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Variant: NM_000260.4(MYO7A):c.3546C>A (p.Asn1182Lys)

Version: 1.2

CA381946913

438177 (ClinVar)

Gene: MYO7A (HGNC:4647)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0ff89378-59ae-459b-9112-e954004ee08d
Approved on: 2023/6/27
Published on: 2023/10/5

HGVS expressions

NM_000260.4(MYO7A):c.3546C>A (p.Asn1182Lys)
NM_000260.4:c.3546C>A
NC_000011.10:g.77189386C>A
CM000673.2:g.77189386C>A
NC_000011.9:g.76900431C>A
CM000673.1:g.76900431C>A
NC_000011.8:g.76578079C>A
NG_009086.1:g.66122C>A
NG_009086.2:g.66141C>A
ENST00000409709.9:c.3546C>A
ENST00000670577.1:c.1387C>A
ENST00000409619.6:c.3513C>A
ENST00000409709.7:c.3546C>A
ENST00000458169.2:c.1089C>A
ENST00000458637.6:c.3546C>A
ENST00000467137.1:n.73C>A
ENST00000481328.7:n.1089C>A
NM_000260.3:c.3546C>A
NM_001127180.1:c.3546C>A
NM_001127180.2:c.3546C>A
NM_001369365.1:c.3513C>A

Likely Pathogenic

Met criteria codes 4

PM3_Strong PM2_Supporting PP3 PP4

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 p.Asn1182Lys variant in MYO7A is a missense variant predicted to cause substitution of asparagine to lysine at amino acid 1182. This variant is absent from large population studies (PM2_Supporting, gnomAD v2.1.1). The computational predictor REVEL gives a score of 0.833 which is above the threshold necessary to apply PP3; however, this information is not predictive of pathogenicity on its own (PP3). This variant has been detected in at least four probands with AR Usher syndrome. Two patients were homozygous for the variant, while the other two were compound heterozygous with a pathogenic or likely pathogenic variant; however only one was confirmed trans (c.721C>T (p.Arg241Cys), 2.0 PM3_Strong points, PMID:27460420, 28041643, 31479088, Invitae Internal Data (SCV001211338.4)). At least one patient with a variant identified in this gene displayed sensorineural hearing loss and retinitis pigmentosa, features consistent with Usher syndrome (PP4). The variant has been reported to segregate with AR Usher syndrome in 1 affected family member from 1 family (PP1; PMID: 31479088). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive Usher syndrome based on ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP; PM2_Supporting, PP3, PM3_Strong, PP1, PP4. (The ClinGen Hearing Loss VCEP Specifications Version 2; 06/27/2023).

Met criteria codes

PM3_Strong	✔	2.0 PM3_Strong points total. 0.5 for proband from Bonnet et al., homozygous. 0.5 for proband from Carss et al., assumed to be in trans with the c.721C>T (Arg241Cys) variant in MYO7A, which is classified as likely pathogenic by Counsyl and NIHR Bioresource Rare Diseases, University of Cambridge. 0.5 from Khateb et al., 2020 proband (CIC00072 Index) with the homozygous variant occurrence. 0.5 for Invitae internal proband with a second pathogenic variant in the gene and an unknown phase.
PM2_Supporting	✔	Absent from gnomAD with high coverage.
PP3	✔	REVEL score 0.833. Splicing not predicted to be impacted by Alamut. No animals in UCSC database have an alternate amino acid at this site.
PP4	✔	Identified in 1 French patient with Usher syndrome type 1 (Bonnet et al.) and 1 European male with Usher syndrome (Carss et al.)

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.3546C>A (p.A...	Likely Pathogenic	Usher Syndrome	2023-10-05	1.2	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_000260.4(MYO7A):c.3546C>A (p.A...	Likely Pathogenic	Usher Syndrome	2023-08-25	1.1	-	MYO7A
View	NM_000260.4(MYO7A):c.3546C>A (p.A...	Likely Pathogenic	Usher Syndrome	2019-10-22	1.0	-	MYO7A

Showing 1 to 3 of 3 rows

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