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Variant: NM_000552.5(VWF):c.6187C>T (p.Pro2063Ser)

Version: 1.0

CA202650

100436 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: hereditary von Willebrand disease (MONDO:0019565)
Inheritance Mode: Undetermined mode of inheritance
UUID: 3e1c6372-35ab-4c65-8f6a-476e7c6e0a3b
Approved on: 2024-08-13
Published on: 2024-08-13

HGVS expressions

NM_000552.5:c.6187C>T
NM_000552.5(VWF):c.6187C>T (p.Pro2063Ser)
NC_000012.12:g.5994484G>A
CM000674.2:g.5994484G>A
NC_000012.11:g.6103650G>A
CM000674.1:g.6103650G>A
NC_000012.10:g.5973911G>A
NG_009072.1:g.135187C>T
NG_009072.2:g.135187C>T
ENST00000261405.10:c.6187C>T
ENST00000261405.9:c.6187C>T
ENST00000538635.5:n.421-550C>T
NM_000552.3:c.6187C>T
NM_000552.4:c.6187C>T

Likely Benign

Met criteria codes 3

BP5 BS1 PP4

Not Met criteria codes 4

BP4 BS3 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.6187C>T is a missense variant that replaces proline with serine at position 2063. The Grpmax filtering allele frequency in gnomAD v4.1 is 0.04661 (based on 4353/91066 alleles in the South Asian population, with 145 homozygotes), which is higher than the ClinGen VWD VCEP BS1 threshold of >0.01 (BS1). At least 1 proband harboring the variant in the homozygous state exhibits a history of severe bleeding and a quantitative defect in VWF, consistent with VWD Type 3 (PMID: 23354996), however, it is not yet clear

whether this phenotype is sufficiently specific to meet PP4. While this variant is also reported to be present in the homozygous state in multiple other affected probands (PMID: 23354996), PS4 cannot be considered because BS1 is met. The recombinant p.Pro2063Ser variant in COS-7 cells matches properties of the wild-type recombinant protein, including normal expression, secretion, and multimer formation, inconsistent with a quantitative defect relevant to VWD Type 3 (PMID: 19566550). BS3_Supporting is not met because this criterion is considered not applicable to this gene-disease relationship. This variant has been observed in affected cases with an alternate molecular basis for disease, including in VWD Type 3 in cis with either the NM_000552.5(VWF):c.970C>T (p.Arg324Ter) variant (PMID: 33550700) or the NM_000552.5(VWF):c.5200C>T (p.Gln1734Ter) variant (PMID: 23702511). Both comparison variants have been classified as Pathogenic by the ClinGen VWD VCEP. Three other reported cases with diverse VWD diagnoses harbor this variant as well as a second variant in VWF (PMID: 19404524, PMID: 21534937, PMID: 16985174), however, the comparison variants have not yet been classified by the ClinGen VWD VCEP. In summary, this variant meets the criteria to be classified as Likely Benign for hereditary von Willebrand disease based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: BS1, BP5, PP4. (VCEP Rule specifications for von Willebrand disease type 2A, 2B and 2M v1.0.0; date of approval 08/13/2024)

Met criteria codes

BP5	✔	This variant has been observed in affected family members with an alternate molecular basis for disease. This variant was present in individuals with VWD Type 3 in the homozygous state and in cis with the homozygous NM_000552.5(VWF):c.970C>T (p.Arg324Ter) variant (PMID: 33550700). The phase of the variants was confirmed by family testing, and the second variant has been classified as Pathogenic by the ClinGen VWD VCEP (BP5). The variant was similarly observed in an individual with VWD Type 3 in the homozygous state and in cis with the homozygous NM_000552.5(VWF):c.5200C>T (p.Gln1734Ter) variant (PMID: 23702511). The second variant has been classified as Pathogenic by the ClinGen VWD VCEP. Three other reported cases with diverse VWD diagnoses harbor this variant as well as a second variant in VWF (PMID: 19404524, PMID: 21534937, PMID: 16985174), however the second variants have not yet been classified by the ClinGen VWD VCEP.
BS1	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.04661 (based on 4353/91066 alleles in the South Asian population, with 145 homozygotes), which is higher than the ClinGen VWD VCEP threshold (>0.01) for BS1, and therefore meets this criterion (BS1).
PP4	✔	At least 1 proband harboring the variant in the homozygous state exhibits a history of severe bleeding and a quantitative defect in VWF, consistent with VWD Type 3. The heterozygous carriers and non-carriers from the proband's family appear to be unaffected (PMID: 23354996; PP4).

Not Met criteria codes

BP4	✖	The computational predictor REVEL gives a score of 0.437, which is above the ClinGen VWD VCEP BP4 threshold of <0.290.
BS3	✖	Transfection of the p.Pro2063Ser variant in COS-7 cells found the properties of the variant to match those of the wild-type recombinant protein, including normal expression, secretion, and multimer formation, inconsistent with a quantitative defect relevant to VWD Type 3 (PMID: 19566550). BS3_Supporting is not met because this criterion is considered not applicable to this gene-disease relationship.
PP3	✖	The computational predictor REVEL gives a score of 0.437, which is below the ClinGen VWD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on VWF function. The computational splicing predictor SpliceAI gives a score of 0.02 for splice donor gain, indicating that the variant likely has no impact on splicing.

PS4		✖	While this variant is reported to be present in the homozygous state in multiple affected probands (PMID: 23354996), this code cannot be considered because BS1 is met.

Curation History

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