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Variant: NM_000552.5(VWF):c.4010C>T (p.Pro1337Leu)

Version: 1.0

CA228510

100314 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2B (MONDO:0015629)
Inheritance Mode: Autosomal dominant inheritance
UUID: d3b39318-cc9e-47d1-9ea2-e7bf53737618
Approved on: 2025/10/7
Published on: 2025/10/10

HGVS expressions

NM_000552.5:c.4010C>T
NM_000552.5(VWF):c.4010C>T (p.Pro1337Leu)
NC_000012.12:g.6019408G>A
CM000674.2:g.6019408G>A
NC_000012.11:g.6128574G>A
CM000674.1:g.6128574G>A
NC_000012.10:g.5998835G>A
NG_009072.1:g.110263C>T
NG_009072.2:g.110263C>T
ENST00000261405.10:c.4010C>T
ENST00000261405.9:c.4010C>T
ENST00000538635.5:n.421-25474C>T
NM_000552.3:c.4010C>T
NM_000552.4:c.4010C>T

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PS4_Supporting PS3 PP4

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 NM_000552.5:c.4010C>T variant in VWF is a missense variant predicted to cause substitution of proline by leucine at amino acid 1377 (p.Pro1377Leu). At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of enhanced RIPA and loss of HMWM, which is specific for VWD type 2B. (PP4, PMID 1373334). This variant has been reported in 1 additional proband meeting VWD 2B PP4 laboratory phenotype of enhanced RIPA (PS4_Supporting; Gold Variant Database). The Grpmax filtering

allele frequency in gnomAD v4.1 is 0.00000183 (based on 6/1179864 alleles in the European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 for type 2B (PM2_Supporting). Platelet binding assay performed with the p.Pro1377Leu recombinant mutant vWF expressed by COS-7 showed increased binding at low doses of ristocetin, indicating that this variant has a gain of function effect on the protein (PMID 1373334)(PS3_supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant von Willebrand disease type 2B based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP4, PS4_Supporting, PM2_Supporting, PS3 (ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0)

Met criteria codes

PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.00000183 (based on 6/1179864 alleles in the European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 for type 2B (PM2_Supporting).
PS4_Supporting	✔	This variant has been reported in 1 additional proband meeting VWD 2B PP4 laboratory phenotype of enhanced RIPA (PS4_Supporting; Gold Variant Database).
PS3	✔	Platelet binding assay performed with the p.Pro1377Leu recombinant mutant vWF expressed by COS-7 showed increased binding at low doses of ristocetin, indicating that this variant has a gain of function effect on the protein (PMID 1373334)(PS3_supporting).
PP4	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of enhanced RIPA and loss of HMWM, which is specific for VWD type 2B. (PP4, PMID 1373334).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.581, 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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