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_001313913.2:c.839T>G

Version: 1.0

CA414444922

Gene: F9 (HGNC:2158)
Condition: hemophilia B (MONDO:0010604)
Inheritance Mode: X-linked inheritance
UUID: aaebf2da-2342-4529-a13a-f304b530bb8a
Approved on: 2024/10/11
Published on: 2024/11/1

HGVS expressions

NM_001313913.2:c.839T>G
NC_000023.11:g.139561638T>G
CM000685.2:g.139561638T>G
NC_000023.10:g.138643797T>G
CM000685.1:g.138643797T>G
NC_000023.9:g.138471463T>G
NG_007994.1:g.35903T>G
ENST00000218099.7:c.953T>G
ENST00000643157.1:n.1620T>G
ENST00000218099.6:c.953T>G
ENST00000394090.2:c.839T>G
NM_000133.3:c.953T>G
NM_001313913.1:c.839T>G
NM_000133.4:c.953T>G

Likely Pathogenic

Met criteria codes 6

PM5 PM6 PP4_Moderate PP3 PM2_Supporting 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.953T>G; p.Leu318Arg variant is completely absent from gnomAD v2.1.1 and v3.1.1 (PM2_Supporting). This missense variant has a REVEL score of 0.979 and meets PP3 criteria (PP3, threshold >0.6). At least 3 patients are reported in the literature with severe hemophilia B and this variant, meeting F9 phenotype criteria (PS4_Moderate, PP4_Moderate; PMID: 29296726, PMID: 1897528, PMID: 12588353). There is at least 1 proband with hemophilia B meeting phenotypic criteria for F9, with assumed de novo (maternity not

confirmed in an affected male) occurrence (PM6, PMID: 30648777). Leu318Phe is another pathogenic variant at the same residue (PM5). In summary, this variant meets criteria to be classified as likely pathogenic. The ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel, for F9: PM5, PM6, PS4_Moderate, PP4_Moderate, PP3, PM2_Supporting.

Met criteria codes

PM5	✔	The F9 p.Leu318Phe variant meets the Coagulation Factor Deficiency VCEP classification for pathogenic.
PM6	✔	Variant reported de novo in a maternal grandfather in the family known as HB143 in PMID: 8434583. The same case was also reported in Bottema, at al 1991, which was used for evidence for PS4.
PP4_Moderate	✔	1 proband with severe hemophilia B from PMID: 29296726 meets F9 phenotype criteria
PP3	✔	REVEL score is 0.979, which is above 0.6 cutoff.
PM2_Supporting	✔	Absent from gnomAD v2.1.1 and v3.1.
PS4_Moderate	✔	Variant identified in at least two probands with severe hemophilia B (PMID: 1897528, PMID: 12588353).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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