The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000552.4(VWF):c.3437A>G (p.Tyr1146Cys)

Version: 1.2

CA228408

31009 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2A (MONDO:0015628)
Inheritance Mode: Autosomal dominant inheritance
UUID: a771d414-f2f6-4f3d-b08a-bb4f6c8303ef
Approved on: 2024/8/13
Published on: 2024/8/19

HGVS expressions

NM_000552.4:c.3437A>G
NM_000552.4(VWF):c.3437A>G (p.Tyr1146Cys)
NC_000012.12:g.6022841T>C
CM000674.2:g.6022841T>C
NC_000012.11:g.6132007T>C
CM000674.1:g.6132007T>C
NC_000012.10:g.6002268T>C
NG_009072.1:g.106830A>G
NG_009072.2:g.106830A>G
ENST00000261405.10:c.3437A>G
ENST00000261405.9:c.3437A>G
ENST00000538635.5:n.421-28907A>G
NM_000552.3:c.3437A>G
NM_000552.5:c.3437A>G

Pathogenic

Met criteria codes 5

PS4_Very Strong | PM2_Supporting | PS3 | PP3 | PP4

Not Met criteria codes 1

PP1

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_000552.4(VWF):c.3437A>G (p.Tyr1146Cys) missense variant has been reported in at least 22 VWD type 2A patients. The Grpmax filtering allele frequency in gnomAD v4.1 is 0 (based on 1/37812 alleles in the African/African-American population), which is lower than the ClinGen VWD VCEP threshold of<0.0001 (PM2_Supporting). The computational predictor REVEL gives a score of 0.872, 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

displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of low VWF activity (VWF:RCo 16, VWF:CB 7) and VWF:Ag of 20 for a low VWF:CB activity/VWF:Ag ratio of 0.35, which is specific for VWD type 2A. (PP4; PMID: 24598842). Eight additional VWD 2A patients, with confirmatory lab values including very low VWF:RCo, low VWF:GPIb, and or low VWF activity/ VWF:Ag ratio, have been reported (PMIDs: 22871923, 16985174, 35452508, 20351307; PS4_VeryStrong). Multimer analysis in 293 cells expressing recombinant variant VWF showed reduced high molecular weight multimers indicating that this variant has a damaging effect on protein function (PMID: 20351307 Figure 3, PMID: 27533707 Figure 2; PS3). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant VWD type 2A based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PS4_VeryStrong, PS3, PM2_supporting, PP3, PP4.

Met criteria codes

PS4_Very Strong	✔	At least 22 patients, heterozygous for the variant, have been reported with type 2A. Eight are included here with confirmatory lab values including very low VWF:RCo, low VWF:GPIb, and or low VWF activity/ VWF:Ag ratio (PMIDs: 22871923, 16985174, 35452508, 20351307; PS4_VeryStrong).
PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0 (based on 1/37812 alleles in the African/African-American population), which is lower than the ClinGen VWD VCEP threshold of<0.0001 (PM2_Supporting).
PS3	✔	Multimer analysis in 293 cells expressing recombinant variant VWF showed reduced high molecular weight multimers indicating that this variant has a damaging effect on protein function (PMID: 20351307 Figure 3, PMID: 27533707 Figure 2; PS3).
PP3	✔	The computational predictor REVEL gives a score of 0.872, 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 0.01 for splice acceptor gain, indicating that the variant likely has no impact on splicing.
PP4	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotypes of low VWF activity (VWF:RCo 16, VWF:CB 7) and VWF:Ag of 20 for a low VWF:CB activity/VWF:Ag ratio of 0.35, which is specific for VWD type 2A. (PP4; PMID: 24598842).

Not Met criteria codes

PP1	✖	The variant has been reported to segregate with VWD type 2A through just 1 affected meiosis from family 16 (PP1_NotMet; PMID: 30722078).

Curation History

Showing 1 to 3 of 3 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.