

Variant: *NM_000132.3(F8):c.2215G>A (p.Glu739Lys)*

Version: 1.0

CA255139 [↗](#)

10247 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 70229bdd-5bf3-4644-8ab6-49706b300e62

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HGVS expressions

NM_000132.3:c.2215G>A

NM_000132.3(F8):c.2215G>A (p.Glu739Lys)

NC_000023.11:g.154931575C>T

CM000685.2:g.154931575C>T

NC_000023.10:g.154159850C>T

CM000685.1:g.154159850C>T

NC_000023.9:g.153813044C>T

NG_011403.1:g.96149G>A

NG_011403.2:g.96149G>A

ENST00000360256.9:c.2215G>A

ENST00000647125.1:c.*1881G>A

ENST00000360256.8:c.2215G>A

NM_000132.4:c.2215G>A

Pathogenic

Met criteria codes **6**

PP1_Moderate

PS3

PS4

PP4_Moderate

PP3

PM2_Supporting

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.2215G>A (p.Glu739Lys) missense variant is absent from males in both gnomAD v2.1.1 and v3.1.1, meeting the PM2_Supporting criteria. The variant has a REVEL score of 0.614 (>0.6), meeting PP3 criteria. At least 13 patients with mild hemophilia A are reported in the literature and internal laboratory data meeting F8 phenotype criteria (PMID: 24452774, 23711237, 21166991, 8547094, 16972227), which meets the PS4_Very strong and PP4_Moderate criteria. This variant has been labeled as an inverse discrepant variant, where the one-stage assays show lower factor VIII levels than the two-stage, or chromogenic, assays (EAHAD database; PMID: 32232366). There were

multiple related individuals across 6 different families reported that were genotyped, but their specific relation was not stated, so the **PP1** was capped at the moderate weight to be conservative (PMID: 24452774). In-vitro assays in COS-1 cells show FVIII-Glu739Lys results in lower FVIII:C in the mild range, as observed in patients with this variant and hemophilia A (PMID: 30997536). 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, PS3, PP1_Moderate, PP4_Moderate, PP3, PM2_Supporting**.

Met criteria codes

PP1_Moderate			Variant was identified in 13 individuals from 6 families. The relationships in these 6 families were not provided, so we assumed a minimal number of 7 meioses and applying at only the PP1_Moderate level to be conservative.
PS3			In-vitro assays in COS-1 cells show FVIII-Glu739Lys results in lower FVIII:C in the mild range, as observed in patients with this variant and hemophilia A (PMID: 30997536).
PS4			At least 13 patients with mild hemophilia A are reported in the literature and internal laboratory data meeting F8 phenotype criteria (PMID: 24452774, 23711237, 21166991, 8547094, 16972227, 29296726), which meets the PS4_Very strong code.
PP4_Moderate			One individual with mild hemophilia A with factor VIII activity level of 32%. Participant had full F8 and F9 gene deletion and duplication analysis through MLOF study.
PP3			The c.2215G>A (p.Glu739Lys) missense variant has a REVEL score of 0.614 (>0.6), meeting PP3 criteria
PM2_Supporting			The variant is absent from males in gnomAD.

Curation History

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