

Variant: NM_000552.5(VWF):c.2635G>A (p.Asp879Asn)

Version: 1.0

CA228357 [↗](#)

100231 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 0532580f-3083-4283-aaf1-01bc8f2819f2

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HGVS expressions

NM_000552.5:c.2635G>A

NM_000552.5(VWF):c.2635G>A (p.Asp879Asn)

NC_000012.12:g.6034738C>T

CM000674.2:g.6034738C>T

NC_000012.11:g.6143904C>T

CM000674.1:g.6143904C>T

NC_000012.10:g.6014165C>T

NG_009072.1:g.94933G>A

NG_009072.2:g.94933G>A

ENST00000261405.10:c.2635G>A

ENST00000261405.9:c.2635G>A

ENST00000538635.5:n.421-40804G>A

NM_000552.3:c.2635G>A

NM_000552.4:c.2635G>A

Pathogenic

Met criteria codes **5**

PP4_Moderate

PP3

PS3

PM3

PM2_Supporting

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.2635G>A variant in VWF is a missense variant predicted to cause substitution of aspartic acid by asparagine at amino acid 879. The Grpmax filtering allele frequency in gnomAD v4.1 is 0.0001409 (based on 14/59994 alleles in the Admixed American population), which is lower than the ClinGen VWD VCEP threshold (<0.005 for type 2N) for PM2_Supporting. At least 1 patient with this variant displayed mildly prolonged mucocutaneous bleeding, low FVIII activity, decreased VWF:FVIII binding, reduced ability to agglutinate

platelets in the presence of ristocetin (VWF:RCo), and reduced VWF expression, which is highly specific for VWD type 2N, despite the reduced HMW multimers (PP4, PMID: 9845532). This patient was compound heterozygous and harbored a second variant (p.Arg1659Ter) in trans that has been classified Pathogenic by the VCEP, (PMID: 9845532, PM3). Factor VIII binding assay performed with the p.Asp879Asn mutant and wild-type recombinant vWF expressed by and purified from HEK293 cells showed dramatically decreased binding, indicating that this variant has a damaging effect on protein function (PMID: 30111575, PMID: 9845532) (PS3). The computational predictor REVEL gives a score of 0.66, 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, PM2_Supporting, PS3, PP3, PP4.

Met criteria codes

PP4_Moderate			At least 1 patient with this variant displayed mildly prolonged mucocutaneous bleeding, low FVIII activity, decreased VWF:FVIII binding, reduced ability to agglutinate platelets in the presence of ristocetin (VWF:RCo), and reduced VWF expression, which is highly specific for VWD type 2N. (PP4, PMID: 9845532). HMW multimers were reduced, however.
PP3			The computational predictor REVEL gives a score of 0.66, 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 0.00 for all splicing types, indicating that the variant has no impact on splicing.
PS3			Factor VIII binding assay performed with the p.Asp879Asn mutant and wild-type recombinant vWF expressed by and purified from HEK293 cells showed dramatically decreased binding indicating that this variant has a damaging effect on protein function (PMID: 30111575, PMID: 9845532) (PS3).
PM3			This variant has been detected in at least 1 individual with VWD Type 2N. The individual was compound heterozygous for the p.Asp879Asn variant and a second variant (p.Arg1659Ter) and was confirmed in trans by genotyping of a heterozygous carrier family member (1 PM3 point awarded, PMID: 9845532, ClinVar Variation ID: 297).
PM2_Supporting			The Grpmax filtering allele frequency in gnomAD v4.1 is 0.0001409 (based on 14/59994 alleles in the Admixed American population), which is lower than the ClinGen VWD VCEP threshold (<0.005 for type 2N) for PM2_Supporting,

Not Met criteria codes

PM5			The D879E variant has been reported (PMID: 26988807) at the same amino acid residue but is not considered here to avoid circularity.
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Curation History 

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