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Variant: NM_000552.5(VWF):c.2546G>A (p.Cys849Tyr)

Version: 1.0

CA383520272

1684006 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2A (MONDO:0015628)
Inheritance Mode: Autosomal dominant inheritance
UUID: a6da2b92-5e98-4a14-981c-3a5872a0a75b
Approved on: 2024/8/13
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HGVS expressions

NM_000552.5(VWF):c.2546G>A (p.Cys849Tyr)
NM_000552.5:c.2546G>A
NC_000012.12:g.6036388C>T
CM000674.2:g.6036388C>T
NC_000012.11:g.6145554C>T
CM000674.1:g.6145554C>T
NC_000012.10:g.6015815C>T
NG_009072.1:g.93283G>A
NG_009072.2:g.93283G>A
ENST00000261405.10:c.2546G>A
ENST00000261405.9:c.2546G>A
ENST00000538635.5:n.421-42454G>A
NM_000552.3:c.2546G>A
NM_000552.4:c.2546G>A

Likely Pathogenic

Met criteria codes 4

PS3 PP3 PP4 PM2_Supporting

Not Met criteria codes 1

BP5

Evidence Links 1

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:c.2546G>A variant encodes a missense substitution of cysteine by tyrosine at codon 849 in VWF. The variant has been reported in at least 1 patient displaying excessive mucocutaneous bleeding as well as laboratory phenotypes of low activity/VWF:Ag ratio and loss of high molecular weight multimers, which together are specific for VWD type 2A. (PP4, PMID: 19422453, PMID: 35452508). The patient had three heterozygous missense mutations (R202W, C849Y, and R1583Q) in the VWF gene. R1583Q is classified Likely Benign by

the VWD VCEP and R202W (ClinVar 619940 VUS) is also considered a VUS at this time. The variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.579, which is below the ClinGen VWD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on VWF function. However, the splicing predictor SpliceAI gives a delta score of 0.72 for donor loss (PP3), which has been functionally confirmed to result in an aberrant splicing product in an affected individual (Figure 3, PMID: 19422453). Multimerization assay performed with the p.Cys849Tyr recombinant mutant and a wild-type control vWF expressed by COS-7 cells showed absence of higher-MW multimers, indicating that this variant has a damaging effect on protein function consistent with the multimerization defect observed in the proband (PS3, PMID: 19422453). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant VWD type 2A based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PS3, PM2_supporting, PP3, PP4.

Met criteria codes

PS3	✔	Multimerization assay performed with the NM_000552.5(VWF):c.2546G>A (p.Cys849Tyr) recombinant mutant and controls including wild-type vWF expressed by COS-7 cells showed absent higher-MW multimers, indicating that this variant has a damaging effect on protein function consistent with the multimerization defect observed in the proband (PS3, PMID: 19422453). The recombinant mutant protein also showed severely defective binding to Factor VIII (Figure 7). Multimerization assay performed with the NM_000552.5(VWF):c.2546G>A (p.Cys849Tyr) recombinant mutant and controls including wild-type vWF expressed by COS-7 cells showed absent higher-MW multimers, indicating that this variant has a damaging effect on protein function consistent with the multimerization defect observed in the proband (PS3_Supporting, PMID: 19422453, Figure 5). One of the other variants in trans (p.Arg202Trp) also showed a severe multimerization defect, raising the possibility of a combined effect. The recombinant mutant protein also showed severely defective binding to Factor VIII (Figure 7). PubMed:19422453
PP3	✔	The computational predictor REVEL gives a score of 0.579, which is below the ClinGen VWD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on VWF function. However, the splicing predictor SpliceAI gives a delta score of 0.72 for donor loss (PP3), which has been functionally confirmed to result in an aberrant splicing product in an affected individual (Figure 3, PMID: 19422453).
PP4	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of VWF:RCo/VWF:Ag ratio (0.51), and loss of high molecular weight multimers, which together are highly specific for VWD type 2A. (PP4, PMID: 19422453, PMID: 35452508). Additional consistent phenotypes were also reported in the patient including low VWF activity indicated by mildly impaired binding of factor VIII to VWF and impaired von Willebrand factor collagen binding activity (59 IU/dL), normal platelet count, FVIII activity consistent with VWF antigen, and an impaired RIPA assay.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

BP5	✖	The patient had three heterozygous missense mutations (R202W, C849Y, and R1583Q) in the VWF gene. R1583Q is classified Likely Benign by the VWD VCEP. R202W (ClinVar 619940 VUS) is not yet evaluated and classification of the variant would not affect the likely pathogenic classification of Cys849Tyr at this time.

Curation History

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