dominant multiplex hearing loss families in our previous series,
- Specifically, we found a p.G38D variant of the *COCH* gene from both of the new DFNA9 families through targeted resequencing and subsequent filtering steps (Figs. 1 and 2), making the total number of Korean families segregating p.G38D to be three (60%) of five total DFNA9 families.

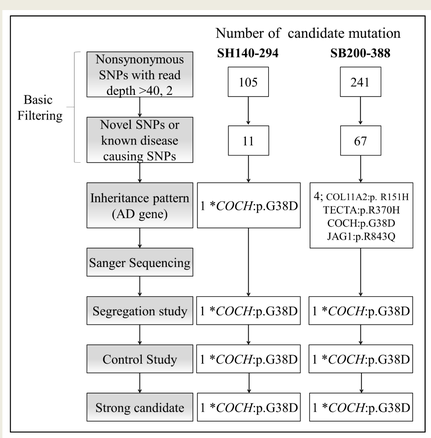

Fig. 1. Process of filtering *COCH*: p.G38D from 105 and 241 candidate mutations to one strong, responsible candidate in SH140-294 and SB 200-388 respectively

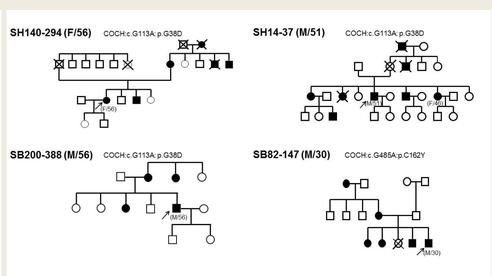

Fig. 2. Pedigree analysis in SH-140, SH-14, SB-200, and SB-82 with sensorineural hearing loss

Analysis of vestibular phenotypes of COCH mutations

- Classifying our cohorts into two groups: one (SB82) with an MD-like phenotype and the other (SH140, SB200 and SH14) with significant bilateral vestibular loss without any diagnostic MD symptoms.
- A 56-year-old female (SH140-294) carrying p.G38D in the LCCL domain of *COCH* complained of bilateral hearing loss (Fig 3a).
- She sometimes complained of mild lightheadedness, but it is notable that classical whirling-type vertigo was not reported. Interestingly, the bithermal caloric test and rotatory chair test revealed complete bilateral vestibular loss (Figs. 3b and 3c).
- A 56-year-old male (SB200-388) manifested an autosomal dominant hearing loss (Fig. 2). His hearing loss began in his-forties (Fig. 3a). He also complained of oscillopsia without definite vertigo attack and the bithermal caloric test documented complete bilateral vestibular loss (Fig. 3b).
- A 51-year-old male (SH14-37) carrying p.G38D was previously reported to have bilateral profound hearing loss without any definite vestibular symptoms (Fig. 3a). Further detailed history-taking revealed that his sister (SH14-38) had a similar pattern of hearing loss with intermittent lightheadedness type of dizziness (Fig. 3a). An additional caloric test and rotatory chair test were performed; the results also indicated complete bilateral vestibular loss (Figs. 3b and 3c).
- In contrast, a 30-year-old male (SB82-147) carrying p.C162Y in the vWFA 1 domain showed a remarkably different phenotype: he manifested asymmetrical bilateral SNHL with left-sided tinnitus and aural fullness (Fig. 4a).
- He also complained of recurrent devastating whirling-type vertigo attacks, which were well controlled by diuretics. Caloric testing showed reduced response on the right side with canal paresis of 56%, which might imply an irritative phase of MD on the left side, and the rotary chair test also demonstrated subtly reduced gain and phase lead features, which are usually evident in patients with vestibular hypofunction (Figs. 4b and 4c). Electrocochleography (ECOG) was later performed—results favored the diagnosis of bilateral MD with Summating Potential/Action Potential ratios of 0.45 and 0.46 on the right and left sides, respectively (Fig. 4d).

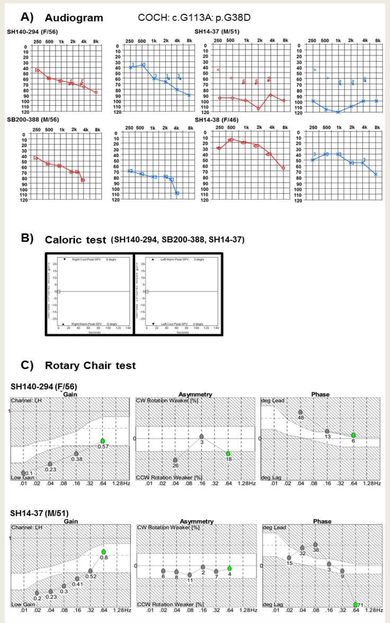

Fig. 3. Audiogram and vestibular function test results in SH-140, SB-200, and SH-14 with sensorineural hearing loss

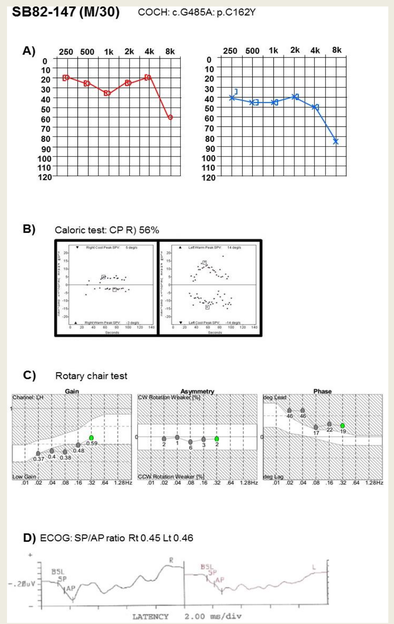

Fig. 4. Audiogram, and vestibular function test results in SB-82 with sensorineural hearing loss

DISCUSSION

- The p.G38D variant of the *COCH* gene accounted for three Korean multiplex families segregating hearing loss as well as vestibular symptoms. Considering the extreme heterogeneity of the molecular genetic etiology of progressive SNHL, detection of this variant in three families suggests it to be a frequent cause of such a phenotype in this population.
- A progressive hearing loss that starts in the 30s or 40s with the need for bilateral hearing aids in the 50s and very slowly progressive bilateral vestibular loss not accompanied by a definite vertigo attack may be a hallmark phenotype of DFNA9 with alterations in the LCCL domain. Moreover, MD-like features may be related to only a subset of DFNA9 subjects with mutations in the vWFA domains.
- This study shows a correlation between p.G38D in *COCH* and complete bilateral vestibular loss, suggesting that significant bilateral vestibular loss may also accompany DFNA9 hearing loss especially when the LCCL domain is mutated, despite the apparent absence of dizziness episodes.
- Collectively, our results expand the vestibular phenotypic spectrum of DFNA9 to range from bilateral vestibular loss without episodic vertigo to MD-like features with devastating episodic vertigo.

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