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Variant: NM_000552.4(VWF):c.1583A>G (p.Asn528Ser)

Version: 1.0

CA114178

318 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2A (MONDO:0015628)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9a7228cc-a4fe-4d5d-ba2a-316baa9e75a9
Approved on: 2024/8/13
Published on: 2024/8/13

HGVS expressions

NM_000552.4:c.1583A>G
NM_000552.4(VWF):c.1583A>G (p.Asn528Ser)
NC_000012.12:g.6057995T>C
CM000674.2:g.6057995T>C
NC_000012.11:g.6167161T>C
CM000674.1:g.6167161T>C
NC_000012.10:g.6037422T>C
NG_009072.1:g.71676A>G
NG_009072.2:g.71676A>G
ENST00000261405.10:c.1583A>G
ENST00000261405.9:c.1583A>G
ENST00000538635.5:n.420+52520A>G
NM_000552.3:c.1583A>G
NM_000552.5:c.1583A>G

Pathogenic

Met criteria codes 5

PM2_Supporting PP1 PM3 PP4_Moderate PS3

Not Met criteria codes 7

PP3 PM6 BS4 BS3 PS2 BP5 BP4

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_000552.4(VWF):c.1583A>G variant in VWF is a missense variant predicted to cause substitution of asparagine by serine at amino acid 528. This variant is absent from gnomAD v4.1 (PM2_Supporting). This variant has been reported homozygous in two homozygous (PM3) probands meeting the VWD type 2A phenotypic criteria (PP4_moderate, PS4_suporting; PMID: 20335223; 9714529). The variant was found to co-segregate with disease in multiple affected family members, with 3 meioses observed in one family (PP1; PMID: 20335223).

There is evidence of defective VWF storage with no response to desmopressin and very little VWF:Ag released after administration. Expression in 293 EBNA cells showed that homozygous N528S-VWF secretion was 7.5% of WT, with a multimer pattern lacking medium and HMWMs (PMID: 20335223 Fig. 4; PS3). Expression in AtT-20 cells showed that the N528S-VWF is not multimerized and is not trafficked to storage granules. In summary, this variant meets the criteria to be classified as pathogenic for von Willebrand disease type 2A. ACMG/AMP criteria applied, as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PM2_supporting, PP4_moderate, PM3, PP1, PS3.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PP1	✔	The variant has been reported to segregate with VWD type 2A in 3 affected family members from 1 family, all homozygous for this variant PMIDs: 20335223
PM3	✔	This variant has been reported in two homozygous probands meeting activity < antigen, loss of HMWMs and abnormal RCo (PMID: 20335223, PMID 9714529). 1pt PM3 An additional compound heterozygote has been reported in PMID: 35452508. Family 1 proband was compound heterozygous for N528S and p. D366LfsX16, confirmed in trans. The second variant has not yet been curated by the VWD VCEP. This could potentially increase the code to PM3_Strong but would not affect the variant classification.
PP4_Moderate	✔	At least one patient with this variant displayed activity<antigen, loss of HMWMs and abnormal RCo assay, which is highly specific for VWD type 2A PMID: 20335223 - Ag plasma: 38,30,33; CB:7,5,6; Ag platelet: <1,<1,nd; FVIII:C: 66,58,91; reduction of medium and HMWMs consistent with 2A; PMID 9714529 - FVIII:C: 25; VWF:Ag: 26; VWF:RCo: <6
PS3	✔	defective VWF storage with no response to desmopressin and very little VWF:Ag released after administration; Expression in 293 EBNA cells showed homozygous variant secretion was 7.5% of WT, with multimer pattern lacking medium and HMWMs (PMID: 20335223 Fig. 4; PS3); AtT-20 cells showed the variant is not multimerized and is not trafficked to storage granules

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Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.555, which is below the ClinGen VWD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on VWF function. The computational splicing predictor SpliceAI gives a score of 0.08 for splice acceptor loss, indicating that the variant likely has no impact on splicing.
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	The computational predictor REVEL gives a score of 0.555, which is above the ClinGen VWD VCEP threshold of <0.290.

Curation History

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