

Variant: *NM_000260.4(MYO7A):c.2476G>A (p.Ala826Thr)*

Version: 1.1

CA180669 [↗](#)

177732 (ClinVar) [↗](#)

Gene: MYO7A ([HGNC:4647](#))

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 99eea1cf-9c28-4b80-9057-8f3ed2a98c2c

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HGVS expressions

NM_000260.4(MYO7A):c.2476G>A (p.Ala826Thr)

NM_000260.4:c.2476G>A

NC_000011.10:g.77179843G>A

CM000673.2:g.77179843G>A

NC_000011.9:g.76890889G>A

CM000673.1:g.76890889G>A

NC_000011.8:g.76568537G>A

NG_009086.1:g.56580G>A

NG_009086.2:g.56598G>A

ENST00000409709.9:c.2476G>A

ENST00000409893.6:c.541G>A

ENST00000670577.1:c.317G>A

ENST00000409619.6:c.2443G>A

ENST00000409709.7:c.2476G>A

ENST00000409893.5:c.2476G>A

ENST00000458169.2:c.19G>A

ENST00000458637.6:c.2476G>A

ENST00000481328.7:n.19G>A

ENST00000620575.4:c.2476G>A

NM_000260.3:c.2476G>A

NM_001127179.2:c.2476G>A

NM_001127180.1:c.2476G>A

NM_001127180.2:c.2476G>A

NM_001369365.1:c.2443G>A

Uncertain Significance

Met criteria codes **4**

BA1 PP1 PP4 PM3

Not Met criteria codes **6**

PS1 PS4 PP3 PM5 BS2

BP4

Evidence Links **6**

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

Evidence submitted by expert panel

Hearing Loss VCEP

The variant NM_000260.4:c.2476G>A in MYO7A is a missense variant predicted to cause substitution of alanine by threonine at amino acid 826 (p.Ala826Thr). The filtering allele frequency of the variant is 0.55% for South Asian chromosomes by gnomAD, including 1 homozygous observation (144/22680 with 95% CI), meeting BA1 criteria. The REVEL computational prediction analysis tool produced a score of 0.54, which meets neither PP3 nor BP4 criteria. This variant has been detected in 2 patients with Usher syndrome in trans with pathogenic variants, and has been observed as homozygous in at least 9 cases (PM3; PMID:27460420, 29490346, 23770805, 22135276, 18181211, 9382091). The evidence originally met PM3_Strong criteria, however was downgraded to PM3 by the VCEP due to the high filtering allele frequency of the variant. The variant has also been reported to segregate with Usher syndrome in at least 12 family members (PP1_Strong; 23770805, 9382091). In most of these cases, the patients were documented to have both hearing loss and retinitis pigmentosa (PP4; PMID:27460420, 29490346, 23770805, 22135276, 9382091). 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: BA1, PM3, PP1_Strong, PP4 (ClinGen Hearing Loss VCEP specifications version 2; 1/18/2023).

Met criteria codes

BA1			This variant is present in 144/22680 South Asian alleles in gnomAD, including 1 homozygote. The FAF is 0.55%, which meets our BA1 cutoff.
PP1			The p.Ala826Thr variant segregated with disease in 12 affected individuals. Of 243 Pakistani families with hearing loss, 34 consanguineous families with apparent linkage to MYO7A, CDH23, or SLC26A4 were tested for variants in 24 genes from the OtoSeq panel. The p.Ala826Thr variant was identified in homozygosity in one affected family. Three affected siblings were homozygous for the p.Ala826Thr variant and the p.Gly434Arg variant (a rare VUS). Parents were carriers for each of those variants. PubMed:23770805 28 families with Usher Type 1B were tested for variants in MYO7A. The p.Ala826Thr variant was identified in the homozygous state in 4 Moroccan families (counting those with different haplotypes) and in the compound heterozygous state in a fifth family in trans with the p.Gly214Arg variant. (p.Gly214Arg is classified as pathogenic by 4 clinical labs in ClinVar). It segregated with disease in 10 affected individuals. PubMed:9382091
PP4			Multiple patients with Usher syndrome were identified with the p.Ala826Thr variant.
PM3			The p.Ala826Thr variant has been identified in 9 homozygous individuals and 2 compound heterozygous individuals (with two pathogenic variants). 3 points for PM3, meeting strong criteria, but was downgraded to moderate based on high FAF. Of 243 Pakistani families with hearing loss, 34 consanguineous families with apparent linkage to MYO7A, CDH23, or SLC26A4 were tested for variants in 24 genes from the OtoSeq panel. The p.Ala826Thr variant was identified in homozygosity in one affected family. The proband was also homozygous for p.Gly434Arg. (A rare VUS) PubMed:23770805 427 individuals with Usher syndrome from various European medical centers were exome sequenced. The p.Ala826Thr was identified in the homozygous state in one individual. This individual was also heterozygous for p.Ser3590Cys in ADGRV1. PubMed:27460420

74 Israeli and Palestinian families with Usher syndrome received whole exome sequencing. The p.Ala826Thr variant was identified in the homozygous state in 1 North African Jewish family and one Moroccan Jewish family. [PubMed:29490346](#)

557 Pakistani families with hearing loss were tested for variants in MYO7A. The p.Ala826Thr variant was identified in the homozygous state in one family. No segregation information was provided. [PubMed:18181211](#)

28 families with Usher Type 1B were tested for variants in MYO7A. The p.Ala826Thr variant was identified in the homozygous state in 4 Moroccan families (counting those with different haplotypes) and in the compound heterozygous state in a fifth family in trans with the p.Gly214Arg variant. (p.Gly214Arg is classified as pathogenic by 4 clinical labs in ClinVar). [PubMed:9382091](#)

188 individuals with Usher were tested for variants in MYO7A, CDH23, PCDH15, USH1C, USH1G, USH2A, GPR98, WHRN, CLRN1, and SLC4A7. The p.Ala826Thr variant was identified in 1 Caucasian compound heterozygous individual who also harbored the p.Trp1431X variant. [PubMed:22135276](#)

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			A summed case control analysis was done using all of the probands and controls from the literature, along with the South Asian controls from gnomAD. In a Chi squared analysis, it was determined that the p.Ala826Thr variant was not enriched in cases v controls with a p value of 0.3262.
PP3			The REVEL score is 0.54, which is inconclusive. Neither BP4 nor PP3 are met.
PM5			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
BP4			The REVEL score is 0.54, which is inconclusive. Neither BP4 nor PP3 are met.

Curation History



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