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Variant: NM_000552.5(VWF):c.8317T>C (p.Cys2773Arg)

Version: 1.1

CA114158

306 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2A (MONDO:0015628)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5cc42018-eb70-41e2-bd19-e80a84e236a0
Approved on: 2024/8/13
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HGVS expressions

NM_000552.5(VWF):c.8317T>C (p.Cys2773Arg)
NM_000552.5:c.8317T>C
NC_000012.12:g.5949140A>G
CM000674.2:g.5949140A>G
NC_000012.11:g.6058306A>G
CM000674.1:g.6058306A>G
NC_000012.10:g.5928567A>G
NG_009072.1:g.180531T>C
NG_009072.2:g.180531T>C
ENST00000261405.10:c.8317T>C
ENST00000261405.9:c.8317T>C
NM_000552.3:c.8317T>C
NM_000552.4:c.8317T>C

Pathogenic

Met criteria codes 7

PM2_Supporting PP3 PM5 PS4_Supporting PP4_Moderate PS2_Supporting PS3

Evidence Links 7

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.8317T>C (p.Cys2773Arg) missense variant is absent from gnomADv4.1 (PM2_Supporting) and the computational predictor REVEL gives a score of 0.903, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). Multimerization assay performed with the Cys2773Arg recombinant mutant and wt vWF expressed by COS7 cells showed abnormal multimers, including loss of HMWM and an extra central band, indicating that this variant has a damaging effect on protein function. Additionally, collagen binding was disrupted (PMID: 11264172; PS3). Similar results were also reported in PMID:24598842. At

least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of very low VWF activity measured by VWF:CBA (0.07 units/ml) and with VWF:Ag at 1.19, a low activity/VWF:Ag ratio, and multimeric structure typical for type IID which includes loss of HMWM. this combination is highly specific for VWD type 2A. (PP4_moderate; PMID: 8622978 patient 1). Additional consistent phenotypes were also reported in the patient including a normal FVIII activity consistent with VWF antigen. This was a de novo occurrence (PS2_supporting). This variant has been reported in 1 additional proband meeting PP4 criteria (PS4_supporting; PMID: 8622978 patient 2). Another missense variant in the same codon has been reported in a patient with VWD Type 2A NM_000552.5(VWF):c.8318G>C (p.Cys2773Ser) and has been classified as pathogenic by the ClinGen VWD VCEP (PM5). 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: PP4_Moderate, PS2_Supporting, PS4_Supporting, PS3, PP3, PM2_Supporting, PM5_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomADv4.1 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.903, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3).
PM5	✔	Another missense variant in the same codon has been reported in a patient with VWD Type 2A NM_000552.5(VWF):c.8318G>C (p.Cys2773Ser) and has been classified as pathogenic by the ClinGen VWD VCEP (PM5).
PS4_Supporting	✔	This variant has been reported in 1 additional proband meeting PP4 criteria (PS4_supporting; PMID: 8622978 patient 2).
PP4_Moderate	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of very low VWF activity measured by VWF:CBA (0.07 units/ml) and with VWF:Ag at 1.19, a low activity/VWF:Ag ratio, and multimeric structure typical for type IID which includes loss of HMWM. this combination is highly specific for VWD type 2A. (PP4; PMID: 8622978 patient 1). Additional consistent phenotypes were also reported in the patient including a normal FVIII activity consistent with VWF antigen.
PS2_Supporting	✔	This variant has been identified as a de novo occurrence in 1 individual with VWD (PM6_supporting; PMID: 8622978 patient 1).
PS3	✔	Multimerization assay performed with the Cys2773Arg recombinant mutant and wt vWF expressed by COS7 cells showed abnormal multimers, including loss of HMWM and an extra central band, indicating that this variant has a damaging effect on protein function. Additionally, collagen binding was disrupted. (PMID: 11264172 Fig. 5; PS3) Similar results were also reported in PMID:24598842. The variant was evaluated by expression of the vWF carboxyl-terminal domain containing residues 1366-2050. Insect cells infected with recombinant baculovirus expressing normal vWF sequence secreted a disulfide linked dimeric molecule with an apparent molecular mass of 150 kDa before reduction, yielding a single band of 80 kDa after disulfide bond reduction. In contrast, cells expressing the mutant fragment secreted a monomeric molecule of apparent molecular mass of 80 kDa, which remained unchanged after reduction, indicating it is essential for normal dimerization of vWF subunits through disulfide bonding of carboxyl-terminal domains. This is not one of the assays the VWD VCEP considers for type 2A. PubMed:8622978 Transient recombinant expression of the mutant in the vWF cDNA was carried out in COS-7 cells. Recombinant WT vWF fragment II assembled correctly into a dimer, whereas recombinant mutant fragments were monomeric. Homozygous expression of recombinant mutant full-length vWF resulted in additional dimers, probably through

disulfide bonding at the amino-terminal multimerization site, whereas recombinant WT vWF correctly assembled into multimers. Coexpression of recombinant mutant and recombinant WT vWF reproduced the multimer patterns observed in heterozygous individuals, including loss of HMWM and an extra central band. Additionally, VWF:CBA was below the limit of detection for the recombinant mutant. PubMed:11264172

A double variant mouse model VWF-DEL/C2773R was reported here, however the single variant C2773R was not reported so was not considered for PS3. PubMed:33047469

mutant VWF, transiently expressed in HEK293 cells showed residual formation of small multimers with up to five bands and normal ER localization. PubMed:24598842

Found similar defects in dimerization using atomic force microscopy. PubMed:30645640

Fibronectin binding to recombinant VWF found p.2773R did not bind. This is not an assay considered by the VWD VCEP for PS3. PubMed:34136746

Myosin binding to recombinant VWF found p.2773R, did not bind to myosin. This is not an assay considered by the VWD VCEP for PS3. PubMed:31935285

Curation History

Showing 1 to 2 of 2 rows

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