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.881G>A (p.Arg294Gln)

Version: 1.0

CA255368

10602 (ClinVar)

Gene: F9 (HGNC:2158)
Condition: hemophilia B (MONDO:0010604)
Inheritance Mode: X-linked inheritance
UUID: 317fdec6-df8d-4c37-90c0-0c5ae79cb5ad
Approved on: 2024/11/1
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HGVS expressions

NM_000133.3:c.881G>A
NM_000133.3(F9):c.881G>A (p.Arg294Gln)
NC_000023.11:g.139561566G>A
CM000685.2:g.139561566G>A
NC_000023.10:g.138643725G>A
CM000685.1:g.138643725G>A
NC_000023.9:g.138471391G>A
NG_007994.1:g.35831G>A
ENST00000218099.7:c.881G>A
ENST00000643157.1:n.1548G>A
ENST00000218099.6:c.881G>A
ENST00000394090.2:c.767G>A
NM_001313913.1:c.767G>A
NM_000133.4:c.881G>A
NM_001313913.2:c.767G>A

Pathogenic

Met criteria codes 6

PM2_Supporting | PP1 | PM1 | PS3_Supporting | PS4_Very Strong | PP4_Moderate

Not Met criteria codes 2

PP3 | PM5

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 F8 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Coagulation Factor Deficiency VCEP

The c.881G>A, p.Arg294Gln variant affects one of the functional domains (aa 227-459; Peptidase S1 domain) in the F9 protein meeting PM1. The variant is absent from male population databases (gnomAD v4.1) meeting PM2_Supporting. At least 30 patients with mild, moderate or severe hemophilia B have been reported in the literature reviewed meeting PS4_Very Strong and PP4_Moderate (PMID:

29296726, 15921378, 8091381). In-vitro functional studies show that the variant causes ER retention of the F9 protein, leading to reduced antigen levels meeting PS3_Supporting. REVEL score for this variant does not fall within the thresholds for pathogenic or benign predictions, and no splicing impact is noted by SpliceAI. 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, PM1, PP4_Moderate, PS3_Supporting, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	The variant is absent from male population databases (gnomAD v4.1)
PP1	✔	2 brothers with non-severe hemophilia B are reported in PMID: 29618686 with the hemizygous Arg294Gln variant.
PM1	✔	The c.881G>A (p.Arg294Gln) variant affects one of the functional domains (aa 227-459; Peptidase S1 domain) in the F9 protein and meets criteria for PM1.
PS3_Supporting	✔	The Arg294Gln variant was transiently expressed in HEK293 and CHO cell systems in PMID: 29993188 and was shown to result in reduced levels of secreted protein (~0.2 - ~0.7% of WT). HEK-293 stable clones expressing the rFIX-R294Gln analyzed by immunostaining showed impaired intracellular trafficking of the variant protein, with retention in the ER. The authors note that the specific coagulant activity (ratio between coagulant activity and secreted protein levels) of the variant was higher (~2-fold) compared to WT. PS3_Supporting is applied since low protein secretion indicates reduced antigen levels.
PS4_Very Strong	✔	At least 30 patients with mild, moderate or severe hemophilia B have been reported in the literature reviewed below. There are several additional probands with the variant reported in the EAHAD database, recorded from the literature and unpublished sources. The number of probands meet threshold for PS4_Very strong (>16 probands).
PP4_Moderate	✔	1 proband with severe hemophilia B in MLOF project.

Not Met criteria codes

PP3	✖	The c.881G>A (p.Arg294Gln) missense variant has a REVEL score of 0.576 and does not meet the threshold (>0.6) for PP3. CADD score is not considered. SpliceAI and MES predict no impact (MES suggests a score difference of -8.18 for the native donor site)
PM5	✖	Other missense variants at this residue include Arg294Gly and Arg294Leu. These variants have not been evaluated by the CFD-VCEP yet.

Curation History

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