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Variant: NM_000441.2(SLC26A4):c.845G>A (p.Cys282Tyr)

Version: 1.1

CA261440

43568 (ClinVar)

Gene: SLC26A4 (HGNC:5172)
Condition: Pendred syndrome (MONDO:0010134)
Inheritance Mode: Autosomal recessive inheritance
UUID: 77c881dd-2f00-4636-a5ae-ac1cae285bee
Approved on: 2023/1/24
Published on: 2023/2/2

HGVS expressions

NM_000441.2(SLC26A4):c.845G>A (p.Cys282Tyr)
NM_000441.2:c.845G>A
NC_000007.14:g.107683281G>A
CM000669.2:g.107683281G>A
NC_000007.13:g.107323726G>A
CM000669.1:g.107323726G>A
NC_000007.12:g.107110962G>A
NG_008489.1:g.27647G>A
ENST00000644269.2:c.845G>A
ENST00000265715.7:c.845G>A
NM_000441.1:c.845G>A

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM3_Strong PM2_Supporting PS3_Supporting

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.845G>A (NM_000441.2) variant in SLC26A4 is a missense variant predicted to cause substitution of cysteine by tyrosine at amino acid 282 (p.Cys282Tyr). The highest population minor allele frequency in gnomAD v.2.1.1 is 0.000053 (6/113490 alleles) in the European non-Finnish population, which is lower than the ClinGen Hearing Loss threshold (<0.0007) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.719 which is above the threshold of 0.7, evidence that correlates with impact to SLC26A4 function (PP3). This variant has been detected in at least 4 individuals with hearing loss. Of those individuals,

three were compound heterozygous for the variant and a pathogenic variant observed in trans and one had a rare VUS variant on other allele (c.1001+1G>A, c.233A > G, 3.25 PM3 points, PMID:26969326,33152970, SCV000060163.6, SCV000343642.4) (PM3_Strong). At least one proband with this variant displayed features of sensorineural hearing loss and enlarged vestibular aqueduct, a phenotype highly specific for Pendred syndrome (PP4, PMID:26969326,33152970, SCV000060163.6). Functional studies including fluorescence assays have demonstrated that this variant impacts protein function (PS3_Supporting; PMID:26752218). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive Pendred syndrome based on the ACMG/AMP criteria applied as specified by the Hearing Loss VCEP: PM2_Supporting, PP3, PM3_Strong, PP4, PS3_Supporting. (ClinGen Hearing Loss VCEP specifications version 2; 1/18/2023).

Met criteria codes

PP3	✔	Residue highly conserved (present in all mammals and primates in UCSC) No predicted effect on splicing REVEL score: 0.719
PP4	✔	Probands from publications and an internal LMM case, all cases have hearing loss with EVA. (PMID:26969326,33152970, SCV000060163.6)
PM3_Strong	✔	Two probands from publications and additional probands (LMM and EGL Genetic Diagnostics Internal Data) with progressive mixed hearing loss with EVA were found to harbor this variant. Three probands also harbored the pathogenic c.1001+1G>A variant in SLC26A4 in trans. The final proband harbored a VUS c.233A>G variant in SLC26A4 in trans. This aggregates to 2 PM3 points which leads to a PM3_Strong classification.
PM2_Supporting	✔	Present in 0.0053% (6/113490) of European (non-Finnish) chromosomes in gnomAD v 2.1.1 and in 0.0015% (1/64560) of European (non-Finnish) chromosomes in v3
PS3_Supporting	✔	Halide-sensitive probe assay as specified in the HL paper suggests the SLC26A4 variant has reduced iodine influx compated to WT, control (empty vector), and benign variant.

Curation History

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