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# *Variant: NM_000552.5(VWF):c.2384A>G (p.Tyr795Cys)*

Version: 1.0

*CA114166*

*312 (ClinVar)*

**Gene**: VWF (HGNC:7450)
**Condition**: von Willebrand disease type 2N (MONDO:0015631)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 51a932c7-ed92-419d-a693-6c18a63a3911
**Approved on**: 2025/1/7
**Published on**: 2025/1/8

## *HGVS expressions*

**NM_000552.5:c.2384A>G**
**NM_000552.5(VWF):c.2384A>G (p.Tyr795Cys)**
NC_000012.12:g.6044349T>C
CM000674.2:g.6044349T>C
NC_000012.11:g.6153515T>C
CM000674.1:g.6153515T>C
NC_000012.10:g.6023776T>C
NG_009072.1:g.85322A>G
NG_009072.2:g.85322A>G
ENST00000261405.10:c.2384A>G
ENST00000261405.9:c.2384A>G
ENST00000538635.5:n.421-50415A>G
NM_000552.3:c.2384A>G
NM_000552.4:c.2384A>G

**Pathogenic**

**Met criteria codes** 5

PM2_Supporting PP3 PM3 PP4_Moderate PS3

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.2384A>G (p.Tyr795Cys) missense variant has a Grpmax filtering allele frequency in gnomAD v4.1 of 2.800e-7 (based on 2/1180036 alleles in the European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.005 for type 2N (PM2_Supporting). The computational predictor REVEL gives a score of 0.688, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). At least three compound heterozygous VWD type 2N patients have been**

**reported with this variant; two (PMIDs: 33807613, 15461624; PM3) compound heterozygous with R854Q (classified Pathogenic by the VWD VCEP), and one (PMID: 15213842) compound heterozygous with R1566X (not yet been evaluated by the VWD VCEP). At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as low FVIII activity (0.13 IU/ml) and decreased VWF:FVIII binding (<1.5%), which is highly specific for VWD type 2N. (PP4_moderate, PMID:15213842). Factor VIII binding assay performed with theY795C recombinant mutant showed severely impaired binding indicating that this variant has a damaging effect on protein function (PMID: 15213842, 15461624; PS3). 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: PM2_supporting, PP3, PM3, PP4_moderate, PS3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PM2_Supporting** | ✔ | The Grpmax filtering allele frequency in gnomAD v4.1 is 2.800e-7 (based on 2/1180036 alleles in the European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.005 for type 2N (PM2_Supporting). |
| **PP3** | ✔ | The computational predictor REVEL gives a score of 0.688, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). |
| **PM3** | ✔ | At least three compound heterozygous VWD type 2N patients have been reported with this variant; two (PMIDs: 33807613 1pt, 15461624 0.5pt) compound heterozygous with R854Q (classified Pathogenic by the VWD VCEP), and one (PMID: 15213842 0pt) compound heterozygous with R1566X (not yet been evaluated by the VWD VCEP). Total 1.5pt (PM3) |
| **PP4_Moderate** | ✔ | At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as low FVIII activity (0.13 IU/ml) and decreased VWF:FVIII binding (<1.5%), which is highly specific for VWD type 2N. (PP4_moderate, PMID:15213842). Additionally a consistent phenotype of normal VWF:Ag (0.91 IU/ml) was reported however, there were aberrant multimers (i) relatively reduced concentration of large multimers in ii) the presence of ‘supranormal’ multimers and iii) a lack of a defined triplet structure of individual multimers which had a smeary appearance rather than displaying sharp bands. |
| **PS3** | ✔ | Factor VIII binding assay performed with the Y795C recombinant mutant showed severely impaired binding indicating that this variant has a damaging effect on protein function (PMID: 15213842, 15461624; PS3). |

Curation History

Showing 1 to 1 of 1 rows

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