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Variant: NM_001313913.2:c.688T>C

Version: 1.0

CA414443534

Gene: F9 (HGNC:2158)
Condition: hemophilia B (MONDO:0010604)
Inheritance Mode: X-linked inheritance
UUID: 1083b043-4e59-4203-a23c-d3fb1a0fc64a
Approved on: 2025/10/3
Published on: 2025/10/7

HGVS expressions

NM_001313913.2:c.688T>C
NC_000023.11:g.139560819T>C
CM000685.2:g.139560819T>C
NC_000023.10:g.138642978T>C
CM000685.1:g.138642978T>C
NC_000023.9:g.138470644T>C
NG_007994.1:g.35084T>C
ENST00000218099.7:c.802T>C
ENST00000643157.1:n.1469T>C
ENST00000218099.6:c.802T>C
ENST00000394090.2:c.688T>C
NM_000133.3:c.802T>C
NM_001313913.1:c.688T>C
NM_000133.4:c.802T>C

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PM5 PS4 PP3

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 c.802T>C (NM_000133.4) variant in F9 is a missense variant predicted to cause substitution of cysteine by arginine at amino acid 268 (p.Cys268Arg). This variant has been reported in >4 probands with severe FIX deficiency, meeting phenotypic criteria for F9 (PS4 - PMIDs :17014892, 24375831, 15921378). This variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3/ gnomAD v4.1.0), meeting PM2_Supporting. The computational predictor REVEL gives a score of 0.958, which is above the threshold of 0.6, evidence that

correlates with impact to F9 function (PP3). A different missense variant causing a change at the same residue (p.Cys268Tyr) has been established as pathogenic for F9 and SpliceAI predicts no impact on splicing (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 F9: PS4 + PM2_supporting + PP3 + PM5. (ClinGen Coagulation Factor Deficiency Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for F9 Version 1.0.0., Released 10/5/2023).

Met criteria codes

PM2_Supporting	✔	Variant is absent in gnomAD v2.1.1, v3.1, and v4.1.0.
PM5	✔	There are many variants at this location, including c.803G>A, p.Cys268Tyr which is classified as pathogenic using PS2_VS + PS4 + PM2_sup + PP3. Of note, SpliceAI scores for all variants at this location are 0, indicating the mechanism of disease for variants at this location is unrelated to splicing.
PS4	✔	The c.802T>C (p.Cys268Arg; legacy c.Cys222Arg) variant has been reported in at least 5 probands (4-7 probands & 0 gnomAD alleles) meeting phenotypic criteria for F9 (PS4; PMIDs: 17014892, 24375831, 15921378).
PP3	✔	REVEL score is 0.958, which meets the 0.6 cutoff.

Not Met criteria codes

PM1	✖	Variant is in the S1 peptidase functional domain, however, this domain does not qualify for PM1.

Curation History

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