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Variant: NM_000552.5(VWF):c.5235G>T (p.Trp1745Cys)

Version: 1.0

CA228706

100421 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2M (MONDO:0015630)
Inheritance Mode: Autosomal dominant inheritance
UUID: bf32ce38-6e86-4b38-a00c-1b86f6b15de8
Approved on: 2024/8/13
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HGVS expressions

NM_000552.5:c.5235G>T
NM_000552.5(VWF):c.5235G>T (p.Trp1745Cys)
NC_000012.12:g.6016592C>A
CM000674.2:g.6016592C>A
NC_000012.11:g.6125758C>A
CM000674.1:g.6125758C>A
NC_000012.10:g.5996019C>A
NG_009072.1:g.113079G>T
NG_009072.2:g.113079G>T
ENST00000261405.10:c.5235G>T
ENST00000261405.9:c.5235G>T
ENST00000538635.5:n.421-22658G>T
NM_000552.3:c.5235G>T
NM_000552.4:c.5235G>T

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PP4 PS3

Not Met criteria codes 2

PP1 PS4

Evidence Links 3

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

NM_000552.5(VWF):c.5235G>T is a missense variant in VWF predicted to cause substitution of tryptophan by cysteine at amino acid 1745 in the collagen-binding A3 domain. The Grpmax filtering allele frequency in gnomAD v4.1 is 0 (based on 1/1180040 alleles in European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 (PM2_Supporting). The computational predictor REVEL gives a score of 0.757, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function

(PP3). At least 1 patient with this variant was diagnosed with VWD Type 2M and displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of normal high-MW multimer pattern and abnormal collagen binding assay (Reduced VWF:CB / VWF:Ag ratio of 0.3 VWF to both type III and type I collagen), which together are specific for VWD type 2M. (PP4, PMID: 19687512). However, the patient's VWF:RCo was impaired in proportion to the decreased amount of VWF:Ag, so that VWF:RCo / VWF:Ag ratio was 0.9 (approximately normal). A hydrodynamic mouse model expressing p.Trp1745Cys showed decreased expression of the variant (VWF:Ag), but did not test other parameters relevant to the VWD Type 2M phenotype (Figure 4, PMID: 25051961). Collagen binding assay performed with the p.Trp1745Cys recombinant mutant and wild-type vWF expressed by HEK-293 cells showed decreased binding to both Type I and Type III collagens in an ELISA-based format, indicating that this variant has a damaging effect on protein function (PS3; PMID: 19687512, PMID: 20345715, PMID: 25051961). In summary, this variant meets the criteria to be classified as likely pathogenic for von Willebrand disease type 2M. ACMG/AMP criteria applied as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PS3, PP4, PM2_Supporting, PP3.

Met criteria codes

PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0 (based on 1/1180040 alleles in European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.757, 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.
PP4	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of normal high-MW multimer pattern and abnormal collagen binding assay (Reduced VWF:CB / VWF:Ag ratio of 0.3 VWF to both type III and type I collagen), which together are specific for VWD type 2M. (PP4, PMID: 19687512). The patient's VWF:RCo was impaired in proportion to the decreased amount of VWF:Ag, so that VWF:RCo / VWF:Ag ratio was 0.9 (approximately normal). Genotyping included all coding exons of VWF and would have been sufficient to rule out the presence of the p.Asp1472His variant.
PS3	✔	A hydrodynamic mouse model expressing p.Trp1745Cys showed decreased expression, but did not test other parameters relevant to the VWD Type 2M phenotype (Figure 4, PMID: 25051961). Collagen binding assay performed with the p.Trp1745Cys recombinant mutant and wild-type vWF expressed by HEK-293 cells showed decreased binding to both Type I and Type III collagens in an ELISA-based format, indicating that this variant has a damaging effect on protein function (PMID: 19687512, PMID: 20345715, PMID: 25051961; PS3). ELISA-based collagen binding assay performed with the p.Trp1745Cys recombinant mutant and wild-type vWF expressed by HEK-293 cells showed decreased binding to both Type I collagen (Figure 4A) and Type III collagen (Figure 4B), indicating that this variant has a damaging effect on protein function (PMID: 19687512). PubMed:19687512 The recombinant variant exhibits barely detectable binding to type I and type III collagen, at <5% of wild-type (Figure 1B). PubMed:20345715 A flow chamber system measuring the ability of immobilized recombinant mouse VWF proteins to mediate platelet adhesion to collagen under physiological high shear detected decreased platelet adhesion to collagen I and collagen III surfaces mediated by the variant (Figure 3). Mice hydrodynamically injected with VWF expression plasmids showed decreased VWF:Ag levels associated with the variant (Figure 4). PubMed:25051961

Not Met criteria codes

PP1	✖	The variant has been reported to segregate with VWD type 2M through 1 affected meiosis from 1 family, which is not sufficient to meet this criterion (PMID: 19687512).

PS4		✖	At least 1 reported patient with this variant has a phenotype specific for VWD type 2M, which is not a sufficient proband number to meet this criterion (PMID: 19687512).

Curation History

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