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.6062A>G (p.Lys2021Arg)

Version: 2.0

CA10576905

228282 (ClinVar)

Gene: MYO7A
Condition: Usher syndrome type 1 (MONDO:0010168)
Inheritance Mode: Autosomal recessive inheritance
UUID: c7b98a09-bc39-416b-af89-f1dfff058317
Approved on: 2023/1/18
Published on: 2023/2/6

HGVS expressions

NM_000260.4(MYO7A):c.6062A>G (p.Lys2021Arg)
NM_000260.4:c.6062A>G
NM_000260.4(MYO7A):c.6062A>G
NC_000011.10:g.77211162A>G
CM000673.2:g.77211162A>G
NC_000011.9:g.76922207A>G
CM000673.1:g.76922207A>G
NC_000011.8:g.76599855A>G
NG_009086.1:g.87898A>G
NG_009086.2:g.87917A>G
ENST00000409709.9:c.6062A>G
ENST00000670577.1:c.3863A>G
ENST00000409619.6:c.5915A>G
ENST00000409709.7:c.6062A>G
ENST00000458169.2:c.3488A>G
ENST00000458637.6:c.5948A>G
ENST00000481328.7:n.3598A>G
ENST00000526863.2:n.25+251A>G
ENST00000605744.1:n.1529A>G
NM_000260.3:c.6062A>G
NM_001127180.1:c.5948A>G
NM_001127180.2:c.5948A>G
NM_001369365.1:c.5915A>G

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PM3 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*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.6062A>G (NM_000260.4(MYO7A):c.6062A>G (p.Lys2021Arg)) variant in MYO7A is a missense variant predicted to cause substitution of lysine by arginine at amino acid 2021. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.748, which is above the threshold of 0.7, evidence that correlates with impact to MYO7A function (PP3). This variant has been detected in at least 4 individuals with Usher Syndrome type 1 (from three families). For one of those individuals, they were compound heterozygous for the variant and a pathogenic/likely pathogenic variant (phase unknown) ((NM_000260.4(MYO7A):c.722G>A (p.Arg241His); 0.5 PM3 points; 21436283). In another family, this variant was found in the homozygous state in a male adolescent, 14 years of age, with bilateral congenital hearing loss and features of night blindness (0.5 PM3 points; Allan, 2014; 1). Due to consanguinity, 2 individuals from the same family were homozygous for the variant (0.25 PM3 points; Allam, 2014; 1) (PM3). At least one patient with this disease displayed sensorineural hearing loss and retinitis pigmentosa, which is highly specific for Usher Syndrome 1 (PMID: 21436283; PP4). This variant was re-reviewed on 1.18.2023 and because no additional evidence is available, professional judgment was used to retain this variant as likely pathogenic for autosomal recessive Usher Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP (PM2_supporting, PP3, PM3, PP4; Version 2; 2022). 1. https://docs.google.com/document/d/17VJ_cidV8dqRQMHTzSVrFa-7PrmJ4trkw2wQsNEPqvk/edit

Met criteria codes

PM2_Supporting	✓	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PM3	✓	Variant was reported in an individual from France with Usher Syndrome 1. This variant was found in the compound heterozygous state with another variant (NM_000260.4(MYO7A):c.722G>A p.Arg241His), which is pathogenic/likely pathogenic. Phase was not reported (0.5 points; PM3; PMID: 21436283). Variant was found in the homozygous state at least two children (boy age nine and girl age thirteen) from the same family, each of whom had sensorineural hearing loss with early symptoms of retinal degeneration. The parents were consanguineous (0.25 points; PM3; Allam, 2014). In another family, this variant was found in the homozygous state in a male adolescent, 14 years of age, with bilateral congenital hearing loss, trouble seeing at night, and chronic pain in the throat (0.5 points; PM3; Allam, 2014).
PP3	✓	The REVEL score 0.748 (above the threshold for pathogenicity set by the Hearing Loss VCEP). The variant is very well-conserved in UCSC database across species, except for 1 mammal (elephant) which has Thr at this site. The results from 3 in silico predictors/lines of evidence, [PolyPhen2, conservation, REVEL score], provide evidence that correlates with impact to MYO7A function (PP3).
PP4	✓	All patients evaluated had hearing loss, which is highly specific for Usher Syndrome Type 1 (PP4).

Curation History

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