The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000552.5(VWF):c.4837T>C (p.Ser1613Pro)

Version: 1.0

CA114131

292 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2A (MONDO:0015628)
Inheritance Mode: Autosomal dominant inheritance
UUID: cf756b09-5a21-46f7-96ac-d8d1c3e2d497
Approved on: 2025-02-04
Published on: 2025-02-05

HGVS expressions

NM_000552.5:c.4837T>C
NM_000552.5(VWF):c.4837T>C (p.Ser1613Pro)
NC_000012.12:g.6018581A>G
CM000674.2:g.6018581A>G
NC_000012.11:g.6127747A>G
CM000674.1:g.6127747A>G
NC_000012.10:g.5998008A>G
NG_009072.1:g.111090T>C
NG_009072.2:g.111090T>C
ENST00000261405.10:c.4837T>C
ENST00000261405.9:c.4837T>C
ENST00000538635.5:n.421-24647T>C
NM_000552.3:c.4837T>C
NM_000552.4:c.4837T>C

Uncertain Significance

Met criteria codes 4

PP3 PP4_Moderate PM2_Supporting PS4_Supporting

Not Met criteria codes 1

PP1

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 c.4837T>C variant in VWF is a missense variant predicted to cause substitution of Serine by Proline at amino acid 1613 (p.Ser1613Pro). At least 1 patient (Patient 14 from PMID: 38053262) with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of very low VWF activity as indicated by a VWF activity-to-antigen ratio <0.7, and loss of high molecular weight multimers, which together are highly specific for VWD type 2A. Additional consistent phenotypes were also reported in the patient

including a FVIII activity consistent with VWF antigen (ratio >0.7) (PP4_Moderate). This variant has been reported in one additional proband (Zimmerman program) with activity/antigen ratio <0.37, abnormal multimers, and normal platelet binding (PS4_Supporting). The computational predictor REVEL gives a score of 0.7, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). This variant is absent from gnomAD v4.1 (PM2_Supporting). In summary, this variant meets the criteria to be classified as VUS for autosomal recessive von Willebrand disease type 2A based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PS4_Supporting, PP4_Moderate, PP3 and PM2_Supporting (VCEP specifications version 1.0.0; date of approval).

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.7, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).
PP4_Moderate	✔	At least 1 patient (Patient 14 from PMID: 38053262) with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of very low VWF activity (VWF:RCo or VWF:GPIbM 12 IU/dL), a VWF activity-to-antigen ratio <0.7, and loss of high molecular weight multimers, which together are highly specific for VWD type 2A. Additional consistent phenotypes were also reported in the patient including a FVIII activity consistent with VWF antigen (ratio >0.7) (PP4_Moderate).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PS4_Supporting	✔	This variant has been reported in one additional proband (Zimmerman program) with activity/antigen ratio <0.37, abnormal multimers, and normal platelet binding (PS4_supoprting).

Not Met criteria codes

PP1	✖	At least one family has been reported (Zimmerman program) with the proband and daughter harboring this variant and a type 2A phenotype. This is insufficient segregations to meet the PP1 criterion.

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.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.