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Variant: NM_000552.5(VWF):c.4121G>A (p.Arg1374His)

Version: 1.0

CA228541

100330 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease 2 (MONDO:0013304)
Inheritance Mode: Autosomal dominant inheritance
UUID: 029492d7-af69-4d07-a762-e986e370328c
Approved on: 2024-12-03
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HGVS expressions

NM_000552.5:c.4121G>A
NM_000552.5(VWF):c.4121G>A (p.Arg1374His)
NC_000012.12:g.6019297C>T
CM000674.2:g.6019297C>T
NC_000012.11:g.6128463C>T
CM000674.1:g.6128463C>T
NC_000012.10:g.5998724C>T
NG_009072.1:g.110374G>A
NG_009072.2:g.110374G>A
ENST00000261405.10:c.4121G>A
ENST00000261405.9:c.4121G>A
ENST00000538635.5:n.421-25363G>A
NM_000552.3:c.4121G>A
NM_000552.4:c.4121G>A

Pathogenic

Met criteria codes 6

PP1_Moderate PP3 PP4 PS3 PS4_Very Strong PM2_Supporting

Not Met criteria codes 1

PM5

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.4121G>A is a missense variant predicted to cause substitution of Arginine by Histidine at amino acid 1374. This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor computational predictor REVEL gives a score of 0.879, which is above the ClinGen VWD VCEP threshold of >0.644 and predicts a damaging effect on VWF function (PP3). Family M proband I.1 (PMID: 7734373) with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of a complete set of vWF

multimers present but relative reduction of the larger multimers, low VWF:RCo/VWF:Ag ratio (<0.4), and VWF:RCo <3-10 IU/dl (PP4). Additional consistent phenotypes included FVIII activity consistent with VWF antigen. This variant has been reported in >8 additional probands with consistent laboratory phenotypes (PS4_VeryStrong; PMIDs: 7620154, 9031470, 11154147, 7734373, 38315875, 28083987, 28536718). The variant has been reported to segregate with VWD type [2A/2M] through at least 2 affected meioses in at least 2 families (PP1_Moderate; PMID: 7734373, PMID: 7620154). A platelet binding assay in COS-7 cells expressing the recombinant VWF variant showed decreased binding indicating that this variant has a damaging effect on protein function relative to the rVWF wild-type control (PMID: 10845912, PS3). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal dominant VWD type 2 based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD VCEP: PS3, PS4_VeryStrong, PM2_supporting, PP1_Moderate, PP3, PP4. Recent analysis (PMID: 38315875) reports that patients with R1374H have severely reduced VWF:GPIbR/VWF:Ag and a modest decrease in VWF:CB/VWF:Ag ratios. This can be explained by 2 defects, (1) a reduced VWF A1 domain binding to GPIb and (2) an altered VWF multimeric pattern in which patients showed a slightly diminished proportion of HMWM and little increase of low and intermediate multimers. They hypothesize that the slight reduction of HMWM (characteristic of type 2A) is primarily responsible for marginally reduced VWF:CB/VWF:Ag ratio, whereas the markedly reduced VWF:GPIbR/VWF:Ag ratio is mainly because of a type 2M defect (diminished binding of A1-GPIb) and propose a subtype designation of 2M/2A for this variant.

Met criteria codes

PP1_Moderate	✔	The variant has been reported to segregate with VWD type [2A/2M] through at least 2 affected meioses in at least 2 families (PP1_moderate; PMID: 7734373, PMID: 7620154).
PP3	✔	The computational predictor REVEL gives a score of 0.879, 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 scores of 0.00 for all splice site types, indicating that the variant has no impact on splicing.
PP4	✔	Family M proband I.1 (PMID: 7734373) with this variant displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of a complete set of vWF multimers present but relative reduction of the larger multimers, low VWF:RCo/VWF:Ag ratio (<0.4), and VWF:RCo <3-10 IU/dl (PP4). Additional consistent phenotypes included FVIII activity consistent with VWF antigen. PP4_Moderate was not applied due to the relative reduction of the larger multimers
PS3	✔	A platelet binding assay in COS-7 cells expressing the recombinant VWF variant showed decreased binding indicating that this variant has a damaging effect on protein function relative to the rVWF wild-type control (PMID: 10845912, PS3).
PS4_Very Strong	✔	This variant has been reported in >8 additional probands with consistent laboratory phenotypes (PS4_VeryStrong; PMIDs: 7620154, 9031470, 11154147, 7734373, 38315875, 28083987, 28536718).
PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 2.800e-7 (based on 2/1179856 alleles in the European non-Finnish population), which is lower than the ClinGen VWD VCEP threshold of <0.0001 (PM2_Supporting).

Not Met criteria codes

PM5	✖	2 different missense variants in the same codon have been reported in patients with VWD (NM_000552.5(VWF):c.4120C>T (p.Arg1374Cys) and NM_000552.5(VWF):c.4121G>T (p.Arg1374Leu))(PMID: 16247740, PMID: 11150026, PMID: 9198195, PMID: 17408416, PMID: 11686104, ClinVar Variation IDs 100331 and 100329). However, these variants have not yet been classified by the ClinGen VWD VCEP.

Curation History

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