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# *Variant: NM_000441.2(SLC26A4):c.1694G>A (p.Cys565Tyr)*

Version: 1.0

*CA261418*

*43519 (ClinVar)*

**Gene**: SLC26A4 (HGNC:5172)
**Condition**: Pendred syndrome (MONDO:0010134)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** c6b044c8-0623-4882-8baa-17bfb6a3ffd6
**Approved on**: 2023/7/19
**Published on**: 2023/10/5

## *HGVS expressions*

**NM_000441.2:c.1694G>A**
**NM_000441.2(SLC26A4):c.1694G>A (p.Cys565Tyr)**
NC_000007.14:g.107700162G>A
CM000669.2:g.107700162G>A
NC_000007.13:g.107340607G>A
CM000669.1:g.107340607G>A
NC_000007.12:g.107127843G>A
NG_008489.1:g.44528G>A
ENST00000644269.2:c.1694G>A
ENST00000644846.1:c.405G>A
ENST00000265715.7:c.1694G>A
ENST00000477350.5:n.541G>A
ENST00000480841.5:n.543G>A
ENST00000492030.2:n.77G>A
NM_000441.1:c.1694G>A

**Likely Pathogenic**

**Met criteria codes** 4

PS3_Supporting PM3_Strong PM2_Supporting PP4

**Not Met criteria codes** 2

PM5 PP3

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.1694G>A variant in SLC26A4 is a missense variant predicted to cause substitution of cysteine by tyrosine at amino acid 565 (p.Cys565Tyr). The highest population minor allele frequency in gnomAD v2.1.1 is 0.006% (1/15418) in European (non-Finnish) population, which is lower than the ClinGen Hearing Loss VCEP threshold ≤0.00007 (0.007%) for PM2_Supporting, meeting this criterion (PM2_Supporting). Radio isotope assays in Xenopus oocytes and HEK293T cell lines demonstrated that cells transfected with mutant SLC26A4 show a statistically significant decreased efflux of iodide compared to wildtype pendrin indicating that this variant impacts protein function (PS3_Supporting; PMID: 19204907, 31599023). This variant has been detected in at least 4 individuals with Pendred syndrome or nonsyndromic hearing loss with enlarged vestibular aqueduct (total of 3.5 PM3 points, PM3_Strong). One individual with Pendred syndrome was compound heterozygous with a pathogenic variant p.Q514R (ClinVar ID 43511, PMID: 19204907, 15689455). The second individual was a Pendred syndrome patient compound heterozygous with a pathogenic variant p.L236P (ClinVar ID 4817, PMID: 9618166). The third individual had nonsyndromic hearing loss with enlarged vestibular aqueduct which is highly specific for Pendred syndrome and was compound heterozygous with pathogenic p.H723R (ClinVar ID 4825, PMID: 14508505, PP4). The fourth individual had sensorineural hearing loss and enlarged vestibular aqueduct and was assumed compound heterozygous with pathogenic c.1342-2_1343dupAGTC (p.Leu450Glyfs*19) but phase unknown (Internal data from LMM). In summary, this variant has been classified as likely pathogenic for AR Pendred syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PM2_Supporting, PS3_Supporting, PM3_Strong, PP4. (VCEP specifications version 2; 07.19.2023).**

**Met criteria codes**

| | | |
|---|---|---|
| **PS3_Supporting** | ✔ | Radio isotope assays in Xenopus oocytes and HEK293T cell lines demonstrated that cells transfected with mutant SLC26A4 show a statistically significant decreased efflux of iodide compared to wildtype pendrin indicating that this variant impacts protein function (PS3_Supporting; PMID: 1920490, 31599023). |
| **PM3_Strong** | ✔ | This variant has been detected in at least 4 individuals with Pendred syndrome or nonsyndromic hearing loss with enlarged vestibular aqueduct (total of 3.5 PM3 points, PM3_Strong). One individual with Pendred syndrome was compound heterozygous with a pathogenic variant p.Q514R (ClinVar ID 43511, PMID: 19204907, 15689455). The second individual was a Pendred syndrome patient compound heterozygous with a pathogenic variant p.L236P (ClinVar ID 4817, PMID: 9618166). The third individual had nonsyndromic hearing loss with enlarged vestibular aqueduct which is highly specific for Pendred syndrome and was compound heterozygous with pathogenic p.H723R (ClinVar ID 4825, PMID: 14508505, PP4). The fourth individual had sensorineural hearing loss and enlarged vestibular aqueduct and was assumed compound heterozygous with pathogenic c.1342-2_1343dupAGTC (p.Leu450Glyfs*19) but phase unknown (Internal data from LMM). |
| **PM2_Supporting** | ✔ | The highest population minor allele frequency in gnomAD v2.1.1 is 0.006% (1/15418) in European (non-Finnish) population, which is lower than the ClinGen Hearing Loss VCEP threshold ≤0.00007 (0.007%) for PM2_Supporting, meeting this criterion (PM2_Supporting). |
| **PP4** | ✔ | Individual with nonsyndromic hearing loss and enlarged vestibular aqueduct which is highly specific for Pendred syndrome and was compound heterozygous with pathogenic p.H723R (ClinVar ID 4825, PMID: 14508505, PP4). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM5** | ✖ | Reported at this position are two variants (p.Cys565Gly, ClinVar ID: 373978 and patient F3IP1 in PMID: 16570074 with p.Cys565Arg) which do not meet likely pathogenic with the HL specifications. |
| **PP3** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |

## Curation History

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