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Variant: NM_000552.5(VWF):c.3178T>C (p.Cys1060Arg)

Version: 1.0

CA114176

317 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2N (MONDO:0015631)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2c90cf2e-6636-48a7-886d-900facd59bba
Approved on: 2025/2/4
Published on: 2025/2/5

HGVS expressions

NM_000552.5:c.3178T>C
NM_000552.5(VWF):c.3178T>C (p.Cys1060Arg)
NC_000012.12:g.6025624A>G
CM000674.2:g.6025624A>G
NC_000012.11:g.6134790A>G
CM000674.1:g.6134790A>G
NC_000012.10:g.6005051A>G
NG_009072.1:g.104047T>C
NG_009072.2:g.104047T>C
ENST00000261405.10:c.3178T>C
ENST00000261405.9:c.3178T>C
ENST00000538635.5:n.421-31690T>C
NM_000552.3:c.3178T>C
NM_000552.4:c.3178T>C

Pathogenic

Met criteria codes 5

PS3 PP3 PM3 PP4_Moderate PM2_Supporting

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.3178T>C (p.Cys1060Arg) missense variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.96, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). At least one homozygote and two compound heterozygotes with R854Q (confirmation of trans phase not reported), which is classified pathogenic by the VWD VCEP (PMID: 12588349; PM3). At least 1 patient with this variant displayed excessive mucocutaneous

bleeding as well as low FVIII activity (FVIII:C 4-10 IU/dL) and absent VWF:FVIII binding, which is highly specific for VWD type 2N. (PP4_moderate, PMID 12406074). Variants in F8 were screened for by sequencing. Site-directed mutagenesis and transient expression in COS-7 cells showed R1060rVWF was completely unable to bind to rFVIII (PMID: 12588349; 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

PS3	✔	Site-directed mutagenesis and transient expression in COS-7 cells, showed R1060rVWF was completely unable to bind to rFVIII (PMID: 12588349; PS3). site-directed mutagenesis and transient expression in COS-7 cells, showed R1060rVWF was completely unable to bind to rFVIII PubMed:12588349
PP3	✔	The computational predictor REVEL gives a score of 0.96, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).
PM3	✔	At least one homozygote and two compound heterozygotes with R854Q (confirmation of trans phase not reported), which is classified pathogenic by the VWD VCEP (PMID: 12588349; PM3).
PP4_Moderate	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as low FVIII activity (FVIII:C 4-10 IU/dL) and absent VWF:FVIII binding, which is highly specific for VWD type 2N. (PP4_moderate, PMID 12406074). Variants in F8 were screened for by sequencing.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

Curation History

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