

Variant: *NM_206933.4(USH2A):c.13396C>T (p.Pro4466Ser)*

Version: 1.1

CA143316 [↗](#)

48417 (ClinVar) [↗](#)

Gene: USH2A ([HGNC:7399](#))

Condition: Usher syndrome ([MONDO:0019501](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: afedcdf5-4814-4f0e-a431-fb76cffe27e8

Approved on: 2022/11/22

Published on: 2023/2/6

HGVS expressions

NM_206933.4:c.13396C>T

NM_206933.4(USH2A):c.13396C>T (p.Pro4466Ser)

NC_000001.11:g.215674515G>A

CM000663.2:g.215674515G>A

NC_000001.10:g.215847857G>A

CM000663.1:g.215847857G>A

NC_000001.9:g.213914480G>A

NG_009497.1:g.753882C>T

NG_009497.2:g.753934C>T

ENST00000307340.8:c.13396C>T

ENST00000674083.1:c.13396C>T

ENST00000307340.7:c.13396C>T

NM_206933.2:c.13396C>T

NM_206933.3:c.13396C>T

Uncertain Significance

Met criteria codes **2**

PM3_Supporting BP4

Not Met criteria codes **24**

PM6 PM2 PM1 PM5 PM4
BS2 BS1 BS4 BS3 PVS1
PS1 PS2 PS3 PS4 BP3 BP1
BP2 BP5 BP7 BA1 PP1 PP2
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*

[↗](#) **PDF**

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Hearing Loss VCEP

The variant NM_206933.4:c.13396C>T in USH2A is a missense variant predicted to cause substitution of proline by serine at amino acid 4466 (p.Pro4466Ser). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00044 (57/128120 alleles) in the European (non-

Finnish) population, which does not meet either PM2_supporting nor BS1 criteria. The REVEL computational prediction analysis tool produced a score of 0.049, which is below the threshold necessary to apply BP4. This variant has been reported in two probands, one with retinitis pigmentosa, however the second variant was not specified and no PM3 points were awarded and the other homozygous with inherited retinal disease (PM3_Supporting; PMID 28041643, 32581362). In summary, the variant meets criteria to be classified as uncertain significance for AR Usher syndrome. ACMG/AMP criteria met, as specified by the ClinGen Hearing Loss VCEP: BP4, PM3_Supporting (ClinGen Hearing Loss VCEP specifications version 2; 11/22/2022)

Met criteria codes

PM3_Supporting			This variant has been reported in two probands, one with retinitis pigmentosa, however the second variant was not specified and no PM3 points were awarded and the other homozygous with inherited retinal disease
BP4			REVEL = 0.049 (<0.15)

Not Met criteria codes

PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00044 (57/128120 alleles) in the European (non-Finnish) population, which does not meet either PM2_supporting nor BS1 criteria.
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
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00044 (57/128120 alleles) in the European (non-Finnish) population, which does not meet either PM2_supporting nor BS1 criteria.
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			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

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			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			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			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline



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