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Variant: NM_000260.4(MYO7A):c.1849T>C (p.Ser617Pro)

Version: 2.0

CA6197628

438172 (ClinVar)

Gene: MYO7A (HGNC:4647)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 91d8a5fd-ca4f-426d-9b06-68e7858e7d7e
Approved on: 2024/6/28
Published on: 2024/6/28

HGVS expressions

NM_000260.4(MYO7A):c.1849T>C (p.Ser617Pro)
NM_000260.4:c.1849T>C
NC_000011.10:g.77172799T>C
CM000673.2:g.77172799T>C
NC_000011.9:g.76883845T>C
CM000673.1:g.76883845T>C
NC_000011.8:g.76561493T>C
NG_009086.1:g.49536T>C
NG_009086.2:g.49554T>C
ENST00000409709.9:c.1849T>C
ENST00000669443.1:c.213T>C
ENST00000409619.6:c.1816T>C
ENST00000409709.7:c.1849T>C
ENST00000409893.5:c.1849T>C
ENST00000458637.6:c.1849T>C
ENST00000620575.4:c.1849T>C
NM_000260.3:c.1849T>C
NM_001127179.2:c.1849T>C
NM_001127180.1:c.1849T>C
NM_001127180.2:c.1849T>C
NM_001369365.1:c.1816T>C

Likely Pathogenic

Met criteria codes 3

PP1_Strong PP3 PM3

Not Met criteria codes 7

BP4 BP1 PP2 PP4 BA1 PM2 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.1849T>C variant in MYO7A is a missense variant predicted to cause substitution of serine by proline at amino acid 617 (p.Ser617Pro). The highest population minor allele frequency in gnomAD v4 is 0.00009496 (8/84244 alleles) in the South Asian population (PM2_Supporting, BS1, and BA1 are not met). The computational predictor REVEL gives a score of 0.922, which is above the threshold of 0.7, evidence that correlates with impact to MYO7A function (PP3). This variant has been detected in 3 individuals with nonsyndromic hearing loss. Of those individuals, 2 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and both of those were confirmed in trans by parental testing (c.20G>T [p.Gly7Val], c.1258A>T [p.K420*], 2 PM3 points, PMIDs: 30303587, 33187236). One individual was homozygous for the variant (0.5 PM3 points, PMIDs: 27344577, 33671976) (PM3). The variant has been reported to segregate with nonsyndromic hearing loss in 7 affected family members from 3 families (PP1_Strong; PMIDs: 27344577, 30303587, 33187236, 33671976). This variant has also been detected in 1 individual with Usher syndrome, with a second variant c.4838delA (p.Asp1613ValfsTer32) without phase confirmation (PMIDs: 28041643, 32581362). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive hearing loss based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PP1_S, PM3, PP3. (Hearing Loss VCEP specifications version 2; 4/22/2024). As cases have been observed with both nonsyndromic hearing loss and Usher syndrome and genotype-phenotype correlation is currently unclear, individuals should be evaluated for both conditions.

Met criteria codes

PP1_Strong	✔	The variant has been reported to segregate with nonsyndromic hearing loss in 7 affected family members from 3 families (PP1_Strong; PMIDs: 27344577, 30303587, 33187236, 33671976).
PP3	✔	The computational predictor REVEL gives a score of 0.922, which is above the threshold of 0.7, evidence that correlates with impact to MYO7A function (PP3).
PM3	✔	This variant has been detected in 3 individuals with nonsyndromic hearing loss. Of those individuals, 2 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and both of those were confirmed in trans by parental testing (c.20G>T [p.Gly7Val], c.1258A>T [p.K420*], 2 PM3 points, PMIDs: 30303587, 33187236). One individual was homozygous for the variant (0.5 PM3 points, PMIDs: 27344577, 33671976) (PM3).

Not Met criteria codes

BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	Not applicable
PP2	✖	Not applicable
PP4	✖	This variant has also been detected in 1 individual with Usher syndrome (HL and RP), with a second variant c.4838delA (p.Asp1613ValfsTer32) without phase confirmation (PMIDs: 28041643, 32581362). This is not scored for PP4 due to being curated for NSGHL.
BA1	✖	

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 v4 is 0.00009496 (8/84244 alleles) in the South Asian population (PM2_Supporting, BS1, and BA1 are 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_000260.4(MYO7A):c.1849T>C (p.S...	Likely Pathogenic	Nonsyndromic Genetic Deafness	2024-06-28	2.0	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	MYO7A
View	NM_000260.3(MYO7A):c.1849T>C (p.S...	Uncertain Significance	Usher Syndrome	2019-10-07	1.0	-	MYO7A

Showing 1 to 2 of 2 rows

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