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.6623A>G (p.Gln2208Arg)

Version: 1.0

CA10567784

368117 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: a4ca4afa-b02a-4de0-b568-7804ab1da46c
Approved on: 2025/8/15
Published on: 2025/8/21

HGVS expressions

NM_000132.4:c.6623A>G
NM_000132.4(F8):c.6623A>G (p.Gln2208Arg)
NC_000023.11:g.154861818T>C
CM000685.2:g.154861818T>C
NC_000023.10:g.154090093T>C
CM000685.1:g.154090093T>C
NC_000023.9:g.153743287T>C
NG_011403.1:g.165906A>G
NG_011403.2:g.165906A>G
ENST00000360256.9:c.6623A>G
ENST00000644698.1:c.356A>G
ENST00000330287.10:c.218A>G
ENST00000360256.8:c.6623A>G
NM_000132.3:c.6623A>G
NM_019863.2:c.218A>G
NM_019863.3:c.218A>G

Likely Pathogenic

Met criteria codes 4

PP3 PM5 PP4_Moderate PS4

Not Met criteria codes 2

PM2 BS1

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_000132.4(F8):c.6623A>G (p.Gln2208Arg) is a missense variant. The computational predictor REVEL gives a score of 0.741, which is above the threshold of 0.6, evidence that correlates with impact to F8 function (PP3_Supporting). This variant has been reported in 4

probands with mild hemophilia A This variant was reported in 2 patients with mild hemophilia A with FVIII:C = 23% and FVIII:C=34%. VWD was excluded. (PMID: 26879396; PMID 27734074). This variant was reported in 1 patient with mild hemophilia A with FVIII:C = 23%. VWD was ruled out (PMID: 27734074). Reported in 1 patient with mild hemophilia A with FVIII:C = 34%. VWD is excluded. Another missense variant c.6622C>G (p.Gln2208Glu) is present at the same codon and has been classified as pathogenic by CFD VCEP. In summary, based on the evidence available at this time, the clinical significance of this variant is likely pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8: PM5, PP3, PS4_Strong.

Met criteria codes

PP3	✔	The variant has a REVEL score: of 0.741 SpliceAI score: AL, DL, DG = 0.0, AG = 0.03, meeting PP3 Criteria.
PM5	✔	Another missense variant c.6622C>G (p.Gln2208Glu) is present at the same codon and has been classified as pathogenic by CFD VCEP.
PP4_Moderate	✔	This variant was reported in 1 patient with mild hemophilia A with FVIII:C = 23%. VWD was excluded. MLPA used to detect del/dups.
PS4	✔	Total of 5 probands noted with mild hemophilia. This variant was reported in 2 probands with mild hemophilia A with FVIII:C = 23% and FVIII:C=34%, but one was used for PP4 code. This variant was reported in 1 proband with mild hemophilia A with FVIII:C = 23%. Reported in 1 proband with mild hemophilia A with FVIII:C = 34%. VWD was excluded in multiple probands. (PMID: 26879396; PMID 27734074).

Not Met criteria codes

PM2	✖	This variant is present in gnomAD v2 with an allele frequency of 0.00002437.
BS1	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00004(4/92592 alleles) in the European (non-finnish) population, which is greater than the ClinGen Coag VCEP's threshold for BS1. However, it doesn't meet the requirement that the population must have a minimum of five variant alleles present.

Curation History

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