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Variant: NM_000552.5:c.5140G>C

Version: 1.0

CA383496428

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2M (MONDO:0015630)
Inheritance Mode: Autosomal dominant inheritance
UUID: 97caccf9-3bae-4a6e-945c-be9298008b62
Approved on: 2024-08-13
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HGVS expressions

NM_000552.5:c.5140G>C
NC_000012.12:g.6016784C>G
CM000674.2:g.6016784C>G
NC_000012.11:g.6125950C>G
CM000674.1:g.6125950C>G
NC_000012.10:g.5996211C>G
NG_009072.1:g.112887G>C
NG_009072.2:g.112887G>C
ENST00000261405.10:c.5140G>C
ENST00000261405.9:c.5140G>C
ENST00000538635.5:n.421-22850G>C
NM_000552.3:c.5140G>C
NM_000552.4:c.5140G>C

Uncertain Significance

Met criteria codes 3

PP4_Moderate PP3 PM2_Supporting

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_000552.5(VWF):c.5140G>C (p.Ala1714Pro) missense variant has been reported in one patient (P9; PMID: 28083987), with excessive mucocutaneous bleeding (bleeding score = 7) as well as laboratory phenotypes of a normal multimer pattern, low VWF:RCo/VWF:Ag ratio of 0.69, and abnormal collagen binding assay (VWF:CIIIB: 11.3% and VWF:CIIIB/VWF:Ag ratio 0.31), which together are highly specific for VWD type 2M. (PP4_moderate). This variant is absent from gnomAD v4.1 (PM2_supporting). The computational predictor REVEL gives a score of 0.662, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF

function (PP3). In summary, the variant meets the criteria to be classified as Uncertain Significance for von Willebrand disease type 2M based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP3, PP4_moderate, and PM2_supporting.

Met criteria codes

PP4_Moderate	✔	One patient (P9; PMID: 28083987) with this variant has excessive mucocutaneous bleeding (bleeding score = 7) as well as laboratory phenotypes of a normal multimer pattern, low VWF:RCo/VWF:Ag ratio of 0.69, and abnormal collagen binding assay (VWF:CIIIB: 11.3% and VWF:CIIIB/VWF:Ag ratio 0.31), which together are highly specific for VWD type 2M. (PP4_moderate).
PP3	✔	The computational predictor REVEL gives a score of 0.662, 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 donor loss, indicating that the variant likely has no impact on splicing.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

PP1	✖	As reported in the PhD thesis of T Fidalgo (https://www.proquest.com/docview/2076363788?pq-origsite=gscholar&fromopenview=true), the daughter of P9 (P48) is also affected with VWD, however P48 is compound heterozygous for Ala1714Pro and a potential splice variant c.5170+10C>T leading to a severe type 1 VWD (VWF:AG 13%, VWF:RCo 10%, ratio 1.13, VWF:CB 12%). Additionally, a single segregation within the family is insufficient to consider PP1.

Curation History

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