

Variant: NM_000552.5(VWF):c.8318G>C (p.Cys2773Ser)

Version: 1.1

CA228847 [↗](#)

100503 (ClinVar) [↗](#)

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

Condition: von Willebrand disease type 2A ([MONDO:0015628](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 7f9772d1-c9d1-448a-855d-4e2b353a4d44

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HGVS expressions

NM_000552.5:c.8318G>C

NM_000552.5(VWF):c.8318G>C (p.Cys2773Ser)

NC_000012.12:g.5949139C>G

CM000674.2:g.5949139C>G

NC_000012.11:g.6058305C>G

CM000674.1:g.6058305C>G

NC_000012.10:g.5928566C>G

NG_009072.1:g.180532G>C

NG_009072.2:g.180532G>C

ENST00000261405.10:c.8318G>C

ENST00000261405.9:c.8318G>C

NM_000552.3:c.8318G>C

NM_000552.4:c.8318G>C

Pathogenic

Met criteria codes **6**

PS3 PP3 PS4_Moderate

PM2_Supporting PP4_Moderate

PS2_Moderate

Not Met criteria codes **5**

BP4 PP1 PM5 BA1 BS1

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.8318G>C variant in VWF is a missense variant predicted to cause substitution of cysteine by serine at amino acid 2773. This variant is absent from gnomAD v4.1 (PM2_Supporting). At least one patients with this variant displayed laboratory phenotypes of excessive mucocutaneous bleeding, very low VWF activity (measured by VWF:RCo assay), low VWF:RCo/VWF:Ag ratio, and loss of high molecular weight multimers, which together are highly specific for VWD Type 2A (PP4_moderate, PMID: 17139364). This variant has been reported in 3 additional probands meeting type 2A laboratory criteria for PP4 (PS4_moderate; PMID: 21979291,

32664776, 28971901), and one was a de novo occurrence with unconfirmed parental relationships (PS2_Moderate; PMID: 32664776). Multimerization assay performed with the p.Cys2773Ser recombinant mutant and wild-type vWF co-expressed by HEK293 cells showed abnormal multimers (PMID: 17139364 Fig. 2) that were counteracted by an allele-specific siRNA targeting the mutant transgene, indicating that this variant has a damaging effect on protein function (PMID: 29734512)(PS3_supporting). The computational predictor REVEL gives a score of 0.876, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). In summary, this variant meets the criteria to be classified as Pathogenic for von Willebrand disease type 2A. ACMG/AMP criteria applied as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PP4_Moderate, PS2_Moderate, PS4_Moderate, PS3, PP3, PM2_Supporting.

Met criteria codes

PS3			Multimerization assay performed with the p.Cys2773Ser recombinant mutant and wild-type vWF co-expressed by HEK293 cells showed abnormal multimers (PMID: 17139364 Fig. 2) that were counteracted by an allele-specific siRNA targeting the mutant transgene, indicating that this variant has a damaging effect on protein function (PMID: 29734512)(PS3).
PP3			The computational predictor REVEL gives a score of 0.876, 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.
PS4_Moderate			This variant has been reported in 3 additional probands meeting type 2A laboratory criteria for PP4 (PS4_supporting; PMID: 21979291, 32664776, 28971901).
PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).
PP4_Moderate			At least one patients with this variant displayed laboratory phenotypes of excessive mucocutaneous bleeding, very low VWF activity (measured by VWF:RCo assay), low VWF:RCo/VWF:Ag ratio, and loss of high molecular weight multimers, which together are highly specific for VWD Type 2A (PP4_moderate, PMID: 17139364).
PS2_Moderate			This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with VWD Type 2A meeting PP4_Moderate (PM6; PMID: 32664776).

Not Met criteria codes

BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			The variant has been reported to segregate with VWD type 2A through only 1 affected meiosis from 1 family, so that the standard for this criterion of 2 segregations in one family is not met (PMID: 17139364).
PM5			Another missense variant in the same codon has been reported in a patient with VWD Type 2A (NM_000552.5(VWF):c.8317T>C (p.Cys2773Arg) but is not considered here to avoid circularity.
BA1			This variant is absent from gnomAD v2.1.1 and v3.1.2. The criterion is not met.

BS1

This variant is absent from gnomAD v2.1.1 and v3.1.2. The criterion is not met.

Curation History

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