

Variant: NM_000132.4:c.686C>A

Version: 1.0

CA414919140 [↗](#)

2775449 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 461d01d4-686b-480b-8a6d-b0e1078b461c

Approved on: 2024/2/2

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HGVS expressions

NM_000132.4:c.686C>A

NC_000023.11:g.154984788G>T

CM000685.2:g.154984788G>T

NC_000023.10:g.154213063G>T

CM000685.1:g.154213063G>T

NC_000023.9:g.153866257G>T

NG_011403.1:g.42936C>A

NG_011403.2:g.42936C>A

ENST00000360256.9:c.686C>A

ENST00000647125.1:c.*472C>A

ENST00000360256.8:c.686C>A

ENST00000423959.5:c.581C>A

NM_000132.3:c.686C>A

Pathogenic

Met criteria codes 4

PS4_Supporting

PVS1

PM2_Supporting

PS2_Moderate

Not Met criteria codes 2

PS1

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 NM_000132.3:c.686C>A variant predicts a nonsense change, Ser229Ter, in exon 6 of the F8 gene and the resulting transcript is predicted to undergo NMD, which meets PVS1 criteria. The variant is absent from gnomAD v2.1.1 and v3, which meets PM2_Supporting. It is not reported in male patients with hemophilia A in the literature; however, another nucleotide change that results in the same nonsense variant is reported in two patients (PMID: 18217193, 22958177). At least one male with severe hemophilia A was found to be de novo for the variant, without confirmation of maternity, from internal laboratory data, which meets the PS2_Moderate and PS4_Supporting criteria.

In summary, this variant meets criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency variant curation expert panel: PVS1, PS2_Moderate, PS4_Supporting, PM2_Supporting.

Met criteria codes

PS4_Supporting			The variant has not been reported in male patients with HA the literature, to the best of our knowledge. From internal laboratory data: the variant is reported de novo in 1 male individual with severe Hemophilia A. Baseline FVIII:C noted to be <1%. Individual meets F8 phenotype criteria specified by the CFD VCEP.
PVS1			The c.686C>A variant introduces a PTC in exon 6/26; NMD is predicted.
PM2_Supporting			The variant is absent from gnomAD v2.1.1 and v3
PS2_Moderate			From internal laboratory data: the variant is reported de novo in 1 male individual with severe Hemophilia A. FVIII:C noted to be <1%. Maternity confirmation is not noted. This evidence is scored 1 point for an assumed de novo occurrence (without confirmation of maternity) in a patient with FVIII:C in the severe range.

Not Met criteria codes

PS1			A different nucleotide change that results in the same nonsense codon has been reported in 1 Italian and 1 Slovenian HA patients (EAHAD database and PMID: 18217193, 22958177. The information is noted for the record, but PS1 is not applicable to nonsense variants.
PM1			The variant occurs in the A1 domain of the F8 protein; however, PM1 is not applied to LOF variants.

Curation History

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