

Variant: *NM_000552.5(VWF):c.3802C>G (p.His1268Asp)*

Version: 1.0

CA228445 [↗](#)

100281 (ClinVar) [↗](#)

Gene: VWF ([HGNC:7450](#))

Condition: von Willebrand disease type 2B ([MONDO:0015629](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: bdbc4c65-f676-4c9a-b80a-d6fd2eb3d76f

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HGVS expressions

NM_000552.5:c.3802C>G

NM_000552.5(VWF):c.3802C>G (p.His1268Asp)

NC_000012.12:g.6019616G>C

CM000674.2:g.6019616G>C

NC_000012.11:g.6128782G>C

CM000674.1:g.6128782G>C

NC_000012.10:g.5999043G>C

NG_009072.1:g.110055C>G

NG_009072.2:g.110055C>G

ENST00000261405.10:c.3802C>G

ENST00000261405.9:c.3802C>G

ENST00000538635.5:n.421-25682C>G

ENST00000539641.1:n.600C>G

NM_000552.3:c.3802C>G

NM_000552.4:c.3802C>G

Pathogenic

Met criteria codes 5

PM2_Supporting

PP4_Moderate

BP4

PS3

PS4

Not Met criteria codes 1

PM5

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.3802C>G (p.His1268Asp) variant is a missense variant with a REVEL score of 0.29, which meets the VWD VCEP threshold of less than or equal to 0.29 and does not predict a damaging effect on VWF function (BP4). However, a patient with the H1268D variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of a partial loss of high molecular weight

multimers and a significant increase in VWF-GPIb showing gain of function which is highly specific for VWF type 2B. Additionally, the patient developed thrombocytopenia during infectious episodes (PMID: 18805962; PP4_Moderate). There are at least 4 additional type 2B probands with this variant and confirmed increased VWF binding (PMID: 8376405, PMID: 16704443, Christopherson, 2020, SCV002515761.1; PS4). The variant is absent from gnomADv4, thus, meeting PM2_Supporting criterion. RIPA assay demonstrated that the variant demonstrated enhanced responsiveness to rVWF-WT at a low concentration of ristocetin. Furthermore, multimer analysis also showed preferential cleavage of HMWMs (PMID: 26345337). The variant also exhibited increased affinity towards the LBD compared to WT AIM-A1 (PS3). In summary, this variant has been classified as 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. BP4, PP4_Moderate, PM2_Supporting, PS3, PS4.

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4, thus, meeting PM2_Supporting criterion.
PP4_Moderate			At lease 1 patient with the H1268D variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of a partial loss of high molecular weight multimers and a significant increase in VWF-GPIb showing gain of function which is highly specific for VWF type 2B. Additionally, the patient developed thrombocytopenia during infectious episodes (PMID: 18805962).
BP4			The computational predictor REVEL gives a score of 0.29, which meets the ClinGen VWD VCEP threshold of <0.290 (or equal to) and does not predict a damaging effect on VWF function (BP4). Additionally, the computational splicing predictor SpliceAI indicated that the variant has no impact on splicing (delta scores 0.00).
PS3			RIPA assay using fresh platelets showed that the H1268D variant demonstrated enhanced responsiveness compared with rVWF-WT at a low concentration of ristocetin (0.5 mg/mL). Multimer analysis also showed preferential cleavage of HMW multimers (PMID: 26345337). The H1268 variant showed increased affinity towards the LBD compared to WT AIM-A1 in transfected Expi293FBirA cells (PMID: 33883551).
PS4			There are at least 4 additional type 2B probands with this variant and confirmed increased VWF binding (PMID: 8376405, PMID: 16704443, Christopherson, 2020, SCV002515761.1).

Not Met criteria codes

PM5			Two additional variants, p.His1268Asn and His1268Tyr, have been reported at the same codon but have not been curated by the VWD VCEP. Use of PM5 would not change the classification of His1268Asp and will not be pursued at this time.
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Curation History 

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