

Variant: *NM_001313913.2:c.138G>C*

Version: 1.0

CA414435594 [↗](#)

Gene: F9 ([HGNC:2158](#))

Condition: hemophilia B ([MONDO:0010604](#))

Inheritance Mode: X-linked inheritance

UUID: 491bbc8e-a398-41a7-8fa1-5ab562f996c1

Approved on: 2026/4/10

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HGVS expressions

NM_001313913.2:c.138G>C

NC_000023.11:g.139537059G>C

CM000685.2:g.139537059G>C

NC_000023.10:g.138619218G>C

CM000685.1:g.138619218G>C

NC_000023.9:g.138446884G>C

NG_007994.1:g.11324G>C

ENST00000218099.7:c.138G>C

ENST00000218099.6:c.138G>C

ENST00000394090.2:c.138G>C

ENST00000479617.2:n.145G>C

NM_000133.3:c.138G>C

NM_001313913.1:c.138G>C

NM_000133.4:c.138G>C

Pathogenic

Met criteria codes 4

PS1_Moderate

PS4_Moderate

PM2_Supporting

PVS1

Not Met criteria codes 3

PS3

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 F9 Version 2.0.0*

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Coagulation Factor Deficiency VCEP

The c.138G>C variant in F9 is a possible cryptic splice variant predicted to cause substitution of arginine by serine at amino acid 46. This variant is completely absent from gnomAD v4.1.0 meeting PM2_Supporting. The variant has a REVEL score of 0.802 (>0.6) and SpliceAI predicts a cryptic donor gain with a score of 0.13. This variant is located within an exonic splicing silencer, and a minigene assay performed in BHK cells demonstrated that c.138G>C results in abnormal splicing and an out-of-frame transcript with a premature

termination codon (PVS1_RNA, PMID: 26063760). An additional, protein-level functional study demonstrated p.Arg46Ser reduced secretion of a reporter protein (PMID: 32766856). However, because this variant has also been shown to disrupt splicing, the extent to which the observed functional effect is attributable to abnormal splicing versus the missense change itself remains unclear. At least 3 probands from the literature and internal laboratory data meet F9 phenotype criteria for PS4_Moderate (PMID: 25251685, PMID: 3461460, PMID: 7937052). Another variant impacting this same codon with a different nucleotide change, F9 c.138G>T, p.Arg46Ser, was classified at pathogenic using CFD VCEP rule specifications meeting PS1_Moderate. In summary, based on the evidence available at this time, this variant is classified as pathogenic for hemophilia B. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel v2.0.0: PVS1_RNA, PS1_Moderate, PS4_Moderate, PM2_Supporting.

Met criteria codes

PS1_Moderate			The Arg46Ser variant is a consequence of c.138G>T and c.138G>C. The c.138G>T variant is reported in moderate-severe HB patients. Both variants alter splicing.
PS4_Moderate			At least 3 probands from the literature and internal laboratory data meet F9 phenotype criteria (PMID: 25251685, PMID: 3461460, PMID: 7937052).
PM2_Supporting			The c.138G>C (p.Arg46Ser) variant is completely absent from population databases (gnomAD v4.1.0).
PVS1			This variant is located within an exonic splicing silencer, and RT-PCR minigene assays performed in BHK cells demonstrated that c.138G>C was associated with abnormal splicing due to increased use of an exonic cryptic 5' splice site, resulting in an out-of-frame transcript with a premature termination codon (PMID: 26063760).

Not Met criteria codes

PS3			The p.Arg46Ser variant was assessed in a cell-based reporter assay in HEK293T cells and was associated with a severely reduced secreted conformation-specific reporter (SCSR) signal, consistent with markedly reduced secretion of properly processed functional reporter protein (PMID: 32766856). Of note, because the assay was performed at the protein level, it is unclear whether the p.Arg46Ser construct corresponds specifically to c.138G>C or c.138G>T, as both encode the same amino acid change and both variants are cited. PS3 evidence was not applied because additional published studies indicate that this variant causes abnormal splicing, making it unclear to what extent any observed functional effect is attributable to the missense change itself.
PP3			The missense variant has a REVEL score of 0.802 (>0.6). SpliceAI predicts a cryptic donor gain with a score of 0.13 but does not meet the threshold of >0.5. Code is not used because PVS1_RNA is applied.
PP4			There are no known reported cases with deletion/duplication reported.

Curation History 

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Showing 1 to 1 of 1 rows

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