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Variant: NM_000552.5(VWF):c.3941T>A (p.Val1314Asp)

Version: 1.1

CA228500

100309 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2B (MONDO:0015629)
Inheritance Mode: Autosomal dominant inheritance
UUID: de8701b6-2c6d-4d47-b019-12ea0f618cb5
Approved on: 2024/8/13
Published on: 2024/8/13

HGVS expressions

NM_000552.5:c.3941T>A
NM_000552.5(VWF):c.3941T>A (p.Val1314Asp)
NC_000012.12:g.6019477A>T
CM000674.2:g.6019477A>T
NC_000012.11:g.6128643A>T
CM000674.1:g.6128643A>T
NC_000012.10:g.5998904A>T
NG_009072.1:g.110194T>A
NG_009072.2:g.110194T>A
ENST00000261405.10:c.3941T>A
ENST00000261405.9:c.3941T>A
ENST00000538635.5:n.421-25543T>A
NM_000552.3:c.3941T>A
NM_000552.4:c.3941T>A

Pathogenic

Met criteria codes 6

PP4_Moderate | PM2_Supporting | PM5 | PS2_Supporting | PS3 | 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.3941T>A (p.Val1314Asp) missense variant has been reported in one patient, Family 1 patient II:1 (PMID: 11325649) who displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of loss of high molecular weight multimers and a high affinity of plasma vWF for ristocetin-dependent platelet receptor was confirmed at 0.4mg/m showing gain of function, which together are highly specific for VWD type 2B (PP4_moderate). The patient was also reported to have thrombocytopenia

(9,600-80,000 platelets/µL) and a VWF antigen/activity ratio of 0.25, consistent with type 2B. The variant was identified de novo with parental relationships not fully confirmed (PS2_supporting). This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.761, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). Platelet binding assay performed with the V1314D recombinant vWF expressed by HEK293 cells showed binding in the absence of ristocetin under rheological shear flow, enhanced relative to wild-type indicating that this variant has a gain of function effect on the protein (PMID: 31628947; PS3). Another type 2B variants have been reported at this amino acid residue Val1314Leu and classified pathogenic by the VWD VCEP (PM5). In summary, the variant meets the criteria to be classified as Pathogenic for von Willebrand disease type 2A based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PS3_supporting, PS2_supporting, PP3, PP4_moderate, PM5 and PM2_supporting.

Met criteria codes

PP4_Moderate	✔	Family 1 patient II:1 (PMID: 11325649) with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of loss of high molecular weight multimers and a high affinity of plasma vWF for ristocetin-dependent platelet receptor was confirmed at 0.4mg/m showing gain of function, which together are highly specific for VWD type 2B. (PP4_moderate). The patient was also reported to have thrombocytopenia (9,600-80,000 platelets/µL) and a VWF antigen/activity ratio of 0.25, consistent with type 2B.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PM5	✔	Another type 2B variants have been reported at this amino acid residue; Val1314Leu and classified pathogenic by the VWD VCEP (PM5). Val1314Phe (classified pathogenic by the VWD VCEP) has also been reported but is not included here to avoid circularity.
PS2_Supporting	✔	The variant was identified de novo in Family 1 patient II:1 (PMID: 11325649) in which parental relationships were not fully confirmed (0.5pt; PS2_supporting). The following microsatellites were analyzed: VNTR3, VNTR1 and VNTR2 (in intron 40 of the vWF gene), and another in the promoter region.
PS3	✔	Platelet binding assay performed with the V1314D recombinant vWF expressed by HEK293 cells showed binding in the absence of ristocetin under rheological shear flow, enhanced relative to wild-type indicating that this variant has a gain of function effect on the protein (PMID: 31628947 Figure 7; PS3).
PP3	✔	The computational predictor REVEL gives a score of 0.761, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).

Curation History

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