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Case Report

Non-Syndromic Sensorineural Prelingual and Postlingual Hearing Loss due to *COL11A1* Gene Mutation

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This paper aims to present a third world case of Non-Syndromic sensorineural hearing loss (NSHL) due to a novel missense variant in *COL11A1* gene, defined as DFNA37 non-syndromic hearing loss. The clinical features of a 6-year-old boy affected by a bilateral moderate to severe down-sloping sensorineural hearing loss are presented, as well as the genetic analysis, the latter identifying a heterozygous missense variation in the COL11A1 gene. In addition, in families with autosomal dominant transmission, *COL11A1* gene should be considered in the genetic workup of the NSHL with prelingual onset.

KEYWORDS: Non-syndromic hearing loss, sensorineural hearing loss *COL11A1* gene mutation

INTRODUCTION

Non-Syndromic hearing loss (NSHL) is the most common congenital sensorineural disorder with a reported frequency of 1/500 live births. NSHL is characterized by a high clinical and genetic heterogeneity with approximately 115 genes and 170 loci identified to date.

Because of this genetic heterogeneity, current genetic tests fail to provide a diagnosis for the vast majority of cases, suggesting that many novel HL genes and mutations remain to be discovered [1]. In this light, next-generation sequencing (NGS) of HL patients and families, together with careful clinical evaluation is a powerful approach to identify the molecular cause of this disease [2, 3].

CASE PRESENTATION

A 6-year-old boy, P.G, (IV:2, please see Figure 1a for the family tree), was born preterm (at 31 weeks and 6 days gestation) by caesarean section in a monochorionic diamniotic twin pregnancy complicated by suspicion of twin-to-twin transfusion and prelabour rupture of membranes (PROM). Since birth, Otoacoustic Emissions (OAE) were bilaterally REFER, and the same result was obtained at the 1-month retest. Maternal serology, blood and urine tests were all in range; renal and brain echo scans revealed no abnormalities. Cytomegalovirus serological and molecular tests resulted negative.

Hearing threshold was firstly defined by Auditory Brainstem Responses (ABR) at the age of 3 months: a replicable wave V was present until 65 dBnHL on the right and until 60 dBnHL on the left (Figure 1b). The same audiological features were found at the retest performed at 5 and at 7 months of age and later at 16 months. At this stage, ABR findings were also confirmed by Auditory Steady State Responses (ASSR).

The first conditioned orienting response (COR) audiometry was performed at 10 months disclosing a behavioural threshold at 55 dB HL (Figure 1c). The following audiological examinations confirmed the presence of a bilateral moderate to severe down-sloping sensorineural hearing loss. The boy was given bilateral hearing aids at the age of 16 months. His twin (IV:3 in Figure 1a) had the same audiological findings and received hearing aids at the same age. In addition, their sister (IV:1 in Figure 1a) was affected by moderate sensorineural bilateral hearing loss involving middle to high frequencies (1-2 kHz) (Figure 1d).

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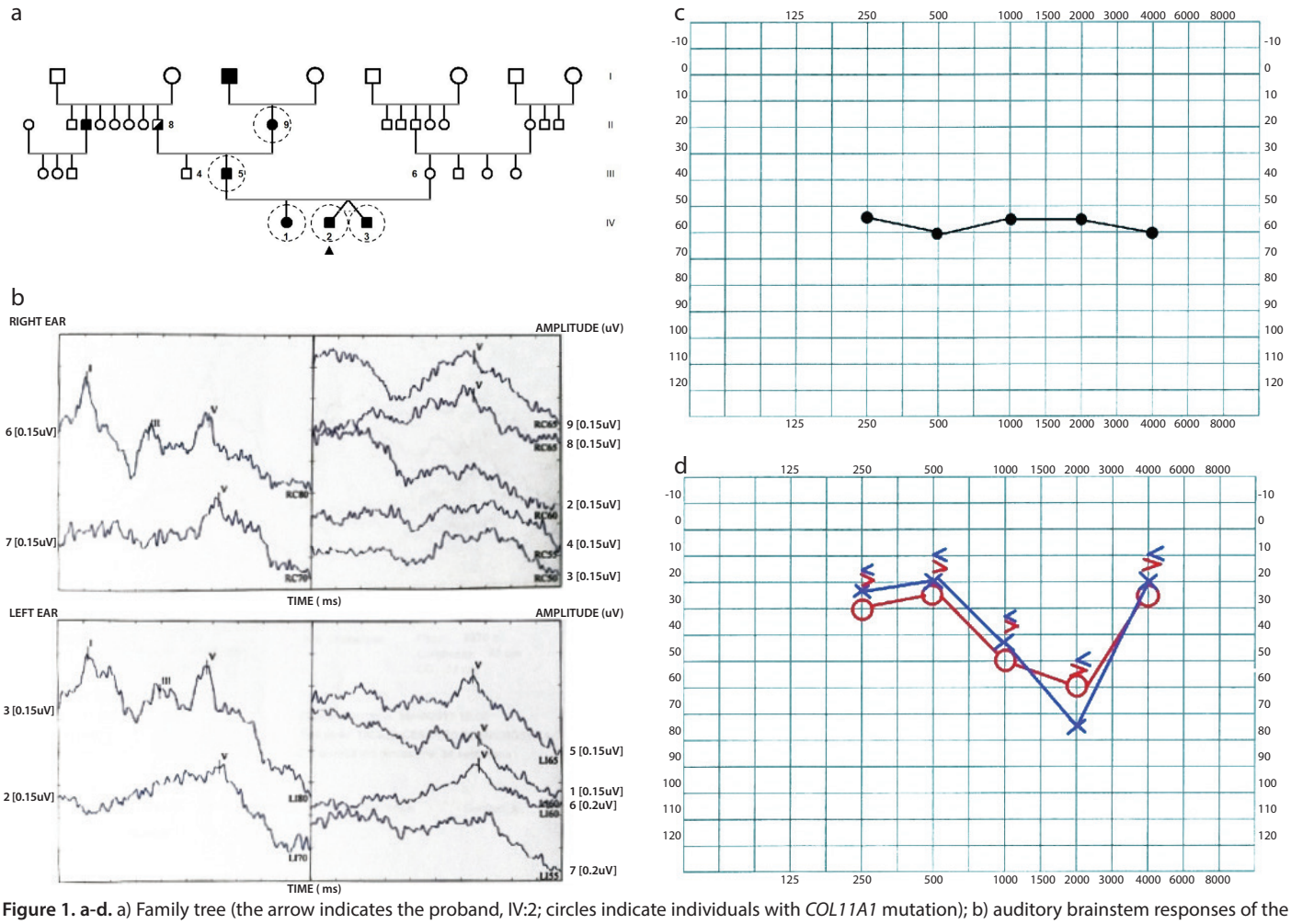

Figure 1. a-d. a) Family tree (the arrow indicates the proband, IV:2; circles indicate individuals with *COL11A1* mutation); b) auditory brainstem responses of the proband at the age 3 months (IV:2) revealed a replicable wave V until 65 dBnHL on the right and until 60 dBnHL on the left; c) the first conditioned orienting response audiometry of the proband (IV:2), revealing a behavioural threshold at 55 dB HL; d) tonal audiometry of the elder sister (IV:1) showing a moderate bilateral sensorineural hearing loss involving middle to high frequencies (1-2 kHz).

Considering the known paternal family history of hearing loss (Figure 1a), a genetic counselling was requested. Dysmorphology evaluation of the proband, the twin, and the father revealed no specific signs evocative of a syndromic hearing loss condition.

The molecular diagnostic approach started with the analysis of mutations in *GJB2* and *GJB6* genes, which resulted negative. Subsequently, the family underwent a targeted re-sequencing (TRS) panel of 96 genes associated with NSHL [4], which also was found to be negative.

For this reason, whole-exome sequencing (WES) using Ion Proton platform (ThermoFisher, Waltham, Massachusetts, USA) was performed in the proband (IV:2 in Fig. 1A), in the father (III:5 in Figure 1a), in the older sister (IV:1 in Figure 1a), in the paternal grandmother (II:9 in Figure 1a) (all affected by moderate postlingual hearing loss), in the mother (III:6 in Figure 1a) (healthy), and the paternal grandfather (II:8 in Fig. 1A) (displaying age-related hearing loss). WES led to the identification of a heterozygous missense variation in the *COL11A1* gene (NM_001854.3) c.494A> T, p.(His165Leu), detected in the proband, his older sister, his father, and his paternal grandmother. The variant is predicted as deleterious (Varsome[0]) by all the bioinformatics prediction tools used (MutationAssessor, MutationTaster, PrimateAI, REVEL and SIFT) and is not reported in the main public databases (e.g., dbSNP, GnomAD, ExAC, 1000 genomes, HGMD Professional 2018.3, Deafness Variation Database, Clin Var, and LOVD).

Sanger sequencing, performed in all the individuals previously sequenced by WES and in the healthy paternal uncle (III:4), confirmed the correct segregation of the variant within the family, being pres-

MAIN POINTS

- To present the third world case of Non-Syndromic sensorineural hearing loss (NSHL) due to a novel missense variant in COL11A1 gene, defined as DFNA37 non-syndromic hearing loss.
- Also considering the case of this family, we would like to highlight the variability of the clinical features of the COL11A1 gene mutations.
- It is important to consider COL11A1 gene in the genetic workup of the NSHL with prelingual onset.

ent in all the affected patients (i.e., IV:2, IV:1, III:5, and II:9) and absent in the remaining individuals (i.e., III:4, III:6, and II:8).

The family agreed to the publication of clinical data.

DISCUSSION

The *COL11A1* gene (located on chromosome 1p21.1 and consisting of 67 exons) belongs to the collagen family gene [5], encoding for one of the two alpha chains of collagen type XI (essential for skeleton and cartilage formation and for sense organ function, such as eyes and ear) [6-9]. Mutations of this gene have been associated with syndromic congenital deafness, such as fibrocondrogenesis type I (code OMIM # 228520), Marshall syndrome (code OMIM # 154780), Stickler syndrome type II (code OMIM # 604841) [6-10], and to an isolated deafness transmitted with an autosomal dominant inheritance. Nowadays only two mutations, one missense [10] and one splicing [6], are considered as causative of non-syndromic postlingual hearing loss; the mutations involve the same protein domain affected by the variant found in the examined family (Laminin G domain), supporting its possible pathogenetic role.

In this light, we strongly believe that the described *COL11A1* mutation can be considered as causative of the sensorineural hearing loss of this family, due to the following reasons: first, the *COL11A1*-related phenotypes are associated to the presence of high-frequency sensorineural hearing loss, according to the current reports available in the literature. The audiometric profile of the affected family members is similar to those reported in literature showing *COL11A1* mutations. Second, the location of the mutation identified in the probands in the literature. Third, the bioinformatic data predictions about the mutation effects, as reported by Annunen S et al [6] and Miyagawa M et al [10], confirm the possible causative effect. Fourth, the co-segregation of the mutation in the hearing loss of different family members following an autosomal dominant model of transmission. Lastly, the heterogeneity of the hearing loss segregating in the family further confirm our findings.

CONCLUSION

The mutation identified represents, to the best of our knowledge, a third world case of mutation in COL11A1 associated with autosomal dominant NSHL.

Moreover, taking into consideration the case of this family, we would like to highlight the variability of the clinical features (as expected in the autosomal dominant conditions), ranging from prelingual severe hearing loss in the proband and his twin to postlingual moderate hearing loss in the sister, father, and grandmother. Therefore, in families with autosomal dominant transmission, it is important to consider *COL11A1* gene in the genetic workup of the NSHL with prelingual onset.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

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Conflict of Interest: The authors have no conflict of interest to declare.

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