

Variant: *NM_000132.4:c.2138A>T*

Version: 1.1

CA414904027 [↗](#)

2691907 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: e39cdc6c-fa4c-483d-bc9e-04b440156fed

Approved on: 2025/3/10

Published on: 2025/3/28

HGVS expressions

NM_000132.4:c.2138A>T

NC_000023.11:g.154931652T>A

CM000685.2:g.154931652T>A

NC_000023.10:g.154159927T>A

CM000685.1:g.154159927T>A

NC_000023.9:g.153813121T>A

NG_011403.1:g.96072A>T

NG_011403.2:g.96072A>T

ENST00000360256.9:c.2138A>T

ENST00000647125.1:c.*1804A>T

ENST00000360256.8:c.2138A>T

NM_000132.3:c.2138A>T

Likely Pathogenic

Met criteria codes **5**

PP1_Moderate

PS4_Supporting

PS3

PM2_Supporting

PP3

Evidence Links **1**

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 c.2138A>T; p.Asn713Ile variant is completely absent from gnomAD v2.1.1 and v3.1.1. This missense variant has a REVEL score of 0.803 and meets PP3 criteria (threshold >0.6). One large Danish family with mild hemophilia A, with well over 3 meioses of variant segregation, is reported in the literature, meeting F8 phenotype criteria for PS4_Supporting and PP1_Moderate (PMID: 10886198). Monkey COS-1 cells with variant demonstrated decreased factor VIII antigen and activity levels discrepant between 1- and 2-stage assays, which meets PS3 criteria. In summary, this variant meets criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8: PS3, PS4_Supporting, PP1_Moderate, PM2_Supporting, PP3.

Met criteria codes

PP1_Moderate		✓	Variant segregates in large Danish family with more than 6 meioses, but capping at PP1_Moderate strength because segregations are from only 1 family.
PS4_Supporting		✓	Variant is absent in gnomAD v2.1.1 and v3.1 and present in a proband from a large Danish family.
PS3		✓	<p>Mutant expressed COS-1 monkey kidney cells showed decreased F8 antigen (~25%) and discrepant F8 activity (1 stage ~20%; 2 stage ~10%).</p> <p>Full-length cDNAs containing variant generated by oligonucleotide site-directed mutagenesis were expressed in COS-1 monkey kidney cells showed decreased F8 antigen (~25%) and discrepant F8 activity (1 stage ~20%; 2 stage ~10%). PubMed:12428094 </p>
PM2_Supporting		✓	Variant is absent from gnomAD v2.1.1 and v3.
PP3		✓	REVEL score is 0.803, which is above 0.6 cutoff.

Curation History

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