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_000132.3(F8):c.980T>C (p.Leu327Pro)

Version: 1.0

CA255086

10199 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: 0359c35e-8a2d-43a2-a9ba-6b9fd5c4cab8
Approved on: 2024/9/30
Published on: 2024/10/1

HGVS expressions

NM_000132.3:c.980T>C
NM_000132.3(F8):c.980T>C (p.Leu327Pro)
NC_000023.11:g.154969360A>G
CM000685.2:g.154969360A>G
NC_000023.10:g.154197635A>G
CM000685.1:g.154197635A>G
NC_000023.9:g.153850829A>G
NG_011403.1:g.58364T>C
NG_011403.2:g.58364T>C
ENST00000360256.9:c.980T>C
ENST00000647125.1:c.*856T>C
ENST00000360256.8:c.980T>C
NM_000132.4:c.980T>C

Likely Pathogenic

Met criteria codes 4

PM5 PP3 PS4_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 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.980T>C (p.Leu327Pro) variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3). The variant has been reported in two probands with severe hemophilia A meeting phenotypic criteria for F8 in PMID: 8644728 and 26897466. This missense variant has a REVEL score of 0.926 (>0.6). A pathogenic variant, Leu327Val, is reported at the same residue meeting PM5. In summary, based on the evidence available at this time, the clinical significance of this variant is likely pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8: PP3, PS4_Moderate, PM2_Supporting, PM5.

Met criteria codes

PM5	✔	Leu327Val is a pathogenic variant classified by the CFD-VCEP
PP3	✔	This missense variant has a REVEL score of 0.926 (>0.6). SpliceAI predicts no splicing impact.
PS4_Moderate	✔	The c.980T>C (p.Leu327Pro) variant has been reported in two probands meeting phenotypic criteria for F8 in PMID: 8644728 and 26897466.
PM2_Supporting	✔	The missense variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3).

Not Met criteria codes

PP1	✖	PMID: 8644728 reports a family in which the origin of the proband's variant has been traced to the maternal grandmother (potentially 2 segregations), however, factor levels of mother and grandmother are not noted. PP1 criteria not met.

Curation History

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