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Variant: NM_000552.5(VWF):c.4195C>T (p.Arg1399Cys)

Version: 2.2

CA228555

100337 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2M (MONDO:0015630)
Inheritance Mode: Autosomal dominant inheritance
UUID: 807b1008-f3f9-4267-96c0-1bbbc7a587ed
Approved on: 2025/10/7
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HGVS expressions

NM_000552.5(VWF):c.4195C>T (p.Arg1399Cys)
NM_000552.5:c.4195C>T
NC_000012.12:g.6019223G>A
CM000674.2:g.6019223G>A
NC_000012.11:g.6128389G>A
CM000674.1:g.6128389G>A
NC_000012.10:g.5998650G>A
NG_009072.1:g.110448C>T
NG_009072.2:g.110448C>T
ENST00000261405.10:c.4195C>T
ENST00000261405.9:c.4195C>T
ENST00000538635.5:n.421-25289C>T
NM_000552.3:c.4195C>T
NM_000552.4:c.4195C>T

Pathogenic

Met criteria codes 4

PP3 PS4_Very Strong PP4_Moderate PM2_Supporting

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 NM_000552.5(VWF):c.4195C>T (p.Arg1399Cys) missense variant has been reported in a proband displaying excessive mucocutaneous bleeding as well as laboratory phenotypes of low VWF:RCo/VWF:Ag ratio (0.67), abnormal collagen binding assay, and normal high molecular weight multimer pattern, which together are highly specific for VWD type 2M (PP4_moderate, PMID: 28083987). Although the patient's multimer pattern did not lack high-molecular weight forms, it was visibly smeared, similar to those associated with the

p.Arg1315Cys and p.Arg1374Cys variants (PMID: 26988807). This variant has been reported in at least 10 additional probands meeting PP4 laboratory phenotype criteria for type 2M VWD (PS4_VS; PMID: 17000885, PMID: 26988807, PMID: 35452508, PMID: 34758185, Internal Laboratory Contributors). The computational predictor REVEL gives a score of 0.712, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). The Grpmax allele frequency in gnomAD v4.1 is 0.00005281 (8/74886 alleles) in the African/African American population, which is lower than the ClinGen VWD VCEP threshold of <0.0001 (PM2_Supporting). In summary, the variant meets the criteria to be classified as Pathogenic for von Willebrand disease Type 2M based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PS4_Very Strong, PP4_Moderate, PP3, and PM2_Supporting. (VCEP Rule specifications for von Willebrand disease type 2A, 2B and 2M v1.0.0)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.712, 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.
PS4_Very Strong	✔	This variant has been reported in at least 10 probands with phenotypes meeting the laboratory phenotype requirements of type 2M PP4 criteria, in addition to the proband used for the PP4_Moderate code (PS4_Very Strong; PMID: 17000885, PMID: 26988807, PMID: 35452508, PMID: 34758185, Internal lab contributors).
PP4_Moderate	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding (bleeding score of 7) as well as laboratory phenotypes that included a normal multimer pattern, low VWF:RCo/VWF:Ag ratio (0.67), and abnormal collagen binding assay, which together are highly specific for VWD type 2M. (PP4_moderate, PMID: 28083987). Please note that the multimer pattern did not lack high-molecular weight forms, but was visibly smeary, similar to the p.Arg1315Cys and p.Arg1374Cys variants (PMID: 26988807).
PM2_Supporting	✔	The Grpmax allele frequency in gnomAD v4.1 is 0.00005281 (8/74886 alleles) in the African/African American population, which is lower than the ClinGen VWD VCEP threshold (<0.0001), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	Another missense variant in the same codon, NM_000552.5(VWF):c.4196G>A (p.Arg1399His), has been reported. This variant has been classified as VUS by the ClinGen VWD VCEP and is not considered here to avoid circularity.

Curation History

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