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Variant: NM_000441.2(SLC26A4):c.706C>G (p.Leu236Val)

CA132738

43565 (ClinVar)

Gene: SLC26A4 (HGNC:5172)
Condition: Pendred syndrome (MONDO:0010134)
Inheritance Mode: Autosomal recessive inheritance
UUID: f3b84ed4-48e1-4d17-8fda-a9bacc5d12b8
Approved on: 2018-09-10
Published on: 2018-12-10

HGVS expressions

NM_000441.2(SLC26A4):c.706C>G (p.Leu236Val)
NM_000441.2:c.706C>G
NC_000007.14:g.107675050C>G
CM000669.2:g.107675050C>G
NC_000007.13:g.107315495C>G
CM000669.1:g.107315495C>G
NC_000007.12:g.107102731C>G
NG_008489.1:g.19416C>G
ENST00000644269.2:c.706C>G
ENST00000265715.7:c.706C>G
NM_000441.1:c.706C>G

Pathogenic

Met criteria codes 4

PM5 PP1_Moderate PM3_VeryStrong PP4

Not Met criteria codes 2

PM2 PP3

Evidence Links 1

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.706C>G variant in SLC26A4 is a missense variant predicted to cause substitution of leucine by valine at amino acid 236 (p.Leu236Val). The variant was identified in 0.01833% (11/59998) of admixed American alleles, which is the highest population minor allele frequency in gnomAD v4.1.0 (PM2_Supporting and BS1 are not met). This variant has been detected in 3 probands in trans with a pathogenic variant, in 5 probands in phase unknown with a pathogenic variant, and in the homozygous state in 3 probands, all of whom had hearing loss and/or inner ear malformations consistent with Pendred syndrome. The variant was also identified with a pathogenic splice site variant in 2 probands (PM3_VeryStrong; Partners Laboratory for Molecular Medicine internal data ClinVar SCV000060159.5,

ARUP internal data ClinVar SCV000605149.1, Chinese PLA General Hospital internal data, Molecular Otolaryngology and Renal Research Laboratories internal data, Revvity ClinVar SCV002023538.3GeneDx internal data ClinVar SCV001783711.3, Invitae internal data ClinVar SCV002234501.3). This variant was seen in two probands with no second variant identified whose phenotypes were consistent with Pendred syndrome (PMID: 34410491, 34515852), as well as in one proband with enlarged vestibular aqueduct who was compound heterozygous with a likely pathogenic variant in phase unknown (PP4; PMID: 36703223). A different pathogenic missense variant (p.Leu236Pro) has been previously identified at this codon of SLC26A4, which may indicate that this residue is critical to the function of the protein (PM5; ClinVar Variation ID 4817). Additionally, the variant was seen in an adult with deafness who had two pathogenic GJB2 variants in trans (Revvity internal data ClinVar SCV002023538.3). The variant has been reported to segregate with hearing loss in two affected family members (PP1_Moderate; Partners Laboratory for Molecular Medicine internal data ClinVar SCV000060159.5). In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive Pendred syndrome based on the ACMG/AMP criteria applied as specified by the Hearing Loss Expert Panel: PM3_VeryStrong, PM5, PP1_Moderate, PP4. (ClinGen Hearing Loss VCEP specifications version 2; 10/16/2024)

Met criteria codes

PM5	✔	PM5 was applied for p.Leu236Pro, which is classified as pathogenic by 10 clinical labs in ClinVar (Variation ID: 4817).
PP1_Moderate	✔	Detected in trans with a frameshift variant in 1 proband (Partners Laboratory for Molecular Medicine internal data, ClinVar SCV000060159.6). It then segregated across five meioses to a distant relative, where it was found in homozygosity in two siblings with congenital hearing loss and a paternal family history of hearing loss.
PM3_Very Strong	✔	This variant has been detected in 3 probands in trans with a pathogenic variant, in 5 probands in phase unknown with a pathogenic variant, and in the homozygous state in 3 probands, all of whom had hearing loss and/or inner ear malformations consistent with Pendred syndrome. The variant was also identified with a pathogenic splice site variant in 2 probands (Partners Laboratory for Molecular Medicine internal data ClinVar SCV000060159.5, ARUP internal data ClinVar SCV000605149.1, Chinese PLA General Hospital internal data, Molecular Otolaryngology and Renal Research Laboratories internal data, Revvity internal data ClinVar SCV002023538.3, GeneDx internal data ClinVar SCV001783711.3, Invitae internal data ClinVar SCV002234501.3). This variant was seen in two probands with no second variant identified whose phenotypes were consistent with Pendred syndrome (PMID: 34410491, 34515852), as well as in one proband with enlarged vestibular aqueduct who was compound heterozygous with a likely pathogenic variant in phase unknown (PMID: 36703223). No other pathogenic variant identified in patient. Patient had bilateral SNHL w/ “atypical phenotype" PubMed:25991456
PP4	✔	Detected in 1 proband with hearing loss and temporal bone abnormality (Partners Laboratory for Molecular Medicine internal data, ClinVar SCV000060159.6).

Not Met criteria codes

PM2	✖	This variant has a minor allele frequency of 0.01833% (11/59998) for the Admixed American population in gnomAD v4.1.0
PP3	✖	REVEL score 0.319

Curation History

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