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.835G>A (p.Ala279Thr)

Version: 1.1

CA277507

216926 (ClinVar)

Gene: F9 (HGNC:2158)
Condition: hemophilia B (MONDO:0010604)
Inheritance Mode: X-linked inheritance
UUID: 4982024e-218e-4597-8dff-d780dd246d0a
Approved on: 2025/2/19
Published on: 2025/2/19

HGVS expressions

NM_000133.3:c.835G>A
NM_000133.3(F9):c.835G>A (p.Ala279Thr)
NC_000023.11:g.139560852G>A
CM000685.2:g.139560852G>A
NC_000023.10:g.138643011G>A
CM000685.1:g.138643011G>A
NC_000023.9:g.138470677G>A
NG_007994.1:g.35117G>A
ENST00000218099.7:c.835G>A
ENST00000643157.1:n.1502G>A
ENST00000218099.6:c.835G>A
ENST00000394090.2:c.721G>A
NM_001313913.1:c.721G>A
NM_000133.4:c.835G>A
NM_001313913.2:c.721G>A

Pathogenic

Met criteria codes 4

PP3 PS4_Very Strong PP4_Moderate PM2_Supporting

Not Met criteria codes 1

PP1

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 NM_000133.3:c.835G>A variant that results in the Ala279Thr missense change is absent from gnomAD v2.1.1 and v3, meeting PM2_Supporting. More than 59 male patients with mild hemophilia B are reported hemizygous for this variant in the literature, meeting PS4_Very strong and PP4_Moderate criteria (PMID: 29296726, 29656491). It is noted as a founder variant but may also have arisen de novo

as a recurrent variant and is found in multiple ethnicities. The variant has a REVEL score of 0.765 (>0.6) which meets the thresholds recommended for PP3. In summary, the 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, PP3, PP4_Moderate, PM2_Supporting.

Met criteria codes

PP3	✔	REVEL score of 0.765 (>0.6) meets the thresholds recommended for PP3 by the CFD VCEP.
PS4_Very Strong	✔	At least 59 patients with the Ala279Thr variant are reported across 27 publications from different ethnicities, meeting criteria for PS4_Very Strong. This is a conservative estimate, it is likely that the variant is present at a higher frequency among HB patients. 94 HB patients are recorded in the EAHAD database. The variant is mostly associated with mild disease, with a mean FIX:C of 11.21 U/dl (PMID: 19699296). Inhibitors are NOT reported in patients.
PP4_Moderate	✔	Male with mild hemophilia B with 6% factor IX activity level who had F8 and F9 full gene sequencing and deletion/duplication analysis.
PM2_Supporting	✔	The variant is absent from gnomAD v2.1.1 and v3.

Not Met criteria codes

PP1	✖	From internal laboratory data: Patient with mild HB (FIX:C = 19%) is reported to have two brothers with HB; however, their genotyping information is unavailable.

Curation History

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