Variant: NM_022124.6(CDH23):c.6866A>G (p.Asn2289Ser)

Version: 1.1

CA10576816

228500 (ClinVar)

Gene: CDH23 (HGNC:64072)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4e5ca14d-cfbf-4aea-a468-9806004f6872
Approved on: 2022-12-21
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HGVS expressions

NM_022124.6:c.6866A>G
NM_022124.6(CDH23):c.6866A>G (p.Asn2289Ser)
NC_000010.11:g.71798390A>G
CM000672.2:g.71798390A>G
NC_000010.10:g.73558147A>G
CM000672.1:g.73558147A>G
NC_000010.9:g.73228153A>G
NG_008835.1:g.406444A>G
ENST00000224721.12:c.6866A>G
ENST00000642965.1:c.799A>G
ENST00000647092.1:c.463A>G
ENST00000224721.10:c.6881A>G
ENST00000398788.4:c.146A>G
ENST00000475158.1:n.402A>G
ENST00000619887.4:c.146A>G
ENST00000622827.4:c.6866A>G
NM_001171933.1:c.146A>G
NM_001171934.1:c.146A>G
NM_022124.5:c.6866A>G

Uncertain Significance

Met criteria codes 2

PP3 **PM2**

Not Met criteria codes 1

PM3

Evidence Links 0

Expert Panel

Hearing Loss VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Hearing Loss Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CDH23, COCH, GJB2, KCNQ4, MYO6, MYO7A, SLC26A4, TECTA and USH2A Version 2*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Hearing Loss VCEP

The NM_022124.6:c.6866A>G variant in the CDH23 gene is a missense variant predicted to cause substitution of asparagine to serine at amino acid 2289 (p.Asn2289Ser). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.534, which is neither above nor below the thresholds predicting a damaging or benign impact. This variant was reported in two individuals with sensorineural hearing loss and one individual with postlingual deafness and bilateral vestibular areflexia (LMM unpublished data SCV000271567.2, ARUP Labs unpublished data SCV000602954.2, University Hospital of Geneva unpublished data SCV000494445.1). One individual had a second variant of uncertain significance in trans, and one had a second variant of uncertain significance phase unknown (SCV000602954.2, SCV000494445.1) (Does not meet PM3). In summary, due to limited evidence, this variant is classified as a variant of uncertain significance based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss Variant Curation Expert Panel: PM2_supporting. (VCEP specifications version 2.0.0; Dec 21, 2022)

Met criteria codes

PP3	✓	The REVEL Score is 0.534, but the nucleotide is highly conserved (all vertebrates in UCSC MSA have Asn at the position). MaxEntScan predicts the creation of cryptic 5' splice site.
PM2	✓	The variant is not present in v2.1.1 or v3 of gnomAD.

Not Met criteria codes

PM3	✗	A proband with sensorineural hearing loss with preauricular pits and a parent with ear pits was found to carry the p.Asn2289Ser variant in CDH23, the p.Ala974Val variant in COL11A2 and a deletion of exon 16-17 in EYA1. This proband was not scored any points (LMM Internal Lab Data, SCV000271567.2). A proband with bilateral postlingual deafness and bilateral vestibular areflexia harbored two variants in CDH23 (the p.Asn2289Ser variant and a c.478G>A/p.Asp160Asn variant). The mother of the proband was confirmed to carry the p.Asp160Asn variant but not the first one and the father was not tested so the variants were not confirmed in trans. The p.Asp160Asn variant is present in 0.0095% of European (Finnish) chromosomes in gnomAD v3 and present in 0.00089% (1/112644) of European (non-Finnish) chromosomes in gnomAD v2.1.1. This proband was given a score of 0 points (University Hospital of Geneva internal data, SCV000494445.1). A 1 y/o female presented with moderate bilateral sensorineural hearing loss and mild bilateral hydronephrosis that resolved spontaneously. The patient had the p.Asn2289Ser variant in CDH23 and the c.8083G>A/p.Asp2695Asn variant in CDH23. The p.Asp2695Asn variant is a VUS in ClinVar and meets PM2 for population frequency. This patient was not scored with any PM3 points because the second variant is rare variant of unknown significance (ARUP Labs Internal Data, SCV000602954.2).

Curation History

Showing 1 to 2 of 2 rows