The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000260.4(MYO7A):c.4115T>G (p.Val1372Gly)

Version: 2.0

CA353603

224749 (ClinVar)

Gene: MYO7A (HGNC:4647)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 580d30fb-1bb1-468a-bb63-1d786dac0556
Approved on: 2024/11/26
Published on: 2025/1/6

HGVS expressions

NM_000260.4(MYO7A):c.4115T>G
NM_000260.4:c.4115T>G
NM_000260.4(MYO7A):c.4115T>G (p.Val1372Gly)
NC_000011.10:g.77192241T>G
CM000673.2:g.77192241T>G
NC_000011.9:g.76903286T>G
CM000673.1:g.76903286T>G
NC_000011.8:g.76580934T>G
NG_009086.1:g.68977T>G
NG_009086.2:g.68996T>G
ENST00000409709.9:c.4115T>G
ENST00000670577.1:c.1956T>G
ENST00000409619.6:c.4082T>G
ENST00000409709.7:c.4115T>G
ENST00000458169.2:c.1658T>G
ENST00000458637.6:c.4115T>G
ENST00000481328.7:n.1658T>G
NM_000260.3:c.4115T>G
NM_001127180.1:c.4115T>G
NM_001127180.2:c.4115T>G
NM_001369365.1:c.4082T>G

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM3 PM5_Supporting PM2_Supporting

Not Met criteria codes 1

BA1

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.4115T>G variant in MYO7A is a missense variant predicted to cause substitution of valine by glycine at amino acid 1372. The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001332 (1/75054 alleles) in the African/African-American population, which is lower than the ClinGen Hearing Loss VCEP threshold (<0.00007) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.869, which is above the threshold of 0.7, evidence that correlates with impact to MYO7A function (PP3). At least one patient with this variant displayed congenital sensorineural hearing loss, delayed gross motor development, and rod-cone dystrophy, which is highly specific for Usher syndrome (PP4, PMID: 31836858). This individual was compound heterozygous for the variant and a pathogenic variant published by multiple submitters in ClinVar (c.6025del (p.Ala2009Profs*32)) and confirmed in trans by parental testing (1 PM3 point, PMID: 31836858). A different missense variant in the same codon (c.4114G>A (p.Val1372Met), PMID: 33576163), has been reported in the homozygous state in a patient with hearing loss and retinitis pigmentosa. However, this other variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen Hearing loss VCEP (PM5_Supporting). In summary, this variant has been classified as a likely pathogenic variant for autosomal recessive Usher syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PM3, PP3, PP4, PM2_Supporting, PM5_Supporting (ClinGen Hearing Loss VCEP specifications version 2; 11/26/2024).

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.869, which is above the threshold of 0.7, evidence that correlates with impact to MYO7A function (PP3).
PP4	✔	At least one patient with this variant displayed congenital sensorineural hearing loss, delayed gross motor development, and rod-cone dystrophy, which is highly specific for Usher syndrome (PP4, PMID: 31836858).
PM3	✔	At least one patient with this variant displayed congenital sensorineural hearing loss, delayed gross motor development, and rod-cone dystrophy, which is highly specific for Usher syndrome (PP4, PMID: 31836858). This individual was compound heterozygous for the variant and a pathogenic variant published by multiple submitters in ClinVar (c.6025del (p.Ala2009Profs*32)) and confirmed in trans by parental testing (1 PM3 point, PMID: 31836858).
PM5_Supporting	✔	An individual with Usher syndrome was reported to be homozygous for a different missense variant at the same amino acid residue NM_000260.3(MYO7A):c.4114G>A(Val1372Met). PMID: 33576163.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001332 (1/75054 alleles) in the African/African-American population, which is lower than the ClinGen Hearing Loss VCEP threshold (<0.00007) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

BA1	✖	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.4115T>G (p.V...	Likely Pathogenic	Usher Syndrome	2025-01-06	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_000260.4(MYO7A):c.4115T>G (p.V...	Uncertain Significance	Usher Syndrome	2020-04-30	1.0	-	MYO7A

Showing 1 to 2 of 2 rows

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