Variant: NM_000441.2(SLC26A4):c.1003T>C (p.Phe335Leu)

Version: 2.6

CA253316

4842 (ClinVar)

Gene: SLC26A4 (HGNC:5172)
Condition: Pendred syndrome (MONDO:0010134)
Inheritance Mode: Autosomal recessive inheritance
UUID: fd54e511-37fc-437e-bf54-4757947ec10f
Approved on: 2020-08-19
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HGVS expressions

NM_000441.2:c.1003T>C
NM_000441.2(SLC26A4):c.1003T>C (p.Phe335Leu)
NC_000007.14:g.107689054T>C
CM000669.2:g.107689054T>C
NC_000007.13:g.107329499T>C
CM000669.1:g.107329499T>C
NC_000007.12:g.107116735T>C
NG_008489.1:g.33420T>C
ENST00000644269.2:c.1003T>C
ENST00000265715.7:c.1003T>C
NM_000441.1:c.1003T>C

Likely Pathogenic

Met criteria codes 6

BS1_Supporting | PP1 | PP3 | PP4 | PM3_Very Strong | PS3_Supporting

Evidence Links 0

Expert Panel

Hearing Loss VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.1003T>C (p.Phe335Leu) variant has been identified in over 20 probands with Hearing loss, 6 of whom had a second pathogenic or suspected pathogenic variant in trans (PM3_VeryStrong; PMIDs: 19509082, 29293505, 25394566, 20668687, 20597900, 19426954, 19204907, 18285825, 17503324, 17357124, 17309986, 15689455, 14679580, 11317356, Laboratory for Molecular Medicine internal data). The variant has been reported to segregate with disease in one affected family member (PP1; PMID: 18285825). Multiple probands presented with hearing loss and enlarged vestibular aqueducts (EVA) which are highly specific to Pendred syndrome (PP4; PMIDs: 14679580, 18285825, 19509082, 25394566, Laboratory for Molecular Medicine internal data). Evidence has been published indicating that the p.Phe335Leu variant may be pathogenic when in trans with a functionally-null or severely hypomorphic variant but not as a mono-allelic variant or in the homozygous state (PMIDs: 19204907, 24051746). The c.1003T>C (p.Phe335Leu) variant was present in 0.203% (76/30612 CI 95%) of South Asian alleles in gnomAD v2.1.1, which is a high enough frequency apply BS1_Supporting. Additionally it was present in 2.1% (27/910 CI 95%) of Amish alleles in gnomAD v3.1 (BA1). The ClinGen Hearing Loss Expert Panel believes that the evidence for the pathogenicity of this variant for Pendred syndrome outweighs the high allele frequency of the variant in population databases.

Therefore, neither BS1_Supporting nor BA1 will contribute to the overall classification. A functional study demonstrates that the p.Phe335Leu variant may impact protein function (PS3_Supporting; PMID: 19204907). Finally, the REVEL computational prediction analysis tool produced a score of 0.828, which is above the threshold necessary to apply PP3. In summary, this variant has been classified as likely pathogenic for autosomal recessive Pendred syndrome based on the ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel: PM3_VeryStrong, PS3_Supporting, PP1, PP3, PP4.

Met criteria codes

BS1_Supporting	✔	0.203% (76/30612 CI 95%) of South Asian alleles in gnomAD v2.1.1
PP1	✔	PMID: 18285825
PP3	✔	REVEL: 0.858
PP4	✔	PMID: 18285825
PM3_Very Strong	✔	6 compound het cases
PS3_Supporting	✔	PMID: 19204907

Curation History

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