

Variant: NM_000132.4:c.1421G>A

Version: 1.1

CA414914388 [🔗](#)

Gene: F8 ([HGNC:2157](#))

Condition: hemophilia A ([MONDO:0010602](#))

Inheritance Mode: X-linked inheritance

UUID: d7b0efe3-746e-4810-9550-36646f76d60b

Approved on: 2025/1/14

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HGVS expressions

NM_000132.4:c.1421G>A

NC_000023.11:g.154965992C>T

CM000685.2:g.154965992C>T

NC_000023.10:g.154194267C>T

CM000685.1:g.154194267C>T

NC_000023.9:g.153847461C>T

NG_011403.1:g.61732G>A

NG_011403.2:g.61732G>A

ENST00000360256.9:c.1421G>A

ENST00000647125.1:c.*1297G>A

ENST00000360256.8:c.1421G>A

ENST00000483822.2:n.241G>A

NM_000132.3:c.1421G>A

Pathogenic

Met criteria codes **3**

PS4_Very Strong

PP3

PM2_Supporting

Not Met criteria codes **2**

PP4

PM1

Evidence Links **0**

Expert Panel

Coagulation Factor Deficiency VCEP [🔗](#)

Criteria Specification Information

[🔗](#) **Criteria Specification:** ClinGen Coagulation Factor Deficiency Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for F8 Version 1.0.0

[🔗](#) **Criteria Specification Approval History**

[🔗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Coagulation Factor Deficiency VCEP

The variant, NM_000132.3(F8):c.1421G>A predicts a missense change, Gly474Glu, which is not reported in gnomAD v2.1 or v3.1.1, meeting PM2_Supporting. This variant has been reported in at least 8 patients with severe hemophilia A (at least one patient with an inhibitor to factor replacement therapy - PMID: 16601827) in the literature (PMID: 31134694, 10404764, and 29296726) and from internal VCEP data; meeting the F8 phenotype criteria at PS4_Very Strong. The variant has a REVEL score of 0.973 (threshold >0.6) meeting PP3. In summary,

the variant meets criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8: PS4_Very Strong, PP3, PM2_Supporting.			
Met criteria codes			
PS4_Very Strong			At least 8 patients from the literature (PMID: 31134694, 10404764, 16601827) and internal laboratory data (3 MLOF participants & 1 clinical lab patient) meet F8 phenotype criteria for PS4_Very strong.
PP3			REVEL score of 0.973 (threshold >0.6) and CADD score of 25.2 (threshold >21) meet criteria for PP3
PM2_Supporting			Gly474Glu is absent from gnomAD v2.1. and v3.1.2.
Not Met criteria codes			
PP4			Male with severe hemophilia A who had full gene sequencing for F8 and F9 genes with deletion/duplication analysis in the MLOF study, but proband used for PS4 to apply at VS strength.
PM1			Gly474Glu occurs in the A2 domain of the F8 protein. PM1 is not applicable at this time.

Curation History

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