Variant: NM_000552.5(VWF):c.2446C>T (p.Arg816Trp)

Version: 1.0

CA114137

295 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2N (MONDO:0015631)
Inheritance Mode: Autosomal recessive inheritance
UUID: 70363cd6-3c5e-4b06-8b9d-206168fc402f
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HGVS expressions

NM_000552.5:c.2446C>T
NM_000552.5(VWF):c.2446C>T (p.Arg816Trp)
NC_000012.12:g.6036488G>A
CM000674.2:g.6036488G>A
NC_000012.11:g.6145654G>A
CM000674.1:g.6145654G>A
NC_000012.10:g.6015915G>A
NG_009072.1:g.93183C>T
NG_009072.2:g.93183C>T
ENST00000261405.10:c.2446C>T
ENST00000261405.9:c.2446C>T
ENST00000538635.5:n.421-42554C>T
NM_000552.3:c.2446C>T
NM_000552.4:c.2446C>T

Pathogenic

Met criteria codes 6

PP3 **PP1_Moderate** **PM2_Supporting**
PM3 **PS3** **PP4_Moderate**

Not Met criteria codes 1

BP2

Evidence Links 1

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.2446C>T variant in VWF is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 816. The Grpmax filtering allele frequency in gnomAD v4.1 is 0.00009000 (based on 10/59984 alleles in the Admixed American population), which is lower than the ClinGen VWD VCEP threshold of <0.005 (PM2_Supporting). At least 8 patients with this variant displayed excessive mucocutaneous bleeding as well as low FVIII activity (1.3% or 9.8%) and decreased VWF:FVIII binding (0.00 to 0.1), which is highly specific

for VWD type 2N (PMID: 28536718, PMID: 1832934, PMID: 28971901), (PP4_Moderate). Five individuals were homozygous for the variant (PM3) and three were compound heterozygous (PMID: 28536718, PMID: 28971901, PMID: 1832934). The variant has been reported to segregate with VWD type 2N in a proband plus two affected family members (PP1_moderate; PMID: 1832934). A hydrodynamic mouse model showed prolonged bleeding time, reduced factor VIII stability, and impaired binding of factor VIII to VWF, indicating that this variant has a damaging effect on protein function (PMID: 28581694)(PS3). The computational predictor REVEL gives a score of 0.756, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). In summary, this variant meets the criteria to be classified as Pathogenic for von Willebrand disease type 2N. ACMG/AMP criteria applied as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PM3, PP1_Moderate, PP3, PP4_Moderate, PS3, PM2_Supporting.

Met criteria codes

PP3	ⓘ	✓	The computational predictor REVEL gives a score of 0.756, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). The computational splicing predictor SpliceAI gives a score of 0.11 for acceptor loss, indicating an inconclusive impact on splicing.
PP1_Moderate	ⓘ	✓	The variant has been reported to segregate with VWD type 2N in the proband plus two affected family members (PP1_moderate; PMID: 1832934).
PM2_Supporting	ⓘ	✓	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.00009000 (based on 10/59984 alleles in the Admixed American population), which is lower than the ClinGen VWD VCEP threshold of <0.005 (PM2_Supporting).
PM3	ⓘ	✓	This variant has been detected in at least 7 individuals with VWD Type 2N. 5 individuals were homozygous for the variant (1 point, PMID: 28536718, PMID: 28971901, PM3). 1 individual was compound heterozygous for the variant and an established pathogenic variant associated with VWD Type 2A/2M, p.Arg1315Cys (PMID: 28971901), but was too ambiguous phenotypically to include in the evaluation of this code. 1 of those individuals was compound heterozygous for the variant and a pathogenic variant (p.Val638Cysfs*13, Canonical Allele Identifier: CA2573105978) without confirmation in trans (NGS-based genotyping but 2 variants are distant from one another), (not scored at this time since quantitative rules are not yet finalized, PMID: 28536718). 1 of those individuals was compound heterozygous for the variant and a pathogenic variant (p.Arg854Gln) confirmed in trans (not counted here to avoid circularity, PMID: 1832934).
PS3	ⓘ	✓	A hydrodynamic mouse model with tail-vein injections of plasma-derived p.Arg816Trp showed prolonged bleeding time, reduced factor VIII stability, and impaired binding of factor VIII to VWF, indicating that this variant has a damaging effect on protein function (PMID: 28581694)(PS3). A hydrodynamic mouse model with tail-vein injections of plasma-derived p.Arg816Trp showed prolonged bleeding time (Figure 4A), reduced factor VIII stability (Figure 2B), and impaired binding of factor VIII to VWF (1D), recapitulating the key phenotypes of VWD Type 2N. **PubMed:28581694**
PP4_Moderate	ⓘ	✓	At least 8 patients with this variant displayed excessive mucocutaneous bleeding as well as low FVIII activity (1.3% or 9.8%) and decreased VWF:FVIII binding (0.00 to 0.1), which is highly specific for VWD type 2N (PMID: 28536718, PMID: 1832934, PMID: 28971901), (PP4_Moderate).

Not Met criteria codes

BP2	✗	1 individual diagnosed with VWD Type 2A/2M was compound heterozygous for the variant and an established pathogenic variant associated with VWD Type 2A, p.Arg1315Cys (PMID: 28971901), but had phenotypes consistent

with both VWD Type 2A and Type 2N and was too ambiguous phenotypically to include in the evaluation of this code.

Curation History

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