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Variant: NM_000020.3(ACVRL1):c.1468C>T (p.Gln490Ter)

Version: 1.0

CA384906013

426040 (ClinVar)

Gene: ACVRL1 (HGNC:94)
Condition: telangiectasia, hereditary hemorrhagic, type 2 (MONDO:0010880)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8ebf9f7a-0a8a-4ed2-924e-83f8991523cc
Approved on: 2024/3/15
Published on: 2024/3/15

HGVS expressions

NM_000020.3:c.1468C>T
NM_000020.3(ACVRL1):c.1468C>T (p.Gln490Ter)
NC_000012.12:g.51920849C>T
CM000674.2:g.51920849C>T
NC_000012.11:g.52314633C>T
CM000674.1:g.52314633C>T
NC_000012.10:g.50600900C>T
NG_009549.1:g.18432C>T
ENST00000547400.6:c.1198C>T
ENST00000551576.6:c.1468C>T
ENST00000388922.9:c.1468C>T
ENST00000388922.8:c.1468C>T
ENST00000419526.6:c.946C>T
ENST00000550683.5:c.1510C>T
NM_000020.2:c.1468C>T
NM_001077401.1:c.1468C>T
NM_001077401.2:c.1468C>T

Pathogenic

Met criteria codes 4

PM2_Supporting | PVS1_Strong | PS4 | PP1_Strong

Evidence Links 0

Expert Panel

Hereditary Hemorrhagic Telangiectasia VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Hereditary Hemorrhagic Telangiectasia Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ACVRL1 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Hereditary Hemorrhagic Telangiectasia VCEP

The NM_000020.3: c.1468C>T (p.Gln490Ter) variant in ACVRL1 is a nonsense variant that may cause a premature stop codon that is predicted to escape nonsense medicated decay, however it is a truncation of a functionally important region (removes amino acids 490-503) in a gene where loss-of-function is an established disease mechanism (PVS1_Strong; PMID: 15879500, 16829353, 20301525). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant has been reported in >4 probands with a phenotype consistent with HHT (PS4; PMID: 16829353, 16540754, 32573726, 11484689, Internal lab contributors). The variant has been reported to segregate with HHT in several affected family members from two large families (PP1_Strong; PMID: 16829353, 11484689). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant hereditary hemorrhagic telangiectasia based on the ACMG/AMP criteria applied, as specified by the ClinGen Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel: PVS1_Strong, PM2_Supporting, PS4, PP1_Strong (specification version 1.0.0; 1/4/2024).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PVS1_Strong	✔	The NM_000020.3: c.1468C>T (p.Gln490Ter) variant in ACVRL1 is a nonsense variant that may cause a premature stop codon that is predicted to escape nonsense medicated decay, however it is a truncation of a functionally important region (removes amino acids 490-503) in a gene where loss-of-function is an established disease mechanism (PVS1_Strong; PMID: 15879500, 16829353, 20301525).
PS4	✔	This variant has been reported in >4 probands with a phenotype consistent with HHT (PS4; PMID: 16829353, 16540754, 32573726, 11484689, Internal lab contributors).
PP1_Strong	✔	The variant has been reported to segregate with HHT in several affected family members from two large families (PP1_Strong; PMID: 16829353, 11484689).

Curation History

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