

Variant: NM_000552.5(VWF):c.3940G>T (p.Val1314Phe)

Version: 1.0

CA228498 [↗](#)

100308 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: f029ee4a-f433-486b-a623-20df4ad77990

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HGVS expressions

NM_000552.5:c.3940G>T

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NC_000012.12:g.6019478C>A

CM000674.2:g.6019478C>A

NC_000012.11:g.6128644C>A

CM000674.1:g.6128644C>A

NC_000012.10:g.5998905C>A

NG_009072.1:g.110193G>T

NG_009072.2:g.110193G>T

ENST00000261405.10:c.3940G>T

ENST00000261405.9:c.3940G>T

ENST00000538635.5:n.421-25544G>T

NM_000552.3:c.3940G>T

NM_000552.4:c.3940G>T

Pathogenic

Met criteria codes **6**

PM2_Supporting

PS3

PS2_Moderate

PP3

PP4

PM5

Evidence Links **3**

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.3940G>T (p.Val1314Phe) missense variant has been reported in at least 1 proband with prolonged bleeding time (>20 minutes), decreased binding capacity to GPIb, vWFAg (25 U/dL) associated with the absence of vWFRCo (<5 U/dL) for a ratio of <0.2, and an absence of high molecular weight and intermediate multimers in the plasma. Additional features included decreased levels of VIIC (30 U/dL) and a total lack of ristocetin platelet aggregation (RIPA) at concentrations of modulator between 0 and 2 mg/mL. His platelet

count is around $120 \times 10^9/L$ and decreases to approximately $50 \times 10^9/L$ at the time of bleeding episodes (PP4; PMID: 8298143). As reported by the authors, there is a discrepancy in this patient between an apparent type 2A phenotype and 2B genotype. This discrepancy can be explained as an extremely severe form of type-IIB vWD, where the variant strongly increases the affinity of vWF for platelet GPIb, which might result in plasma in a spontaneous binding of both HMW and intermediate-sized multimers to the platelets. This could explain the thrombocytopenia of the propositus and the clearance of the large and intermediate forms of vWF from the patient’s plasma. The variant was identified as a de novo occurrence in this patient (PS2_moderate; PMIDs: 1419803). This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.741, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).A GP1b binding assay performed with the recombinant Val1314Phe mutant vWF expressed by COS-7 cells showed spontaneous binding at low doses of ristocetin (PMID: 8298143 and PMID: 8630394), and enhanced binding to platelets in the presence of low-dose ristocetin compared with WT (PMID: 8630394), indicating that this variant has a gain of function effect on the protein (PS3_supporting). Another type 2B variants have been reported at this amino acid residue; Val1314Leu and classified pathogenic by the VWD VCEP (PM5). In summary, the variant meets the criteria to be classified as Pathogenic for von Willebrand disease type 2B based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PS3, PS2_moderate, PP3, PP4, PM5, and PM2_supporting.

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).
PS3			A GP1b binding assay performed with the recombinant Val1314Phe mutant vWF expressed by COS-7 cells showed spontaneous binding at low doses of ristocetin (PMID: 8298143 and PMID: 8630394), and enhanced binding to platelets in the presence of low-dose ristocetin compared with WT (PMID: 8630394), indicating that this variant has a gain of function effect on the protein (PS3). This variant lead to significantly decreased heparin-binding in plasma and corresponding rVWF, reaching 68% of control plasma or WT-rVWF. This is not an assay considered for this criteria. PubMed:11776314  Found V1314F rVWF exhibited a significantly increased to rADAMTS-13-mediated proteolysis, both in low and in physiological ionic strength conditions as compared with rVWF-WT (fig 5). PubMed:17087728  V1314F (referred to here as V551F) rVWF had spontaneous binding to GPIb ($22.1\% \pm 3.5\%$) and increased binding at low doses of ristocetin ($41.3\% \pm 3.1\%$ at 0.2mg). PubMed:10845912 
PS2_Moderate			The Val1314Phe variant (referred to as Val551Phe in PMID: 8298143) was identified in the patient but not in the parents. Additionally, the authors studied the variable number of tandemly repeated (VNTR) DNA sequences in the 3’ hypervariable region of the apolipoprotein B gene of the patient and his parents, and together with the available blood group data, confirmed parental relationships (PS2_moderate).
PP3			The computational predictor REVEL gives a score of 0.741, 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 0.01 for splice donor gain, indicating that the variant likely has no impact on splicing.
PP4			The patient, in PMID: 8298143, had prolonged bleeding time (>20 minutes), decreased binding capacity to GPIb, vWFag (25 U/dL) associated with the absence of vWFRCo (<5 U/dL) for a ratio of <0.2, and an absence of high molecular weight and intermediate multimers in the plasma. Additional features included decreased levels of VIIC (30 U/dL) and a total lack of ristocetin platelet aggregation (RIPA) at concentrations of modulator between 0 and 2 mg/mL. His platelet count is around $120 \times 10^9/L$ and decreases to approximately $50 \times 10^9/L$ at the time of bleeding episodes. As reported by the authors, there is a discrepancy in this patient between an apparent type 2A phenotype and 2B genotype. The patient meets criteria for PP4_moderate for type 2A but this is likely actually a type 2B variant and PP4 is applied at the supporting level based on loss of HMWM. This discrepancy can be explained as an extremely severe form of type-IIB vWD, where the variant strongly increases the affinity of vWF for

platelet GPIb, which might result in plasma in a spontaneous binding of both HMW and intermediate-sized multimers to the platelets. This could explain the thrombocytopenia of the propositus and the clearance of the large and intermediate forms of vWF from the patient’s plasma.

PM5

Another type 2B variants have been reported at this amino acid residue; Val1314Leu and classified pathogenic by the VWD VCEP (PM5). Val1314Asp (classified pathogenic by the VWD VCEP) has also been reported but is not included here to avoid circularity.

Curation History [↗](#)

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