

Variant: NM_000132.3:c.1214T>C

Version: 1.1

CA414916092 [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: f44dc699-f004-4b89-8b19-a925f15d2fa4

Approved on: 2024/12/6

Published on: 2024/12/6

HGVS expressions

NM_000132.3:c.1214T>C

NC_000023.11:g.154966483A>G

CM000685.2:g.154966483A>G

NC_000023.10:g.154194758A>G

CM000685.1:g.154194758A>G

NC_000023.9:g.153847952A>G

NG_011403.1:g.61241T>C

NG_011403.2:g.61241T>C

ENST00000360256.9:c.1214T>C

ENST00000647125.1:c.*1090T>C

ENST00000360256.8:c.1214T>C

ENST00000483822.2:n.34T>C

NM_000132.4:c.1214T>C

Pathogenic

Met criteria codes **3**

PP3

PS4_Very Strong

PM2_Supporting

Not Met criteria codes **3**

PM1

PM5

PP4

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 missense variant, NM_000132.3:c.1214T>C (p.Ile405Thr), is not reported in gnomAD v2.1.1 or v3 (PM2_Supporting). This variant has been reported in at least six male patients with moderate and severe Hemophilia A in the literature and meet phenotype criteria for F8 (PS4, PP4_Moderate, PMID: 29296726, 22103590, 24845853). The variant has a REVEL score of 0.981 (PP3, threshold >0.6). This variant reaches a classification of Pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8: PS4, PP4_Moderate, PP3, PM2_Supporting.

Met criteria codes

PP3			REVEL score of 0.981 (threshold: >0.6) and CADD score of 25.4 (threshold: >25.4) meet criteria for PP3
PS4_Very Strong			8 patients reported with moderate or severe Hemophilia A reported in the literature (PMID: 29296726, 22103590, 24845853) or by a clinical laboratory meet F8 phenotype criteria.(4 patients from the MLOF project are reported with FVIII:C <1%, confirmed upon expert review). One proband from Gulf States Hemophilia and Thrombophilia Center, Houston, TX with FVIII:C 4%. PS4 is applied at the very strong level.
PM2_Supporting			The variant is absent from gnomAD v2.1.1 and v3.

Not Met criteria codes

PM1			Ile405Thr occurs in the A2 domain of the F8 protein. PM1 is not applied at this time.
PM5			c.1213T>C (p.Ile405Phe) is a variant at the same codon and is curated by the Coagulation Factor Deficiency VCEP to be likely pathogenic. c.1213T>C (p.Ile405Ser) is also a variant at the same codon and is curated by the Coagulation Factor Deficiency VCEP to be likely pathogenic so PM5 is met, however, the (p.Ile405Ser) was at VUS, so the (p.Ile405Phe) variant was used to apply PM5_Supporting to move it to LP.
PP4			MLOF probands were used for PS4_very strong.

Curation History

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