

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

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HGVS expressions

NM_001114753.3:c.1645T>G

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

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**

PS4_Moderate

PP3

PM2_Supporting

PM1

PM5

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

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).
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).
PM2_Supporting			This variant is absent from gnomAD v.2.1.1 (PM2_Supporting).
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).

Curation History

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