

Variant: NM_000132.4:c.1420G>A

Version: 1.3

CA414914390 [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 3beb4702-1e52-4da0-bd95-488b63916bbc

Approved on: 2024/9/30

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HGVS expressions

NM_000132.4:c.1420G>A

NC_000023.11:g.154965993C>T

CM000685.2:g.154965993C>T

NC_000023.10:g.154194268C>T

CM000685.1:g.154194268C>T

NC_000023.9:g.153847462C>T

NG_011403.1:g.61731G>A

NG_011403.2:g.61731G>A

ENST00000360256.9:c.1420G>A

ENST00000647125.1:c.*1296G>A

ENST00000360256.8:c.1420G>A

ENST00000483822.2:n.240G>A

NM_000132.3:c.1420G>A

Likely Pathogenic

Met criteria codes **6**

PS4_Moderate

PP4_Moderate

PP3

PS1_Moderate

PM5

PM2_Supporting

Not Met criteria codes **1**

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>A, predicts a missense change, Gly474Arg, which is not reported in gnomAD v2.1.1 or v3. This variant has been reported in at least three patients with severe or mild-moderate Hemophilia A in the literature (PMID: 9603440, 16972227, 29296726) meeting PS4_Moderate and PP4_Moderate criteria. The variant has a REVEL score of 0.972 (threshold >0.6) meeting criteria for PP3. Another nucleotide change at the same codon, c.1421G>A (p.Gly474Glu) is classified as pathogenic by CFD-VCEP meeting

criteria for PM5. 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: PS4_Moderate, PM5, PP4_Moderate, PP3, PM2_Supporting.

Met criteria codes		
PS4_Moderate		Two patients with severe and mild-moderate hemophilia A reported in PMID: 9603440 and PMID: 16972227, respectively, meeting F8 phenotype criteria.
PP4_Moderate		1 patient with the c.1420G>A variant and severe hemophilia A (FVIII:C <1%) is reported in the MLOF study, wherein full gene sequencing of F8 and F9 and deletion/duplication analysis of F8 were performed.
PP3		REVEL score of 0.972 (threshold: >0.6) and CADD score of 27.5 (threshold: >21) meet criteria for PP3
PS1_Moderate		Another nucleotide change at the same position, c.1420G>T (p.Gly474Trp), is also reported. PS1_Moderate is applied as c.1420G>T is evaluated by the CFD-VCEP as a likely pathogenic.
PM5		Another nucleotide change at the same codon, c.1421G>A (p.Gly474Glu) is classified as pathogenic by CFD-VCEP, and it does not appear to causing a splicing defect (SpliceAI = Acceptor Gain 0.02).
PM2_Supporting		Gly474Arg (c.1420G>A) is absent from gnomAD v2.1.1 and v3.

Not Met criteria codes

PM1Gly474Arg occurs in the A2 domain. PM1 is not applied at this time.

Curation History

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