

Variant: *NM_000132.3:c.1420G>T*

Version: 1.1

CA414914394 [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 64af1bb4-86df-41c1-adc6-2b041e26e8d8

Approved on: 2025/3/10

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HGVS expressions

NM_000132.3:c.1420G>T

NC_000023.11:g.154965993C>A

CM000685.2:g.154965993C>A

NC_000023.10:g.154194268C>A

CM000685.1:g.154194268C>A

NC_000023.9:g.153847462C>A

NG_011403.1:g.61731G>T

NG_011403.2:g.61731G>T

ENST00000360256.9:c.1420G>T

ENST00000647125.1:c.*1296G>T

ENST00000360256.8:c.1420G>T

ENST00000483822.2:n.240G>T

NM_000132.4:c.1420G>T

Likely Pathogenic

Met criteria codes **4**

PP3

PM5

PM2_Supporting

PP4_Moderate

Not Met criteria codes **2**

PS4

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.1420G>T, predicts a missense change, Gly474Trp, which is not reported in gnomAD v2.1.1 or v3. This variant has been reported in at least one male patient with severe hemophilia A in the literature meeting PP4_Moderate criteria (PMID: 19473408). Another nucleotide change at the same codon, c.1421G>A; p.Gly474Glu is classified as pathogenic by CFD-VCEP meeting the PM5 criteria. The variant has a REVEL score of 0.952 (threshold >0.6) meeting PP3 criteria. In summary, the clinical significance of this

variant is likely pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8: PP4_Moderate, PP3, PM2_Supporting, PM5.

Met criteria codes

PP3			REVEL score of 0.952 (threshold: >0.6) and CADD score of 28.1 (threshold: >21) meet criteria for PP3. SpliceAI acceptor/donor loss score of 0.01.
PM5			Another nucleotide change at the same codon, c.1421G>A (p.Gly474Glu) is classified as pathogenic by CFD-VCEP
PM2_Supporting			Gly474Trp is absent from gnomAD v2.1.1 and v3.
PP4_Moderate			Proband with severe hemophilia A. Performed MLPA to access for del/dups.

Not Met criteria codes

PS4			Applying proband for PP4 code
PM1			Gly474Trp occurs in the A2 domain. PM1 is not applied at this time.

Curation History

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