

Variant: NM_016239.4(MYO15A):c.4642G>A (p.Ala1548Thr)

Version: 1.0

CA8423973 [↗](#)

228954 (ClinVar) [↗](#)

Gene: MYO15A ([HGNC:51168](#))

Condition: autosomal recessive nonsyndromic hearing loss 3 ([MONDO:0010860](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 99de4974-7876-4054-8f80-a4970421a472

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HGVS expressions

NM_016239.4(MYO15A):c.4642G>A (p.Ala1548Thr)

NM_016239.4:c.4642G>A

NC_000017.11:g.18136462G>A

CM000679.2:g.18136462G>A

NC_000017.10:g.18039776G>A

CM000679.1:g.18039776G>A

NC_000017.9:g.17980501G>A

NG_011634.1:g.32757G>A

NG_011634.2:g.32757G>A

ENST00000647165.2:c.4642G>A

ENST00000205890.9:c.4642G>A

ENST00000615845.4:c.4642G>A

NM_016239.3:c.4642G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting

PP3

PS3_Supporting

PM3_Strong

Not Met criteria codes 5

BP4

PS1

BA1

BS1

BS2

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 OTOF and MYO15A Version 1

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

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

Evidence submitted by expert panel

Hearing Loss VCEP

The NM_016239.4(MYO15A):c.4642G>A variant is a missense variant predicted to cause a substitution of alanine to threonine at amino acid 1548. This variant has been reported in 2 probands with hearing loss. Both were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and were confirmed in trans by family testing (PMIDs : 26561413, 33398081). An additional patient with congenital profound HL were compound heterozygous for this variant and another rare missense of unknown significance (PMID : 26915297) (PM3_Strong). The allele frequency of this variant is 0.005% (76/1180010) of European non-finnish chromosomes by gnomAD

v.4, which is lower than the thresholds defined by the ClinGen Hearing Loss Expert Panel for PM2_Supporting, meeting this criterion (PM2_Supporting). A study reporting Inner hair cells derived from patient iPSc compound for this variant and another missense showed stereocilia length, electrophysiological and F-actin organization abnormalities. This phenotype has been rescued after CRISPR-Cas9 correction of the c.4642G>A variant, indicating that this variant impacts protein function (PMID: 26915297)(PS3_P). The REVEL computational prediction analysis tool produced a score of 0.884, which is above the threshold necessary to apply PP3 (PP3). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive hearing loss based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: (PS3_P, PM2_P, PM3_S, PP3) (ClinGen Hearing Loss VCEP specifications version 1; 10/8/2025)

Met criteria codes

PM2_Supporting			The allele frequency of this variant is 0.005% (76/1180010) of European non-finnish chromosomes by gnomAD v.4, which is lower than the thresholds defined by the ClinGen Hearing Loss Expert Panel for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP3			The REVEL computational prediction analysis tool produced a score of 0.884, which is above the threshold necessary to apply PP3 (PP3).
PS3_Supporting			Inner hair cells derived from patient iPSc compound for this variant and another missense showed stereocilia length, electrophysiological and F-actin organization abnormalities. This phenotype has been rescued after CRISPR-Cas9 correction of the c.4642G>A variant, indicating that this variant impacts protein function (PMID: 26915297)(PS3_P).
PM3_Strong			This variant has been detected in 2 probands with hearing loss. Both were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and were confirmed in trans by family testing), (optional - provide list of variants, PM3 points, PMIDs : 26561413, 33398081). Another patient with congenital profound HL were compound heterozygous for this variant and another rare missense of unknown significance (PMID : 26915297) (PM3_Strong).

Not Met criteria codes

BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			Same amino acid change reported in a single patient with congenital severe HL PMID : 26969326 (c.4643C>T - p.Ala1548Thr), associated with another missense of unknown significance (c.5866C>T - p.(Arg1956Trp : rare, well predicted, never reported). These arguments doesn't allow to use PS1
BA1			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
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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