

Variant: *NM_000133.3(F9):c.1009G>A (p.Ala337Thr)*

Version: 1.0

CA414445354 [↗](#)

626950 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 29ecb66b-21ba-432d-8d33-c05913d46900

Approved on: 2024/4/26

Published on: 2024/7/11

HGVS expressions

NM_000133.3:c.1009G>A

NM_000133.3(F9):c.1009G>A (p.Ala337Thr)

NC_000023.11:g.139561694G>A

CM000685.2:g.139561694G>A

NC_000023.10:g.138643853G>A

CM000685.1:g.138643853G>A

NC_000023.9:g.138471519G>A

NG_007994.1:g.35959G>A

ENST00000218099.7:c.1009G>A

ENST00000643157.1:n.1676G>A

ENST00000218099.6:c.1009G>A

ENST00000394090.2:c.895G>A

NM_001313913.1:c.895G>A

NM_000133.4:c.1009G>A

NM_001313913.2:c.895G>A

Pathogenic

Met criteria codes **3**

PS4

PP3

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 c.1009G>A (NM_000133.4) variant in F9 is a missense variant predicted to cause substitution of alanine by threonine at amino acid 337 (p.Ala337Thr). This variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3). This variant has been reported in at least 8 unique probands with mild to severe hemophilia B (PMID: 8091381; PMID: 11013449; PMID: 2726481), meeting phenotypic

criteria for F9. The computational predictor REVEL gives a score of 0.783, which is above the threshold of 0.6, evidence that correlates with impact to F9 function (PP3). In summary, this variant meets criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F9: PS4_Very Strong + PM2_Supporting + PP3. (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

PS4			Refresh 4/2/24: Variant is seen in at least 8 unrelated patients, meets criteria for PS4_VS-APM. The Ala337Thr variant has been reported in at least 6 unrelated probands (≥ 4 probands & 0 gnomAD alleles) from PMID: 8091381 meeting phenotypic criteria for F9.
PP3			The variant has a REVEL score of 0.783 (>0.6) and a CADD score of 26.5 (>21). Note: Variant has a SpliceAI score of 0.00 (Max distance 10,000; masked scores), which qualifies it to be used as evidence of pathogenicity for other missense variants at this location (PM5) which also do not predict a splice impact.
PM2_Supporting			The c.1009G>A (p.Ala337Thr) variant is completely absent from males in population databases (gnomAD v2.1.1/gnomAD v3).

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.
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Curation History



 

 

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