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Variant: NM_000552.5(VWF):c.3939G>C (p.Trp1313Cys)

Version: 1.0

CA114121

287 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2B (MONDO:0015629)
Inheritance Mode: Autosomal dominant inheritance
UUID: 75526f4e-8e39-403b-b27e-fb45a7312cbb
Approved on: 2025/4/1
Published on: 2025/4/15

HGVS expressions

NM_000552.5(VWF):c.3939G>C (p.Trp1313Cys)
NM_000552.5:c.3939G>C
NC_000012.12:g.6019479C>G
CM000674.2:g.6019479C>G
NC_000012.11:g.6128645C>G
CM000674.1:g.6128645C>G
NC_000012.10:g.5998906C>G
NG_009072.1:g.110192G>C
NG_009072.2:g.110192G>C
ENST00000261405.10:c.3939G>C
ENST00000261405.9:c.3939G>C
ENST00000538635.5:n.421-25545G>C
NM_000552.3:c.3939G>C
NM_000552.4:c.3939G>C

Likely Pathogenic

Met criteria codes 4

PS4_Supporting PS3 PP4_Moderate PM2_Supporting

Not Met criteria codes 1

PP3

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 p.Trp1313Cys variant has a REVEL score of 0.629, which is below the VWD VCEP threshold of > 0.644 and therefore, the variant does not predict a damaging effect on VWF function. The variant is absent from gnomADv4, thus, meeting PM2_Supporting criteria. There is at least one proband with the variant exhibiting a risk of excessive bleeding, RIPA assay showing GOF, and a loss of HMWM which is consistent with VWD type 2B (PP4_Moderate). This patient is also a carrier for the p.Val1565Leu variant (PMID: 35772170) which has been

classified as Benign by the VWD VCEP. "Genotyping previously confirmed the diagnosis in each patient with type 2B VWD" (PMID: 35772170). Functional data demonstrated that mammalian CHO-K1 cells transfected with mutant plasmid (p.W1313C) exhibited a 10-fold affinity to GPIb in the presence of ristocetin compared to wildtype cells (PMID: 2011604) (PS3). This variant has been reported in at least 1 additional proband meeting PP4 laboratory phenotype criteria (PS4_supporting); PMIDs: 31939074. Taken together, the variant has been classified as likely pathogenic for VWD type 2B by the Von Willebrand Disease variant curation expert panel. PP4_Moderate, PM2_Supporting, PS3, PS4_Supporting.

Met criteria codes

PS4_Supporting	✔	This variant has been reported in at least 1 additional proband meeting PP4 laboratory phenotype criteria (PS4_supporting); PMID: 31939074.
PS3	✔	The authors transfected mammalian CHO-K1 cells with mutant plasmid. The Cys mutant demonstrated interaction with GPIb even in the absence of modulators. In the presence of ristocentin, the Cys mutant had a 10-fold affinity to GPIb compared to molecules with the normal sequence (PMID: 2011604).
PP4_Moderate	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of an assay of increased RIPA, showing gain of function, which is highly specific for VWD type 2B (PP4_moderate) (PMID: 35772170).
PM2_Supporting	✔	The p.Trp1313Cys variant is absent from gnomad v4 (PM2_Supporting).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.629, which is below the ClinGen VWD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on VWF function.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000552.5(VWF):c.3939G>C (p.Trp1...	Likely Pathogenic	Von Willebrand Disease Type 2B	2025-04-15	1.0	ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0	VWF

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