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Variant: NM_000132.4(F8):c.6622C>G (p.Gln2208Glu)

Version: 1.0

CA414905992

811219 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: e33fd50a-49ea-4ff8-a27c-3458a35b6532
Approved on: 2025/8/15
Published on: 2025/8/21

HGVS expressions

NM_000132.4(F8):c.6622C>G (p.Gln2208Glu)
NM_000132.4:c.6622C>G
NC_000023.11:g.154861819G>C
CM000685.2:g.154861819G>C
NC_000023.10:g.154090094G>C
CM000685.1:g.154090094G>C
NC_000023.9:g.153743288G>C
NG_011403.1:g.165905C>G
NG_011403.2:g.165905C>G
ENST00000360256.9:c.6622C>G
ENST00000644698.1:c.355C>G
ENST00000330287.10:c.217C>G
ENST00000360256.8:c.6622C>G
NM_000132.3:c.6622C>G
NM_019863.2:c.217C>G
NM_019863.3:c.217C>G

Pathogenic

Met criteria codes 4

PP3 | PS4_Very Strong | PP4_Moderate | PM2_Supporting

Not Met criteria codes 1

PM5

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.6622C>G (p.Gln2208Glu) variant is absent in gnomAD v2.1.1 and 3.1.2 meeting PM2_Supporting. The variant has a REVEL score of 0.799 meeting PP3. There have been more than 10 probands reported with mild hemophilia A, and at least one proband with FVIII:C 24%

had VWD type 2N ruled out (PMID: 29296726, 21645180, 16769589 & EAHAD Database), meeting PP4_Moderate and PS4_Very strong. There is another variant at the codon, c.6622C>G, p.Gln2208Arg, and has been classified as pathogenic by CFD VCEP. However, PM5 will not be applied to avoid circularity. In summary, based on the evidence available at this time, the clinical significance of this variant is pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8: PM2_Supporting, PP3, PP4_Moderate, PS4_Very strong.

Met criteria codes

PP3	✔	This variant has a REVEL score of 0.799 meeting and a SpliceAI score of 0.00, acceptor gain of 0.01 meeting PP3.
PS4_Very Strong	✔	More than 10 probands are reported with mild hemophilia A, and 1 proband was applied to PP4. 1 proband with mild hemophilia A with FVIII:C 24% and VWD type 2N ruled out (PMID: 21645180). 3 probands reported with mild hemophilia A with FVIII levels of 30%, 26%, and 14%. From unpublished McVey and Tuddenham, et al. 5 probands with FVIII:C (%): 23.5%, 27.6%, 28%, 20%, 23% (PMID: 16769589). There are other unpublished probands in the EAHAD Database that were not used for this curation for brevity.
PP4_Moderate	✔	1 proband with mild hemophilia A with s FVIII level of 6% in MLOF.
PM2_Supporting	✔	The c.6622C>G (p.Gln2208Glu) variant is males in gnomAD v2.1.1 and gnomAD 3.1.2.

Not Met criteria codes

PM5	✖	Another missense variant c.6622C>G (p.Gln2208Arg) is present at the same codon and has been classified as pathogenic by CFD VCEP. It will not be counted to avoid circularity.

Curation History

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