

Variant: *NM_000132.4(F8):c.6658G>C (p.Ala2220Pro)*

Version: 1.0

CA10567779 [↗](#)

1029498 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: f0c59eaf-6cee-4161-957b-83eb0a2a4db2

Approved on: 2025/8/15

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HGVS expressions

NM_000132.4(F8):c.6658G>C (p.Ala2220Pro)

NM_000132.4:c.6658G>C

NC_000023.11:g.154861783C>G

CM000685.2:g.154861783C>G

NC_000023.10:g.154090058C>G

CM000685.1:g.154090058C>G

NC_000023.9:g.153743252C>G

NG_011403.1:g.165941G>C

NG_011403.2:g.165941G>C

ENST00000360256.9:c.6658G>C

ENST00000644698.1:c.391G>C

ENST00000330287.10:c.253G>C

ENST00000360256.8:c.6658G>C

NM_000132.3:c.6658G>C

NM_019863.2:c.253G>C

NM_019863.3:c.253G>C

Pathogenic

Met criteria codes **5**

PP4_Moderate

PS4_Very Strong

PM2_Supporting

PP3

PP1_Moderate

Not Met criteria codes **3**

BS1

BS3

BA1

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.6658G>C; p.Ala2220Pro is absent in males in gnomAD database v.2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.713, which is above the threshold of 0.6, evidence that correlates with impact to F8 function (PP3). This

variant has been reported in at least 17 individuals with mild/moderate hemophilia A (PMID: 18034765 ; 20536985, 10910913, 29296726), meeting the PS4_Very Strong & PP4_Moderate criteria. This variant was found to co-segregate with the disease in multiple affected family members, with 7 meioses observed in one family (PP1_Moderate; PMID: 20536985). This variant has also been associated with incidence of inhibitor development to factor replacement products (PMID: 18034765). In summary, this variant meets criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the ClinGen Coagulation Factor Deficiency Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for F8 Version 1.0.0: PM2_Supporting, PP3, PS4_Very Strong, PP4_Moderate, PP1_Moderate.

Met criteria codes

PP4_Moderate			1 proband with moderate hemophilia A genotyped through My Life Our Future (MLOF).
PS4_Very Strong			This variant has been reported in at least 17 unrelated patients with mild hemophilia A, with one proband being used for PP4 (PMID: 10910913, 29296726, 18034765, 20536985). In summary, it fits the PS4_Very strong criteria.
PM2_Supporting			The variant is absent in males in GnomAD database v.2.1.1 (PM2_Supporting).
PP3			The computational predictor REVEL gives a score of 0.713, which is above the threshold of 0.6, evidence that correlates with impact to F8 function (PP3_Supporting).
PP1_Moderate			This variant was found to segregate with the disease in multiple affected family members, with 4 meioses observed in one family (PMID: 20536985).

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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