

Variant: *NM_000133.3(F9):c.88G>C (p.Val30Leu)*

Version: 1.0

CA414434503 [↗](#)

627400 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 3b97275b-1610-4c8c-aa33-afd4f5c09395

Approved on: 2026/4/10

Published on: 2026/4/12

HGVS expressions

NM_000133.3(F9):c.88G>C (p.Val30Leu)

NM_000133.3:c.88G>C

NC_000023.11:g.139530852G>C

CM000685.2:g.139530852G>C

NC_000023.10:g.138613011G>C

CM000685.1:g.138613011G>C

NC_000023.9:g.138440677G>C

NG_007994.1:g.5117G>C

ENST00000218099.7:c.88G>C

ENST00000218099.6:c.88G>C

ENST00000394090.2:c.88G>C

ENST00000479617.2:n.95G>C

NM_001313913.1:c.88G>C

NM_000133.4:c.88G>C

NM_001313913.2:c.88G>C

Likely Pathogenic

Met criteria codes **5**

PS1_Moderate

PP3

PS4_Moderate

PM2_Supporting

PS3_Supporting

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 F9 c.88G>C, p.Val30Leu variant is completely absent from gnomAD v4.1.0 meeting PM2_Supporting. The computational splicing predictor SpliceAI gives a score of 0.97 for donor loss, predicting that the variant disrupts the donor splice site of intron 1 of F9 meeting PP3. Additionally, the c.88G>A, p.Val30Ile variant is also predicted to impact splicing (SpliceAI donor loss score of 0.96) and was previously

classified as a likely pathogenic variant using the CFD VCEP rule specifications, meeting **PS1_Moderate**. Two probands with the Val30Leu variant have been reported with moderate or severe hemophilia B meeting **PS4_Moderate** (PMID: 31064749, EAHAD Factor IX (F9) Database). Secreted conformation-specific reporter (SCSR) assay in HEK293T cells showed decreased SCSR levels compared to that of the WT, indicating that this variant impacts protein function (PMID: 32766856; **PS3_Supporting**). 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 F9 v2.0.0: **PS1_Moderate, PS4_Moderate, PP3, PM2_Supporting, PS3_Supporting**.

Met criteria codes

PS1_Moderate			Val30Ile is a variant at the same residue and is classified as likely pathogenic by the CFD-VCEP yet. Both Val30Leu and Val30Ile are predicted to impact splicing. The computational splicing predictor SpliceAI gives a score of 0.97 for donor loss, predicting that the variant disrupts the donor splice site of intron 1 of F9. For the F9 c.88G>A, p.Val30Ile variant, the computational splicing predictor SpliceAI gives a score of 0.96 for donor loss.
PP3			The c.88G>C (p.Val30Leu) missense variant has a REVEL score of 0.787 (>0.6). The variant affects the last codon of exon 1 and spliceAI predicts a splicing impact with delta score of 0.97.
PS4_Moderate			1 proband with the Val30Leu variant and moderate hemophilia B is reported in the literature (PMID: 31064749) and 1 proband with severe hemophilia B is listed in the EAHAD factor IX (F9) database.
PM2_Supporting			The c.88G>C; p.Val30Leu variant is completely absent from gnomAD v4.1.1.
PS3_Supporting			PMID: 32766856 analyzed variants in a cell-based reporter assay with levels of secreted conformation-specific reporter with a functional γ-carboxyglutamate (Gla) domain of FIX. The Val30Leu variant showed less secretion of functional protein. The actual levels of FIX:C and FIX:Ag are not available; however, since this assay has been accepted as valid by the CFD VCEP, PS3_Supporting criteria is met.

Curation History

▼

▼

Showing 1 to 1 of 1 rows

--

