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Variant: NM_000133.3(F9):c.1009G>C (p.Ala337Pro)

Version: 2.0

CA255378

10606 (ClinVar)

Gene: F9 (HGNC:2158)
Condition: hemophilia B (MONDO:0010604)
Inheritance Mode: X-linked inheritance
UUID: 79a87499-0c15-4285-b320-7feb19194468
Approved on: 2024/9/30
Published on: 2024/10/1

HGVS expressions

NM_000133.3:c.1009G>C
NM_000133.3(F9):c.1009G>C (p.Ala337Pro)
NC_000023.11:g.139561694G>C
CM000685.2:g.139561694G>C
NC_000023.10:g.138643853G>C
CM000685.1:g.138643853G>C
NC_000023.9:g.138471519G>C
NG_007994.1:g.35959G>C
ENST00000218099.7:c.1009G>C
ENST00000643157.1:n.1676G>C
ENST00000218099.6:c.1009G>C
ENST00000394090.2:c.895G>C
NM_001313913.1:c.895G>C
NM_000133.4:c.1009G>C
NM_001313913.2:c.895G>C

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PM5 PS4_Moderate

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.1009G>C (NM_000133.4) variant in F9 is a missense variant predicted to cause substitution of alanine by proline at amino acid 337 (p.Ala337Pro). This variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3). This variant has been previously reported in at least one patient with mild hemophilia B (PMID: 1998585), meeting phenotypic criteria for F9. An additional proband with

severe hemophilia B has been reported in the EAHAD Factor IX (F9) variant database. The computational predictor REVEL gives a score of 0.617, which is above the threshold of 0.6, evidence that correlates with impact to F9 function (PP3). Different missense variants causing a change at the same residue (p.Ala337Thr and p.Ala337Val) have been established as pathogenic for F9 and SpliceAI predicts no impact on splicing meeting PM5. In summary, based on the evidence available at this time, the clinical significance of this variant is uncertain. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F9: PS4_Moderate + 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	✔	The c.1009G>C (p.Ala337Pro) variant is completely absent from males in population databases (gnomAD v2.1.1/gnomAD v3).
PP3	✔	The variant has a REVEL score of 0.617 (>0.6) and a CADD score of 22.8 (>21) and meets criteria for PP3. SpliceAI predicts no splicing impact with scores <=0.01
PM5	✔	Different missense variants causing a change at the same residue (p.Ala337Thr and p.Ala337Val) have been established as pathogenic for F9 and SpliceAI predicts no impact on splicing. Notes, bring up for discussion upgrading PM5 to strong when there are 2 or more pathogenic variants at the same location (Missense variants with no impact on splicing).
PS4_Moderate	✔	At least 1 patient with severe HB reported in the EAHAD and 1 with moderate HB reported in PMID: 1998585 meets criteria for PS4_Moderate.

Not Met criteria codes

PM1	✖	Variant refresh 4/1/24: Variant no longer qualifies for PM1. The variant affects the Peptidase S1 domain (aa 227-459) in the F9 protein deemed critical for protein function by the CFD-VCEP.

Curation History

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