Variant: NM_000552.5(VWF):c.2561G>A (p.Arg854Gln)

Version: 1.0

CA114139

296 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2N (MONDO:0015631)
Inheritance Mode: Autosomal recessive inheritance
UUID: 01c59bbd-0d03-488a-94f1-fa68f3b2e083
Approved on: 2024-07-09
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HGVS expressions

NM_000552.5:c.2561G>A
NM_000552.5(VWF):c.2561G>A (p.Arg854Gln)
NC_000012.12:g.6034812C>T
CM000674.2:g.6034812C>T
NC_000012.11:g.6143978C>T
CM000674.1:g.6143978C>T
NC_000012.10:g.6014239C>T
NG_009072.1:g.94859G>A
NG_009072.2:g.94859G>A
ENST00000261405.10:c.2561G>A
ENST00000261405.9:c.2561G>A
ENST00000538635.5:n.421-40878G>A
NM_000552.3:c.2561G>A
NM_000552.4:c.2561G>A

Pathogenic

Met criteria codes 4

PS3 PP1 PM3_Strong PP4_Moderate

Not Met criteria codes 5

BS1 BP4 PP3 PM5 PM2

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.2561G>A variant in VWF is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 854. The Grpmax filtering allele frequency in gnomAD v4.0 is 0.005857 (based on 7050/1180026 alleles, with 24 homozygotes) in the European non-Finnish population. This allele frequency is above the ClinGen VWD VCEP threshold for VWD Type 2N (<0.005) for PM2_Supporting but below the threshold (>0.01) for BS1 and therefore does not meet any population criterion. At least 9 patients with

this variant displayed excessive mucocutaneous bleeding, low FVIII activity, and decreased VWF:FVIII binding, which is highly specific for VWD type 2N (PP4_Moderate, PMID: 28971901, PMID: 22875612). Four individuals were homozygous for the variant (PMID: 28971901, PMID: 22875612, PMID: 1832934) and one of those individuals was compound heterozygous for the variant and a pathogenic variant (p.Arg816Trp) confirmed in trans (PMID: 1832934), additional compound heterozygotes have been reported but were not considered here (PM3_Strong). In one family, the variant segregated with VWD type 2N in the proband and a second affected family member (PP1; PMID: 28971901). A hydrodynamic mouse model showed reduced factor VIII stability and impaired binding of factor VIII to VWF, indicating that this variant has a damaging effect on protein function (PMID: 28581694)(PS3). In summary, this variant meets the criteria to be classified as Pathogenic for von Willebrand disease type 2N. ACMG/AMP criteria applied as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PS3, PM3_Strong, PP4_Moderate, PP1.

Met criteria codes

PS3	✔	A hydrodynamic mouse model with wild-type and p.Arg854Gln mutant VWF proteins was generated from the plasma of VWF/FVIII double knockout mice, and p.Arg854Gln samples showed reduced factor VIII stability and impaired binding of factor VIII to VWF, indicating that this variant has a damaging effect on protein function (PMID: 28581694) (PS3).
PP1	✔	The variant has been reported to segregate with VWD type 2N in the proband plus one affected family member (PP1; PMID: 28971901).
PM3_Strong	✔	This variant has been detected in at least 9 individuals with VWD Type 2N. 4 individuals were homozygous for the variant (1 point maximum, PMID: 28971901, PMID: 22875612, PMID: 1832934). 1 of those individuals was compound heterozygous for the variant and a pathogenic variant (p.Arg816Trp) confirmed in trans (1 point, PMID: 1832934). Total 2pt (PM3_Strong) 2 additional individuals were compound heterozygous for the p.Arg854Gln variant with a second variant confirmed in trans (p.Arg324Ter and p.Pro2558GlyfsTer7, respectively, 2 points, PMID: 28971901) but quantitative VWD classification rules are not yet finalized.
PP4_Moderate	✔	At least 4 patients with this variant displayed excessive mucocutaneous bleeding (score between 6 and 16) as well as low FVIII activity (between 3 and 24) and decreased VWF:FVIII binding (between 0.02 and 0.11), which is highly specific for VWD type 2N. (PP4_Moderate, PMID: 28971901). Additional consistent phenotypes were also reported in the patients including normal HMW multimers. While NGS was used for genotyping, it is not clear whether the alternate diagnosis of Hemophilia A was successfully ruled out in these patients. Two additional homozygous affected individuals have been found in PMID: 22875612.

Not Met criteria codes

BS1	✖	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.005857 (based on 7050/1180026 alleles, with 24 homozygotes) in the European non-Finnish population. This allele frequency is below the ClinGen VWD VCEP threshold (>0.01) for VWD Type 2N variants for BS1.
BP4	✖	The computational predictor REVEL gives a score of 0.487, which is above the ClinGen VWD VCEP PP3 threshold of <0.290.
PP3	✖	The computational predictor REVEL gives a score of 0.487, 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 acceptor gain, indicating that the variant likely has no impact on splicing.

PM5	✖	Another missense variant NM_000552.5(VWF):c.2560C>T (p.Arg854Trp) (PMID: 9684781, PMID: 20586924, ClinVar Variation ID: 100228) in the same codon has not yet been classified for VWD Type 2N by the ClinGen VWD VCEP, and PM5 will not be evaluated in this curation to avoid circularity.
PM2	✖	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.005857 (based on 7050/1180026 alleles, with 24 homozygotes) in the European non-Finnish population. This allele frequency is above the ClinGen VWD VCEP threshold (<0.005) for VWD Type 2N variants for PM2_Supporting.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000552.5(VWF):c.2561G>A (p.Arg...)	Pathogenic	Von Willebrand Disease Type 2N	2024-08-12	1.0	ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0	VWF

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