

Variant: NM_000552.5(VWF):c.4541T>G (p.Phe1514Cys)

Version: 1.0

CA114154 [↗](#)

304 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: c90dcedf-05f4-4c7d-883e-1b316a64d157

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HGVS expressions

NM_000552.5:c.4541T>G

NM_000552.5(VWF):c.4541T>G (p.Phe1514Cys)

NC_000012.12:g.6018877A>C

CM000674.2:g.6018877A>C

NC_000012.11:g.6128043A>C

CM000674.1:g.6128043A>C

NC_000012.10:g.5998304A>C

NG_009072.1:g.110794T>G

NG_009072.2:g.110794T>G

ENST00000261405.10:c.4541T>G

ENST00000261405.9:c.4541T>G

ENST00000538635.5:n.421-24943T>G

NM_000552.3:c.4541T>G

NM_000552.4:c.4541T>G

Likely Pathogenic

Met criteria codes **5**

PS4_Supporting

PM2_Supporting

PP4_Moderate

PP1

PP3

Not Met criteria codes **6**

BS2

BS1

BP4

BP5

BA1

PM5

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.4541T>G p.(Phe1514Cys) variant in VWF is a missense variant predicted to cause substitution of phenylalanine by cysteine at amino acid 1514. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.93, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). At least 1 proband with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of very low VWF activity

(measured by VWF:RCo), low activity/VWF:Ag ratio and loss of high molecular weight multimers, which together are highly specific for VWD type 2A. (PP4_moderate, PMID 8435341). The variant has been reported to segregate with VWD type 2A through >2 affected meioses from 1 family (PP1; PMID: 8435341). This variant has been reported in at least 1 additional proband with reduced VWF:Ag to activity ratio (PS4_supporting; PMID: 40393667). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant von Willebrand disease Type 2A based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP (v1): PP1, PP3, PP4_Moderate, PM2_Supporting, PS4_Supporting.

Met criteria codes

PS4_Supporting			This variant has been reported in at least 1 additional proband with reduced VWF:Ag to activity ratio (PS4_supporting; PMID: 40393667).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP4_Moderate			At least 1 proband with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of very low VWF activity (measured by VWF:RCo), low activity/VWF:Ag ratio and loss of high molecular weight multimers, which together are highly specific for VWD type 2A. (PP4_moderate, PMID 8435341).
PP1			The variant has been reported to segregate with VWD type 2A through >2 affected meioses from 1 family (PP1; PMID: 8435341).
PP3			The computational predictor REVEL gives a score of 0.93, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).

Not Met criteria codes

BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			Phe1514Ser has been reported in at least one type 2A patient (PMID: 40393667) but has not yet been classified by the VWD VCEP.

Curation History 

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