

Variant: *NM_000133.4(F9):c.802T>A (p.Cys268Ser)*

Version: 1.1

CA414443531 [↗](#)

627143 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 27098047-1cd6-476e-980b-90322be70d28

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HGVS expressions

NM_000133.4:c.802T>A

NM_000133.4(F9):c.802T>A (p.Cys268Ser)

NC_000023.11:g.139560819T>A

CM000685.2:g.139560819T>A

NC_000023.10:g.138642978T>A

CM000685.1:g.138642978T>A

NC_000023.9:g.138470644T>A

NG_007994.1:g.35084T>A

ENST00000218099.7:c.802T>A

ENST00000643157.1:n.1469T>A

ENST00000218099.6:c.802T>A

ENST00000394090.2:c.688T>A

NM_000133.3:c.802T>A

NM_001313913.1:c.688T>A

NM_001313913.2:c.688T>A

Likely Pathogenic

Met criteria codes **5**

PP4_Moderate

PS4_Moderate

PP3

PM5

PM2_Supporting

Not Met criteria codes **1**

PM1

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 1.0.0

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

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

Evidence submitted by expert panel

Coagulation Factor Deficiency VCEP

The F9 c.802T>A (p.Cys268Ser) variant is completely absent from gnomAD v2.1.1 and v3.1.1 meeting PM2_Supporting. This missense variant has a REVEL score of 0.969 and meets PP3 criteria (threshold >0.6 - PP3). Three probands are reported in the literature with moderate and severe hemophilia B meeting F9 criteria (PMID: 31064749, PMID: 8091381, PMID: 21263151 - PS4_Moderate &

PP4_Moderate). The c.802T>A (p.Cys268Ser) variant is a missense change at the same residue (p.Cys268) where at least 3 different missense changes have been previously established as pathogenic/likely pathogenic variants (p.Cys268Gly, p.Cys268Arg, p.Cys268Tyr) using CFD-VCEP rules for F9 and SpliceAI shows no splicing impact (PM5). In summary, this variant meets criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8/F9: **PS4_Moderate, PP4_Moderate, PM5, PM2_Supporting, PP3.**

Met criteria codes

PP4_Moderate			PMID: 31064749: Proband with hemophilia B from the ThromboGenomics cohort.
PS4_Moderate			2 probands with hemophilia B reported in literature counted for PS4. PMID: 8091381, PMID: 21263151. Note, the third proband in the literature from PMID: 31064749 is counted under PP4_Moderate.
PP3			REVEL score is 0.969, which is above the 0.6 cutoff.
PM5			The c.5186G>A (p.Gly1729Glu) variant is a missense change at the same residue (p.1729) where at least 3 different missense changes have been previously established as pathogenic/likely pathogenic variants using CFD-VCEP rules for F8/F9 and RNA data or agreement in splicing predictors (SpliceAI <0.01) show no splicing impact.
PM2_Supporting			Variant is absent in gnomAD v2.1.1 or v3.1.

Not Met criteria codes

PM1			Variant is not within exons 4, 5 or 6.
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Curation History

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