Variant: NM_000552.5(VWF):c.3926T>A (p.Ile1309Asn)

Version: 1.0

CA383506185

1684483 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2B (MONDO:0015629)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3f3d0c7b-a702-4ea7-a03a-15e8fc2e2fb8
Approved on: 2025-05-06
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HGVS expressions

NM_000552.5:c.3926T>A
NM_000552.5(VWF):c.3926T>A (p.Ile1309Asn)
NC_000012.12:g.6019492A>T
CM000674.2:g.6019492A>T
NC_000012.11:g.6128658A>T
CM000674.1:g.6128658A>T
NC_000012.10:g.5998919A>T
NG_009072.1:g.110179T>A
NG_009072.2:g.110179T>A
ENST00000261405.10:c.3926T>A
ENST00000261405.9:c.3926T>A
ENST00000538635.5:n.421-25558T>A
NM_000552.3:c.3926T>A
NM_000552.4:c.3926T>A

Likely Pathogenic

Met criteria codes 4

PP3 PM5 PM2_Supporting PP4_Moderate

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.3926T>A (p.Ile1309Asn) missense variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.886, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). Another type 2B missense change (p.I1309V) has been reported at this amino acid residue and has been classified Pathogenic for type 2B VWD by the VWD VCEP (PM5). At least one patient with this variant displayed excessive mucocutaneous bleeding

as well as a laboratory phenotypes of thrombocytopenia and an assay showing gain of function (flow cytometry showed markedly increased baseline activity), which together are highly specific for VWD type 2B. (PP4_moderate, SCV002515788.1). The patient was also reported to a VWF antigen/activity ratio (0.2) consistent with type 2B. In summary, this variant has been classified as likely 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, PM5, PP4_moderate.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.886, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).
PM5	✔	Another type 2B missense change (p.I1309V) has been reported at this amino acid residue and has been classified Pathogenic for type 2B VWD by the VWD VCEP.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PP4_Moderate	✔	At least one patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of thrombocytopenia and an assay showing gain of function (flow cytometry showed markedly increased baseline activity), which together are highly specific for VWD type 2B. (PP4_moderate, SCV002515788.1). The patient was also reported to a VWF activity/antigen ratio (0.2) consistent with type 2B.

Curation History

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