

Variant: *NM_000132.4(F8):c.599A>G (p.Glu200Gly)*

Version: 1.0

CA10568575 [↗](#)

449370 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: e4caf4f4-de49-400d-96ab-e40e0ec2c926

Approved on: 2024/2/2

Published on: 2024/7/11

HGVS expressions

NM_000132.4:c.599A>G

NM_000132.4(F8):c.599A>G (p.Glu200Gly)

NC_000023.11:g.154992938T>C

CM000685.2:g.154992938T>C

NC_000023.10:g.154221213T>C

CM000685.1:g.154221213T>C

NC_000023.9:g.153874407T>C

NG_011403.1:g.34786A>G

NG_011403.2:g.34786A>G

ENST00000360256.9:c.599A>G

ENST00000647125.1:c.*385A>G

ENST00000360256.8:c.599A>G

ENST00000423959.5:c.494A>G

NM_000132.3:c.599A>G

Pathogenic

Met criteria codes 4

PP4_Moderate

PP3

PS4

PP1_Moderate

Not Met criteria codes 1

PM2

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 c.599A>G (p.Glu200Gly) missense variant has a REVEL score of 0.779 which meets PP3 criteria (threshold >0.6). This variant is present in 1 hemizygot in gnomAD v2.1.1 and v3.1 and therefore, does not meet criteria for rarity in the population. At least 9 patients with mild hemophilia A are reported in literature, meeting F8 phenotype criteria for PS4_Very strong and PP4_Moderate (PMID: 29296726, 29388750). Three related individuals were reported in Reitter, et al (PMID: 20431853), and two were specifically mentioned to be uncle and

a nephew, which counts as 2 meioses. Additionally, authors of the Boylan, et al. paper informed this VCEP that one of the probands had an affected relative who also has this variant, which is counted as 1 meioses (PMID: 25780857). This gives a total of 3 meioses and meeting PP1_Moderate 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 for F8: PS4_Very strong, PP1_Moderate, PP4_Moderate, PP3.

Met criteria codes

PP4_Moderate			Male with mild hemophilia A with 12% factor VIII activity level who had full gene sequencing in F8 and F9 genes with deletion/duplication analysis.
PP3			REVEL score is 0.779, which is above the 0.6 cutoff.
PS4			At least 8 individuals with mild hemophilia A with only 1 hemizygote in gnomAD v2.1.1 and v3.1.
PP1_Moderate			Variant reported in uncle and nephew with mild hemophilia A (2 meioses). There are also 2 affected individuals from a CDC family cohort, but only 1 meiosis is counted because their relationship is unknown.

Not Met criteria codes

PM2		Present in one hemizygote in gnomAD v2.1.1.
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Curation History

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