Variant: NM_000552.5(VWF):c.4130C>T (p.Ala1377Val)

Version: 1.0

CA6402597

619750 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: hereditary von Willebrand disease (MONDO:0019565)
Inheritance Mode: Autosomal dominant inheritance
UUID: 7b5db5e9-0875-4a2d-876d-618ab52f4c15
Approved on: 2024-08-12
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HGVS expressions

NM_000552.5:c.4130C>T
NM_000552.5(VWF):c.4130C>T (p.Ala1377Val)
NC_000012.12:g.6019288G>A
CM000674.2:g.6019288G>A
NC_000012.11:g.6128454G>A
CM000674.1:g.6128454G>A
NC_000012.10:g.5998715G>A
NG_009072.1:g.110383C>T
NG_009072.2:g.110383C>T
ENST00000261405.10:c.4130C>T
ENST00000261405.9:c.4130C>T
ENST00000538635.5:n.421-25354C>T
NM_000552.3:c.4130C>T
NM_000552.4:c.4130C>T

Uncertain Significance

Met criteria codes 3

PP4_Moderate **PP1** **PP3**

Not Met criteria codes 6

PS3 **PS4** **PM2** **BP5** **BP2** **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

NM_000552.5(VWF):c.4130C>T is a missense variant in VWF that replaces alanine with valine at position 1377. At least 1 patient with this variant, in combination with p.Arg1379Cys (ClinVar 100333; Pathogenic VWD type 1) in cis, displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of a normal multimer pattern, low VWF:RCo/VWF:Ag ratio (0.6 to 0.7), and decreased GP1b binding assay which together are highly specific for VWD type 2M (PP4_moderate, PMID: 27785872). The p.Ala1377Val and p.Arg1379Cys variants have

been reported in cis in 3 additional probands with high mucocutaneous bleeding as well as laboratory phenotypes of a normal multimer pattern, low VWF:RCo/VWF:Ag ratio (0.6 to 0.7), and decreased GP1b binding assay, but the four patients from Milan show the same short tandem repeats nearby, indicating the possibility of a common ancestor. The proband of Family VIII (PMID: 35452508) has 3 additional type 2M diagnosed individuals, 2 are counted here with VWF Act/ VWF:Ag ratio <=0.42 (the other is 0.75). Each individual is heterozygous for p.A1377V; p.R1379C (PP1). The Grpmax filtering allele frequency of this variant in gnomAD v4.1 is 0.001967 (based on 170/75034 alleles in the African / African-American population), which is lower than the ClinGen VWD VCEP threshold for BS1 (>0.01) and higher than the threshold for PM2_Supporting (<0.0001). GP1b-alpha binding assay performed with recombinant VWF expressed by HEK-293 cells showed severely decreased binding when p.Ala1377Val was combined with the p.Arg1379Cys variant, indicating that the combination of these two variants has a damaging effect on protein function. PS3_Supporting was not met because the individual p.Ala1377Val and p.Arg1379Arg mutants showed approximately wild-type binding to GpIb-alpha (PMID: 27785872). The computational predictor REVEL gives a score of 0.805, 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 a variant of unknown significance for hereditary von Willebrand disease based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP4_Moderate, PP3, PP1. (Rule specifications for von Willebrand disease type 2A, 2B and 2M v1.0.0; date of approval 08/12/2024)

Met criteria codes

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 (0.6 to 0.7), and decreased GP1b binding assay which together are highly specific for VWD type 2M (PP4_moderate, PMID: 27785872).
PP1	✓	Family VIII (PMID: 35452508) has 4 type 2M diagnosed individuals, 3 are counted here with VWF Act/ VWF:Ag ratio <=0.42 (the fourth is 0.75). Each individual is heterozygous for p.A1377V; p.R1379C.
PP3	✓	The computational predictor REVEL gives a score of 0.805, 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.

Not Met criteria codes

PS3	✗	GP1b-alpha binding assay performed with the p.Ala1377Val and p.Arg1379Cys recombinant mutant expressed by HEK-293 cells showed severely decreased binding relative to the wild-type and the individual mutants, indicating that the combination of these two variants has a damaging effect on protein function. PS3_Supporting was not met because the individual p.Ala1377Val mutant showed approximately wild-type binding to GpIb-alpha (PMID: 27785872).
PS4	✗	This variant has been reported in 4 probands with high mucocutaneous bleeding as well as laboratory phenotypes of a normal multimer pattern, low VWF:RCo/VWF:Ag ratio (0.6 to 0.7), and decreased GP1b binding assay. The four patients are reportedly unrelated, yet show the same short tandem repeats nearby, indicating the possibility of a common ancestor (PMID: 27785872 and PMID: 35452508).
PM2	✗	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.001967 (based on 170/75034 alleles in the African / African-American population), which is higher than the ClinGen VWD VCEP threshold for PM2_Supporting (<0.0001 for type 2A/B/M), failing to meet this criterion.
BP5	✗	The additional substitution p.Arg1379Cys (ClinVar 100333; Pathogenic VWD type 1) is found in cis with this variant in all four patients. However, the patients present with a 2M subtype so Arg1379Cys does not fully explain their

phenotype.

BP2		✖	The additional substitution p.Arg1379Cys (ClinVar 100333; Pathogenic VWD type 1) in found in cis with this variant in all four patients. This criteria is not considered by the VWD VCEP.
BS1	ℹ	✖	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.001967 (based on 170/75034 alleles in the African / African-American population), which is lower than the ClinGen VWD VCEP threshold (>0.01) for BS1, failing to meet this criterion.

Curation History

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