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Variant: NM_001114753.3(ENG):c.1145G>A (p.Cys382Tyr)

Version: 1.0

CA374978902

430375 (ClinVar)

Gene: ENG (HGNC:2022)
Condition: telangiectasia, hereditary hemorrhagic, type 1 (MONDO:0008535)
Inheritance Mode: Autosomal dominant inheritance
UUID: 495f0389-0c66-4d9f-ab7f-f1bf5d4cfa68
Approved on: 2025/2/4
Published on: 2025/3/26

HGVS expressions

NM_001114753.3:c.1145G>A
NM_001114753.3(ENG):c.1145G>A (p.Cys382Tyr)
NC_000009.12:g.127820027C>T
CM000671.2:g.127820027C>T
NC_000009.11:g.130582306C>T
CM000671.1:g.130582306C>T
NC_000009.10:g.129622127C>T
NG_009551.1:g.39742G>A
ENST00000480266.6:c.599G>A
ENST00000373203.9:c.1145G>A
ENST00000344849.4:c.1145G>A
ENST00000373203.8:c.1145G>A
ENST00000480266.5:c.599G>A
ENST00000486329.1:n.113G>A
NM_000118.3:c.1145G>A
NM_001114753.2:c.1145G>A
NM_001278138.1:c.599G>A
NR_136302.1:n.1569-1168C>T
NM_001278138.2:c.599G>A

Pathogenic

Met criteria codes 6

PM1 PP4_Moderate PS4 PP1 PM2_Supporting PS3_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.1145G>A variant in ENG is a missense variant predicted to cause substitution of cysteine by tyrosine at amino acid 382 (p.Cys382Tyr). This variant alters amino acid C382 of ENG that is defined as a critical residue (previously reported to be likely pathogenic or pathogenic) by the ClinGen Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel (PM1; PMID: 17786384). This variant has been reported in more than 4 probands with a phenotype consistent with HHT (PS4; 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; PMID: 30763665). The variant has been reported to segregate with HHT in 3 affected family members from a single family (PP1; PMID: 30763665, Internal lab contributors). This variant is absent from gnomAD v.2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.56, which is neither above nor below the thresholds predicting a damaging or benign impact on ENG function. Functional assays showed the variant protein to have reduced protein expression in CHO-K1 cells, indicating that this variant impacts protein function (PS3_Supporting, PMID: 30763665). 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: PS4, PM1, PP4_Moderate, PM2_Supporting, PS3_Supporting, PP1 (specifications version 1.1.0; 02/04/2025).

Met criteria codes

PM1	✔	This variant alters amino acid C382 of ENG that is defined as a critical residue (previously reported to be likely pathogenic or pathogenic) by the ClinGen Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel (PM1; PMID: 17786384).
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; PMID: 30763665).
PS4	✔	This variant has been reported in more than 4 probands with a phenotype consistent with HHT (PS4; Internal lab contributors).
PP1	✔	The variant has been reported to segregate with HHT in 3 affected family members from a single family (PP1; PMID: 30763665, Internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v.2.1.1 (PM2_Supporting).
PS3_Supporting	✔	Functional assays showed the variant protein to have reduced protein expression in CHO-K1 cells, indicating that this variant impacts protein function (PS3_Supporting, PMID: 30763665).

Curation History

Showing 1 to 1 of 1 rows

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