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Variant: NM_001114753.3(ENG):c.662T>C (p.Leu221Pro)

Version: 1.0

CA374983528

435060 (ClinVar)

Gene: ENG (HGNC:2022)
Condition: telangiectasia, hereditary hemorrhagic, type 1 (MONDO:0008535)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3d717ef0-3d29-4ae8-92c1-13c6f812bf95
Approved on: 2024/3/15
Published on: 2024/3/15

HGVS expressions

NM_001114753.3:c.662T>C
NM_001114753.3(ENG):c.662T>C (p.Leu221Pro)
NC_000009.12:g.127825722A>G
CM000671.2:g.127825722A>G
NC_000009.11:g.130588001A>G
CM000671.1:g.130588001A>G
NC_000009.10:g.129627822A>G
NG_009551.1:g.34047T>C
ENST00000480266.6:c.116T>C
ENST00000373203.9:c.662T>C
ENST00000344849.4:c.662T>C
ENST00000373203.8:c.662T>C
ENST00000480266.5:c.116T>C
NM_000118.3:c.662T>C
NM_001114753.2:c.662T>C
NM_001278138.1:c.116T>C
NM_001278138.2:c.116T>C

Likely Pathogenic

Met criteria codes 4

PS3_Supporting PP4_Moderate PM2_Supporting PS4

Not Met criteria codes 1

PP3

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.662T>C variant in ENG is a missense variant predicted to cause substitution of leucine by proline at amino acid 221 (p.Leu221Pro). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant has been reported in >10 probands with a phenotype consistent with HHT (PS4; PMID: 10545596, 15880681, 17384219, 18498373, 20414677, 22991266, 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 computational predictor REVEL gives a score of 0.478, which is neither above nor below the thresholds predicting a damaging or benign impact on ENG function. However, protein expression assays in cell lines showed the variant causes reduced endoglin expression (PS3_Supporting; PMID: 10545596). In summary, this variant meets the criteria to be classified as likely 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: PS4, PP4_Moderate, PS3_Supporting, PM2_Supporting (specification version 1.0.0; 1/4/2024).

Met criteria codes

PS3_Supporting	✔	Protein expression assays in cell lines showed the variant causes reduced endoglin expression (PS3_Supporting; PMID: 10545596).
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).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS4	✔	This variant has been reported in >10 probands with a phenotype consistent with HHT (PS4; PMID: 10545596, 15880681, 17384219, 18498373, 20414677, 22991266, Internal lab contributors).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.478, which is neither above nor below the thresholds predicting a damaging or benign impact on ENG function.

Curation History

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