

Variant: NM_000441.1(SLC26A4):c.412G>T (p.Val138Phe)

CA253312 [↗](#)

4835 (ClinVar) [↗](#)

Gene: SLC26A4 ([HGNC:5172](#))

Condition: Pendred syndrome ([MONDO:0010134](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: c400a0f9-d38a-4d2e-9b96-5829547c6b19

Approved on: 2018-09-19

Published on: 2018-12-10

HGVS expressions

NM_000441.1:c.412G>T

NM_000441.1(SLC26A4):c.412G>T (p.Val138Phe)

NC_000007.14:g.107672245G>T

CM000669.2:g.107672245G>T

NC_000007.13:g.107312690G>T

CM000669.1:g.107312690G>T

NC_000007.12:g.107099926G>T

NG_008489.1:g.16611G>T

ENST00000265715.7:c.412G>T

Pathogenic

Met criteria codes 7

PS3_Supporting PM3_Very Strong
PP3 PP4 PS4 PM2_Supporting
PP1_Moderate

Not Met criteria codes 16

PVS1 BA1 BP4 BP3 BP2
BP7 BP5 BS2 BS1 BS4 PS1
PS2 PM6 PM5 PM4 PM1

Evidence Links 14

Expert Panel

Hearing Loss VCEP [↗](#)

Criteria Specification Information !

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The p.Val138Phe variant in SLC26A4 has been detected in over 4 patients with Pendred syndrome or hearing loss with enlarged vestibular aqueducts who harbored a pathogenic or suspected pathogenic variant in trans with p.Val138Phe (PM3_VS; PMID: 17503324, 15689455, 20597900, 18285825, 23965030, 24224479, 21551164, 23273637, 12788906, 16570074). This variant was found to have a statistically higher prevalence in affected individuals over controls (PS4; PMID: 25999548, 23336812, 26683941). The p.Val138Phe variant in SLC26A4 has been reported to segregate with hearing loss in at least 2 family members (PP1_M; PMID: 12788906). The allele frequency of the p.Val138Phe variant in the SLC26A4 gene is 0.03% (38/126540) of European chromosomes by the Genome Aggregation Database (<http://gnomad.broadinstitute.org>), which is a low enough frequency to award PM2_Supporting based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss (PM2_P). Computational prediction tools and conservation analysis

suggest that the p.Val138Phe variant may impact the protein (PP3). At least one patient with a variant in this gene displayed features of EVA and/or Mondini malformation which are consistent with Pendred syndrome (PP4; PMID: 12788906, 23273637). A functional study performed in HeLa and human embryonic kidney cell lines demonstrated that pendrin harboring the p.Val138Phe variant did not localize to the cell membrane. However, there was no effect on iodide efflux (PS3_P; PMID: 11932316). In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive Pendred syndrome/EVA based on the ACMG/AMP criteria applied: PM3_VS, PS4, PP1_M, PM2_Supporting, PP3, PP4, PS3_P.

Met criteria codes

PS3_Supporting  

SLC26A4 has been shown to be integral to hearing loss function through its effects as a transmembrane protein. Therefore mislocalization of the protein may be sufficient evidence to support this variant's effect on the phenotype.

This paper showed that the V138F variant, among other SLC26A4 variants was not able to reach the cell membrane and appeared to localize to distinct areas of the cytoplasm. They hypothesized that the mutants caused aberrant protein processing in either the ER or the Golgi. This study only shows mislocalization and the variant did not have an effect on iodide efflux. Therefore, there is no direct implication of the variant causing disease (other than the SLC26A4's known LOF mechanism) as this does not prove that the mislocalization causes LOF. [PubMed:11932316](#) 

PM3_Very Strong  

PM3_VS met. There were at least 6 cases of homozygous p.V138F induced PS/EVA and there were at least 10 cases of the variant being in trans with a P/LP variant.

This study found 2 probands. One was heterozygous for the V138F variant who had LE Cophosis RE normal hearing. And the other patient and sibling had the V138F variant in trans with the p.Q514 variant. [PubMed:18285825](#) 

This study identified a 46 year old Caucasian female who was diagnosed with Pendred syndrome. "This case illustrates that, although pendrin is not usually required to maintain acid-base homeostasis under ambient condition, loss of renal bicarbonate excretion by pendrin during a metabolic alkalotic challenge may contribute to life-threatening acid-base disturbances in patients with Pendred syndrome". This patient was homzoygous for the variant. Sequencing of the SLC26A4 gene revealed the genotype. Consanguinity was not discussed.

[PubMed:21551164](#) 

4 Patients with Pendred syndrome sequenced for SLC26A4 variants as well as FOXI1 and KCNJ10. They found 3 p.Val138Phe homozygotes and 1 compound heterozygote (p.Leu597Ser). Leu597Ser is actually classified as a Benign/LB variant in ClinVar by 4 labs. [PubMed:23965030](#) 

This paper identified the V138F variant in a Brazilian patient with NSHL and EVA. THe patient had a compound heterozygous genotype with the variant in trans with a p.Q413R variant which has been classified as LP by counsyl in 2016. [PubMed:23273637](#) 

This study identified a French patient with EVA and Mondini malformation with a homozygous p.V138F genotype. [PubMed:16570074](#) 

This study identified 2 patients with Pendred syndrome adn one patient with an indeterminate EVA phenotype. The patient with indeterminate phenotype had a c.1343_1344insAGTC variant in trans with the p.V138F variant. One Pendred patient was homozygous for the p.V138F variant and another patient was compound het with a p.E384G variant (P/LP). [PubMed:15689455](#) 

Total: 2 comp het probands with Path variants in trans and 2 homzygous probands. This paper identified 4 families who had the p.Val138Phe identified with disease. The variant was present in a homozygous individual with Pendred syndrome in family A and segregated from two unaffected nonconsanguineous Turkish parents who were het carriers. Family B (German nonconsanguineous): Father had the p.Y530H (Path in GI) variant, mother had the p.V138F variant, 2 affected compound het children. Family C (German nonconsanguineous), Father and sister were affected by Pendred syndrome and had the p.V138F and E384G variants, but his p.E384G (Path in GI) heterozygous son was unaffected. Family D (German nonconsanguineous): Pendred syndrome in homozygous p.V138F German boy who had heterozygous mother, aunt and uncle. [PubMed:12788906](#) 

Total: 2 compound het with path variant. Identified two brothers who have Pendred syndrome. Both were positive for the p.Val138Phe and p.Leu445Trp (Path in ClinVar by 4 labs including LMM & GeneDx). Also identified a female patient with Pendred who had the variant in trans with p.Glu384Gly variant (Path/LP in ClinVar by LMM, GeneDx, Counsyl) [PubMed:24224479](#)

This study identified 6 patients with the p.V138F varaint who had PS-EVA, and they found that 4 of them had a second mutation identified however they don't describe what the other mutations were. [PubMed:17503324](#)

This study identified the p.Val138Phe variant in 6 patients with EVA and hearing loss. However, there were only 2 patietns with biallelic pathogenic SLC26A4 mutations. One patient had a c.1001+1G>A varaint and the other had the Leu445Trp variant. Of note, there were 4 affected heterozygotes. [PubMed:20597900](#)

PP3			REVEL reports a score of 0.898. Our cutoff for PP3 is > 0.7.
PP4			<div>Several cases identified with HL and EVA and Mondini</div> <div>ID'd an affected patient with EVA and HL PubMed:23273637</div> <div>ID'd families with Pendred syndrome PubMed:12788906</div>
PS4			<div>This meta analysis of SLC26A4 variants showed that p.V138F had a significantly higher frequency in hearing loss populations than in controls. They used a cohort of 2294 HL cases and 3193 multiethnic controls. They also found that this difference was sig among just European affected vs controls.</div> <div>This meta analysis shows that the origin of the p.V138F variant is likely from Western Europe and that it is a founder mutation in Caucasians. However, there is no statistical analysis proving this variants pathogenicity. PubMed:25999548</div> <div>This study found the p.V138F variant in 17% of their Pendred/DFNB4 cohort but did not report this as statistically higher than controls. PubMed:23336812</div> <div>Meta analysis of frequencies of SLLC26A4 variants among cases and controlsThis study found 185 indiviudals with the variant and found that the frequency in hearing loss was significantly higher (p<0.001) Used data from 24 articles from Asia, Europe and North America including 2294 cases and 3193 controls in multiethnic cohorts. Furthermore, there was a statistically significant increase in frequency of the variant within just European cases-European controls. The difference in frequencies for EVA vs non-EVA populations was insignificant for this variant. PubMed:26683941</div>
PM2_Supporting			38/126540 European (non-finnish) 0.03%
PP1_Moderate			<div>There are 2 affected segregations and 0 unaffected segregations which means we should apply PP1_M. This variant has been shown to be a founder variant in German families. See pedigrees in Borck et al. 2003</div> <div>Total: 2 affected segs and 0 unaffected segs from parents with the p.V138F Variant. 2 comp het probands with Path variants in trans and 2 homzygous probands. This paper identified 4 families who had the p.Val138Phe identified with disease. Family B (German nonconsanguineous): Father had the p.Y530H (Path in GI) variant, mother had the p.V138F variant, 2 affected compound het children. Family C (German nonconsanguineous), Father and sister were affected by Pendred syndrome and had the p.V138F and E384G variants, but his p.E384G (Path in GI) heterozygous son was unaffected. Family D (German nonconsanguineous): Pendred syndrome in homozygous p.V138F German boy who had heterozygous mother, aunt and uncle. PubMed:12788906</div>

Not Met criteria codes

PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			38/126540 European (non-finnish) 0.03%
BP4			REVEL reports a score of 0.898. Our cutoff for PP3 is > 0.7.
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			<p>This study found 2 probands. One was heterozygous for the V138F variant who had LE Cophosis RE normal hearing. And the other patient and sibling had the V138F variant in trans with the p.Q514 variant. PubMed:18285825 </p> <p>This study identified a 46 year old Caucasian female who was diagnosed with Pendred syndrome. "This case illustrates that, although pendrin is not usually required to maintain acid-base homeostasis under ambient condition, loss of renal bicarbonate excretion by pendrin during a metabolic alkalotic challenge may contribute to life-threatening acid-base disturbances in patients with Pendred syndrome". This patient was homzygous for the variant. Sequencing of the SLC26A4 gene revealed the genotype. Consanguinity was not discussed. PubMed:21551164 </p> <p>4 Patients with Pendred syndrome sequenced for SLC26A4 variants as well as FOXI1 and KCNJ10. They found 3 p.Val138Phe homozygotes and 1 compound heterozygote (p.Leu597Ser). Leu597Ser is actually classified as a Benign/LB variant in ClinVar by 4 labs. PubMed:23965030 </p> <p>This paper identified the V138F variant in a Brazilian patient with NSHL and EVA. The patient had a compound heterozygous genotype with the variant in trans with a p.Q413R variant which has been classified as LP by counsyl in 2016. PubMed:23273637 </p> <p>This study identified a French patient with EVA and Mondini malformation with a homozygous p.V138F genotype. PubMed:16570074 </p> <p>This study identified 2 patients with Pendred syndrome adn one patient with an indeterminate EVA phenotype. The patient with indeterminate phenotype had a c.1343_1344insAGTC variant in trans with the p.V138F variant. One Pendred patient was homozygous for the p.V138F variant and another patient was compound het with a p.E384G variant (P/LP). PubMed:15689455 </p> <p>Total: 2 comp het probands with Path variants in trans and 2 homzygous probands. This paper identified 4 families who had the p.Val138Phe identified with disease. The variant was present in a homozygous individual with Pendred syndrome in family A and segregated from two unaffected nonconsanguineous Turkish parents who were het carriers. Family B (German nonconsanguineous): Father had the p.Y530H (Path in GI) variant, mother had the p.V138F variant, 2 affected compound het children. Family C (German nonconsanguineous), Father and sister were affected by Pendred syndrome and had the p.V138F and E384G variants, but his p.E384G (Path in GI) heterozygous son was unaffected. Family D (German nonconsanguineous): Pendred syndrome in homozygous p.V138F German boy who had heterozygous mother, aunt and uncle. PubMed:12788906 </p> <p>Total: 2 compound het with path variant. Identified two brothers who have Pendred syndrome. Both were positive for the p.Val138Phe and p.Leu445Trp (Path in ClinVar by 4 labs including LMM & GeneDx). Also identified a female patient with Pendred who had the variant in trans with p.Glu384Gly variant (Path/LP in ClinVar by LMM, GeneDx, Counsyl) PubMed:24224479 </p> <p>This study identified 6 patients with the p.V138F varaint who had PS-EVA, and they found that 4 of them had a second mutation identified however they don't describe what the other mutations were. PubMed:17503324 </p> <p>This study identified the p.Val138Phe variant in 6 patients with EVA and hearing loss. However, there were only 2 patietns with biallelic pathogenic SLC26A4 mutations. One patient had a c.1001+1G>A varaint and the other had the Leu445Trp variant. Of note, there were 4 affected heterozygotes. PubMed:20597900 </p>

BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			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
BS1			38/126540 European (non-finnish) 0.03%
BS4			Total: 2 affected segs and 0 unaffected segs from parents with the p.V138F Variant. 2 comp het probands with Path variants in trans and 2 homzygous probands. This paper identified 4 families who had the p.Val138Phe identified with disease. Family B (German nonconsanguineous): Father had the p.Y530H (Path in GI) variant, mother had the p.V138F variant, 2 affected compound het children. Family C (German nonconsanguineous), Father and sister were affected by Pendred syndrome and had the p.V138F and E384G variants, but his p.E384G (Path in GI) heterozygous son was unaffected. Family D (German nonconsanguineous): Pendred syndrome in homozygous p.V138F German boy who had heterozygous mother, aunt and uncle. PubMed:12788906 
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			In the LMM database, there is a c.412_415+21delinsTGACA that causes p.Val138X but it is currently not classified.
PM4			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

Curation History 

▼

▼

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.