Variant: NM_001114753.3(ENG):c.1517T>A (p.Leu506His)

Version: 1.0

CA5252743

1466744 (ClinVar)

Gene: ENG (HGNC:2022)
Condition: telangiectasia, hereditary hemorrhagic, type 1 (MONDO:0008535)
Inheritance Mode: Autosomal dominant inheritance
UUID: c4aa1004-6cff-4317-b302-93c0aeff6eea
Approved on: 2025-02-04
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HGVS expressions

NM_001114753.3:c.1517T>A
NM_001114753.3(ENG):c.1517T>A (p.Leu506His)
NC_000009.12:g.127818289A>T
CM000671.2:g.127818289A>T
NC_000009.11:g.130580568A>T
CM000671.1:g.130580568A>T
NC_000009.10:g.129620389A>T
NG_009551.1:g.41480T>A
ENST00000480266.6:c.971T>A
ENST00000373203.9:c.1517T>A
ENST00000344849.4:c.1517T>A
ENST00000373203.8:c.1517T>A
ENST00000480266.5:c.971T>A
NM_000118.3:c.1517T>A
NM_001114753.2:c.1517T>A
NM_001278138.1:c.971T>A
NR_136302.1:n.1378-22A>T
NM_001278138.2:c.971T>A

Likely Pathogenic

Met criteria codes 4

PS1 PP3 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.1517T>A variant in ENG is a missense variant predicted to cause substitution of leucine by histidine at amino acid 506 (p.Leu506His). This variant has been reported in 2 probands with a phenotype consistent with HHT (PS4_Moderate; Internal lab contributors). The computational predictor REVEL gives a score of 0.88, which is above the threshold of ≥0.644, evidence that correlates with impact to ENG function (PP3). The overall minor allele frequency in gnomAD v2.1.1 is 0.000004 (1/250772 alleles), which is lower than the ClinGen Hereditary Hemorrhagic Telangiectasia VCEP threshold (<6 total alleles) for PM2_Supporting, meeting this criterion (PM2_Supporting). Another missense variant, c.1517T>C, p.Leu506Pro (PMID: 24196379, 30073140; ClinVar Variation ID: 1774348), in the same codon has been classified as likely pathogenic for autosomal dominant Hereditary Hemorrhagic Telangiectasia by the ClinGen Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel (PM5). 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, PP3, PM2_Supporting, PM5 (specifications version 1.1.0; 02/04/2025).

Met criteria codes

PS1	✔	Another missense variant, c.1517T>C, p.Leu506Pro (PMID: 24196379, 30073140; ClinVar Variation ID: 1774348), in the same codon has been classified as likely pathogenic for autosomal dominant Hereditary Hemorrhagic Telangiectasia by the ClinGen Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel (PM5).
PP3	✔	The computational predictor REVEL gives a score of 0.88, which is above the threshold of ≥0.644, evidence that correlates with impact to ENG function (PP3).
PS4_Moderate	✔	This variant has been reported in 2 probands with a phenotype consistent with HHT (PS4_Moderate; Internal lab contributors).
PM2_Supporting	✔	The overall minor allele frequency in gnomAD v2.1.1 is 0.000004 (1/250772 alleles), which is lower than the ClinGen Hereditary Hemorrhagic Telangiectasia VCEP threshold (<6 total alleles) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Curation History

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