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Variant: NM_000441.2(SLC26A4):c.2145G>T (p.Lys715Asn)

Version: 2.1

CA261425

43541 (ClinVar)

Gene: SLC26A4 (HGNC:5172)
Condition: Pendred syndrome (MONDO:0010134)
Inheritance Mode: Autosomal recessive inheritance
UUID: b6f4c008-3e27-485a-bddb-183a7f974693
Approved on: 2023-08-22
Published on: 2023-10-05

HGVS expressions

NM_000441.2:c.2145G>T
NM_000441.2(SLC26A4):c.2145G>T (p.Lys715Asn)
NC_000007.14:g.107710109G>T
CM000669.2:g.107710109G>T
NC_000007.13:g.107350554G>T
CM000669.1:g.107350554G>T
NC_000007.12:g.107137790G>T
NG_008489.1:g.54475G>T
ENST00000644269.2:c.2145G>T
ENST00000644846.1:c.801G>T
ENST00000265715.7:c.2145G>T
ENST00000492030.2:n.377-46G>T
NM_000441.1:c.2145G>T

Likely Pathogenic

Met criteria codes 3

PP4 PS3_Supporting PM3_Strong

Not Met criteria codes 2

BS1 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.2145G>T variant in SLC26A4 is a missense variant predicted to cause substitution of lysine by asparagine at amino acid 715 (p.Lys715Asn). The highest population minor allele frequency in gnomAD v2.1.1 is 0.06777% (95% CI of 29/30610) in the South Asian population (PM2_supporting, BS1, and BA1 not met). This variant has been observed in 3 probands with hearing loss in trans with another

pathogenic or likely pathogenic variant (PM3_Strong; PMID: 26969326, PMID: 32417962, LMM unpublished data SCV000060131.6). At least one proband with this variant presented with clinical features of sensorineural hearing loss and enlarged vestibular aqueduct, a phenotype specific for Pendred syndrome (PP4; LMM unpublished data SCV000060131.6).This variant has been observed in several other cases where a second variant in SLC26A4 was not found (PMID: 19509082, 19287372, 26188157, 32417962). Functional studies including fluorescence assays and chloride exchange experiments have demonstrated that this variant impacts protein function (PS3_Supporting; PMID: 19509082). Computational prediction tools and conservation analyses do not provide strong support for or against an impact to the protein. 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 08/22/23: PM3_Strong, PS3_Supporting, PP4.

Met criteria codes

PP4	✔	2yo female with congenital SNHL and EVA. Het. for this variant as well as c.1229C>T (p.Thr410Met), classified as Pathogenic by VCEP (LMM internal data, SCV000060131.6)
PS3_Supporting	✔	Fluorescence assay performed by Dai et al. 2009 indicates the K715N mutant exhibits decreased trafficking efficiency to the surface of Xenopus oocytes.
PM3_Strong	✔	LMM internal data: 2yo female with congenital sensorineural hearing loss and EVA. Heterozygous. Also het. for p.Thr410Met, classified as P by VCEP (0.5 PM3 points)

Not Met criteria codes

BS1	✖	v2: Present in 0.09474% (29/30610) of South Asian chromosomes. v3: Present in 0.1312% (4/3048) of South Asian chromosomes. Using v2, BS1_P is not met because the filtering allele frequency is only 0.06777%.
BP4	✖	REVEL score 0.352. Conserved in UCSC database (no mammals have Asn at this site). Splicing is not predicted to be impacted in Alamut.

Curation History

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