

Variant: NM_000552.5(VWF):c.5347T>G (p.Ser1783Ala)

Version: 1.0

CA228715 [↗](#)

31012 (ClinVar) [↗](#)

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

Condition: von Willebrand disease type 2M ([MONDO:0015630](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: d91ee10f-1f19-432f-a68e-c32a9dff069f

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HGVS expressions

NM_000552.5(VWF):c.5347T>G (p.Ser1783Ala)

NM_000552.5:c.5347T>G

NC_000012.12:g.6016197A>C

CM000674.2:g.6016197A>C

NC_000012.11:g.6125363A>C

CM000674.1:g.6125363A>C

NC_000012.10:g.5995624A>C

NG_009072.1:g.113474T>G

NG_009072.2:g.113474T>G

ENST00000261405.10:c.5347T>G

ENST00000261405.9:c.5347T>G

ENST00000538635.5:n.421-22263T>G

NM_000552.3:c.5347T>G

NM_000552.4:c.5347T>G

Likely Pathogenic

Met criteria codes **3**

PS3

PP3

PP4_Moderate

Not Met criteria codes **2**

PS4

PM2

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.5347T>G variant in VWF is a missense variant predicted to cause substitution of Serine by Alanine at amino acid 1783 (p.Ser1783Ala). 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: 19687512). A hydrodynamic mouse model expressing the p.Ser1783Ala variant showed severely reduced type I

and type III collagen binding, indicating that this variant has a damaging effect on protein function (PMID: 25051961)(PS3). The computational predictor REVEL gives a score of 0.687, 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 autosomal dominant von Willebrand disease type 2M based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP4_Moderate, PS3 and PP3 (VCEP specifications version 1.0.0).

Met criteria codes

PS3			A hydrodynamic mouse model expressing the p.Ser1783Ala variant showed severely reduced type I and type III collagen binding, indicating that this variant has a damaging effect on protein function (PMID: 25051961)(PS3). Collagen binding assay performed with the c.5347T>G (p.Ser1783Ala) recombinant mutant and wt vWF expressed in HEK293 cells showed decreased binding indicating that this variant has a damaging effect on protein function (PMID: 19687512)(PS3_supporting).
PP3			The computational predictor REVEL gives a score of 0.687, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).
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: 19687512).

Not Met criteria codes

PS4			Although an additional VWD patient asserted was found who carried this variant, the patient had a VWF:RCo/VWF:Ag ratio greater than 0.7 as well as normal collagen binding.
PM2			The Grpmax filtering allele frequency in gnomAD v4.1 is 0.0005233 (based on 63/91072 alleles in the South Asian population). This intermediate allele frequency is lower than the ClinGen VWD VCEP threshold (>0.01) for BS1 but higher than the threshold of <0.0001 for type 2M for PM2_Supporting.

Curation History



 

 

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