The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001114753.3(ENG):c.447G>C (p.Trp149Cys)

Version: 1.0

CA10582615

237027 (ClinVar)

Gene: ENG (HGNC:2022)
Condition: telangiectasia, hereditary hemorrhagic, type 1 (MONDO:0008535)
Inheritance Mode: Autosomal dominant inheritance
UUID: 81eb6b2e-96ac-4bf0-bfce-6ca2da09ea81
Approved on: 2024/3/15
Published on: 2024/3/15

HGVS expressions

NM_001114753.3:c.447G>C
NM_001114753.3(ENG):c.447G>C (p.Trp149Cys)
NC_000009.12:g.127826586C>G
CM000671.2:g.127826586C>G
NC_000009.11:g.130588865C>G
CM000671.1:g.130588865C>G
NC_000009.10:g.129628686C>G
NG_009551.1:g.33183G>C
ENST00000480266.6:c.-100G>C
ENST00000373203.9:c.447G>C
ENST00000344849.4:c.447G>C
ENST00000373203.8:c.447G>C
ENST00000462196.1:n.347G>C
ENST00000480266.5:c.-100G>C
NM_000118.3:c.447G>C
NM_001114753.2:c.447G>C
NM_001278138.1:c.-100G>C
NM_001278138.2:c.-100G>C

Pathogenic

Met criteria codes 6

PS3_Supporting PS4 PM2_Supporting PP1 PP3 PP4_Moderate

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 ENG Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hereditary Hemorrhagic Telangiectasia VCEP

The NM_001114753.3: c.447G>C variant in ENG is a missense variant predicted to cause substitution of tryptophan by cysteine at amino acid 149 (p.Trp149Cys). 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: 9554745, 22022569, 22991266, 32300199, Internal lab contributors). At least one patient's phenotype meets Curacao Criteria for HHT, and sequencing and large deletion/duplication analysis was performed for ENG and ACVRL1, which is highly specific for HHT (PP4_Moderate; Internal lab contributors). The variant has been reported to segregate with HHT in 3 affected individuals of a family (4 generations) (PP1; PMID: 10545596). The computational predictor REVEL gives a score of 0.762, which is above the threshold of ≥0.644, evidence that correlates with impact to ENG function (PP3). Additionally, expression studies in endoglin-deficient mice, human umbilical vein endothelial cells (HUVECs) and peripheral blood activated monocytes showed reduced expression of fully processed normal endoglin indicating that this variant impacts protein function (PS3_Supporting; PMID: 10545596, 11343967, 10749981). 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: PM2_Supporting, PP3, PP4_Moderate, PS4, PS3_Supporting, PP1 (specification version 1.0.0; 1/4/2024).

Met criteria codes

PS3_Supporting	✔	Expression studies in endoglin-deficient mice, human umbilical vein endothelial cells (HUVECs) and peripheral blood activated monocytes showed reduced expression of fully processed normal endoglin indicating that this variant impacts protein function (PS3_Supporting; PMID: 10545596, 11343967, 10749981).
PS4	✔	This variant has been reported in >4 probands with a phenotype consistent with HHT (PS4; PMID: 9554745, 22022569, 22991266, 32300199, Internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP1	✔	The variant has been reported to segregate with HHT in 3 affected individuals of a family (4 generations) (PP1; PMID: 10545596).
PP3	✔	The computational predictor REVEL gives a score of 0.762, which is above the threshold of ≥0.644, evidence that correlates with impact to ENG function (PP3).
PP4_Moderate	✔	At least one patient's phenotype meets Curacao Criteria for HHT, and sequencing and large deletion/duplication analysis was performed for ENG and ACVRL1, which is highly specific for HHT (PP4_Moderate; Internal lab contributors).

Curation History

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