

Variant: NM_000132.4(F8):c.222G>A (p.Thr74=)

Version: 1.0

CA519384276 [↗](#)

618103 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 2ec7722b-a6c2-463a-aa7e-28c6c77f9d07

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HGVS expressions

NM_000132.4(F8):c.222G>A (p.Thr74=)

NM_000132.4:c.222G>A

NC_000023.11:g.154999522C>T

CM000685.2:g.154999522C>T

NC_000023.10:g.154227797C>T

CM000685.1:g.154227797C>T

NC_000023.9:g.153880991C>T

NG_011403.1:g.28202G>A

NG_011403.2:g.28202G>A

ENST00000360256.9:c.222G>A

ENST00000647125.1:c.*8G>A

ENST00000360256.8:c.222G>A

ENST00000423959.5:c.117G>A

ENST00000453950.1:c.204G>A

NM_000132.3:c.222G>A

Uncertain Significance

Met criteria codes **1**

BS1

Not Met criteria codes **6**

BP4

PVS1

BP7

PS4

PP3

PP4

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.222G>A (p.Thr74=) variant is a synonymous change that may result in abnormal gene splicing. The Grpmax filtering allele frequency in gnomad V4.1.0 is 0.0001184 (BS1). This variant has been reported in at least nine males with mild hemophilia A (PMIDs: 35770352, 35743412, 30690819; Fernández-Artazcoz (2024), and Internal Laboratory Data), including at least one patient who underwent

comprehensive testing with F8 sequencing and CNV analysis, and at least one patient with type 2N von Willebrand disease excluded by normal 2N binding. Patients have also been reported with reduced factor VIII activity levels >40% (PMIDs: 25652415, Fernández-Artazcoz (2024)), indicating that the variant is associated with a spectrum of factor VIII reduction extending into the low-normal range. Patient mRNA analyses show variable splicing patterns, with some samples containing both full length and exon 2 skipped transcripts, while others predominantly express the wildtype transcript. (PMIDs: 25652415, 34962362, 23088352). This variability is consistent with incomplete or leaky splicing, likely reflecting differences in individual sensitivity to the splice defect. No PS4 or PP4 points have been applied due to the variant meeting BS1. A minigene assay showed normal exon 2 splicing for c.222G>A in HeLa and in Huh7 hepatocyte derived cells (PMID: 30690819). In summary, the clinical significance of this variant is uncertain. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8/F9: BS1.

Met criteria codes

BS1			The Grpmax filtering AF in gnomad V4.1.0 is 0.0001184 (meets BS1) with greater than 45000 alleles tested for the subpopulation in which this variant was detected (Admixed American).
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Not Met criteria codes

BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			This variant may alter normal splicing and result in transcripts lacking exon 2, introducing a frameshift and premature termination codon predicted to undergo nonsense mediated decay (p.Phe30Serfs*7). Patient mRNA analyses show variable splicing patterns, with some samples containing both full length and exon 2 skipped transcripts, while others predominantly express the wildtype transcript. (PMIDs: 25652415, 34962362, 23088352). This variability is consistent with incomplete or leaky splicing, likely reflecting differences in individual sensitivity to the splice defect. Such variability in splicing efficiency corresponds with the variable reduction in factor VIII levels observed among patients, ranging from normal to mildly decreased. A minigene assay showed normal exon 2 splicing for c.222G>A in HeLa and in Huh7 hepatocyte derived cells (PMID: 30690819). Due to conflicting evidence, PVS1 has not been applied at any strength.
BP7			The variant has a PhyloP 100 vertebrate score of -1.16, which suggests it is not conserved, however this variant does not meet BP4 requirements and therefore BP7 cannot be applied.
PS4			This variant has been reported in at least nine males with mild hemophilia A (PMIDs: 35770352, 35743412, 30690819; Fernández-Artazcoz (2024), and Internal Laboratory Data), including at least one patient who underwent comprehensive testing with F8 sequencing and CNV analysis, and at least one patient with type 2N von Willebrand disease excluded by normal 2N binding. Patients have also been reported with reduced factor VIII activity levels >40% (PMIDs: 25652415, Fernández-Artazcoz (2024)), indicating that the variant is associated with a spectrum of factor VIII reduction extending into the low-normal range. Of note, PS4 points have not been applied due to this variant meeting BS1. Fernández-Artazcoz (2024) can be accessed here: https://www.postersessiononline.eu/173580348_eu/congresos/WFH2024/aula/-PO_32_WFH2024.pdf
PP3			The variant has a SpliceAI score of: 0.06, 0.05, 0, 0. This is below the threshold for PP3 (>0.5), but above the threshold for BP4 (<0.05).
PP4			1 patient in MLOF with a FVIII level of 26%, which typically counts at PP4_moderate, however PP4 points cannot be applied due to the variant meeting BS1.

Curation History 

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