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Variant: NM_000552.5(VWF):c.3925A>G (p.Ile1309Val)

Version: 1.0

CA228492

100305 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2B (MONDO:0015629)
Inheritance Mode: Autosomal dominant inheritance
UUID: 24d7382b-1d45-46f2-be36-0ae3ad44145b
Approved on: 2025/2/4
Published on: 2025/2/5

HGVS expressions

NM_000552.5(VWF):c.3925A>G (p.Ile1309Val)
NM_000552.5:c.3925A>G
NC_000012.12:g.6019493T>C
CM000674.2:g.6019493T>C
NC_000012.11:g.6128659T>C
CM000674.1:g.6128659T>C
NC_000012.10:g.5998920T>C
NG_009072.1:g.110178A>G
NG_009072.2:g.110178A>G
ENST00000261405.10:c.3925A>G
ENST00000261405.9:c.3925A>G
ENST00000538635.5:n.421-25559A>G
NM_000552.3:c.3925A>G
NM_000552.4:c.3925A>G

Pathogenic

Met criteria codes 6

PS3 PP1 PP3 PS4_Moderate PP4_Moderate PM2_Supporting

Not Met criteria codes 3

PM5 BP5 BP2

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.3925A>G (p.Ile1309Val) missense variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.851, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). The Ile1309Val rVWF resulted in enhanced affinity for the GP1b receptor (PMID: 8621553; PS3). At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of loss of high molecular weight multimers and an

assay showing gain of function (enhanced RIPA at 0.3 mg/mL), which together are highly specific for VWD type 2B. (PP4_moderate; PMID: 9308766). This variant has been reported in at least 3 additional type 2B probands with enhanced RIPA reported (PS4_Moderate; PMIDs: 23005922, 18805962, 9198195). The variant has been reported to segregate with VWD type 2B through >2 affected meioses from at least 1 family (PP1; PMID: 18805962). In summary, this variant has been classified as Pathogenic for type 2B Von Willebrand Disease based on the ACMG/AMP criteria applied as specified by the von Willebrand Disease Variant Curation Expert Panel. PM2_supporting, PP3, PS3, PP4_moderate, PS4_moderate, PP1

Met criteria codes

PS3	✔	The Ile1309Val (reported here as I564V) substitution in rVWF resulted in enhanced inhibition of LJ-Ib1 (a monoclonal antibody that recognizes the 45-kDa amino-terminal domain of GP Ibα and is a competitive inhibitor of vWF binding to this receptor) binding, suggesting that the mutation conferred greater affinity for the receptor (PMID: 8621553; PS3).
PP1	✔	The variant has been reported to segregate with VWD type 2B through >2 affected meioses from at least 1 family (PP1; PMID: 18805962).
PP3	✔	The computational predictor REVEL gives a score of 0.851, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).
PS4_Moderate	✔	This variant has been reported in at least 3 additional type 2B probands with enhanced RIPA reported (PS4_Moderate; PMIDs: 23005922, 18805962, 9198195).
PP4_Moderate	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of loss of high molecular weight multimers and an assay showing gain of function (enhanced RIPA at 0.3 mg/mL), which together are highly specific for VWD type 2B. (PP4_moderate; PMID: 9308766). The patient was also reported to have thrombocytopenia consistent with type 2B.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

PM5	✖	NM_000552.5(VWF):c.3926T>A (p.Ile1309Asn) has been reported at the same residue but will not be considered here to avoid circularity.
BP5	✖	The patient in PMID: 22871923 also carries Pro1240Leu on the opposite allele, which is not yet classified by the VWF VCEP. This patient is not contributing to the classification of NM_000552.5(VWF):c.3925A>G (p.Ile1309Val).
BP2	✖	The patient also carries Pro1240Leu on the opposite allele, which is not yet classified by the VWF VCEP.

Curation History

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