The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000552.5(VWF):c.5173C>T (p.Pro1725Ser)

Version: 1.0

CA6402355

619937 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: hereditary von Willebrand disease (MONDO:0019565)
Inheritance Mode: Undetermined mode of inheritance
UUID: c93db46c-aaf6-440c-b520-b2c990937f25
Approved on: 2024/8/13
Published on: 2024/8/13

HGVS expressions

NM_000552.5(VWF):c.5173C>T (p.Pro1725Ser)
NM_000552.5:c.5173C>T
NC_000012.12:g.6016654G>A
CM000674.2:g.6016654G>A
NC_000012.11:g.6125820G>A
CM000674.1:g.6125820G>A
NC_000012.10:g.5996081G>A
NG_009072.1:g.113017C>T
NG_009072.2:g.113017C>T
ENST00000261405.10:c.5173C>T
ENST00000261405.9:c.5173C>T
ENST00000538635.5:n.421-22720C>T
NM_000552.3:c.5173C>T
NM_000552.4:c.5173C>T

Likely Benign

Met criteria codes 1

BS1

Not Met criteria codes 3

PP3 BS2 BP4

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.5173C>T is a missense variant that replaces proline with serine at position 1725. T The Grpmax filtering allele frequency in gnomAD v4.1 is 0.02354 (based on 1836/75022 alleles in the African / African-American population, with 27 homozygotes), which is higher than the ClinGen VWD VCEP threshold of >0.01 for BS1. While this variant has been reported in healthy control individuals

(PMID: 22197721), BS2 is not being used due to penetrance issues. 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.

Met criteria codes

BS1	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.02354 (based on 1836/75022 alleles in the African / African-American population, with 27 homozygotes), which is higher than the ClinGen VWD VCEP threshold of >0.01 for BS1.

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.352, 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 0.07 for splice acceptor gain, indicating that the variant likely has no impact on splicing.
BS2	✖	The variant has been reported in multiple control individuals (PMID: 22197721), however, this criterion is considered not applicable to the gene-disease relationship due to incomplete penetrance.
BP4	✖	The computational predictor REVEL gives a score of 0.352, which is above the ClinGen VWD VCEP BP4 threshold of <0.290.

Curation History

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