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Variant: NM_001313913.2:c.1121G>A

Version: 1.0

CA414446709

2775451 (ClinVar)

Gene: F9 (HGNC:2158)
Condition: hemophilia B (MONDO:0010604)
Inheritance Mode: X-linked inheritance
UUID: 45aad5b1-fcb9-4818-8df5-a5b8fe03662b
Approved on: 2024/2/9
Published on: 2024/7/11

HGVS expressions

NM_001313913.2:c.1121G>A
NC_000023.11:g.139561920G>A
CM000685.2:g.139561920G>A
NC_000023.10:g.138644079G>A
CM000685.1:g.138644079G>A
NC_000023.9:g.138471745G>A
NG_007994.1:g.36185G>A
ENST00000218099.7:c.1235G>A
ENST00000643157.1:n.1723+179G>A
ENST00000218099.6:c.1235G>A
ENST00000394090.2:c.1121G>A
NM_000133.3:c.1235G>A
NM_001313913.1:c.1121G>A
NM_000133.4:c.1235G>A

Pathogenic

Met criteria codes 4

PP3 PM2_Supporting PP4_Moderate PS4

Not Met criteria codes 1

PM5

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.1235G>A (NM_000133.4) variant in F9 is a missense variant predicted to cause substitution of Glycine by Glutamate at amino acid 412 (p.Gly412Glu). This variant has been reported in at least 8 probands meeting the hemophilia B phenotype criteria specified by the Coagulation Factor Deficiency VCEP (PS4_VeryStrong; PMID: 10874302, 29296726, 1680287, 8055323, 12588353). At least one patient with this variant meets the VCEP specification for PP4 (PP4_Moderate, MLOF study). This variant is absent from gnomAD v2.1.1 and v3.1.1

(PM2_Supporting). The computational predictor REVEL gives a score of 0.981, which is above the threshold of 0.6, evidence that correlates with impact to F9 function (PP3). In summary, this variant meets the criteria to be classified as Pathogenic for X-linked recessive hemophilia B based on the ACMG/AMP criteria applied, as specified by the ClinGen Coagulation Factor Deficiency VCEP: PS4_VeryStrong, PP4_Moderate, PP3, 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

PP3	✔	The computational predictor REVEL gives a score of 0.981, which is above the threshold of 0.6, evidence that correlates with impact to F9 function (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and v3.1.1 (PM2_Supporting).
PP4_Moderate	✔	Male with severe hemophilia B with F8 and F9 full gene sequencing and deletion/duplication analysis.
PS4	✔	This variant has been reported in at least 8 probands meeting the hemophilia B phenotype criteria specified by the Coagulation Factor Deficiency VCEP (PS4_VeryStrong; PMID: 10874302, 29296726, 1680287, 8055323, 12588353).

Not Met criteria codes

PM5	✖	This criteria is met. However, this variant meets pathogenic without using this code, so it is no longer needed for this variant. Gly412Trp and Gly412Ala are two variants at the same residue that are curated by the CFD-VCEP to be VUS with 1 supporting code short of a likely pathogenic classification. PM5_Supporting is applied based on two "highly suspicious VUS" at the same residue.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001313913.2:c.1121G>A	Pathogenic	Hemophilia B	2024-07-11	1.0	ClinGen Coagulation Factor Deficiency Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for F9 Version 1.0.0	F9

Showing 1 to 1 of 1 rows

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