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Variant: NM_000552.5(VWF):c.4213AAG[3] (p.Lys1408del)

Version: 1.0

CA228561

100340 (ClinVar)

Gene: VWF (HGNC:7450)
Condition: von Willebrand disease type 2M (MONDO:0015630)
Inheritance Mode: Autosomal dominant inheritance
UUID: d2894595-214e-4bcc-9af1-7bd1ab5c5eee
Approved on: 2025/10/7
Published on: 2025/10/10

HGVS expressions

NM_000552.5:c.4222_4224del
NM_000552.5:c.4222_4224delAAG
NM_000552.5:c.4213AAG[3]
NM_000552.5(VWF):c.4213AAG[3] (p.Lys1408del)
NC_000012.12:g.6019204_6019206del
CM000674.2:g.6019204_6019206del
NC_000012.11:g.6128370_6128372del
CM000674.1:g.6128370_6128372del
NC_000012.10:g.5998631_5998633del
NG_009072.1:g.110475_110477del
NG_009072.2:g.110475_110477del
ENST00000261405.10:c.4222_4224del
ENST00000261405.9:c.4222_4224del
ENST00000538635.5:n.421-25262_421-25260del
NM_000552.3:c.4222_4224del
NM_000552.4:c.4222_4224del

Pathogenic

Met criteria codes 6

PP4_Moderate PP1_Strong PM2_Supporting PM4 PS3 PS4_Moderate

Not Met criteria codes 1

BS4

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.4222_4224del (p.Lys1408del), in vWF is an in-frame deletion predicted to cause deletion of amino acid residue 1408, which is predicted to cause a change in the length of the protein in a non-repeat region meeting criteria for PM4. The variant is absent in

gnomAD v4.1 meeting criteria for PM2_Supporting. At least 3 probands have displayed excessive mucocutaneous bleeding as well as laboratory phenotypes of a normal multimer pattern, low VWF:RCo/VWF:Ag ratio and decreased platelet/GP1b binding assay, which is highly specific for VWD type 2M (PP4_Moderate PMID: ; PS4_Moderate PMID: 28971901 & 10959688). The variant has been reported to segregate with VWD type 2M through at least 12 meioses across 3 different families (PP1_Strong; PMID: 28971901 & 10959688). Platelet/GP1b binding assay performed with the c.4222_4224del recombinant mutant vWF expressed by cos-7 cells showed decreased binding indicating that this variant has a damaging effect on protein function meeting criteria for PS3 (PMID:10959688). In summary, this variant meets the criteria to be classified as pathogenic for von Willebrand disease type 2M. ACMG/AMP criteria applied as specified by the ClinGen von Willebrand disease Variant Curation Expert Panel: PS3, PS4_Moderate, PM4, PP1_Strong, PP4_Moderate, PM2_Supporting.

Met criteria codes

PP4_Moderate	✔	Female proband with bleeding score of 19 and the following lab phenotype: vWF ant 21%, vWF act 9%, factor VIII 43%, collagen binding 27% and multimer analysis was performed (PP4_Moderate, PMID: 28971901).
PP1_Strong	✔	The variant has been reported to segregate with VWD type 2M through at least 12 affected meioses from 3 different families. At least 10 meioses from the Hilbert, et al (PMID: 10959688) and 2 meioses from the Borras, et al. family (PMID: 28971901).
PM2_Supporting	✔	Variant is absent in gnomAD v4.1.
PM4	✔	This variant is predicted to cause a change in the length of the protein due to an in-frame deletion of Lys1408 amino acid in a non-repeat region (PM4)
PS3	✔	Platelet/GP1b binding assay performed with the c.4222_4224del recombinant mutant vWF expressed by cos 7 showed decreased binding indicating that this variant has a damaging effect on protein function (PMID: 10959688)
PS4_Moderate	✔	This variant has been reported in at least 2 probands meeting laboratory phenotype criteria (PS4_Moderate, PMIDs: 28971901 & 10959688)

Not Met criteria codes

BS4	✖	Variant segregates with disease in reported families.

Curation History

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