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# *Variant: NM_000552.4(VWF):c.3970G>A (p.Gly1324Ser)*

Version: 1.0

*CA114147*

*300 (ClinVar)*

**Gene**: VWF (HGNC:7450)
**Condition**: von Willebrand disease type 2M (MONDO:0015630)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** 8c83fcdc-3afc-44f1-a269-c2f1e73f9298
**Approved on**: 2024/8/13
**Published on**: 2024/8/13

## *HGVS expressions*

**NM_000552.4(VWF):c.3970G>A (p.Gly1324Ser)**
**NM_000552.4:c.3970G>A**
NC_000012.12:g.6019448C>T
CM000674.2:g.6019448C>T
NC_000012.11:g.6128614C>T
CM000674.1:g.6128614C>T
NC_000012.10:g.5998875C>T
NG_009072.1:g.110223G>A
NG_009072.2:g.110223G>A
ENST00000261405.10:c.3970G>A
ENST00000261405.9:c.3970G>A
ENST00000538635.5:n.421-25514G>A
NM_000552.3:c.3970G>A
NM_000552.5:c.3970G>A

**Pathogenic**

**Met criteria codes** 6

PP4_Moderate | PM2_Supporting | PS3 | PS4_Moderate | PP1 | PP3

**Not Met criteria codes** 1

PM5

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.3970G>A (p.Gly1324Ser) variant is a missense variant predicted to cause substitution of Glycine by Serine at amino acid 1324. 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, and a decreased GP1b binding assay, which together are highly specific for VWD type 2M (PP4_moderate, PMID: 30084138). The variant has been reported to segregate with VWD type 2M through 2 affected meioses from 1**

**family (PP1; PMID: 29341351). At least 3 additional VWD type 2M probands have been reported with this variant (PMIDs: 29341351, 22102201, 1409710; PS4_moderate). The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000003650 (based on 2/91074 alleles in the South Asian population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 (PM2_Supporting). The computational predictor REVEL gives a score of 0.718, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). A platelet binding assay in COS-7 cells expressing recombinant VWF showed decreased binding indicating that this variant has a damaging effect on protein function. In a direct binding assay, the ristocetin-induced binding of rvWF(G1324S) to platelets was markedly reduced compared with rvWF(wt). (PMID: 1409710) (PS3). 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, PP1, PP3, PP4_moderate, PS4_moderate. (VCEP specifications version Pilot; date of approval).**

**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, and a decreased GP1b binding assay, which together are highly specific for VWD type 2M (PP4_moderate PMID: 30084138). Additional consistent phenotypes were also reported in the patient including FVIII activity consistent with VWF antigen level. |
| **PM2_Supporting** | ✔ | The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000003650 (based on 2/91074 alleles in the South Asian population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 (PM2_Supporting). |
| **PS3** | ✔ | A platelet binding assay in COS-7 cells expressing recombinant VWF showed decreased binding indicating that this variant has a damaging effect on protein function. In a direct binding assay, the ristocetin-induced binding of rvWF(G1324S) to platelets was markedly reduced compared with rvWF(wt). (PMID: 1409710) (PS3). |
| **PS4_Moderate** | ✔ | At least 3 additional VWD type 2M probands have been reported with this variant (PMIDs: 29341351, 22102201, 1409710; PS4_moderate) |
| **PP1** | ✔ | The variant has been reported to segregate with VWD type 2M through 2 affected meioses from 1 family (PP1; PMID: 29341351). |
| **PP3** | ✔ | The computational predictor REVEL gives a score of 0.718, 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**

| | | |
|---|---|---|
| **PM5** | ✖ | Another missense variant in the same codon has been reported in a patient with VWD type 2 [c.3971G>C, p.Gly1324Ala] (PMID: 9198195). However, this is not considered here to avoid circularity (PM5 not met). |

Curation History

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