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Variant: NM_000551.4(VHL):c.257C>T (p.Pro86Leu)

Version: 1.0

CA020186

182977 (ClinVar)

Gene: VHL (HGNC:7428)
Condition: von Hippel-Lindau disease (MONDO:0008667)
Inheritance Mode: Autosomal dominant inheritance
UUID: 318690ae-2743-4195-8d9b-e2e84ff94494
Approved on: 2024/6/25
Published on: 2024/6/25

HGVS expressions

NM_000551.4(VHL):c.257C>T (p.Pro86Leu)
NM_000551.4:c.257C>T
NC_000003.12:g.10142104C>T
CM000665.2:g.10142104C>T
NC_000003.11:g.10183788C>T
CM000665.1:g.10183788C>T
NC_000003.10:g.10158788C>T
NG_008212.3:g.5470C>T
ENST00000696142.1:c.257C>T
ENST00000696143.1:c.257C>T
ENST00000696153.1:c.257C>T
ENST00000256474.3:c.257C>T
ENST00000256474.2:c.257C>T
ENST00000345392.2:c.257C>T
NM_000551.3:c.257C>T
NM_198156.2:c.257C>T
NM_001354723.1:c.257C>T
NM_001354723.2:c.257C>T
NM_198156.3:c.257C>T

Pathogenic

Met criteria codes 3

PP1_Strong | PS4 | PM2_Supporting

Evidence Links 0

Expert Panel

VHL VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen VHL Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VHL Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

VHL VCEP

The variant NM_000551.4(VHL):c.257C>T (p.Pro86Leu) is a missense variant predicted to cause substitution of Proline by Leucine. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This is identified in over 10 probands meeting either Danish criteria for VHL, or harboring other consistent features with VHL. The total phenotype points is 7.5, which meets the VHL VCEP specification of PS4 (5-15 phenotype points) (PMIDs:7728151; 27527340; 29437867; 21463266). The variant has been reported to segregate with von Hippel Lindau syndrome in at least 7 affected family members from 2 families (PP1_Strong; PMID: 7728151). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal-dominant von Hippel Lindau syndrome (VHL syndrome) based on the ACMG/AMP criteria applied, as specified by the ClinGen VHL VCEP Version 1.0 (Specifications approval date: 02/26/2024 Variant Approval Date 06/25/2024).

Met criteria codes

PP1_Strong	✔	Two unrelated VHL families with a total of 12 affected individuals with this VHL variant. Detailed relationship not provided but this would meet ">7 meioses across >=2 families" criteria for PP1_Strong.
PS4	✔	At least 10 probands either meeting Danish criteria (1 point each) or minor features of VHL (0.5 points for consistent with VHL phenotype, and 0.25 points for nonspecific features). Total proband points reached is 7.5 (5-15 points = PS4)
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Curation History

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