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_206933.4(USH2A):c.956G>A (p.Cys319Tyr)

Version: 2.0

CA252231

2355 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: de5c11cc-0c72-45e3-a3d9-8708277e343d
Approved on: 2022/8/3
Published on: 2022/8/3

HGVS expressions

NM_206933.4:c.956G>A
NM_206933.4(USH2A):c.956G>A (p.Cys319Tyr)
NC_000001.11:g.216325492C>T
CM000663.2:g.216325492C>T
NC_000001.10:g.216498834C>T
CM000663.1:g.216498834C>T
NC_000001.9:g.214565457C>T
NG_009497.1:g.102905G>A
NG_009497.2:g.102957G>A
ENST00000307340.8:c.956G>A
ENST00000674083.1:c.956G>A
ENST00000307340.7:c.956G>A
ENST00000366942.3:c.956G>A
NM_007123.5:c.956G>A
NM_206933.2:c.956G>A
NM_206933.3:c.956G>A
NM_007123.6:c.956G>A

Pathogenic

Met criteria codes 3

PP1 PP4 PM3_Very Strong

Not Met criteria codes 5

PP3 PM2 BA1 BS1 BP4

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.956G>A variant in USH2A is a missense variant predicted to cause substitution of cysteine by tyrosine at amino acid 319. The highest population minor allele frequency in gnomAD v2.1.1 is 0.0002679 (15/34508 alleles) in the Latino/Admixed American population (PM2_Supporting, BS1, and BA1 are not met). The computational predictor REVEL gives a score of 0.524, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function. At least one patient was homozygous for this variant and displayed moderate to severe sensorineural hearing loss and progressive retinitis pigmentosa, which is highly specific for Usher syndrome (PP4, PMID:10729113). This variant has been detected in 5 individuals with Usher syndrome. For 5 of those individuals, 4 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and all of those were confirmed in trans by family testing (c.3408T>A (p.Ser1136Arg), c.12067-2A>G, c.5329C>T (p.Arg1777Trp), c.15089C>A (p.S5030X)), (4 PM3 points, PMID: 26969326, 33089500, LMM internal data, EGL internal data). One individual was homozygous for the variant (0.5 PM3 points, PMID:10729113) (PM3_VeryStrong). One of the individuals who was compound heterozygous for the variant and another pathogenic variant in USH2A (RCV000599950.1), had an affected sibling in whom both variants segregated (PP1). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive Usher syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PP4, PM3_VS, PP1 (Hearing Loss VCEP specifications version 2; 6/15/2022).

Met criteria codes

PP1	✔	One of the individuals who was compound heterozygous for the variant and another pathogenic variant in USH2A (RCV000599950.1), had an affected sibling in whom both variants segregated (PP1).
PP4	✔	At least one patient was homozygous for this variant and displayed moderate to severe sensorineural hearing loss and progressive retinitis pigmentosa, which is highly specific for Usher syndrome (PP4, PMID:10729113).
PM3_Very Strong	✔	This variant has been detected in 5 individuals with Usher syndrome. For 5 of those individuals, 4 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and all of those were confirmed in trans by family testing (c.3408T>A (p.Ser1136Arg), c.12067-2A>G, c.5329C>T (p.Arg1777Trp), c.15089C>A (p.S5030X)), (4 PM3 points, PMID: 26969326, 33089500, LMM internal data, EGL internal data). One individual was homozygous for the variant (0.5 PM3 points, PMID:10729113) (PM3_VeryStrong). 1 proband het. with VUS variant c.5329C>T (p.Arg1777Trp) PubMed:26969326 1 proband homozygous. PubMed:10729113

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.524, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function.
PM2	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.0002679 (15/34508 alleles) in the Latino/Admixed American population (PM2_Supporting, BS1, and BA1 are not met).
BA1	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.0002679 (15/34508 alleles) in the Latino/Admixed American population (PM2_Supporting, BS1, and BA1 are not met).
BS1	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.0002679 (15/34508 alleles) in the Latino/Admixed American population (PM2_Supporting, BS1, and BA1 are not met).

BP4		✖	The computational predictor REVEL gives a score of 0.524, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function.

Curation History

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