

Variant: NM_000552.5(VWF):c.3946G>A (p.Val1316Met)

Version: 1.2

CA114127 [↗](#)

290 (ClinVar) [↗](#)

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

Condition: von Willebrand disease type 2B ([MONDO:0015629](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: b78eb887-2dcf-44f2-bf99-7f0aa13fad67

Approved on: 2024/8/13

Published on: 2024/8/19

HGVS expressions

NM_000552.5:c.3946G>A

NM_000552.5(VWF):c.3946G>A (p.Val1316Met)

NC_000012.12:g.6019472C>T

CM000674.2:g.6019472C>T

NC_000012.11:g.6128638C>T

CM000674.1:g.6128638C>T

NC_000012.10:g.5998899C>T

NG_009072.1:g.110199G>A

NG_009072.2:g.110199G>A

ENST00000261405.10:c.3946G>A

ENST00000261405.9:c.3946G>A

ENST00000538635.5:n.421-25538G>A

NM_000552.3:c.3946G>A

NM_000552.4:c.3946G>A

Pathogenic

Met criteria codes **7**

PS3 PP1 PP3 PS4_Very Strong

PS2_Moderate PP4_Moderate

PM2_Supporting

Not Met criteria codes **1**

PM6

Evidence Links **1**

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.3946G>A variant in VWF is a missense variant predicted to cause substitution of valine by methionine at amino acid 1316. This variant is absent from gnomADv4.1 (PM2_Supporting). This variant has been reported in at least 9 probands showing excessive mucocutaneous bleeding as well as a laboratory phenotype of loss of high molecular weight multimers and/or enhanced platelet aggregation at low doses of ristocetin (PS4_VeryStrong, PMID: 19060241, PMID: 27885890, PMID: 28640903). At least 1 patient showed

excessive mucocutaneous bleeding, loss of high molecular weight multimers, and enhanced platelet aggregation at low doses of ristocetin, which together are specific for VWD type 2B, along with consistent features of thrombocytopenia and low VWF antigen/activity ratio (PP4_Moderate, PMID: 28640903). Two additional affected patients harbored the variant in an apparent de novo heterozygous state (PS2_Moderate, PMID: 7909449, PMID: 2010538). The variant has been reported to segregate with VWD type 2B through 3 affected meioses from 1 family (PP1; PMID: 19060241). The computational predictor REVEL gives a score of 0.74, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). A knock-in mouse model expressing VWF p.Val1316Met has shown prolonged bleeding time, absence of high-MW multimers, large platelet aggregates, decreased in vitro platelet adhesion to thrombin or collagen, and enhanced in vivo VWF/platelet string formation, indicating that this variant has a damaging effect on protein function that is consistent with phenotypes of VWD Type 2B (PMID: 27212476, PS3). In summary, this variant meets the criteria to be classified as Pathogenic for von Willebrand disease type 2A. ACMG/AMP criteria applied as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PS3, PS4_VeryStrong, PP4_Moderate, PS2_Moderate, PP1, PP3, PM2_Supporting.

Met criteria codes

PS3			A knock-in mouse model expressing VWF p.Val1316Met showed prolonged bleeding time (Figure 3A), absence of high-MW multimers (Figure 2D), large platelet aggregates (Figure 2C), decreased in vitro platelet adhesion to thrombin or collagen (Figure 4), and enhanced in vivo VWF/platelet string formation (Figure 5), indicating that this variant has a damaging effect on protein function that is consistent with phenotypes of VWD Type 2B (PMID: 27212476, PS3).
			A knock-in mouse model expressing VWF p.Val1316Met showed prolonged bleeding time (Figure 3A), absence of high-MW multimers (Figure 2D), large platelet aggregates (Figure 2C), decreased in vitro platelet adhesion to thrombin or collagen (Figure 4), and enhanced in vivo VWF/platelet string formation (Figure 5), indicating that this variant has a damaging effect on protein function that is consistent with phenotypes of VWD Type 2B (PMID: 27212476, PS3). PubMed:27212476 
PP1			The variant has been reported to segregate with VWD type 2B through 3 affected meioses from 1 family (PP1; PMID: 19060241).
PP3			The computational predictor REVEL gives a score of 0.74, 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.
PS4_Very Strong			This variant has been reported in 9 probands showing excessive mucocutaneous bleeding as well as a laboratory phenotype of loss of high molecular weight multimers and/or enhanced platelet aggregation at low doses of ristocetin (PS4_VeryStrong, PMID: 19060241, PMID: 27885890, PMID: 28640903, PMID: 18805962, PMID: 7909449).
PS2_Moderate			This variant has been identified as a de novo occurrence with confirmed paternal but not maternal relationships in 2 individuals with VWD Type 2B (PS2_Moderate, PMID: 7909449, PMID: 2010538).
PP4_Moderate			At least 4 probands with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of loss of high molecular weight multimers and/or enhanced platelet aggregation at low doses of ristocetin (PMID: 27885890, PMID: 19060241, PMID: 28640903). One patient in particular has excessive mucocutaneous bleeding, loss of high molecular weight multimers, and enhanced platelet aggregation at low doses of ristocetin, which together are specific for VWD type 2B. (PP4_Moderate, PMID: 28640903). The patient was also reported to have thrombocytopenia and a VWF antigen/activity ratio consistent with type 2B, and the alternate diagnosis of platelet-type VWD was not reported in this patient, which is consistent with VWD type 2B.

PM2_Supporting	 	This variant was not found in gnomAD v4.1 (PM2_Supporting).
Not Met criteria codes		
PM6		No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
		<div></div> <div></div> <div></div>
Showing 1 to 3 of 3 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.