

Variant: NM_000552.5:c.4225G>T

Version: 1.0

CA383503778 [↗](#)

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

Condition: von Willebrand disease type 2M ([MONDO:0015630](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 2af4a425-9cc1-4fdf-b9c8-e03d528eaedf

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HGVS expressions

NM_000552.5:c.4225G>T

NC_000012.12:g.6019193C>A

CM000674.2:g.6019193C>A

NC_000012.11:g.6128359C>A

CM000674.1:g.6128359C>A

NC_000012.10:g.5998620C>A

NG_009072.1:g.110478G>T

NG_009072.2:g.110478G>T

ENST00000261405.10:c.4225G>T

ENST00000261405.9:c.4225G>T

ENST00000538635.5:n.421-25259G>T

NM_000552.3:c.4225G>T

NM_000552.4:c.4225G>T

Likely Pathogenic

Met criteria codes **5**

PP4_Moderate

PP3

PP1_Moderate

PS4_Moderate

PM2_Supporting

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(VWF):c.4225G>T variant in VWF is a missense variant predicted to cause substitution of valine by phenylalanine at amino acid 1409. This variant has been reported in at least 3 apparently unrelated probands exhibiting a VWD Type 2M phenotype (PMID: 28971901 and PMID: 19404524, PS4_Moderate). The two probands of PMID: 28971901, exhibit excessive mucocutaneous bleeding as well as a laboratory phenotype of normal multimers, low VWF:RCo/VWF:Ag ratio and low collagen binding, which together are specific for VWD type 2M (PP4_Moderate). Low FVIII activity, an inconsistent phenotype, was also reported in these patients. The variant has been reported

to segregate with VWD type 2M through at least 2 affected meioses from 2 different families (PP1_Moderate; PMID: 28971901). This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.722, 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 indicates that the variant has no impact on splicing. In summary, this variant meets the criteria to be classified as Likely Pathogenic for von Willebrand disease type 2A. ACMG/AMP criteria applied as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PP1_Moderate, PP3, PM2_Supporting, PS4_Moderate, PP4_Moderate.

Met criteria codes

PP4_Moderate			At least 2 patients with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of low VWF:RCo/VWF:Ag ratio and low collagen binding, as well as normal multimer distribution, which together are specific for VWD type 2M. (PP4_Moderate, PMID: 28971901). Low FVIII activity, an inconsistent phenotype, was also reported in these patients . The D1472H variant was ruled out in these patients (PMID: 28971901). An additional proband is described in PMID: 19277422, but it is likely that this individual has also been reported in PMID: 28971901 and is a family member of one of the previously scored probands.
PP3			The computational predictor REVEL gives a score of 0.722, 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 0.00 for all splicing types, indicating that the variant has no impact on splicing.
PP1_Moderate			The variant has been reported to segregate with VWD type 2M through >2 affected meioses in 2 different families (PP1_moderate; PMID: 28971901).
PS4_Moderate			This variant has been reported in 2 additional probands meeting at least the laboratory criteria of PP4 (PMID: 28971901 and PMID: 19404524, PS4_Moderate). An additional proband is described in PMID: 19277422, but it is not clear whether this individual is unrelated to the others.
PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).

Curation History

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