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Variant: NM_000552.5(VWF):c.3940G>C (p.Val1314Leu)

Version: 1.1

CA114151

302 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2B (MONDO:0015629)
Inheritance Mode: Autosomal dominant inheritance
UUID: ab78c79b-78a9-47d5-8200-5964fbaf737a
Approved on: 2024/8/12
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HGVS expressions

NM_000552.5:c.3940G>C
NM_000552.5(VWF):c.3940G>C (p.Val1314Leu)
NC_000012.12:g.6019478C>G
CM000674.2:g.6019478C>G
NC_000012.11:g.6128644C>G
CM000674.1:g.6128644C>G
NC_000012.10:g.5998905C>G
NG_009072.1:g.110193G>C
NG_009072.2:g.110193G>C
ENST00000261405.10:c.3940G>C
ENST00000261405.9:c.3940G>C
ENST00000538635.5:n.421-25544G>C
NM_000552.3:c.3940G>C
NM_000552.4:c.3940G>C

Pathogenic

Met criteria codes 5

PS2_Moderate PS4_Moderate PS3 PP4_Moderate PM2_Supporting

Not Met criteria codes 3

PM5 BP4 PP3

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.3940G>C (p.Val1314Leu) missense variant has been reported in at least 3 probands with VWD 2B phenotypes (PS4_moderate; PMIDs: 1419803, 27215777, ISTH 2015 Congress Poster). At least one proband displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of loss of high molecular weight multimers and an increased response to LD-RIPA showing gain of function, which together are highly specific for VWD type 2B (PP4_moderate; PMID: 1419803). The variant was identified as a de

novo occurrence in this patient (PS2_Moderate; PMIDs: 1419803). This variant is absent from gnomAD v4.1 (PM2_Supporting). A Platelet binding assay performed with the Val1314Leu recombinant mutant vWF expressed by COS-7 showed increased binding in the absence of, or at low doses, of ristocetin, indicating that this variant has a gain of function effect on the protein (PMID: 8630394; PS3). 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: PS3, PS4_moderate, PS2_Moderate, PP4_moderate, and PM2_supporting.

Met criteria codes

PS2_Moderate	✔	This variant has been identified as a de novo occurrence without confirmation of parental relationships (PS2_Moderate; PMID: 1419803).
PS4_Moderate	✔	This variant has been reported in 2 additional probands meeting the PP4 or PP4_moderate criteria for highly specific phenotypes (PS4_moderate; PMIDs: 27215777, ISTH 2015 Congress Poster).
PS3	✔	A Platelet binding assay performed with the Val1314Leu recombinant mutant vWF expressed by COS-7 showed increased binding in the absence of, or at low doses, of ristocetin, indicating that this variant has a gain of function effect on the protein (PMID: 8630394; PS3).
PP4_Moderate	✔	At least one proband displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of loss of high molecular weight multimers and an increased response to LD-RIPA showing gain of function, which together are highly specific for VWD type 2B. (PP4_moderate; PMID: 1419803).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

PM5	✖	Two additional type 2 variants have been reported at this amino acid residue; Val1314Phe and Val1314Asp but are not considered here to avoid circularity.
BP4	✖	The computational predictor REVEL gives a score of 0.597, which is above the ClinGen VWD VCEP BP4 threshold of <0.290.
PP3	✖	The computational predictor REVEL gives a score of 0.597, which is below the ClinGen VWD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on VWF function. Additionally, SpliceAI does not predict a splice effect of this variant either.

Curation History

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