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Variant: NM_000552.4(VWF):c.2372C>T (p.Thr791Met)

Version: 1.0

CA114135

294 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2N (MONDO:0015631)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3b27668f-206c-4b22-a66d-e407aaee7010
Approved on: 2024/8/13
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HGVS expressions

NM_000552.4(VWF):c.2372C>T (p.Thr791Met)
NM_000552.4:c.2372C>T
NC_000012.12:g.6044361G>A
CM000674.2:g.6044361G>A
NC_000012.11:g.6153527G>A
CM000674.1:g.6153527G>A
NC_000012.10:g.6023788G>A
NG_009072.1:g.85310C>T
NG_009072.2:g.85310C>T
ENST00000261405.10:c.2372C>T
ENST00000261405.9:c.2372C>T
ENST00000538635.5:n.421-50427C>T
NM_000552.3:c.2372C>T
NM_000552.5:c.2372C>T

Pathogenic

Met criteria codes 5

PM3 PS3 PM2_Supporting PP3 PP4_Moderate

Not Met criteria codes 2

BA1 PP1

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_000552.4(VWF):c.2372C>T variant in VWF is a missense variant predicted to cause substitution of threonine by methionine at amino acid 791. The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000006150 (based on 2/64030alleles in European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold <0.005 for PM2_Supporting, meeting this criterion (PM2_Supporting). At least four patients with this variant displayed excessive mucocutaneous bleeding as well as a low VWF:FVIII/VWF:Ag ratio which is highly

specific for VWD type 2N (PP4_moderate, PMIDs: 2018834; 31741138; 22871923; 10706867). This variant has been detected in at least six individuals with VWD type 2N, with absent VWF:FVIII binding, compound heterozygous with a second variant (including Arg854Gln classified Pathogenic by the VWD VCEP without reported confirmation of trans phase 0.5pt PMID: 22102197) and two individuals were homozygous for the variant (PMIDs: 2018834; 22871923) (PM3). Factor VIII binding assay in HEK293 expressing recombinant VWF showed decreased binding indicating that this variant has a damaging effect on protein function (PMID: 19088379; PS3_supporting). The computational predictor REVEL gives a score of 0.869, 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: PM2_supporting, PP4_moderate, PM3, PS3, PP3.

Met criteria codes

PM3	✔	This variant has been detected in at least six individuals with VWD type 2N, with absent VWF:FVIII binding, compound heterozygous with a second variant (Arg854Gln classified Pathogenic by the VWD VCEP without reported confirmation of trans phase 0.5pt, Cys858Trp classified VUS by the VWD VCEP not considered here to avoid circularity, c.2435del classified as Pathogenic by the VWD VCEP confirmed in trans not considered here until quantitative VWD rules are complete; Arg365Ter; c.3379+G>A; not yet evaluated by the VWD VCEP, PMIDs: 22102197, 21371195, 28536718, 10494764, 8903002, 31741138). Two individuals were homozygous for the variant (1 point maximum, PMIDs: 2018834; 22871923) (PM3). Total 1.5pt
PS3	✔	Factor VIII binding assay in HEK293 expressing recombinant VWF showed decreased binding (<10%) indicating that this variant has a damaging effect on protein function (PMID: 19088379)(PS3).
PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000006150 (based on 2/64030alleles in European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold <0.005 for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.869, 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 0.01 for splice donor loss, indicating that the variant likely has no impact on splicing.
PP4_Moderate	✔	At least four patients with this variant displayed excessive mucocutaneous bleeding as well as low FVIII:C and decreased VWF:FVIII binding which is highly specific for VWD type 2N. (PP4; 2018834; 31741138; 22871923; 10706867).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	✖	Two patients from one family were compound heterozygous (PMID: 8903002); insufficient segregation for PP1

Curation History

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