The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000441.2(SLC26A4):c.1963A>G (p.Ile655Val)

Version: 1.3

CA261421

43528 (ClinVar)

Gene: SLC26A4 (HGNC:5172)
Condition: Pendred syndrome (MONDO:0010134)
Inheritance Mode: Autosomal recessive inheritance
UUID: d41262ab-283b-474c-bf6b-db76d1311e8b
Approved on: 2023/8/27
Published on: 2023/10/5

HGVS expressions

NM_000441.2(SLC26A4):c.1963A>G (p.Ile655Val)
NM_000441.2:c.1963A>G
NC_000007.14:g.107701986A>G
CM000669.2:g.107701986A>G
NC_000007.13:g.107342431A>G
CM000669.1:g.107342431A>G
NC_000007.12:g.107129667A>G
NG_008489.1:g.46352A>G
ENST00000644269.2:c.1963A>G
ENST00000644846.1:c.674A>G
ENST00000265715.7:c.1963A>G
ENST00000492030.2:n.250A>G
NM_000441.1:c.1963A>G

Likely Pathogenic

Met criteria codes 4

PM3 PP1 PP4 PM2_Supporting

Not Met criteria codes 1

BP4

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 c.1963A>G variant in SLC26A4 is a missense variant predicted to cause substitution of isoleucine by valine at amino acid 655 (p.Ile655Val). The highest population minor allele frequency in gnomAD v2.1.1 is .005% (2/34558) in the Latino population, which is lower than the ClinGen Hearing Loss VCEP threshold (<0.007) for PM2_Supporting, meeting this criterion (PM2_Supporting). This variant has

been detected in 2 probands with hearing loss and enlarged vestibular aqueducts (PP4; Laboratory for Molecular Medicine internal data, PMID: 26894580). In one of those probands, a pathogenic variant (VCV000004818.5) was observed in trans, and the variant was observed in the homozygous state in the other proband (PM3; Laboratory for Molecular Medicine internal data, PMID: 26894580).The compound heterozygous individual had an affected sibling in whom both variants segregated (PP1; Laboratory for Molecular Medicine internal data). Computational prediction tools and conservation analyses do not provide strong support for or against an impact to the protein. This variant was re-reviewed on 8.22.23 and because no additional evidence is available, professional judgment was used to retain this variant as likely pathogenic for autosomal recessive Pendred syndrome. In summary, this variant is classified as likely pathogenic for autosomal recessive Pendred syndrome. ACMG/AMP Criteria applied as specified by the Hearing Loss Expert Panel 8/22/2023 (PM2_Supporting, PP4, PM3, PP1)

Met criteria codes

PM3	✔	1 proband compound heterozygous for variant and c.1246A>C (p.Thr416Pro) in SLC26A4 (VCV000004818.5). Proband and affected sibling present with sensorineural hearing loss, enlarged vestibular aqueducts, cochlea abnormalities and delayed walking. Parents identified as carriers (Laboratory for Molecular Medicine internal data). 1 South Italian child homozygous for I655V variant. Presented with SNHL and EVA. Parents were both carriers and their great-great grandparents were consanguineous
PP1	✔	1 proband compound heterozygous for variant and c.1246A>C (p.Thr416Pro) in SLC26A4 (VCV000004818.5). Proband and affected sibling present with sensorineural hearing loss, enlarged vestibular aqueducts, cochlea abnormalities and delayed walking. Parents identified as carriers (Laboratory for Molecular Medicine internal data).
PP4	✔	Probands with SNHL and EVA (Laboratory for Molecular Medicine internal data, PMID: 26894580)
PM2_Supporting	✔	.005% (2/34558) Latino alleles in gnomAD

Not Met criteria codes

BP4	✖	The REVEL score is 0.236

Curation History

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