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Clinical characterization of a novel *COCH* mutation G87V in a Chinese DFNA9 family

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ABSTRACT

Objectives: To characterize the clinical features of a Chinese DFNA9 family associated with a novel *COCH* mutation and to confirm the proposed genotype–phenotype correlation of *COCH*.
Methods: Mutation screening of 79 deafness genes was performed in the proband by targeted next-generation sequencing. Co-segregation of the disease phenotype and the detected variants was confirmed in all family members by PCR amplification and Sanger sequencing. The progression of hearing impairment in affected family members was followed and the concomitant vestibular dysfunction was verified by the caloric vestibulo-ocular reflex test.
Results: A novel *COCH* mutation p.G87V was identified in the family segregating with late-onset, progressive sensorineural hearing impairment and consistent vestibular dysfunction.
Conclusion: The p.G87V mutation leads to a very similar phenotype as a previously reported p.G87W mutation of *COCH*. Our study suggested that the G87 residue is critical for function of *COCH* and further confirms a previously proposed genotype–phenotype correlation for DFNA9.
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1. Introduction

Deafness or severe hearing impairment affects about 1 in 1000 children; and more than half of these cases are estimated to be genetic in etiology [1]. To date, more than 60 genes and 130 loci have been identified to be associated with non-syndromic hearing impairment [2]. Mutations in the *COCH* gene (OMIM 603196) lead to autosomal dominant non-syndromic deafness DFNA9. *COCH* encodes a 550 amino acid extracellular protein cochlin that consists of a signal peptide, an LCCL module, and two von Willebrand factor A (vWFA) domains [3,4]. Proteomic analysis identified cochlin as the most abundant protein in the inner ear [5,6]. It is predominantly expressed in the spiral ligament, spiral limbus and osseous spiral lamina of the cochlea and in the stromal fibrocytes and ampullary wall of the vestibular labyrinth and cristae [7]. Consistent with its inner ear expression profile, histopathology and immunohistochemistry analyses of the inner ear tissues from post-mortem DFNA9 temporal bone samples showed major loss of fibrocytes in the spiral ligament and limbus of the cochlear duct and in the vestibular organs. In the same areas, aggregation of abundant homogeneous acellular eosinophilic deposits was observed containing extracellularly deposited cochlin [6].

Though many knock-out mouse models of the deafness genes displayed vestibular dysfunctions in addition to the hearing impairment, the vestibular phenotype was less commonly seen in human patients carrying mutations in the same deafness genes (e.g. *SLC26A4*, *MYO6*, *MYO15A*). Among non-syndromic deafness genes, *COCH* is the only one frequently associated with concomitant vestibular dysfunctions [3,8]. Interestingly, a genotype–phenotype correlation is proposed based on the limited observation that patients with mutations in the LCCL domain of *COCH* were more likely to have vestibular dysfunctions than those with mutations outside the LCCL domain [9].

Recently we identified causative mutations in a large cohort of deaf probands by targeted next-generation sequencing (NGS) of all known non-syndromic deafness genes (manuscript in preparation). Among them, a novel missense mutation in *COCH* was identified in a Chinese DFNA9 family. In this study, we characterized and compared the clinical phenotype associated with this novel mutation, which supported a possible genotype–phenotype correlation for *COCH* mutations in the LCCL domain.

2. Materials and methods

2.1. Subjects and clinical evaluations

This study included a Chinese dominant deaf family (D882) in which five family members were diagnosed as sensorineural

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hearing impairment with vestibular dysfunction (Fig. 1A). All affected subjects were clinically evaluated in the Department of Otolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai, China. The evaluation included a complete medical history inquiry and detailed physical examination to exclude the possibility of environmental or syndromic hearing impairment. Auditory evaluations were performed including otoscopic examination, otoacoustic emission and pure tone audiometry. Hearing thresholds of subjects were determined by the air-conduction pure-tone average thresholds at four frequencies (0.5, 1, 2 and 4 kHz). All hearing thresholds reported in this study were averages from the right and left ears. Caloric vestibulo-ocular reflex (VOR) test was performed in individual II-5 using electronystagmography with computer analysis. Based on the dominant time constant (T), the severity of VOR was determined as areflexia ($T = 0$ s), severe hyporeflexia ($T < 5$ s), hyporeflexia ($T = 5$–12 s), normal ($T = 12$–23 s) and hyperreflexia ($T > 23$ s) as previously described [10].

2.2. Mutation identification

Informed consent for genetic investigation was obtained from all subjects according to the guidelines of the ethics committee of the Xinhua Hospital, Shanghai Jiao Tong University School of Medicine. Peripheral blood samples were collected and genomic DNA was extracted from blood lymphocytes using a commercially available Blood DNA kit (TIANGEN BIOTECH Inc., Beijing, China). Targeted next-generation sequencing was performed in individual II-5 as previously described [11]. Briefly, the exon and flanking

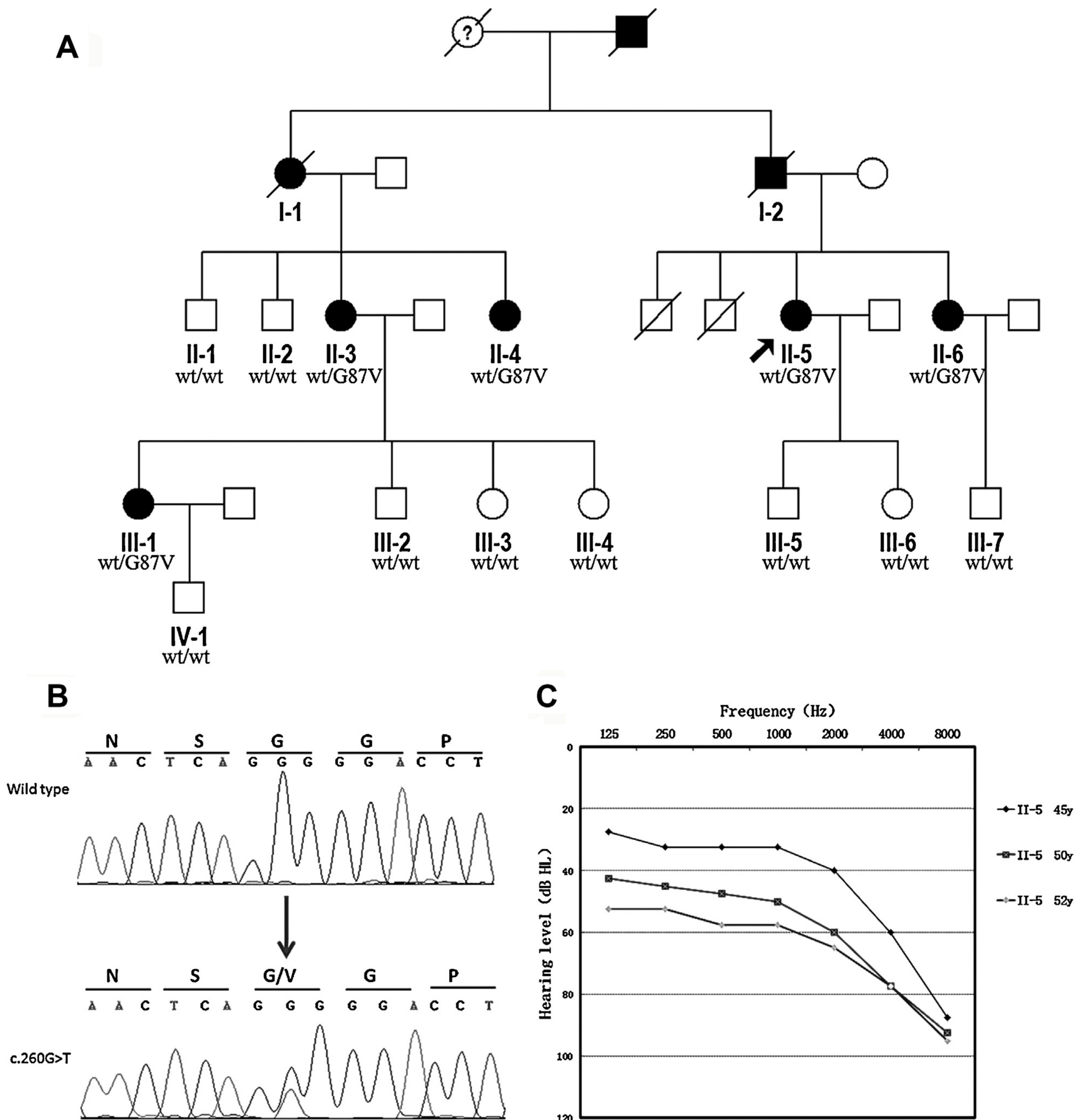

Fig. 1. (A) Pedigree of Family D882 segregating with the p.G87V mutation in *COCH*; (B) chromatograms showing the heterozygous c.260G>T nucleotide substitution; (C) audiograms of the proband II-5 showing the progressive hearing impairment.

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