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Variant: NM_000551.4(VHL):c.408del (p.Phe136fs)

Version: 1.0

CA020343

43601 (ClinVar)

Gene: VHL (HGNC:7428)
Condition: von Hippel-Lindau disease (MONDO:0008667)
Inheritance Mode: Autosomal dominant inheritance
UUID: dd17e816-b08e-439f-8c0e-1fdaf81ed144
Approved on: 2024/6/25
Published on: 2024/6/25

HGVS expressions

NM_000551.4:c.408del
NM_000551.4(VHL):c.408del (p.Phe136fs)
NC_000003.12:g.10146581del
CM000665.2:g.10146581del
NC_000003.11:g.10188265del
CM000665.1:g.10188265del
NC_000003.10:g.10163265del
NG_008212.3:g.9947del
ENST00000696142.1:c.*85del
ENST00000696143.1:c.600-3206del
ENST00000696153.1:c.408del
ENST00000256474.3:c.408del
ENST00000256474.2:c.408del
ENST00000345392.2:c.341-3206del
ENST00000477538.1:n.544del
NM_000551.3:c.408del
NM_198156.2:c.341-3206del
NM_001354723.1:c.*18-3206del
NM_001354723.2:c.*18-3206del
NM_198156.3:c.341-3206del

Pathogenic

Met criteria codes 3

PS4_Supporting PVS1 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.408del (p.Phe136fs) is a frameshift variant in a biologically relevant exon, altering the sequence starting at amino acid 136 and truncating 25 amino acids downstream. It is predicted to cause nonsense mediated decay (though not proven) and is in a critical domain (first beta domain, 63-155) of the protein (PVS1). Aronoff et al reports 5 affected family members with this variant. Proband III-I meets Danish criteria with pancreatic cyst or tumor, cerebellar haemangioblastoma and first degree member affected (1 point, PS4_Supporting. PMID:29437867). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). 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

PS4_Supporting	✔	5 members of same family with this variant. In family pedigree A, proband III-I meets Danish criteria with pancreatic cyst or tumour, cerebellar haemangioblastoma and first degree member affected (mom). (PS4_Supporting).
PVS1	✔	The c.408delT variant in VHL is a frameshift variant in a biologically relevant exon. It is predicted to cause nonsense mediated decay (though not proven) and is in a critical domain (first beta domain, 63-155) of the protein (PVS1).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Curation History

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