

Variant: NM_000552.5(VWF):c.3854C>T (p.Ser1285Phe)

Version: 1.0

CA114164 [↗](#)

311 (ClinVar) [↗](#)

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

Condition: von Willebrand disease type 2M ([MONDO:0015630](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 7b2b1d12-ff49-4d9c-a7d8-afb13b3adf39

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HGVS expressions

NM_000552.5:c.3854C>T

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NC_000012.12:g.6019564G>A

CM000674.2:g.6019564G>A

NC_000012.11:g.6128730G>A

CM000674.1:g.6128730G>A

NC_000012.10:g.5998991G>A

NG_009072.1:g.110107C>T

NG_009072.2:g.110107C>T

ENST00000261405.10:c.3854C>T

ENST00000261405.9:c.3854C>T

ENST00000538635.5:n.421-25630C>T

ENST00000539641.1:n.652C>T

NM_000552.3:c.3854C>T

NM_000552.4:c.3854C>T

Likely Pathogenic

Met criteria codes **4**

PM2_Supporting

PS3

PP3

PP4_Moderate

Not Met criteria codes **3**

PS4

PP1

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(VWF):c.3854C>T variant in VWF is a missense variant predicted to cause substitution of serine by phenylalanine at amino acid 1285. This variant is absent from gnomAD v4.1 (PM2_supporting). At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of a normal multimer pattern, low VWF:RCo/VWF:Ag ratio (<0.5), and markedly

reduced ristocetin-induced VWF binding to GPIb, which together are highly specific for VWD type 2M. (PP4_moderate, PMID: 12588351). The computational predictor REVEL gives a score of 0.946, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). The A1 domain from this variant exhibited complete loss of shear-flow-dependent platelet adhesion (PMID: 25185554, PS3).This variant is classified as Likely Pathogenic for von Willebrand disease type 2M based on the ACMG/AMP criteria applied as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PM2_supporting, PP4_Moderate, PP3, PS3.

Met criteria codes			
PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).
PS3			The A1 domain from this variant exhibited complete loss of shear-flow-dependent platelet adhesion (PMID: 25185554), while circular dichroism of the recombinant protein, immunocytochemistry in HEK293 cells, and limited trypsinolysis combined with hydrogen deuterium exchange in E. coli showed abnormal folding by the variant, relative to wild-type VWF (PMID: 31628947). The assay from PMID: 25185554 meets the requirements for use by the ClinGen VWD VCEP (PS3).
PP3			The computational predictor REVEL gives a score of 0.946, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). The computational splicing predictor SpliceAI gives a score of 0.00 for all splicing types, indicating that the variant has no impact on splicing.
PP4_Moderate			At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of a normal multimer pattern, low VWF:RCo/VWF:Ag ratio (<0.5), and markedly reduced ristocetin-induced VWF binding to GPIb, which together are highly specific for VWD type 2M. (PP4_moderate, PMID: 12588351).

Not Met criteria codes			
PS4			Two additional patients have been reported with this variant, PMID: 17488667 reports a "type 1 von Willebrand disease case" and PMID: 17681836 reports a type 2M case with insufficient information to count here.
PP1			The variant has been reported to segregate with VWD type 2M through 1 affected meiosis from 1 family (Not Met; PMID: 12588351).
PM5			NM_000552.5(VWF):c.3853T>C (p.Ser1285Pro) at the same amino acid residue has not yet been classified by the VWD VCEP but is thought to disrupt secretion, leading to a type 1 VWD, and has insufficient evidence to reach a Pathogenic classification at this time.

Curation History 

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