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_000441.2(SLC26A4):c.1262A>G (p.Gln421Arg)

Version: 2.0

CA4432734

430229 (ClinVar)

Gene: SLC26A4 (HGNC:5172)
Condition: Pendred syndrome (MONDO:0010134)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6cd4c29c-1de2-43d9-b801-d783fce7e382
Approved on: 2023-06-21
Published on: 2024-01-10

HGVS expressions

NM_000441.2:c.1262A>G
NM_000441.2(SLC26A4):c.1262A>G (p.Gln421Arg)
NC_000007.14:g.107690236A>G
CM000669.2:g.107690236A>G
NC_000007.13:g.107330681A>G
CM000669.1:g.107330681A>G
NC_000007.12:g.107117917A>G
NG_008489.1:g.34602A>G
ENST00000644269.2:c.1262A>G
ENST00000265715.7:c.1262A>G
NM_000441.1:c.1262A>G

Uncertain Significance

Met criteria codes 4

PP3 PP4 PM5 PM2_Supporting

Not Met criteria codes 1

PM3

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.1262A>G variant in SLC26A4 is a missense variant predicted to cause substitution of glutamine by arginine at amino acid 421 (p.Gln421Arg). The highest population minor allele frequency in gnomAD v2.1.1 is 0.003% (3/113084) in the European (non-Finnish) population, which is lower than the ClinGen Hearing Loss VCEP threshold (<0.007%) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.954, which is above the threshold of 0.7, evidence that correlates with impact to SLC26A4 function (PP3). Another missense variant, c.1262A>C (p.Gln421Pro), at the same codon has been classified as

likely pathogenic for autosomal recessive Pendred syndrome (PM5; PMID: 17718863, 23918157, 24224479, 28964290). The p.Gln421Arg variant has been reported in five individuals with hearing loss and inner ear abnormalities, which is highly specific for Pendred syndrome (PP4). Two individuals did not have a variant on the second allele identified (PMIDs: 23965030, 14679580). Two individuals were compound heterozygous for the CEVA haplotype, and one individual was compound heterozygous for a variant of uncertain significance, c.284G>A p.Gly95Glu. Phase for these individuals was unknown (0 PM3 points, PMID: 36833263). This variant was re-reviewed on 6.27.2023, and PM2 was downgraded to PM2_Supporting following the most recent specification criteria. Because no contradictory evidence was added, this variant was retained at likely pathogenic for autosomal recessive Pendrome syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PM5, PM2_Supporting, PP3, PP4. (VCEP specifications version 2; 06.21.2023).

Met criteria codes

PP3	✔	REVEL score 0.954. Splicing is not predicted to be impacted by Alamut (Lee et al. 2019 also showed that this variant did not affect splicing in HeLa cells). No animals in UCSC database have an alternate amino acid at this site.
PP4	✔	Applied for proband form Prasad et al. 2004 who had hearing loss plus either dilated VA or Mondini dysplasia (did not specify which, but either temporal bone computed tomography or MRI was done)
PM5	✔	The Gln421Pro variant (variation ID: 556159) is classified as likely pathogenic, but not pathogenic, in ClinVar. 2 other missense changes in this residue (Gln421Lys and Gln421Leu) have also been observed in literature. UPDATE 6.27.2023 making sure this variant is P or LP. c.1262A>G (p.Gln421Arg): 0.005 (1/19939) East Asian PM2_SUPPORTING . PMID: 17718863: 1 individual with H723R (P by >10 labs in ClinVar) with moderate HL. Per text cohort has EVA or EVA+Mondini, and "we genotyped all the parents in 93 simplex families)..." IN TRANS (1pt). PMID: 23918157: Q421P with c.1595G > T S532I (absent gnomAD, P/LP by 3 labs in ClinVar) in table III in one individual with nonsyndromic EVA. Phase unknown, 0.5pt). PMID: 24224479: In one individual with p.Cys400Valfs*32 (NMD+), with EVA and congenital hypothyroidism, nodular goiter. Phase unknown (0.5pt). PMID: 28964290 - Q421P homozygous in family 1555-1000 with EVA. Also reported in family 1040 cmp het with p.Cys400Valfs*32 (same variant reported in 24224479 but that study was done in France). This cohort is probands with hearing loss and inner ear anomalies. Phase unknown, 1pt total. CRITERIA APPLIED: PM3_STRONG, PP4, PM2_SUPPORTING. AT LEAST LIKELY PATHOGENIC
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.003% (3/113084) in the European (non-Finnish) population

Not Met criteria codes

PM3	✖	Identified in 2 patients, but no PM3 points since variants on other allele were not found. Two individuals were compound heterozygous for the CEVA haplotype, and one individual was compound heterozygous for a variant of uncertain significance, c.284G>A p.Gly95Glu. Phase for these individuals was unknown (0 PM3 points, PMID: 36833263).

Curation History

Showing 1 to 2 of 2 rows