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Variant: NM_000133.3(F9):c.88G>A (p.Val30Ile)

Version: 1.0

CA414434500

651569 (ClinVar)

Gene: F9 (HGNC:2158)
Condition: hemophilia B (MONDO:0010604)
Inheritance Mode: X-linked inheritance
UUID: b731a335-3a67-4702-b7ce-39076c05c72e
Approved on: 2024/5/9
Published on: 2024/7/11

HGVS expressions

NM_000133.3:c.88G>A
NM_000133.3(F9):c.88G>A (p.Val30Ile)
NC_000023.11:g.139530852G>A
CM000685.2:g.139530852G>A
NC_000023.10:g.138613011G>A
CM000685.1:g.138613011G>A
NC_000023.9:g.138440677G>A
NG_007994.1:g.5117G>A
ENST00000218099.7:c.88G>A
ENST00000218099.6:c.88G>A
ENST00000394090.2:c.88G>A
ENST00000479617.2:n.95G>A
NM_001313913.1:c.88G>A
NM_000133.4:c.88G>A
NM_001313913.2:c.88G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PS3_Supporting PS4

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.88G>A (NM_000133.3) variant in F9 is a missense variant predicted to cause substitution of Valine by Isoleucine at amino acid 30 (p.Val30Ile). This variant has been reported in at least 5 probands meeting the hemophilia B phenotype criteria specified by the Coagulation Factor Deficiency VCEP (PS4; PMID: 10094553, 23093250, 1680287, 11122099). This variant is absent from gnomAD v2.1.1 and

v3.1.2 (PM2_Supporting). Secreted conformation-specific reporter (SCSR) assay in HEK293T cells showed decreased SCSR level at ~60% of that of the WT, indicating that this variant impacts protein function (PMID: 32766856; the study is approved by the VCEP, applicable at the Supporting strength; PS3_Supporting). The computational predictor REVEL gives a score of 0.787, which is above the threshold of 0.6, evidence that correlates with impact to F9 function. The variant is the last amino acid of exon 1. The computational splicing predictor SpliceAI gives a score of 0.96 for donor loss, predicting that the variant disrupts the donor splice site of intron 1 of F9 (PP3). In summary, this variant meets the criteria to be classified as Likely Pathogenic for X-linked recessive hemophilia B based on the ACMG/AMP criteria applied, as specified by the ClinGen Coagulation Factor Deficiency VCEP: PS4, PP3, PS3_Supporting, PM2_Supporting. (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	✔	This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.787, which is above the threshold of 0.6, evidence that correlates with impact to F9 function. The variant is the last amino acid of exon 1. The computational splicing predictor SpliceAI gives a score of 0.96 for donor loss, predicting that the variant disrupts the donor splice site of intron 1 of F9 (PP3).
PS3_Supporting	✔	Secreted conformation-specific reporter (SCSR) assay in HEK293T cells showed decreased SCSR level at ~60% of that of the WT, indicating that this variant impacts protein function (PMID: 32766856; the study is approved by the VCEP, applicable at the Supporting strength; PS3_Supporting).
PS4	✔	This variant has been reported in at least 5 probands meeting the hemophilia B phenotype criteria specified by the Coagulation Factor Deficiency VCEP (PS4; PMID: 10094553, 23093250, 1680287, 11122099).

Curation History

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