

Variant: *NM_000552.5(VWF):c.2278C>T (p.Arg760Cys)*

Version: 1.0

CA228314 [↗](#)

100208 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: d000f4f9-fefb-4a45-9939-a12016651e14

Approved on: 2025/1/7

Published on: 2025/1/8

HGVS expressions

NM_000552.5(VWF):c.2278C>T (p.Arg760Cys)

NM_000552.5:c.2278C>T

NC_000012.12:g.6046726G>A

CM000674.2:g.6046726G>A

NC_000012.11:g.6155892G>A

CM000674.1:g.6155892G>A

NC_000012.10:g.6026153G>A

NG_009072.1:g.82945C>T

NG_009072.2:g.82945C>T

ENST00000261405.10:c.2278C>T

ENST00000261405.9:c.2278C>T

ENST00000538635.5:n.421-52792C>T

NM_000552.3:c.2278C>T

NM_000552.4:c.2278C>T

Likely Pathogenic

Met criteria codes **5**

PP4_Moderate

PM2_Supporting

BP4

PS3

PM3

Not Met criteria codes **2**

PP1

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 c.2278C>T variant in VWF is a missense variant predicted to cause substitution of Arginine by Cysteine at amino acid 760 (p.Arg760Cys). This variant lies 4 amino acids before the cleavage site for pro-VWF. At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as low FVIII activity and decreased VWF:FVIII binding of 0.23, which is highly specific for VWD type 2N. (PP4_moderate, PMID: 12393698). This individual was compound heterozygous (confirmed in trans by parental testing) for this variant and

the p.R854Q variant which was classified as pathogenic by the VCEP (1 PM3 points, PM3). Factor VIII binding assay performed with the p.Arg760Cys recombinant mutant and wt vWF expressed by FUR4BHK cells showed absent binding indicating that this variant has a damaging effect on protein function (PMID: 12393698)(PS3). The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000007410 (based on 2/60034 alleles in the Admixed American population), which is lower than the ClinGen VWD VCEP threshold of <0.005 for type 2N VWD (PM2_Supporting). The computational predictor REVEL gives a score of 0.219, which is below the ClinGen VWD VCEP threshold of <0.290 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 (BP4). In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal recessive von Willebrand disease type 2N based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP4_Moderate, PM2_Supporting, PM3, PS3, and BP4 (VCEP specifications version 1.0.0; 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: 12393698). The binding capacity of VWF:FVIII was found to be decreased both as an absolute value (11.9 U/dL versus normal range, 70-140 U/dL) and a ratio (0.23 versus normal > 0.75).
PM2_Supporting			The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000007410 (based on 2/60034 alleles in the Admixed American population), which is lower than the ClinGen VWD VCEP threshold of <0.005 for type 2N VWD (PM2_Supporting).
BP4			The computational predictor REVEL gives a score of 0.219, which is below the ClinGen VWD VCEP threshold of <0.290 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 (BP4).
PS3			Factor VIII binding assay performed with the p.Arg760Cys recombinant mutant and wt vWF expressed by FUR4BHK cells showed absent binding indicating that this variant has a damaging effect on protein function (PMID: 12393698)(PS3).
PM3			This variant has been detected in at least 1 individual with VWF Type 2N (PMID: 12393698) This individual was compound heterozygous (confirmed in trans by parental testing) for this variant and the p.R854Q variant which was classified as pathogenic by the VCEP (1 PM3 points, PM3).

Not Met criteria codes

PP1			PMID: 12393698 Father carries variant, but has VWF:FVIII/VWF:Ag of 0.45. * Addition of PP1 would not change classification
PM5			Another missense variant NM_000552.5(VWF):c.2279G>A (p.Arg760His) (ClinVar 31011, Pathogenic) in the same codon has not yet been classified by the ClinGen VWD VCEP. However, this variant is consistently associated with type 1 VWD.

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