

Variant: NM_000552.4(VWF):c.3929C>T (p.Ser1310Phe)

Version: 1.0

CA228494 [↗](#)

100306 (ClinVar) [↗](#)

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

Condition: von Willebrand disease type 2B ([MONDO:0015629](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 23ca549c-5557-4dbe-b8f1-c87ae80467a7

Approved on: 2024/8/12

Published on: 2024/8/12

HGVS expressions

NM_000552.4(VWF):c.3929C>T (p.Ser1310Phe)

NM_000552.4:c.3929C>T

NC_000012.12:g.6019489G>A

CM000674.2:g.6019489G>A

NC_000012.11:g.6128655G>A

CM000674.1:g.6128655G>A

NC_000012.10:g.5998916G>A

NG_009072.1:g.110182C>T

NG_009072.2:g.110182C>T

ENST00000261405.10:c.3929C>T

ENST00000261405.9:c.3929C>T

ENST00000538635.5:n.421-25555C>T

NM_000552.3:c.3929C>T

NM_000552.5:c.3929C>T

Likely Pathogenic

Met criteria codes **5**

PM2_Supporting

PS4_Moderate

PP1

PP3

PP4_Moderate

Not Met criteria codes **2**

PS3

PM5

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_000552.4(VWF):c.3929C>T (p.Ser1310Phe) missense variant has been identified in at least three unrelated patients, with phenotypes specific to VWD type 2B (PS4_moderate; PMIDs: 27978591, 8815591). At least 2 patients with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of loss of high molecular weight multimers and a GP1b assay with enhanced low-dose RIPA showing gain of function, which together are highly specific for VWD type 2B (PP4_moderate; PMID: 27978591). The variant

has been reported to segregate with VWD type 2M through 3 affected siblings from 1 family (PP1; PMID: 27978591). This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.937, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). In summary, the variant meets the criteria to be classified as Likely Pathogenic for von Willebrand disease type 2B based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP1, PP3, PP4_moderate, PM2_supporting, and PS4_moderate.

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).
PS4_Moderate			This variant has been reported in 2 additional probands with VWD type 2B phenotypes (PS4_moderate; PMIDs: 27978591, 8815591).
PP1			The variant has been reported to segregate with VWD type 2B through 2 affected meioses from 1 family (PP1; PMID: 27978591).
PP3			The computational predictor REVEL gives a score of 0.937, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).
PP4_Moderate			At least 2 patients with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of loss of high molecular weight multimers and a GPIb assay with enhanced low-dose RIPA showing gain of function, which together are highly specific for VWD type 2B. (PP4_moderate; PMID: 27978591). The patients were also reported to have thrombocytopenia.

Not Met criteria codes

PS3			Use of directed evolution in yeast to identify further gain-of-function mutations that enhance A1 and GPIbα interaction, identified clone 5, with high affinity for GPIbα selected by yeast surface display, as a double mutant for V1279A and S1310F (PMID: 24391089). The variants were not studied independently so V1279A variant can not be ruled out as contributing to the gain-of-function effect at this time and PS3 is not applied.
PM5			PMID: 26986123 reports S1310P in a type 2B case. That variant occurs at the same codon but it has not yet been evaluated by the VWD VCEP.

Curation History 

▼

▼

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.