The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000132.4(F8):c.6089G>A (p.Ser2030Asn)

Version: 1.0

CA10567911

439683 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: 02958bef-ef7e-40eb-a41a-a45bb873a1b0
Approved on: 2025-03-10
Published on: 2025-03-10

HGVS expressions

NM_000132.4:c.6089G>A
NM_000132.4(F8):c.6089G>A (p.Ser2030Asn)
NC_000023.11:g.154902077C>T
CM000685.2:g.154902077C>T
NC_000023.10:g.154130352C>T
CM000685.1:g.154130352C>T
NC_000023.9:g.153783546C>T
NG_011403.1:g.125647G>A
NG_011403.2:g.125647G>A
ENST00000360256.9:c.6089G>A
ENST00000360256.8:c.6089G>A
NM_000132.3:c.6089G>A

Pathogenic

Met criteria codes 3

PS3 PP4 PS4_Very Strong

Not Met criteria codes 2

PP3 PM2

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

c.6089G>A (p.Ser2030Asn) is a pathogenic with no predicted deleterious effect due to the REVEL score of .573, just below meeting criteria for PP3 (>=.6) It also has a SpliceAI score of .05, not meeting criteria for PP3 (>=.5). The c.6089G>A (p.Ser2030Asn) variant is present in gnomAD v2 with a MAF of 0.00002729 (5/81740) for the European (non-Finnish) population. There are 3 hemizygotes and 2 homozygotes. It was absent from gnomAD v3 meeting PM2_supporting. There are 13 probands with this variant reported in MLoF with mild hemophilia, meeting PP4. There were 24 probands reported but only 20 met criteria making it PS4_very-strong. Cells were measured by ELISA and chromogenic assays showing a deleterious effect on rFVIII expression, as shown by the reduced but appreciable levels of rFVIII protein

(25%–70% of wild-type) and activity (10%–50%), meeting PS3_Moderate. This variant is classified as Pathogenic for Hemophilia A based on the ACMG/AMP criteria applied, as specified by the ClinGen Coagulation Factor Deficiency Variant Curation Expert Panel for F8 (version 1.0.0, released 10/5/2023): PS4_Very-strong, PP4, PS3

Met criteria codes

PS3	✔	Measured by ELISA and chromogenic assays, the variant was associated with 27% factor VIII activity level.
		Measured by ELISA and chromogenic assays, the variant was associated with 27% factor VIII activity level. PubMed:34242570
PP4	✔	1 patient with mild hemophilia A reported in MLOF.
PS4_Very Strong	✔	24 probands reported, 20 counted

Not Met criteria codes

PP3	✖	For the c.6089G>A (p.Ser2030Asn) variant, the REVEL score is .573, not meeting criteria for PP3 (>=.6) It also has a SpliceAI score of .05, not meeting criteria for PP3 (>=.5).
PM2	✖	The c.6089G>A (p.Ser2030Asn) variant is present in gnomAD v2 with a MAF of 0.00002729 (5/81740) for the European (non-Finnish) population. There are 3 hemizygotes and 2 homozygotes. It was absent from gnomAD v3.

Curation History

Showing 1 to 1 of 1 rows