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Variant: NM_001114753.3(ENG):c.1645T>G (p.Cys549Gly)

Version: 1.0

CA374974153

995686 (ClinVar)

Gene: ENG (HGNC:2022)
Condition: telangiectasia, hereditary hemorrhagic, type 1 (MONDO:0008535)
Inheritance Mode: Autosomal dominant inheritance
UUID: f3f7c1fb-c482-43ee-a390-bca0624aa03a
Approved on: 2024/9/11
Published on: 2024/9/19

HGVS expressions

NM_001114753.3(ENG):c.1645T>G (p.Cys549Gly)
NM_001114753.3:c.1645T>G
NC_000009.12:g.127818161A>C
CM000671.2:g.127818161A>C
NC_000009.11:g.130580440A>C
CM000671.1:g.130580440A>C
NC_000009.10:g.129620261A>C
NG_009551.1:g.41608T>G
ENST00000480266.6:c.1099T>G
ENST00000373203.9:c.1645T>G
ENST00000344849.4:c.1645T>G
ENST00000373203.8:c.1645T>G
ENST00000480266.5:c.1099T>G
NM_000118.3:c.1645T>G
NM_001114753.2:c.1645T>G
NM_001278138.1:c.1099T>G
NR_136302.1:n.1378-150A>C
NM_001278138.2:c.1099T>G

Likely Pathogenic

Met criteria codes 5

PP3 PM1 PM5 PS4_Moderate PM2_Supporting

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 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hereditary Hemorrhagic Telangiectasia VCEP

The NM_001114753.3: c.1645T>G variant in ENG is a missense variant predicted to cause substitution of cysteine by glycine at amino acid 549 (p.Cys549Gly). This variant has been reported in 3 probands with a phenotype consistent with Hereditary Hemorrhagic Telangiectasia (PS4_Moderate, Internal lab contributors, Invitae, Victorian Clinical Genetics Service). This variant is absent from gnomAD v.2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.861 which is above the threshold of 0.644, evidence that correlates with impact to ENG function (PP3). Another missense variant c.1646G>A, p.Cys549Tyr (PMIDs: 38828001, 20414677, 21158752; ClinVar Variation ID: 407135) in the same codon has been classified as pathogenic for Hereditary Hemorrhagic Telangiectasia by the ClinGen Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel (PM5). This variant resides within a region, amino acid C549, of ENG that is defined as a mutational hotspot or critical functional domain by the ClinGen Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel (PMIDs: 28564608, 25312062) (PM1). 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_Moderate, PM2_Supporting, PP3, PM5, PM1 (specifications version 1.1.0; 09/11/2024).

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.861 which is above the threshold of 0.644, evidence that correlates with impact to ENG function (PP3).
PM1	✔	This variant resides within a region, amino acid C549, of ENG that is defined as a mutational hotspot or critical functional domain by the ClinGen Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel (PMIDs: 28564608, 25312062) (PM1).
PM5	✔	Another missense variant c.1646G>A, p.Cys549Tyr (PMIDs: 38828001, 20414677, 21158752; ClinVar Variation ID: 407135) in the same codon has been classified as pathogenic for Hereditary Hemorrhagic Telangiectasia by the ClinGen Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel (PM5).
PS4_Moderate	✔	This variant has been reported in 3 probands with a phenotype consistent with Hereditary Hemorrhagic Telangiectasia (PS4_Moderate, Internal lab contributors, Invitae, Victorian Clinical Genetics Service).
PM2_Supporting	✔	This variant is absent from gnomAD v.2.1.1 (PM2_Supporting).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001114753.3(ENG):c.1645T>G (p....	Likely Pathogenic	Telangiectasia, Hereditary Hemorrhagic, Type 1	2024-09-19	1.0	ClinGen Hereditary Hemorrhagic Telangiectasia Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ENG Version 1.1.0	ENG

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