

Variant: NM_000552.5(VWF):c.3971G>C (p.Gly1324Ala)

Version: 1.0

CA228508 [↗](#)

100313 (ClinVar) [↗](#)

Gene: VWF ([HGNC:7450](#))

Condition: von Willebrand disease type 2M ([MONDO:0015630](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 57dada4b-031c-4efd-b870-6f4f6fa2a1b3

Approved on: 2024/8/13

Published on: 2024/8/13

HGVS expressions

NM_000552.5(VWF):c.3971G>C (p.Gly1324Ala)

NM_000552.5:c.3971G>C

NC_000012.12:g.6019447C>G

CM000674.2:g.6019447C>G

NC_000012.11:g.6128613C>G

CM000674.1:g.6128613C>G

NC_000012.10:g.5998874C>G

NG_009072.1:g.110224G>C

NG_009072.2:g.110224G>C

ENST00000261405.10:c.3971G>C

ENST00000261405.9:c.3971G>C

ENST00000538635.5:n.421-25513G>C

NM_000552.3:c.3971G>C

NM_000552.4:c.3971G>C

Pathogenic

Met criteria codes 6

PM5

PS3

PP1

PP3

PM2_Supporting

PS4_Supporting

Not Met criteria codes 1

PP4

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.3971G>C (p.Gly1324Ala) missense variant has been reported in at least one type 2M patient with VWF:RCo/VWF:Ag ratio of 0.44 (PMID: 12008946; PS4_supporting). The variant segregated with VWD type 2M through 3 affected meioses from this family (PP1; PMID:12008946). Another missense variant in the same codon has been reported in a patient with VWD type 2 Gly1324Ser, which has been classified likely pathogenic by the ClinGen VWD VCEP (PM5). The computational predictor REVEL gives a score

of 0.719, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). Platelet/GP1b binding assays performed with the Gly1324Ala recombinant mutant vWF expressed by COS-7 showed no binding indicating that this variant has a damaging effect on protein function (PMIDs: 12008946, 10845912; PS3). This variant is absent from gnomAD v4.1 (PM2_Supporting). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal dominant VWD type 2M based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PS3, PM2_supporting, PM5, PP1, PP3, PS4_supporting.

Met criteria codes

PM5			Another missense variant in the same codon has been reported in a patient with VWD type 2 Gly1324Ser, which has been classified pathogenic by the ClinGen VWD VCEP (PM5).
PS3			Platelet/GP1b binding assays performed with the Gly1324Ala recombinant mutant vWF expressed by COS-7 showed no binding indicating that this variant has a damaging effect on protein function (PMIDs: 12008946, 10845912; PS3).
PP1			The variant has been reported to segregate with VWD type 2M through 3 affected meioses from 1 family (PP1; PMID:12008946).
PP3			The computational predictor REVEL gives a score of 0.719, 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.
PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).
PS4_Supporting			At least one type 2M patient has been reported with VWF:RCo/VWF:Ag ratio of 0.44 (PMID: 12008946; PS4_supporting).

Not Met criteria codes

PP4			At least one patient has been reported with this variant with VWF:RCo 25 IU/dl, VWF:Ag 57 IU/dl (ratio 0.44), normal multimers, normal RIPA, and normal platelet count, however they do not exhibit bleeding symptoms (PP4_NotMet).
-----	---	---	---

Curation History





Showing 1 to 1 of 1 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.

[ClinGen Terms of Use.](#)

[✕ Powered by BCM's Genboree.](#)