

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

NM_206933.4:c.956G>A

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**

PM3_Very Strong

PP1

PP4

Not Met criteria codes **5**

BP4

PP3

PM2

BA1

BS1

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

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 
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).

Not Met criteria codes

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.
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).

Curation History 



Showing 1 to 2 of 2 rows

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