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Letter to Editor

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Nonsyndromic Deafness Due to A Peculiar Compound Heterozygous Genotype of Novel Nonsense and Missense *CEACAM16* Variants

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ABSTRACT

A peculiar compound heterozygous genotype of gene *CEACAM16* associated to non-syndromic hearing loss (NSHL) is reported, of two novel variants of terminal *IgV-like domain N2* domain of *CEACAM16*, different in nature, nonsense p.Trp370Ter and missense p.Ala375Thr, that would have a pathogenic effect (hearing loss) by impairing the interaction of *CEACAM16* with other prominent glycoproteins, mainly with TECTA and TECTB, introducing structural changes in the tectorial membrane (TM) of the *organ of Corti*.

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Dear Editor-in-Chief,

We hereby report on a peculiar case of *non-syndromic hearing loss* (NSHL) due to a novel compound heterozygous genotype, of mutations p.Trp370Ter and p.Ala375Thr, in gene *CEACAM16* (*CEA cell adhesion molecule 16, tectorial membrane component*) located at 19q13.31-q13.32. *CEACAM16*, previously described as *carcinoembryonic antigen-related cell adhesion molecule* 16, coding for a glycoprotein selectively expressed in the mammalian inner ear, secreted by cochlear outer hair cells of the *organ of Corti*, and localized to the tips of the tallest stereocilia and in the *tectorial membrane* (TM). In the TM, *CEACAM16* interacts with other molecules such as glycoproteins α-tectorin (TECTA) and β-tectorin (TECTB), coded by *TECTA* and *TECTB* genes respectively, being a prominent component of TM's striated sheet structure relevant for hearing, resulting its targeted deletion in mice in patho-morphological TM defects and hearing loss [1-4]. Accordingly, *CEACAM16* is a rare cause of NSHL in man, described in counted familial or in single cases, carriers of *heterozygous* or *homozygous* distinct sequence variants associated to dominant (ADNSHL; 1, 5-7) or recessive (ARNSHL) disease, also known as DFNA4B (*Deafness, autosomal dominant* 4B) and DFNB113 (*Deafness, autosomal recessive* 113) as referred in OMIM database (*https://www.omim.org/entry/614591*) [8-10].

As depicted by Figure. 1 and Table 1, only 8 *CEACAM16* mutations had so far been reported associated to NSHL, found dispersed throughout the gene sequence. Of them, 4 heterozygous missense variants, p.Thr140Pro (1), p.Gly169Arg (5), p.Leu365Arg (6) and p.Arg255Gly (7), associated to dominant DFNA4B cases. The remaining 4 are *homozygous* variants of recessive DFNB113 cases: *splice-altering* variants c.37G>T and c.662-1G>C (8), *nonsense* p.Arg146Ter (9), and *missense* variant p.Arg235Cys [10]. These findings would thus point to a broad pathogenic mechanism of *CEACAM16*, due haploinsufficiency or altered function (eventually considered *gain-of-function*) by deleterious, slice-site and missense variants. Further, and irrespective of the type, mutations located without an apparent selective disposition and disease association (Figure. 1), in cases of postlingual onset, in childhood or later in the second decade of life, with moderate but progressive affectation (Table 1).

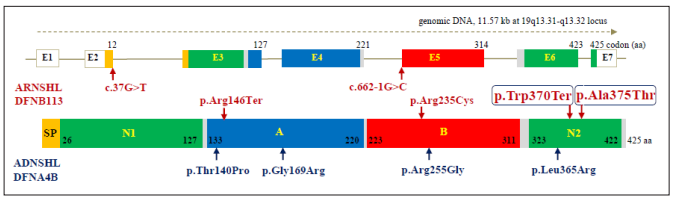

Figure 1: *CEACAM16* mutations associated to NSHL to date described, indicated on schematic genomic (top) and polypeptide (bottom) gene sequence representations. Genomic sequence expands around 11.57 kb in 7 exons, the first (E1) of them non-coding, the remaining 6 (E2-E7) with the coding sequence for a protein molecule of 425 amino acids (aa) that contains a signal peptide sequence (SP), two Ig variable-like domains (N1 and N2) at N- and C-terminus, respectively, and two Ig constant-like domains (A and B), but lacks a transmembrane domain. They are named and of size according to Hofrichter et al. (*Mol Syndromol* 2015;6:156-63): SP: signal peptide; N1: IgV-like domain N1; A: IgC-like domain A; B: IgC-like domain B; and, N2: IgV-like domain N2.

Mutations, also presented with additional data in Table 1, are 10 sequence variants. Of them, 4 (indicated at the bottom, in blue) are monoallelic heterozygous variants of dominant cases (ADNSHL DFNA4B). The remaining 6 (at the top, in red) are of recessive cases (ARNSHL DFNB113), including 4 homozygous variants and the 2 (encircled) of the compound heterozygous genotype of our patient. NSHL: Non-Syndromic Hearing Loss. ADNSHL: Autosomal Dominant Non-Syndromic Hearing Loss. ARNSHL: Autosomal Recessive Non-Syndromic Hearing Loss. DFNA4B: Deafness, autosomal dominant 4B; DFNB113: Deafness, autosomal recessive 113.

Table 1: *CEACAM16* mutations described to date. Data on type of pathogenic variants, zygosity, associated disease (NSHL), onset, and ethnicity

Variant						
Nucleotide	**Amino acid**	**Zygosity**	**NSHL Type**	**Onset**	**Ethnicity**	**Reference**
c.418A>C	p.Thr140Pro	heterozygous	ADNSHL DFNA4B	postlingual, adolescence, progressive	American family	Zheng et al. 2011[1]
c.505G>A	p.Gly169Arg	heterozygous	ADNSHL DFNA4B	postlingual, adolescence, progressive	Chinese family,	Wang et al. 2015[5]
c.1094T>G[a]	p.Leu365Arg	heterozygous	ADNSHL DFNA4B	postlingual, 11 year old	German boy	Hofrichter et al. 2015[6]
c.763A>G	p.Arg255Gly	heterozygous	ADNSHL DFNA4B	postlingual, 7-10 years, progressive	Chinese family	Zhang et al. 2022[7]
c.37G>T[b]	p.Ala13Ser	heterozygous	ARNSHL DFNB113	postlingual, second decade, progressive	Iranian family	Booth et al. 2018[8]
c.662-1G>C[c]	F221CfsX16[c]	heterozygous	ARNSHL DFNB113	postlingual, second decade, progressive	Iranian family	Booth et al. 2018[8]
c.436C>T	p.Arg146Ter	heterozygous	ARNSHL DFNB113	postlingual, second decade, progressive	Brazilian family	Dias et al. 2019[9]
c.703C>T	p.Arg235Cys	heterozygous	ARNSHL DFNB113	postlingual, childhood, progressive	Jewish Iranian families	Brownstein et al. 2020[10]
c.1110G>A / c.1123G>A [p.Trp370Ter / p.Ala375Thr]		compound heterozygous	ARNSHL DFNB113	postlingual, second decade, progressive	Spaniard woman	Nogueira et al. 2023 (present case)

[a]c.1094T>G: *de novo* (not inherited) variant[6]
[b]c.37G>T: *homozygous* splice-altering variant resulting in complete skipping of exon 2 and loss of the AUG start site[8]
[c]c.662-1G>C: *homozygous* splice-altering variant that predicts two abnormal splicing events: an *in-frame* deletion, p.Phe221_Ala313delinsSer, and a *frameshift* change p.Phe221CysfsTer16 (F221CfsX16) proposed as most robust and pathogenic[8]
NSHL: Non-Syndromic Hearing Loss. ADNSHL: Autosomal Dominant Non-Syndromic Hearing Loss. ARNSHL: Autosomal Recessive Non-Syndromic Hearing Loss. DFNA4B: Deafness, autosomal dominant 4B; DFNB113: Deafness, autosomal recessive 113.

In addition, we describe here two *CEACAM16* mutations identified in an adopted 40-year-old Spaniard woman asking for a genomic analysis by lacking any data of her biological parents. To this end, a comprehensive sequencing analysis according to procedures and software for WES (*Whole Exome Sequencing*, with the use of IDT probes), as described in detail at Illumina (*https://www.illumina.com*), led to identification of *CEACAM16* variants p.Trp370Ter and p.Ala375Thr, first of them (p.Trp370Ter) inherited by the two young patient daughters of 6 and 4 years, both healthy and with normal audiogram results (as shown in detail in Figure. 2). It was held as the unique finding of possible interest of the *presymptomatic analysis*, considered potentially relevant by location of the two neighbor mutations in different alleles, thus raising the possibility of a peculiar and so far unknown compound heterozygous genotype of *CEACAM16* associated to a hearing loss. Confirming this suspicion, the "patient" recognized her complaints of long-term hearing loss although without medical evaluation, until recently, following genomic analysis, of a diagnosis of *moderate bilateral hearing loss*, with pure-tone audiometry values of 55 and 45 dB in left and right ears, respectively, and with *tinnitus*.

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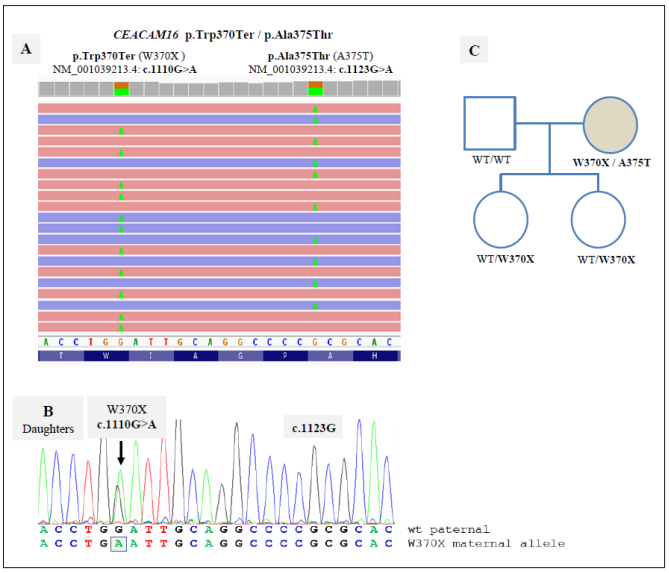

Figure 2: *CEACAM16* mutations p.Trp370Ter and p.Ala375Thr
A: Detail of BAM file of the patient (of WES sequencing, with Illumina NGS procedures) viewed under the IGV software (*https://software. broadinstitute.org*), to show novel mutations p.Trp370Ter (W370X) and p.Ala375Thr (A375T), due to transitions c.1110G>A and c.1123G>A of *CEACAM16* exon 6 (in sequence NM_001039213.4), found in different alleles, each in ~50% single sequences, and therefore most probably inherited.
B: Sanger sequencing analysis detail of *CECAM16* mutations W370X and A375T in the patient daughters, with same results: occurrence of mutation c.1110G>A (W370X) but not of c.1123G>A (A375T).
C: Familial tree showing occurrence of *CEACAM16* mutations W370X (p.Trp370Ter) and 375T (p.Ala375Thr) in the patient and transmission of W370X to daughters, of 6 and 4 years, both healthy and with normal results in pure-tone audiograms.

The contribution of the two *CEACAM16* mutations to the patient hearing loss would mainly be suggested by both nature and exceptional occurrence of them. Thus, on one side, nonsense variant p.Trp370Ter, never described before in patients and healthy individuals, is considered relevant as other deleterious variants of recessive DFNB113 cases, such as c.37G>T, c.662-1G>C, p.Arg146Ter that resulted silent in monoallelic *CEACAM16* variant carriers as the daughters of our patient, both heterozygous for p.Trp370Ter (Figure. 2). On the other hand, missense variant p.Ala375Thr, of exceptional occurrence in healthy individuals (observed only in 2/244.400 heterozygous alleles of *genomAD* exome database), would be considered by paucity of data a *variant of uncertaing significance* (VUS) according to a rigorous evaluation of the ACMG criteria, as it is proposed in knowledge bases VarSome (*https://varsome.com/variant/hg19/NM_001039213:c.1123G>A*) and Franklin (*https://franklin.genoox.com/clinical-db/variant/snp/chr19-45211315-G-A*). However, its occurrence in our patient would prompt us to consider p.Ala375Thr likely *pathogenic*, as other missense variants. In these regard, it might be mentioned that a similar evaluation (likely *pathogenic*) has been given for neighbor *CEACAM16* similar variant p.Thr396Ala associated, according to dominant inheritance, to hearing loss in a familial case reported in the ClinVar database (*https://www.ncbi.nlm.nih.gov/clinvar/variation/228513*). Thus, the discovered novel *CEACAM16* genotype, a compound heterozygote of variants of different types, would be responsible for the patient's hearing loss, most likely due to TM structural damage caused by defective interaction of *CEACAM16* with other TM molecules, such as TECTA and TECTB, by the absence and/or altered function of the IgV-like domain N2, as speculated for other known *CEACAM16* mutations.

Furthermore, it is reasonable to speculate that such an altered TM molecular complex would enhance the effect of non-genetic factors involved in sensorineural hearing loss along the vestibular auditory nerve from the cochlea to the brain, including noise exposure and ischaemia [11, 12]. It would be an example of the proposed involvement of proteinopathies and neurotrauma in neurodegeneration [13].

Authors get permission for publication of patient and family data. They declare that there is no conflict of interests regarding the publication of this paper.

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