

Variant: NM_000552.4(VWF):c.3916C>T (p.Arg1306Trp)

Version: 1.0

CA114123 [↗](#)

288 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: e404894e-1382-496e-825f-e3097e47da53

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HGVS expressions

NM_000552.4(VWF):c.3916C>T (p.Arg1306Trp)

NM_000552.4:c.3916C>T

NC_000012.12:g.6019502G>A

CM000674.2:g.6019502G>A

NC_000012.11:g.6128668G>A

CM000674.1:g.6128668G>A

NC_000012.10:g.5998929G>A

NG_009072.1:g.110169C>T

NG_009072.2:g.110169C>T

ENST00000261405.10:c.3916C>T

ENST00000261405.9:c.3916C>T

ENST00000538635.5:n.421-25568C>T

NM_000552.3:c.3916C>T

NM_000552.5:c.3916C>T

Pathogenic

Met criteria codes **7**

PP1_Moderate

PS3

PS4

PP4_Moderate

PS2_Supporting

PP3

PM2_Supporting

Not Met criteria codes **1**

PM5

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 c.3916C>T (p.Arg1306Trp) variant in VWF has been reported in several dozen vWD type 2B patients (PS4). At least 4 (PMIDs: 1419803, 19740526 and 15041272) have sufficient information reported to meet the PP4_moderate criteria. In vitro studies have shown increased platelet binding in COS-7 cells and a VWF -/- mouse with R1306-vWF hydrodynamic expression recapitulated patient phenotypes (PMID: 20371742). This variant is absent from population databases, including gnomADv4.1 (PM2_supporting). It is predicted deleterious by

REVEL which gives a score of 0.769, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). This variant has been observed both de novo (PMID: 1419803; PS2_supporting) and segregating in multiple families (PMID: 15041272 and 1419803; PP1_moderate). In summary, this variant meets criteria to be classified as pathogenic for vWD type 2B with specified criteria PS3, PS4, PM2_supporting, PS2_supporting, PP1_moderate, PP3, and PP4_moderate.

Met criteria codes

PP1_Moderate			At least 5 unrelated families have been reported with at least 2 informative meiosis, where the R1306W variant cosegregates with disease. At least 2 of these families from PMID: 15041272 and Family 5 of PMID: 1419803 have sufficient phenotypic information on all affected individuals (bleeding phenotype and LD-RIPA response) to confirm they are genotype/phenotype positive.
PS3			<p>The R1306W variant, expressed in COS-7 cells, has been shown to have increased platelet binding by PMID: 1557393 and PMID: 8630394. Additionally a VWF -/- mouse with R1306W-vWF hydrodynamic expression recapitulated patient phenotypes including increased platelet binding, reduced VWF:Ag, thrombocytopenia, and loss of HMW multimers (PMID: 20371742) (PS3).</p> <p>R1306 was introduced into the mouse Vwf cDNA and expression vectors were delivered to VWF-/- mice by hydrodynamic injection. The resultant phenotypes recapitulated those observed in patients: (1) Platelet binding ability (using formalin-fixed, washed mouse platelets, mVWF expressing the 2B VWD mutations of interest, and botrocetin) was significantly increase compared to WT at 3 ug/mL botrocetin and 12.7% spontaneous aggregation was observed without botrocetin (2) VWF:Ag was reduced to 1.47 +/- 0.56 U/mL for R1306W compared to 4.02 +/- 1.21 for WT (3) Thrombocytopenia with platelet count of 150x10^9/L and small platelet aggregates with some large platelets (4) There was a complete loss of HMW multimers by day 7 post injection. PubMed:20371742 </p>
PS4			At least six additional type 2B patients have been reported with this variant (PMIDs: 1419803, 15041272; PS4).
PP4_Moderate			Several dozen vWD type 2B patients have been described with the R1306W variant. At least 6 (PMIDs: 1419803, 19740526 and 15041272) have sufficient information reported to meet the PP4_moderate criteria, including mucocutaneous bleeding and a positive GOF assay. With 4 (PMIDs: 1419803, 19740526 and 15041272) also having reduced VWF:RCo/VWF:Ag ratios reported.
PS2_Supporting			At least three cases have been reported with de novo occurrence of R1306W, one of which (Family 4 of PMID: 1419803) provided sufficient phenotypic information to confirm the proband has type 2B VWD >1200s bleeding time Simplate II)); spontaneous thrombocytopenia (platelet count of 18x10^9/L); moderately decreased VWF:Ag 61 IU/dl and VWF:RCo 20 IU/dl; VWF:Rco/VWF:Ag ratio of 0.33; absence of large multimers in plasma; LD-RIPA response at 0.7 mg/mL). Maternity and paternity were not confirmed.
PP3			The computational predictor REVEL gives a score of 0.769, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).
PM2_Supporting			This variant is absent from population databases, including gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

PM5		
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Additional missense changes at this amino acid residue include R1306L (PMID: 10233434), R1306P (PMID: 26986123), and R1306Q (PMID: 9198195). These have not been included in the analysis of R1306W as they have not yet been classified by the ClinGen VWD VCEP

Curation History

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