

Variant: NM_000552.5(VWF):c.3569G>A (p.Cys1190Tyr)

Version: 1.0

CA383510975 [↗](#)

626960 (ClinVar) [↗](#)

Gene: VWF ([HGNC:7450](#))

Condition: von Willebrand disease type 2A ([MONDO:0015628](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 7451c2f1-7e09-46f1-be83-ab46032458b5

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HGVS expressions

NM_000552.5(VWF):c.3569G>A (p.Cys1190Tyr)

NM_000552.5:c.3569G>A

NC_000012.12:g.6022005C>T

CM000674.2:g.6022005C>T

NC_000012.11:g.6131171C>T

CM000674.1:g.6131171C>T

NC_000012.10:g.6001432C>T

NG_009072.1:g.107666G>A

NG_009072.2:g.107666G>A

ENST00000261405.10:c.3569G>A

ENST00000261405.9:c.3569G>A

ENST00000538635.5:n.421-28071G>A

NM_000552.3:c.3569G>A

NM_000552.4:c.3569G>A

Pathogenic

Met criteria codes **5**

PP3

PM5

PP4_Moderate

PS4

PM2_Supporting

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>A variant in VWF is a missense variant predicted to cause substitution of cysteine by tyrosine at amino acid 1190 (p.Cys1190Tyr). At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of very low VWF activity, low activity/VWF:Ag ratio, and loss of high molecular weight multimers, which together are highly specific for VWD type 2A. (PP4_moderate, PMID 34532631). Additional consistent phenotypes were also reported in the patient, specifically, FVIII activity

consistent with VWF antigen. This variant has been reported in 5 additional probands meeting PP4 laboratory phenotype criteria (PS4; PMID 20351307, 32864553, 32803740, 34355501). 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). The Grpmax filtering allele frequency in gnomAD v4.1 is 0.0000006195 (1/1180046 European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 for type 2A (PM2_Supporting). The computational predictor REVEL gives a score of 0.947, 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 pathogenic for autosomal dominant VWF type 2A based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP4_Moderate, PS4, PM5, PM2_Supporting, PP3. (ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0)

Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.947, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).
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).
PP4_Moderate			At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of very low VWF activity, low activity/VWF:Ag ratio, and loss of high molecular weight multimers, which together are highly specific for VWD type 2A. (PP4_moderate, PMID 34532631). Additional consistent phenotypes were also reported in the patient, specifically, FVIII activity consistent with VWF antigen.
PS4			This variant has been reported in 6 additional probands meeting PP4 laboratory phenotype criteria (PS4; PMID 20351307, 32864553, 32803740, 34355501, 36696193, GoldVariantDatabase PersonalCommunication).
PM2_Supporting			The Grpmax filtering allele frequency in gnomAD v4.1 is 0.0000006195 (1/1180046 European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 for type 2A (PM2_Supporting).

Curation History

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