Variant: NM_000260.4(MYO7A):c.6560G>A (p.Gly2187Asp)

Version: 1.1

CA278713

43335 (ClinVar)

Gene: MYO7A (HGNC:4647)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8815458c-46db-44af-b7e7-82344035be79
Approved on: 2022-08-03
Published on: 2022-08-03

HGVS expressions

NM_000260.4:c.6560G>A
NM_000260.4(MYO7A):c.6560G>A
NM_000260.4(MYO7A):c.6560G>A (p.Gly2187Asp)
NC_000011.10:g.77214608G>A
CM000673.2:g.77214608G>A
NC_000011.9:g.76925653G>A
CM000673.1:g.76925653G>A
NC_000011.8:g.76603301G>A
NG_009086.1:g.91344G>A
NG_009086.2:g.91363G>A
ENST00000409709.9:c.6560G>A
ENST00000670577.1:c.4361G>A
ENST00000409619.6:c.6413G>A
ENST00000409709.7:c.6560G>A
ENST00000458169.2:c.3986G>A
ENST00000458637.6:c.6440G>A
ENST00000481328.7:n.5110G>A
ENST00000605744.1:n.2074G>A
NM_000260.3:c.6560G>A
NM_001127180.1:c.6440G>A
NM_001127180.2:c.6440G>A
NM_001369365.1:c.6413G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PP4 PM3

Not Met criteria codes 22

BP5 BP7 BP4 BP3 BP1 BP2
BS2 BS1 BS4 BS3 PP1 PP2
PVS1 PM6 PM1 PM5 PM4
PS1 PS2 PS3 PS4 BA1

Evidence Links 2

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.6560G>A variant in MYO7A is a missense variant predicted to cause substitution of glycine by aspartic acid at amino acid 2187. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00001190 (1/84018 alleles) in the European (non-Finnish) 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 0.915, which is above the threshold of 0.7, evidence that correlates with impact to MYO7A (PP3). At least one patient with this variant displayed profound congenital deafness and retinitis pigmentosa, which is highly specific for Usher syndrome (PP4, PMID:10930322). This variant has been detected in at least two individuals with Usher syndrome. Of those individuals, both were compound heterozygous for the variant and a pathogenic or likely pathogenic variant published by multiple submitters in ClinVar (c.2904G>T (p.Glu968Asp) and c.3719G>A (p.R1240Q)) and both of those were presumed in trans (1 PM3 point, PMID:10930322, LMM) (PM3). In summary, this variant was reviewed by the ClinGen Hearing Loss VCEP and 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_P, PP3, PP4, PM3 (ClinGen Hearing Loss VCEP specifications version 2; 7/20/2022).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00001190 (1/84018 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Hearing Loss VCEP threshold (<0.00007) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.915, which is above the threshold of 0.7, evidence that correlates with impact to MYO7A (PP3).
PP4	✔	At least one patient with this variant displayed profound congenital deafness and retinitis pigmentosa, which is highly specific for Usher syndrome (PP4, PMID:10930322). All patients had profound congenital deafness and RP PubMed:10930322
PM3	✔	This variant has been detected in at least two individuals with Usher syndrome. Of those individuals, both were compound heterozygous for the variant and a pathogenic or likely pathogenic variant published by multiple submitters in ClinVar (c.2904G>T (p.Glu968Asp) and c.3719G>A (p.R1240Q)) and both of those were presumed in trans (1 PM3 point, PMID:10930322, LMM) (PM3). Found presumed in trans with p.Glu968Asp (a two star pathogenic variant in clinvar). 0.5 points. PubMed:10930322

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
BP4	✖	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
BP2		✖	Found presumed in trans with p.Glu968Asp (a two star pathogenic variant in clinvar). 0.5 points. PubMed:10930322
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	Disrupts interaction with the PDZ3 domain of USH1C. However, the experiment does not have great controls and this type of assay is not listed as adequate for PS3_Supporting PubMed:28439001
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
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	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
PM5		✖	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
PS1		✖	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
PS3		✖	Disrupts interaction with the PDZ3 domain of USH1C. However, the experiment does not have great controls and this type of assay is not listed as adequate for PS3_Supporting
			Disrupts interaction with the PDZ3 domain of USH1C. However, the experiment does not have great controls and this type of assay is not listed as adequate for PS3_Supporting PubMed:28439001
PS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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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