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Variant: NM_000552.5(VWF):c.4021C>T (p.Arg1341Trp)

Version: 1.0

CA228514

100316 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2B (MONDO:0015629)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9495e59e-f337-4608-8889-8f33e41feae1
Approved on: 2025/10/7
Published on: 2025/10/10

HGVS expressions

NM_000552.5(VWF):c.4021C>T (p.Arg1341Trp)
NM_000552.5:c.4021C>T
NC_000012.12:g.6019397G>A
CM000674.2:g.6019397G>A
NC_000012.11:g.6128563G>A
CM000674.1:g.6128563G>A
NC_000012.10:g.5998824G>A
NG_009072.1:g.110274C>T
NG_009072.2:g.110274C>T
ENST00000261405.10:c.4021C>T
ENST00000261405.9:c.4021C>T
ENST00000538635.5:n.421-25463C>T
NM_000552.3:c.4021C>T
NM_000552.4:c.4021C>T

Pathogenic

Met criteria codes 5

PP4_Moderate | PM2_Supporting | PM5 | PS4 | 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.4021C>T variant in VWF is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 1341. At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of loss of high molecular weight multimers and an enhanced RIPA assay showing gain of function, which together are highly specific for VWD type 2B. (PP4_moderate, PMID 20118404). VWF antigen/activity ratio was consistent with type 2B which is consistent with VWD type 2B. This

variant has been reported in 4 additional probands meeting PP4 laboratory phenotype criteria for VWD 2B (PS4; PMIDs 26456374, 18805962, 9723578). The Grpmax filtering allele frequency in gnomAD v4.1 is 0.00006615 (based on 8/60002 alleles in the admixed American population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 for type 2B (PM2_Supporting). The computational predictor REVEL gives a score of 0.889, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). Another missense variant c.4022G>A (p.Arg1341Gln) in the same codon has been classified as pathogenic for VWD 2B by the ClinGen VWD VCEP (PM5). Splicing prediction using SpliceAI revealed no expected effects on splicing due to any of these variants. In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant von Willebrand disease 2B based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP4_Moderate, PS4, PM2_Supporting, PP3, PM5 (ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0)

Met criteria codes

PP4_Moderate	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of loss of high molecular weight multimers and an enhanced RIPA assay showing gain of function, which together are highly specific for VWD type 2B. (PP4_moderate, PMID 20118404). VWF antigen/activity ratio was consistent with type 2B which is consistent with VWD type 2B.
PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.00006615 (based on 8/60002 alleles in the admixed American population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 for type 2B (PM2_Supporting).
PM5	✔	Another missense variant c.4022G>A (p.Arg1341Gln) in the same codon has been classified as pathogenic for VWD 2B by the ClinGen VWD VCEP (PM5). Splicing prediction using SpliceAI revealed no expected effects on splicing due to any of these variants.
PS4	✔	This variant has been reported in 4 additional probands meeting PP4 laboratory phenotype criteria for VWD 2B (PS4; PMIDs 26456374, 18805962, 9723578).
PP3	✔	The computational predictor REVEL gives a score of 0.889, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).

Curation History

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