The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000133.3(F9):c.1009G>A (p.Ala33...	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

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