Variant: NM_000552.5(VWF):c.4082T>C (p.Leu1361Ser)

Version: 1.0

CA228528

100323 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2M (MONDO:0015630)
Inheritance Mode: Autosomal dominant inheritance
UUID: 52bc28a8-fba4-4efe-8942-07926de29016
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HGVS expressions

NM_000552.5:c.4082T>C
NM_000552.5(VWF):c.4082T>C (p.Leu1361Ser)
NC_000012.12:g.6019336A>G
CM000674.2:g.6019336A>G
NC_000012.11:g.6128502A>G
CM000674.1:g.6128502A>G
NC_000012.10:g.5998763A>G
NG_009072.1:g.110335T>C
NG_009072.2:g.110335T>C
ENST00000261405.10:c.4082T>C
ENST00000261405.9:c.4082T>C
ENST00000538635.5:n.421-25402T>C
NM_000552.3:c.4082T>C
NM_000552.4:c.4082T>C

Likely Pathogenic

Met criteria codes 5

PP1 PP3 PM2_Supporting PP4_Moderate PS4_Moderate

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:c.4082T>C variant in VWF is a missense variant predicted to cause substitution of leucine by serine at amino acid 1361. At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of a normal multimer pattern, low VWF:RCo/VWF:Ag ratio and abnormal collagen binding assay, which together are highly specific for VWD type 2M. (PP4_moderate, PMID 16985174). Additionally, FVIII activity is consistent with VWF antigen. This variant has been reported in 2 additional

families meeting activity/antigen ratio <0.7 and normal multimers (PS4_Moderate; Versiti Lab personal communication). The variant has been reported to segregate with VWD type 2M through >2 affected meioses from 1 family (PP1; Versiti Lab personal communication). The Grpmax filtering allele frequency in gnomAD v4.1 is 0.00000068 (based on 3/1179846 alleles in the European non Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 for type 2M (PM2_Supporting). The computational predictor REVEL gives a score of 0.846, 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 likely pathogenic for von Willebrand disease 2M based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP4_Moderate, PS4_Moderate, PP1, PM2_Supporting, PP3 (ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0)

Met criteria codes

PP1	✔	The variant has been reported to segregate with VWD type 2M through >2 affected meioses from 1 family (PP1; Versiti Lab personal communication).
PP3	✔	The computational predictor REVEL gives a score of 0.846, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).
PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.00000068 (based on 3/1179846 alleles in the European non Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 for type 2M (PM2_Supporting).
PP4_Moderate	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of a normal multimer pattern, low VWF:RCo/VWF:Ag ratio and abnormal collagen binding assay, which together are highly specific for VWD type 2M. (PP4_moderate, PMID 16985174). Additionally, FVIII activity is consistent with VWF antigen.
PS4_Moderate	✔	This variant has been reported in 2 additional families meeting activity/antigen ratio <0.7 and normal multimers (PS4_Moderate; Versiti Lab personal communication).

Not Met criteria codes

PM5	✖	PMID: 22329792 reported c.4082T>G p.L1361W in a type 2M patient, it has not yet been evaluated by the VWD VCEP.

Curation History

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