Variant: NM_000441.1(SLC26A4):c.-103T>C

Version: 1.2

CA253314

4838 (ClinVar)

Gene: SLC26A4 (HGNC:5172)
Condition: Pendred syndrome (MONDO:0010134)
Inheritance Mode: Autosomal recessive inheritance
UUID: 52e44005-97e2-4a07-a71a-1f9957307a4b
Approved on: 2024-01-17
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HGVS expressions

NM_000441.1:c.-103T>C
NM_000441.1(SLC26A4):c.-103T>C
NC_000007.14:g.107660756T>C
CM000669.2:g.107660756T>C
NC_000007.13:g.107301201T>C
CM000669.1:g.107301201T>C
NC_000007.12:g.107088437T>C
NG_008489.1:g.5122T>C
ENST00000265715.7:c.-103T>C
NR_028137.1:n.198-550A>G

Uncertain Significance

Met criteria codes 4

PP4 **PM3** **PS3_Supporting** **BS1**

Not Met criteria codes 22

PP1 **PP2** **PP3** **PM1** **PM5**
PM4 **PM6** **PM2** **BS2** **BS4**
BS3 **BP4** **BP3** **BP1** **BP2** **BP5**
BP7 **PVS1** **BA1** **PS1** **PS2**
PS4

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.-103T>C (NM_000441.2) variant is a substitution in the 5’ UTR of SLC26A4. Because the variant is located in the 5’ UTR, it is not expected to alter the amino acid sequence. The highest population minor allele frequency in gnomAD v4.0.0 is 0.3% (262/68066 alleles) in the European (non-Finnish) population, which is a high enough frequency to be classified as likely benign based on the thresholds defined by the ClinGen Hearing Loss Expert Panel (HL EP) for autosomal recessive hearing loss variants (BS1). This variant has been detected in 2 individuals with hearing loss and additional features of Pendred syndrome (enlarged vestibular aqueducts (EVA) and Mondini dysplasia) who were compound heterozygous for the variant and a pathogenic variant with phase confirmed in trans in one individual (PMID:

19204907, 25991456). It has also been identified in two additional compound heterozygous individuals with hearing loss, one with a likely pathogenic and one with a variant of uncertain significance, though phase was not confirmed in either individual (SCV000491274.5). However, due to the allele frequency meeting BS1 criteria, PP4 and PM3 were not applied. There have been many reported heterozygous observations in individuals with EVA/Pendred syndrome (PMID:17503324, 23208854, 23965030, 25991456). Functional studies imply that the variant occurs in a binding site that is a major transcriptional regulatory element of SLC26A4 and is necessary for FOXI1-induced transcriptional activation of SLC26A4 (PMID:25910213, 17503324; PS3_Supporting). Due to conflicting evidence, this variant is classified as a variant of uncertain significance for autosomal recessive Pendred syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: BS1, PS3_P (ClinGen Hearing Loss VCEP specifications version 2; 01/17/2024).

Met criteria codes

PP4	ℹ	✓	At least one patient who was compound heterozygous for this variant and the p.L236P variant displayed hearing loss with enlarged vestibular aqueduct (EVA), which is highly specific for Pendred syndrome (PP4, PMID:19204907).
PM3	ℹ	✓	Heterozygous observations of the c.-103T>C variant were observed in at least 12 individuals with EVA/Pendred syndrome (PMID:17503324, 23208854, 23965030, 25991456). The variant was observed in one affected individual in compound heterozygosity with p.L236P. The p.L236P variant has been reported as pathogenic in ClinVar by five clinical testing labs (PM3).
PS3_Supporting	ℹ	✓	Functional studies imply that the variant occurs in a binding site that is a major transcriptional regulatory element of SLC26A4 and is necessary for FOXI1-induced transcriptional activation of SLC26A4 (PMID:25910213, 17503324; PS3_Supporting).
BS1	ℹ	✓	GnomAD v4 filtering allele frequency 0.3466% (262/68066) European non-Finnish chromosomes with 3 homozygotes.

Not Met criteria codes

PP1	ℹ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2		✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	ℹ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	ℹ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	ℹ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM6	ℹ	✖	No reported de novo cases.
PM2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	25910213, 17503324: Functional studies imply that the variant occurs in a binding site that is a major transcriptional regulatory element of SLC26A4 and is necessary for FOXI1-induced transcriptional activation of SLC26A4.
BP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	This variant is absent from ExAC. The filtering allele frequency is 0.28% (53/14998) of European (Non-Finnish) alleles in gnomAD.
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	No reported de novo cases.

PS4	ℹ	✖	Only 1 case with a confirmed pathogenic variant in trans out of 47 tested EVA subjects. Compared to 53/14998 European (non-Finnish) alleles in gnomAD. Association is not statistically significant.

Curation History

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