Variant: NM_000552.5(VWF):c.2411G>T (p.Cys804Phe)

Version: 1.0

CA114168

313 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2N (MONDO:0015631)
Inheritance Mode: Autosomal recessive inheritance
UUID: e928df71-3a57-4f25-9303-36b69f384f15
Approved on: 2025-02-04
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HGVS expressions

NM_000552.5:c.2411G>T
NM_000552.5(VWF):c.2411G>T (p.Cys804Phe)
NC_000012.12:g.6044322C>A
CM000674.2:g.6044322C>A
NC_000012.11:g.6153488C>A
CM000674.1:g.6153488C>A
NC_000012.10:g.6023749C>A
NG_009072.1:g.85349G>T
NG_009072.2:g.85349G>T
ENST00000261405.10:c.2411G>T
ENST00000261405.9:c.2411G>T
ENST00000538635.5:n.421-50388G>T
NM_000552.3:c.2411G>T
NM_000552.4:c.2411G>T

Likely Pathogenic

Met criteria codes 5

PM3_Supporting **PM2_Supporting**
PS3 **PP4_Moderate** **PP3**

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(VWF):c.2411G>T (p.Cys804Phe) missense variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.935, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). Factor VIII binding assay performed with the C804F recombinant mutant showed severely impaired binding indicating that this variant has a damaging effect on protein function (PMID: 15461624; PS3). At least 1 patient (Patient B) with this variant displayed

excessive mucocutaneous bleeding as well as low FVIII activity (20 IU/dl) and dramatically decreased VWF:FVIII binding, which is highly specific for VWD type 2N. (PP4_moderate, PMID:15213842). Patient B (PMID: 15461624) is compound heterozygous for R854Q (classified Pathogenic by the VWD VCEP; PM3_supporting). In summary, this variant meets the criteria to be classified as Likely Pathogenic for von Willebrand disease type 2N. ACMG/AMP criteria applied as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PM2_supporting, PP3, PM3_supporting, PP4_moderate, PS3.

Met criteria codes

PM3_Supporting	✓	Patient B (PMID: 15461624) is compound heterozygous for R854Q (classified Pathogenic by the VWD VCEP) and C804F; confirmation of trans phase was not reported. 0.5pt (PM3_supporting).
PM2_Supporting	✓	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PS3	✓	Factor VIII binding assay performed with the C804F recombinant mutant showed severely impaired binding indicating that this variant has a damaging effect on protein function (PMID: 15461624; PS3). Expression studies in Cos-7 cells showed C804F failed to bind FVIII. **PubMed:15461624**
PP4_Moderate	✓	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as low FVIII activity (20 IU/dl) and dramatically decreased VWF:FVIII binding, which is highly specific for VWD type 2N. (PP4_moderate, PMID:15213842).
PP3	✓	The computational predictor REVEL gives a score of 0.935, 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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