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Variant: NM_001114753.3(ENG):c.991G>A (p.Gly331Ser)

Version: 1.0

CA16612528

407115 (ClinVar)

Gene: ENG (HGNC:2022)
Condition: telangiectasia, hereditary hemorrhagic, type 1 (MONDO:0008535)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3ce6893b-d576-45bb-b69c-edf517fe12d9
Approved on: 2024/3/15
Published on: 2024/3/15

HGVS expressions

NM_001114753.3:c.991G>A
NM_001114753.3(ENG):c.991G>A (p.Gly331Ser)
NC_000009.12:g.127824800C>T
CM000671.2:g.127824800C>T
NC_000009.11:g.130587079C>T
CM000671.1:g.130587079C>T
NC_000009.10:g.129626900C>T
NG_009551.1:g.34969G>A
ENST00000480266.6:c.445G>A
ENST00000373203.9:c.991G>A
ENST00000344849.4:c.991G>A
ENST00000373203.8:c.991G>A
ENST00000480266.5:c.445G>A
NM_000118.3:c.991G>A
NM_001114753.2:c.991G>A
NM_001278138.1:c.445G>A
NM_001278138.2:c.445G>A

Pathogenic

Met criteria codes 5

PS3 PS4 PP1 PM2_Supporting PP4_Moderate

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.991G>A variant in ENG is a missense variant predicted to cause substitution of glycine by serine at amino acid 331 (p.Gly331Ser). 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: 19767588, 34872578, 16690726, 34880085, 15517393, 25970827, 29171923, 32573726, 21158752, 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: 19767588, 21158752). The variant has been reported to segregate with HHT in 3 affected meioses from 2 families (PP1; PMID: 19767588, 34872578). The computational predictor REVEL gives a score of 0.202, which is neither above nor below the thresholds predicting a damaging or benign impact on ENG function. However, RT-PCR analysis of cDNA demonstrated that the variant impacts splicing by leading to exon 7 skipping (PS3; PMID: 16690726). 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: PS3, PS4, PP4_Moderate, PP1, PM2_Supporting (specification version 1.0.0; 1/4/2024).

Met criteria codes

PS3	✔	RT-PCR analysis of cDNA demonstrated that the variant impacts splicing by leading to exon 7 skipping (PS3; PMID: 16690726).
PS4	✔	This variant has been reported in >10 probands with a phenotype consistent with HHT (PS4; PMID: 19767588, 34872578, 16690726, 34880085, 15517393, 25970827, 29171923, 32573726, 21158752, Internal lab contributors).
PP1	✔	The variant has been reported to segregate with HHT in 3 affected meioses from 2 families (PP1; PMID: 19767588, 34872578).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
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: 19767588, 21158752).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.202, which is neither above nor below the thresholds predicting a damaging or benign impact on ENG function.

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.991G>A (p.G...	Pathogenic	Telangiectasia, Hereditary Hemorrhagic, Type 1	2024-03-15	1.0	ClinGen Hereditary Hemorrhagic Telangiectasia Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ENG Version 1.0.0	ENG

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