Variant: NM_000552.5(VWF):c.3788C>T (p.Ser1263Leu)

Version: 1.0

CA6402670

1703401 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: hereditary von Willebrand disease (MONDO:0019565)
Inheritance Mode: Autosomal dominant inheritance
UUID: 79ef832a-3ca0-4760-a3fd-221316a3f0f7
Approved on: 2024-08-12
Published on: 2024-08-12

HGVS expressions

NM_000552.5:c.3788C>T
NM_000552.5(VWF):c.3788C>T (p.Ser1263Leu)
NC_000012.12:g.6019630G>A
CM000674.2:g.6019630G>A
NC_000012.11:g.6128796G>A
CM000674.1:g.6128796G>A
NC_000012.10:g.5999057G>A
NG_009072.1:g.110041C>T
NG_009072.2:g.110041C>T
ENST00000261405.10:c.3788C>T
ENST00000261405.9:c.3788C>T
ENST00000538635.5:n.421-25696C>T
ENST00000539641.1:n.586C>T
NM_000552.3:c.3788C>T
NM_000552.4:c.3788C>T

Uncertain Significance

Met criteria codes 3

PP4 PM2_Supporting BP4

Not Met criteria codes 2

PP3 PS4

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

NM_000552.5(VWF):c.3788C>T is a missense variant in VWF predicted to encode substitution of serine by leucine at amino acid 1263. The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000008780 (based on 2/91076 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 0.143, which is

below the ClinGen VWD VCEP PP3 threshold of <0.290 and does not predict a damaging effect on VWF function (BP4). Additionally, the computational splicing predictor SpliceAI indicates that the variant has no impact on splicing. At least 2 patients with this variant have been reported, only 1 of whom displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of low VWF:RCo/VWF:Ag ratio, which together are specific for VWD type 2M (PP4, PMID: 28971901). Both reported patients exhibited low FVIII activity relative to VWF antigen, leading one to be diagnosed with VWD Type 1-2N (PMID: 22315491). This variant is classified as a variant of unknown significance for VWD based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PP4, PM2_Supporting, BP4.

Met criteria codes

PP4	✔	At least 1 patient with this variant displayed excessive mucocutaneous bleeding as well as a laboratory phenotype of low VWF:RCo/VWF:Ag ratio (0.62), which together are specific for VWD type 2M (PP4, PMID: 28971901). A second patient with this variant was diagnosed with VWD Type 1-2N but exhibited low VWF:Co (0.49) without a low VWF:RCo/VWF:Ag ratio (1), (PMID: 22315491). Both patients had the inconsistent feature of low FVIII activity (0.12-20) relative to VWF antigen (0.49-0.78), resulting in one publication flagging the patient / variant as having "a discrepant phenotype-genotype correlation" (PMID: 28971901). The presence of the D1472H variant was ruled out by the use of next-generation sequencing-based genotyping in both patients.
PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000008780 (based on 2/91076 alleles in the South Asian population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 (PM2_Supporting).
BP4	✔	The computational predictor REVEL gives a score of 0.143, which is below the ClinGen VWD VCEP threshold of <0.290 and does not predict a damaging effect on VWF function (PP3).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.143, which is below the ClinGen VWD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on VWF function. Additionally, the computational splicing predictor SpliceAI indicates that the variant has no impact on splicing.
PS4	✖	This variant has been reported in 2 probands, 1 of whom has met PP4. PS4_Supporting cannot be applied because the second proband has not met PP4, and because it is not clear whether the two probands are unrelated (PMID: 28971901, PMID: 22315491).

Curation History

Showing 1 to 1 of 1 rows