Variant: NM_000552.5(VWF):c.3797C>A (p.Pro1266Gln)

Version: 1.0

CA228441

100279 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease 2 (MONDO:0013304)
Inheritance Mode: Undetermined mode of inheritance
UUID: 2614b957-fb3f-4223-b866-4b4c8b149e15
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HGVS expressions

NM_000552.5:c.3797C>A
NM_000552.5(VWF):c.3797C>A (p.Pro1266Gln)
NC_000012.12:g.6019621G>T
CM000674.2:g.6019621G>T
NC_000012.11:g.6128787G>T
CM000674.1:g.6128787G>T
NC_000012.10:g.5999048G>T
NG_009072.1:g.110050C>A
NG_009072.2:g.110050C>A
ENST00000261405.10:c.3797C>A
ENST00000261405.9:c.3797C>A
ENST00000538635.5:n.421-25687C>A
ENST00000539641.1:n.595C>A
NM_000552.3:c.3797C>A
NM_000552.4:c.3797C>A

Uncertain Significance

Met criteria codes 1

PP4

Not Met criteria codes 9

PS3 PS4 PP1 PP3 PM5 PM2 BS2 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:c.3797C>A variant in VWF is a missense variant predicted to cause substitution of proline by glutamine at amino acid 1266. Population and in silico predictors were between the pathogenic and benign thresholds for the respective codes. At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of low VWF:RCo/VWF:Ag ratio and no loss

of HMW multimers (described as non-selective loss and low intensity but high molecular weight bands are still present), which is specific for VWD type 2M (PP4, PMID 23179108). The majority of reported cases were asserted as VWD type 2M but there were also assertions for type 2B and type 1. No reported case in the literature had a combination of activity/antigen ratio <0.7, documented abnormal bleeding phenotype, and enhanced platelet binding. There is conflicting evidence of altered platelet binding phenotype evidenced by in vitro assays showing both enhanced GPIb and decreased GPIb binding (PMIDs 23179108, 30488424). In summary, this variant meets the criteria to be classified as a variant of uncertain significance for autosomal dominant VWD type 2 based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP4. (ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0; May 6th, 2025)

Met criteria codes

PP4	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of low VWF:RCo/VWF:Ag ratio and no loss of HMW multimers (described as non-selective loss and low intensity but high molecular weight bands are still present), which is specific for VWD type 2M. (PP4, PMID 23179108)

Not Met criteria codes

PS3	✖	In vitro expression studies of P1266Q from PMIDs: 23179108 and 30488424 respectively report GP1ba binding activity at 54.76 and 94.05% compared to WT. While PMID 23179108 reports GPIb binding activity of 169% when variant and WT rVWF are expressed, the second report PMID 30488424 reports that binding activity is 89% of WT in the same assay. An increased binding activity for GP1ba has not been consistently demonstrated. Further, this variant has more often been described in cases diagnosed as VWD type 2M, not 2B.
PS4	✖	This variant has been reported in 1 family meeting laboratory phenotype for VWD type 2B, RIPA ,<1mg/mL. No thrombocytopenia was observed in cases carrying the variant and multimers were normal in multiple cases. The scored case is compound heterozygous for the Asn1231Thr variant which has been curated likely benign by the VWD VCEP. Only 1 variant with a positive bleeding phenotype, however while the case has VWF:Activity/VWF:Ag <0.7 which is indicative of type 2 VWD, absence of RIPA data means this case is not counted as a positive instance of bleeding phenotype positive case of VWD type 2B for this curation.
PP1	✖	At least 5 families have been described, each with 2 affected individuals harboring P1266Q, however all either carry additional variants as a result of a gene conversion or do not meet the laboratory phenotype for VWD type 2B.
PP3	✖	The computational predictor REVEL gives a score of 0.405, which is below the ClinGen VWD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on VWF function. And the computational splicing predictor SpliceAI indicated that the variant has no impact on splicing.
PM5	✖	Another missense variant NM_000552.5:c.3797C>T (p.Pro1266Leu) in the same codon has been classified as likely benign for VWD by ClinGen VWD VCEP. Splicing prediction using SpliceAI revealed no expected effects on splicing due to this variant.
PM2	✖	This variant has an gnomAD v4.1 Grpmax FAF of 0.003524 (351/91018 alleles) South Asian population, including 3 homozygotes, which is neither higher nor lower than thresholds predicting benign or pathogenic impact to VWF.
BS2	✖	PMID 34807970 identified 3 variant carriers in the control data set but given that this variant is associated with type 2B with normal multimers and no thrombocytopenia, affected status can not be ruled out without more thorough phenotyping

BP5		✖	The VWD VCEP has curated the NM_000552.5:c.4135C>T (p.Arg1379Cys) variant as a VUS for VWD type 2B
BP2		✖	At least 10 of 11 patients with P1266Q harbored additional VWF variants, primarily as a result of gene conversion events, however ClinVar interpretations for these additional variants are Benign to VUS. One patient from PMID: 26456374 also had the Arg1379Cys (curated likely pathogenic by the VWD VCEP), however the cis/trans relationship was not defined. This code is not allowed under the ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0

Curation History

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