

Variant: NM_000552.5:c.2637C>A

Version: 1.0

CA383520062 [↗](#)

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

Condition: von Willebrand disease type 2N ([MONDO:0015631](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 2a3e00c1-568c-483f-b048-6a9f3000f56a

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HGVS expressions

NM_000552.5:c.2637C>A

NC_000012.12:g.6034736G>T

CM000674.2:g.6034736G>T

NC_000012.11:g.6143902G>T

CM000674.1:g.6143902G>T

NC_000012.10:g.6014163G>T

NG_009072.1:g.94935C>A

NG_009072.2:g.94935C>A

ENST00000261405.10:c.2637C>A

ENST00000261405.9:c.2637C>A

ENST00000538635.5:n.421-40802C>A

NM_000552.3:c.2637C>A

NM_000552.4:c.2637C>A

Likely Pathogenic

Met criteria codes 4

PP4_Moderate

PM2_Supporting

PM3

PM5

Not Met criteria codes 2

PP1

PP3

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.2637C>A variant in VWF is a missense variant predicted to cause substitution of aspartate by glutamate at amino acid 879 (p.Asp879Glu). At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as low FVIII activity and decreased VWF:FVIII binding, which is highly specific for VWD type 2N. (PP4_moderate, PMID 26988807). Additional consistent phenotypes were also reported in the patient including normal VWF:Ag, and normal HMW multimers. This variant has been detected in 1 individual with von Willebrand Disease type 2N. The individual is compound heterozygous for the variant and a pathogenic variant as determined by

the ClinGen VWD VCEP, confirmed in trans by the authors (p.Arg854Gln) (PM3, PMID 26988807). This variant is absent from gnomAD v4.1 (PM2_Supporting). Another missense variant c.2635G>A, p.Asp879Asn (PMIDs 9845532, 34298581) in the same codon has been classified as pathogenic for VWD type 2N by the ClinGen VWD VCEP (PM5). Splicing prediction using SpliceAI revealed no expected effects on splicing due to any of these variants. In summary, this variant meets the criteria to be classified as a variant of likely pathogenic for von Willebrand Disease type 2N based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP4_Moderate, PM3, PM2_Supporting, and PM5. (ClinGen VWD VCEP, VWD type 2N rule specifications v1.0.0; date of approval)

Met criteria codes

PP4_Moderate			At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as low FVIII activity and decreased VWF:FVIII binding, which is highly specific for VWD type 2N. (PP4_moderate, PMID 26988807). Additional consistent phenotypes were also reported in the patient including normal VWF:Ag, and normal HMW multimers.
PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).
PM3			This variant has been detected in 1 individual with von Willebrand Disease type 2N. The individual is compound heterozygous for the variant and a type 2N pathogenic variant as determined by the ClinGen VWD VCEP, confirmed in trans by the authors (p.Arg854Gln) (PM3, PMID 26988807).
PM5			Another missense variant c.2635G>A, p.Asp879Asn (PMIDs 9845532, 34298581) in the same codon has been classified as pathogenic for VWD type 2N by the ClinGen VWD VCEP (PM5). Splicing prediction using SpliceAI revealed no expected effects on splicing due to any of these variants.

Not Met criteria codes

PP1			Segretation is asserted but affected status of other family members is not confirmed.
PP3			The computational predictor REVEL gives a score of 0.626, which is below the ClinGen VWD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on VWF function. Additionally, the computational splicing predictor SpliceAI indicated that the variant has no impact on splicing.

Curation History

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