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Variant: NM_000552.5(VWF):c.3445T>C (p.Cys1149Arg)

Version: 1.0

CA228410

309 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2A (MONDO:0015628)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6195b75d-26f1-412c-bb98-bfca1d29e273
Approved on: 2024/7/9
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HGVS expressions

NM_000552.5(VWF):c.3445T>C (p.Cys1149Arg)
NM_000552.5:c.3445T>C
NC_000012.12:g.6022833A>G
CM000674.2:g.6022833A>G
NC_000012.11:g.6131999A>G
CM000674.1:g.6131999A>G
NC_000012.10:g.6002260A>G
NG_009072.1:g.106838T>C
NG_009072.2:g.106838T>C
ENST00000261405.10:c.3445T>C
ENST00000261405.9:c.3445T>C
ENST00000538635.5:n.421-28899T>C
NM_000552.3:c.3445T>C
NM_000552.4:c.3445T>C

Pathogenic

Met criteria codes 6

PM2_Supporting PP3 PP4_Moderate PS3 PS4 PP1_Moderate

Not Met criteria codes 3

BA1 PM5 BS1

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.3445T>C variant in VWF is a missense variant predicted to cause substitution of cysteine by arginine at amino acid 1149 in the D3 (multimerization) domain. This variant has been reported in at least 8 apparently unrelated families exhibiting a VWD Type 2A phenotype (PMID: 19286880, PMID: 8839833, PMID: 28971901, PS4). At least 7 patients with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of very low VWF activity measured by VWF:RCo, activity/VWF:Ag ratio <0.7, and

loss of high molecular weight multimers, which together are highly specific for VWD type 2A (PP4_moderate, PMID: 19286880, PMID: 28971901). The variant has been reported to segregate with VWD type 2A through at least 2 affected meioses from 3 different families (PP1_Moderate; PMID: 8839833, PMID: 19286880, PMID: 28971901). The Grpmax filtering allele frequency in gnomAD v4.1 is 0 (based on 1/316464 alleles in the 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 0.971, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). Multimerization assays performed with the p.Cys1149Arg recombinant mutant and wild-type vWF expressed by 293T cells showed an overall decrease in secreted multimers, with particular loss of high-molecular weight multimers), indicating that this variant has a damaging effect on protein function (PMID: 839833 Fig. 3, PMID: 14995987)(PS3). Additional functional characterization studies have found that the variant protein exhibits characteristics of a quantitative VWF defect as well, as it is retained in the endoplasmic reticulum, exerts a partially dominant negative effect on VWF secretion, and is more rapidly cleared from circulation (PMID: 11698279, PMID: 8839833, PMID: 21596755, PMID: 16194200). In summary, this variant meets the criteria to be classified as Pathogenic for von Willebrand disease type 2A. ACMG/AMP criteria applied as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PS4, PP4_Moderate, PP1_Moderate, PS3, PP3, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0 (based on 1/316464 alleles in the 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 0.971, 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 0.03 for splice acceptor gain, indicating that the variant likely has no impact on splicing.
PP4_Moderate	✔	At least 7 patients with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of very low VWF activity measured by VWF:RCo, activity/VWF:Ag ratio <0.7, and loss of high molecular weight multimers, which together are highly specific for VWD type 2A. Low collagen binding and reduced RIPA assay were also observed (PP4_moderate, PMID: 19286880, PMID: 28971901).
PS3	✔	Multimerization assays performed with the p.Cys1149Arg recombinant mutant and wild-type vWF expressed by 293T cells showed abnormal secreted multimers (decreased overall, with particular loss of high-molecular weight multimers), indicating that this variant has a damaging effect on protein function (PMID: 8839833 Fig. 3, PMID: 14995987)(PS3). Secretion assays in 293 cells or BHK cells showed a defect in secretion of the p.Cys1149Arg variant (PMID: 11698279) that has partially dominant negative consequences on wild-type VWF secretion (PMID: 8839833). Immunofluorescent staining further indicates that when expressed in HEK293 cells, the p.Cys1149Arg variant fails to localize to pseudo-Weibel–Palade bodies and instead exhibits mislocalized retention in the ER (PMID: 21596755). A mouse model also exhibited faster clearance of the recombinant variant from circulation (PMID: 16194200). However, these latter assays are more consistent with a quantitative defect in VWF characteristic of VWD Type 1, and so do not meet the requirements for use by the ClinGen VWD VCEP.
PS4	✔	This variant has also been reported in at least 8 families meeting PP4_Moderate (PMID: 19286880, PMID: 28971901) and an additional family meeting PP4 (PMID: 8839833) (PS4). Despite the finding that the prevalence of the variant in individuals affected with VWD is significantly increased compared with the prevalence in controls (Odds ratio 14.7, 95% confidence interval 4.546-47.98, PMID: 29423401), scoring of this study was avoided due to uncertainty about relatedness of the affected group members.
PP1_Moderate	✔	The variant has been reported to segregate with VWD type 2A through at least 2 affected meioses from 2 different families (PP1_Moderate; PMID: 8839833, PMID: 19286880).

Not Met criteria codes

BA1	✖	This variant is absent from gnomAD v2.1.1.
PM5	✖	Another missense variant in the same codon has been reported in a patient with VWD Type 2A, c.3446G>A (p.Cys1149Tyr), (PMID: 19404524, CAID: CA383511350). However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen VWD VCEP, and this code has not been evaluated to avoid circularity.
BS1	✖	This variant is absent from gnomAD v2.1.1.

Curation History

Showing 1 to 1 of 1 rows

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