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Variant: NM_022124.6(CDH23):c.9569C>T (p.Ala3190Val)

Version: 1.1

CA137643

46076 (ClinVar)

Gene: CDH23 (HGNC:64072)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7f246a3f-3877-4e1c-b536-a8da21fcd3b6
Approved on: 2023/11/15
Published on: 2024/4/1

HGVS expressions

NM_022124.6(CDH23):c.9569C>T (p.Ala3190Val)
NM_022124.6:c.9569C>T
NC_000010.11:g.71812826C>T
CM000672.2:g.71812826C>T
NC_000010.10:g.73572583C>T
CM000672.1:g.73572583C>T
NC_000010.9:g.73242589C>T
NG_008835.1:g.420880C>T
ENST00000224721.12:c.9569C>T
ENST00000642965.1:c.3502C>T
ENST00000647092.1:c.3166C>T
ENST00000224721.10:c.9584C>T
ENST00000398788.4:c.2849C>T
ENST00000475158.1:n.3105C>T
ENST00000619887.4:c.2849C>T
ENST00000622827.4:c.9569C>T
NM_001171933.1:c.2849C>T
NM_001171934.1:c.2849C>T
NM_001171935.1:c.260C>T
NM_001171936.1:c.260C>T
NM_022124.5:c.9569C>T

Uncertain Significance

Met criteria codes 2

PP3 BS2

Not Met criteria codes 4

PP4 PM2 PM3 BS1

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 c.9569C>T variant (NM_022124.6(CDH23):c.9569C>T (p.Ala3190Val)) in CDH23 is a missense variant predicted to cause substitution of alanine by valine at amino acid 3190 (p.Ala3190Val). The highest minor allele frequency in gnomAD v4.0.0 is 694/1179698 alleles (0.0005517), in the European (non-Finnish) population (no population codes met). This variant has been observed in a homozygous state in one parent reported to have no features of Usher syndrome (BS2; Invitae internal data; ClinVar SCV001110059.2). The computational predictor REVEL gives a score of 0.836, which is above the Hearing Loss VCEP threshold of 0.7, evidence that correlates with impact to CDH23 function (PP3). The variant was found in a compound heterozygous state with a deletion of exon 29, a variant which was not able to be confirmed by aCGH (PMID: 25404053). The variant was also found in an unknown phase with p.Arg3206Cys (c.9616C>T), a variant of uncertain significance, in an affected patient with nonsyndromic hearing loss (PMID: 27068579; PM3 not met). In summary, the clinical significance of this variant is uncertain. ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss Expert Panel: BS2, PP3 (Version 2; 11/15/2023).

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.836, which is above the Hearing Loss VCEP threshold of 0.7, evidence that correlates with impact to CDH23 function (PP3). Nucleotide is very well-conserved among 100 vertebrates in UCSC database. Variant is not predicted to impact splicing according to splice AI scores.
BS2	✔	This variant has been observed in a homozygous state in one parent reported to have no features of Usher Syndrome (BS2; Invitae internal data; ClinVar SCV001110059.2).

Not Met criteria codes

PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✖	The highest major allele frequency in gnomAD v4.0.0 is is 694/1179698 (0.0005883) in the European (non-Finnish) population (no population codes met).
PM3	✖	The variant was found in a compound heterozygous state with a deletion of exon 29, a variant which was not confirmed. The variant was also found in an unknown phase with p.Arg3206Cys (c.9616C>T), a variant of uncertain significance, in an affected patient with nonsyndromic hearing loss (PM3 not met).
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_022124.6(CDH23):c.9569C>T (p.Al...	Uncertain Significance	Usher Syndrome	2024-04-01	1.1	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_022124.6(CDH23):c.9569C>T (p.Al...	Uncertain Significance	Usher Syndrome	2020-09-24	1.0	-	CDH23

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