

Variant: NM_022124.6(CDH23):c.380A>G (p.Asp127Gly)

CA10576804 [↗](#)

228491 (ClinVar) [↗](#)

Gene: CDH23 ([HGNC:64072](#))

Condition: Usher syndrome ([MONDO:0019501](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 637bd8ea-a91f-4012-9a60-43d0bfce68ad

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HGVS expressions

NM_022124.6(CDH23):c.380A>G (p.Asp127Gly)

NM_022124.6:c.380A>G

NC_000010.11:g.71511163A>G

CM000672.2:g.71511163A>G

NC_000010.10:g.73270920A>G

CM000672.1:g.73270920A>G

NC_000010.9:g.72940926A>G

NG_008835.1:g.119217A>G

ENST00000224721.12:c.380A>G

ENST00000398809.9:c.380A>G

ENST00000442677.4:n.380A>G

ENST00000646131.1:n.44A>G

ENST00000224721.10:c.380A>G

ENST00000299366.11:c.380A>G

ENST00000398809.8:c.380A>G

ENST00000398842.7:c.203A>G

ENST00000461841.7:c.380A>G

ENST00000616684.4:c.380A>G

ENST00000622827.4:c.380A>G

NM_001171930.1:c.380A>G

NM_001171931.1:c.380A>G

NM_001171932.1:c.380A>G

NM_022124.5:c.380A>G

NM_052836.3:c.380A>G

NR_120672.1:n.143+615T>C

NM_001171930.2:c.380A>G

NM_001171931.2:c.380A>G

NM_052836.4:c.380A>G

NM_001171932.2:c.380A>G

Likely Pathogenic

Met criteria codes 4

PP4 PP3 PM3 PM2_Supporting

Not Met criteria codes 22

BP5 BP7 BP2 BP3 BP1 BP4
BS4 BS3 BS1 BS2 PP1 PP2

Expert Panel

Hearing Loss VCEP [↗](#)

Criteria Specification Information

PM1PM4PM5PS2PS4

PS3PS1BA1PM6PVS1

Evidence Links

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[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 c.380A>G (NM_022124.6(CDH23):c.380A>G (p.Asp127Gly)) variant in CDH23 is a missense variant predicted to cause substitution of aspartate by glycine at amino acid 127. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.796 which is above the threshold of 0.7, evidence that correlates with impact to CDH23 function (PP3). This variant has been detected in one individual with autosomal recessive Usher syndrome. For this individual, they were compound heterozygous for the variant and a pathogenic variant (NM_022124.6(CDH23):c.1949dup (p.Leu651fs) (SCV000271345.2)) and this individual was confirmed in trans by family testing (1.0 point, PM3; LMM internal data). The patient with the variant had congenital severe-profound hearing loss with vestibular complications and ophthalmology-related issues, features highly specific to Usher syndrome (LMM Internal Data; PP4). This variant was re-reviewed on 1.18.2023 and because no additional evidence is available, professional judgment was used to retain this variant as likely pathogenic for autosomal recessive Usher syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP. In summary, this variant is classified as likely pathogenic for autosomal recessive Usher Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PM2_supporting, PP3, PM3, PP4 (ClinGen Hearing Loss VCEP Specifications Version 2; 6/27/2022).

Met criteria codes

PP4			The patient with the variant had congenital severe-profound hearing loss with vestibular complications and ophthalmology-related issues, features highly specific to Usher syndrome (Laboratory for Molecular Medicine Internal Data; PP4).
PP3			REVEL score is 0.796, which is above 0.7, the threshold for pathogenicity set by the hearing loss VCEP. Amino acid is very well-conserved. The results from three in silico predictors/lines of evidence (PolyPhen, REVEL score, conservation) provide evidence that correlates with impact to CDH23 function (PP3).
PM3			This variant was detected in trans with NM_022124.5:c.1949_1950insC (p.Leu651fs)(a pathogenic variant) in CDH23 in a patient with Usher Syndrome (Laboratory for Molecular Medicine Internal Data).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP4			REVEL score is 0.796.
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			The variant is absent from gnomAD.
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			The variant is absent from gnomAD.
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PVS1



No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History [↗](#)

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