Variant: NM_022124.5(CDH23):c.2866G>A (p.Glu956Lys)

Version: 2.1

CA5544361

444219 (ClinVar)

Gene: CDH23 (HGNC:64072)
Condition: sensorineural hearing loss disorder (MONDO:0020678)
Inheritance Mode: Autosomal recessive inheritance
UUID: ad55f8aa-c75a-44f6-9a6e-2344d0525a05
Approved on: 2023-06-27
Published on: 2023-10-05

HGVS expressions

NM_022124.5:c.2866G>A
NM_022124.5(CDH23):c.2866G>A (p.Glu956Lys)
NC_000010.11:g.71705043G>A
CM000672.2:g.71705043G>A
NC_000010.10:g.73464800G>A
CM000672.1:g.73464800G>A
NC_000010.9:g.73134806G>A
NG_008835.1:g.313097G>A
ENST00000224721.12:c.2866G>A
ENST00000398809.9:c.2866G>A
ENST00000442677.4:c.2866G>A
ENST00000466757.8:c.2297G>A
ENST00000224721.10:c.2881G>A
ENST00000299366.11:c.2866G>A
ENST00000398809.8:c.2866G>A
ENST00000442677.3:c.1641G>A
ENST00000466757.7:c.2297G>A
ENST00000616684.4:c.2866G>A
ENST00000622827.4:c.2866G>A
NM_001171930.1:c.2866G>A
NM_001171931.1:c.2866G>A
NM_001171930.2:c.2866G>A
NM_001171931.2:c.2866G>A
NM_022124.6:c.2866G>A

Pathogenic

Met criteria codes 3

PM3_Very Strong **PP3** **PM5**

Not Met criteria codes 2

BP4 **PM2**

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*
- **Criteria Specification Approval History**

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The p.Glu956Lys variant in CDH23 is a missense variant predicted to cause substitution of glutamic acid to lysine at amino acid 956. The highest population minor allele frequency in gnomAD v3.1.2 is 0.02895% (12/41444) in African/African American population which is greater than the PM2_Supporting thresholds defined by the ClinGen Hearing Loss Expert Panel (≤0.007%) and less than the BS1_supporting MAF of ≥0.0007 (0.07%) for autosomal recessive disorders (no codes met). The computational predictor REVEL produced a score of 0.616, which was just below the threshold to automatically apply PP3, but the Expert Panel decided to apply PP3 based upon manual review of alignments to examine homology. This variant has been detected in at least six probands with hearing loss without evidence of retinal disease (5 PM3_Very Strong points, PMID: 26763877,25963016, 22899989, Invitae Internal Data (SCV001228538.3)). Of those individuals, four harbored the p.Pro240Leu pathogenic variant in CDH23 with three individuals confirmed in trans (PMID 25963016, 22899989). The fifth individual harbored the p.Asp645Gly variant in CDH23, but phasing was not performed (PMID 25963016). The sixth proband carried a second pathogenic CDH23 variant in trans (Invitae Internal Data). 1 different missense variant, c.2867A>G (p.Glu956Gly) ClinVar Variation ID:1180655, in the same codon has been classified as likely pathogenic for AR sensorineural hearing loss by two submitters in ClinVar (PM5). In summary, this variant meets the criteria to be classified as pathogenic for AR hearing loss based on ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP; PP3, PM3_Very Strong, PM5. (The ClinGen Hearing Loss VCEP Specifications Version 2; 06/27/2023)

Met criteria codes

PM3_Very Strong	ⓘ	✓	Six probands (5 PM3 points, PMID: 26763877,25963016, 22899989, Invitae Internal Data (SCV001228538.3)). Four harbored the p.Pro240Leu pathogenic variant in CDH23 with three individuals confirmed in trans (3.5 PM3 points, PMID 25963016, 22899989). One individual harbored the p.Asp645Gly variant in CDH23, but phasing was not performed (0.5 PM3 points,PMID 25963016). The sixth proband carried a second pathogenic CDH23 variant in trans (1.0 PM3 points, Invitae Internal Data). PM3_Very Strong met.
PP3	ⓘ	✓	The REVEL computational prediction analysis tool produced a score of 0.616, which was just below the threshold to automatically apply PP3, but the Expert Panel decided to apply PP3 based upon manual review of alignments to examine homology.
PM5	ⓘ	✓	c.2867A>G (p.Glu956Gly) ClinVar Variation ID:1180655; a missense change in the same codon has been classified as likely pathogenic for AR sensorineural hearing loss by two submitters in ClinVar (ClinVar Variation ID: 1180655, PM5 met)

Not Met criteria codes

BP4	ⓘ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2		✗	The highest population minor allele frequency in gnomAD v3.1.2 is 0.02895% (12/41444) in African/African American population which is greater than the PM2_Supporting thresholds defined by the ClinGen Hearing Loss Expert Panel (≤0.007%) and less than the BS1_supporting MAF of ≥0.0007 (0.07%) for autosomal recessive disorders (no codes met).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_022124.5(CDH23):c.2866G>A (p.G...	Pathogenic	Sensorineural Hearing Loss Disorder	2023-10-05	2.1	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	CDH23
View	NM_022124.5(CDH23):c.2866G>A (p.G...	Pathogenic	Sensorineural Hearing Loss Disorder	2023-08-25	2.0	-	CDH23
View	NM_022124.5(CDH23):c.2866G>A (p.G...	Likely Pathogenic	Sensorineural Hearing Loss Disorder	2020-11-02	1.1	-	CDH23
View	NM_022124.5(CDH23):c.2866G>A (p.G...	Likely Pathogenic	Sensorineural Hearing Loss Disorder	2019-08-16	1.0	-	CDH23

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