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_000441.1(SLC26A4):c.349C>T

CA132727

43555 (ClinVar)

Gene: SLC26A4 (HGNC:5172)
Condition: Pendred syndrome (MONDO:0010134)
Inheritance Mode: Autosomal recessive inheritance
UUID: 67c2f97e-385f-494a-b06e-701135ace536
Approved on: 2018-09-26
Published on: 2018-12-10

HGVS expressions

NM_000441.1(SLC26A4):c.349C>T
NM_000441.1:c.349C>T
NC_000007.14:g.107672182C>T
CM000669.2:g.107672182C>T
NC_000007.13:g.107312627C>T
CM000669.1:g.107312627C>T
NC_000007.12:g.107099863C>T
NG_008489.1:g.16548C>T
ENST00000644269.2:c.349C>T
ENST00000265715.7:c.349C>T
ENST00000440056.1:c.349C>T
NM_000441.2:c.349C>T

Pathogenic

The Expert Panel has overridden the computationally generated classification - "*Uncertain Significance - Conflicting Evidence, Benign*"

Met criteria codes 6

PP4 PP3 PM3_Very Strong BA1 BS3_Supporting PP1_Strong

Not Met criteria codes 20

PS2 PS4 PS3 PS1 PP2 PM1 PM4 PM5 PM6 PM2 BS2 PVS1 BS4 BS1 BP5 BP7 BP2 BP3 BP1 BP4

Evidence Links 5

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*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.349C>T variant in SLC26A4 is a missense variant predicted to cause substitution of leucine by phenylalanine at amino acid 117. The filtering allele frequency of the p.Leu117Phe variant is 0.005208 (54/10368 alleles) for Ashkenazi Jewish chromosomes in gnomAD v2.1.1, which is a high enough frequency to be classified as benign based on thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss variants (BA1). The ClinGen Hearing Loss Expert Panel believes that the evidence for the pathogenicity of this variant for hearing loss outweighs the high allele frequency of the variant in population databases. Therefore, the BA1 code will not

contribute to the overall classification. The computational predictor REVEL gives a score of 0.982, which is above the threshold of 0.7, evidence that correlates with impact to SLC26A4 function (PP3). This variant has been detected in 8 individuals with hearing loss. For 5 of those individuals, they were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and all of those were confirmed in trans by (c.1246A>C (p.Thr416Pro), c.1708G>A (p.Val570Ile), c.1522A>G (p.Thr508Ala), c.578C>T (p.Thr193Ile), 5.75 PM3 points, SCV000060146.7, SCV000282017.1). (PM3_VeryStrong). This variant has been identified in patients with EVA, which is a phenotype that was deemed to be highly specific for SLC26A4 by the ClinGen Hearing Loss Expert Panel (LMM) (PP4). The variant has been reported to segregate with hearing loss in at least 5 affected and 4 unaffected family members, across 2 Ashkenazi Jewish families with hearing loss (PP1_Strong; Karen Avraham Lab internal data SCV000282016.1, SCV000282017.1). A functional study demonstrated that this variant may not impact localization or the iodide efflux capacity (BS3_Supporting; PMID: 27771369, 11932316), however, the functional study may not assess all ion transport functions of the protein and/or ensure that the assay reflects the true biological environment and therefore the ClinGen Hearing Loss Expert Panel (HL EP) chose not to consider this evidence fully in conflict with the pathogenic evidence (BS3_Supporting). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive Pendred syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PM3_VS, PP1_S, PP4, PP3, BS3_P (Hearing Loss VCEP specifications version 2; 11/22/2022).

Met criteria codes

PP4 ✔

This variant has been identified in patients with EVA, which is a phenotype that was deemed to be highly specific for SLC26A4 by the ClinGen Hearing Loss Expert Panel.

Patient with EVA and variant. PubMed:16570074
Patient with EVA and variant PubMed:10700480

PP3 ✔

The computational predictor REVEL gives a score of 0.982, which is above the threshold of 0.7, evidence that correlates with impact to SLC26A4 function (PP3).

PM3_Very Strong ✔

This variant has been detected in 8 individuals with hearing loss. For 5 of those individuals, they were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and all of those were confirmed in trans by (c.1246A>C (p.Thr416Pro), c.1708G>A (p.Val570Ile), c.1522A>G (p.Thr508Ala), c.578C>T (p.Thr193Ile), 5.75 PM3 points, SCV000060146.7, SCV000282017.1). (PM3_VeryStrong).

109 patients from 100 families with nonsyndromic hearing loss and EVA. 50 control individuals, study in France. The variant was seen in one affected patient without a second variant. PubMed:16570074
1119 patients with hearing loss tested. Found one compound heterozygote with this variant in trans with a splicing c.-4+1G>C variant with severe to profound hearing loss, but not noted if they tested temporal bone imaging. Shouldn't be used for PM3, as the splice variant is VUS. PubMed:26969326
57 EVA patients screened for SLC26A4. Found in one patinet with HL and EVA but a normal perchlorate test. Did not note a second variant. Variant was absent from 100 control chromosomes-no family/race info PubMed:10700480

BA1 ✔

The filtering allele frequency of the p.Leu117Phe variant is 0.005208 (54/10368 alleles) for Ashkenazi Jewish chromosomes in gnomAD v2.1.1, which is a high enough frequency to be classified as benign based on thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss variants (BA1). The ClinGen Hearing Loss Expert Panel believes that the evidence for the pathogenicity of this variant for hearing loss outweighs the high allele frequency of the variant in population databases. Therefore, the BA1 code will not contribute to the overall classification.

BS3_Supporting ✔

A functional study demonstrated that this variant may not impact localization or the iodide efflux capacity (BS3_Supporting; PMID: 27771369, 11932316), however, the functional study may not assess all ion transport functions of the protein and/or ensure that the assay reflects the true biological environment and therefore the

ClinGen Hearing Loss Expert Panel (HL EP) chose not to consider this evidence fully in conflict with the pathogenic evidence (BS3_Supporting).

Noted variant lacking experimentally validated functional information. Conserved and gives NeEMO stability 1.37. Predicted Benign in silico. predicted molecular effect maintenance of hydrophobicity. PubMed:27771369
This study investigated the impact of 9 different SLC26A4 variants on protein function. They found that the L117F variant showed a cell membrane protein distribution similar to that of the wild type protein and exhibited a rate of iodide efflux statistically similar to that of the WT. this study actually questioned as to whether there was an alternate cause in the case from the study. This study would support a benign impact of the variant, however it is also important to note that this study didn't investigate all ion transport functions. PubMed:11932316

PP1_Strong	✔	The variant has been reported to segregate with hearing loss in at least 5 affected and 4 unaffected family members, across 2 Ashkenazi Jewish families with hearing loss (PP1_Strong; Karen Avraham Lab internal data SCV000282016.1, SCV000282017.1).

Not Met criteria codes

PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	This variant was found in 3 patients in the published literature. It has also been reported in ClinVar in another case from Prof. Karen Avraham @ Tel Aviv Univ.'s lab with congenital profound HL. There are 9 cases in the LMM database with HL/HL + EVA and this variant, however one of them also has a pathogenic AD KCNQ4 variant so this proband was not counted. Reardon 1/114 alleles in HL+ EVA cohort Albert 1/218 alleles in HL + EVA cohort Sloan Heggen: 1/2238 in HL cohort LMM internal 5/3884 SLC26A4 tested alleles as of last NVA 8/6454 Alleles Tested in HL/HL+EVA cohorts vs. gnomAD: 22/126640 European alleles in gnomAD. AND 52/10150 Ashkenazi alleles in gnomAD = 74/136790 ~ 67/123456 In contingency table: 8 to 6446 vs 67 to 123389 p = 0.0448. Applied Moderate evidence. Note: if you add in the internal proband with the KCNQ4 variant the significance is higher but it doesn't seem logical to use a proband with alternate cause in this exercise. Also, Karen Avraham's proband was not counted here because the denominator is unknown. I removed this criteria (was previously scored as PS4_Moderate), but we did not use it in our final classification listed in the Human Mutation manuscript. - Andrea 7.31.18
PS3	✖	109 patients from 100 families with nonsyndromic hearing loss and EVA. 50 control individuals, study in France. The variant was seen in one affected patient without a second variant. PubMed:16570074 1119 patients with hearing loss tested. Found one compound heterozygote with this variant in trans with a splicing c.-4+1G>C variant with severe to profound hearing loss, but not noted if they tested temporal bone imaging. Shouldn't be used for PM3, as the splice variant is VUS. PubMed:26969326 57 EVA patients screened for SLC26A4. Found in one patinet with HL and EVA but a normal perchlorate test. Did not note a second variant. Variant was absent from 100 control chromosomes-no family/race info. PubMed:10700480
PS1	✖	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

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	There is a reported genotype of a compund het case with the c.578C>T variant that was interpreted as pathogenic by a zero star submitter, but there are no other missense variants reported at this codon in ClinVar.
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	There are 2 family members in LMM's internal data who are unaffected but are heterozygous for the p.Leu117Phe variant. However, they don't have the other variant that is in trans in the affected individual.
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	✖	While this variant has been suspected to have an alternate cause in patients due to its lack of known functional implications and the patient in Taylor et al. 2002's lack of thyroid dysfunction at age 18 yr, but a second variant was not identified. In an LMM case, there was a patient without EVA that had this variant as well as a heterozygous pathogenic c.459delC KCNQ4 variant which is known to cause AD HL. Therefore, BP5 could be applied here. RS 9/18/18 After review, this criteria has been determined not met. Mutant performed as wild type pendrin on iodide efflux assay and also showed normal localization. Unclear of the variant impacts another ion transport function of the protein as OH, HCO3, Cl were not assessed. PubMed:11932316
BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	109 patients from 100 families with nonsyndromic hearing loss and EVA. 50 control individuals, study in France. The variant was seen in one affected patient without a second variant. PubMed:16570074

1119 patients with hearing loss tested. Found one compound heterozygote with this variant in trans with a splicing c.-4+1G>C variant with severe to profound hearing loss, but not noted if they tested temporal bone imaging. Shouldn't be used for PM3, as the splice variant is VUS. PubMed:26969326

57 EVA patients screened for SLC26A4. Found in one patinet with HL and EVA but a normal perchlorate test. Did not note a second variant. Variant was absent from 100 control chromosomes-no family/race info PubMed:10700480

BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	z=-3.23
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 2 of 2 rows

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