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Variant: NM_000552.5(VWF):c.3569G>T (p.Cys1190Phe)

Version: 1.0

CA383510973

2572159 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2A (MONDO:0015628)
Inheritance Mode: Autosomal dominant inheritance
UUID: 382a0334-162b-4fa9-87f7-d77a6aea64cb
Approved on: 2025/4/2
Published on: 2025/4/2

HGVS expressions

NM_000552.5(VWF):c.3569G>T (p.Cys1190Phe)
NM_000552.5:c.3569G>T
NC_000012.12:g.6022005C>A
CM000674.2:g.6022005C>A
NC_000012.11:g.6131171C>A
CM000674.1:g.6131171C>A
NC_000012.10:g.6001432C>A
NG_009072.1:g.107666G>T
NG_009072.2:g.107666G>T
ENST00000261405.10:c.3569G>T
ENST00000261405.9:c.3569G>T
ENST00000538635.5:n.421-28071G>T
NM_000552.3:c.3569G>T
NM_000552.4:c.3569G>T

Likely Pathogenic

Met criteria codes 4

PP4_Moderate | PM2_Supporting | PM5 | PP3

Evidence Links 0

Expert Panel

von Willebrand Disease VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

von Willebrand Disease VCEP

The NM_000552.5:c.3569G>T variant in VWF is a missense variant predicted to cause substitution of cysteine by phenylalanine at amino acid 1190. At least 1 patient with this variant displayed excessive mucocutaneous bleeding (evidenced by inclusion in a VWD diagnosed cohort) as well as laboratory phenotypes of very low VWF activity VWF:GP1b and VWF:Collagen binding assay, low activity/VWF:Ag ratio, and loss of high molecular weight multimers, which together are highly specific for VWD type 2A. (PP4_moderate, PMID 36299619).

Another missense variant NM_000552.5:c.3568T>C (p.Cys1190Arg) in the same codon has been classified as likely pathogenic for VWD type 2A by the ClinGen VWD VCEP (PM5). The computational predictor REVEL gives a score of 0.955, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). The computational predictor REVEL gives a score of 0.955, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant VWD type 2A based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PS4_Supporting, PM5_Supporting, PP3, PM2_Supporting. (ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0; date of approval)

Met criteria codes

PP4_Moderate	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding (evidenced by inclusion in a VWD diagnosed cohort) as well as laboratory phenotypes of very low VWF activity VWF:GP1b and VWF:Collagen binding assay, low activity/VWF:Ag ratio, and loss of high molecular weight multimers, which together are highly specific for VWD type 2A. (PP4_moderate, PMID 36299619).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PM5	✔	Another missense variant NM_000552.5:c.3568T>C (p.Cys1190Arg) in the same codon has been classified as pathogenic for VWD type 2A by the ClinGen VWD VCEP (PM5).
PP3	✔	The computational predictor REVEL gives a score of 0.955, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).

Curation History

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