

Variant: *NM_000132.3(F8):c.979C>G (p.Leu327Val)*

Version: 1.0

CA414917679 [↗](#)

627165 (ClinVar) [↗](#)

Gene: F8 ([HGNC:2157](#))

Condition: hemophilia A ([MONDO:0010602](#))

Inheritance Mode: X-linked inheritance

UUID: 064ef5ee-aea8-46c8-8afe-cf0716e645fa

Approved on: 2024/2/2

Published on: 2024/7/11

HGVS expressions

NM_000132.3(F8):c.979C>G (p.Leu327Val)

NM_000132.3:c.979C>G

NC_000023.11:g.154969361G>C

CM000685.2:g.154969361G>C

NC_000023.10:g.154197636G>C

CM000685.1:g.154197636G>C

NC_000023.9:g.153850830G>C

NG_011403.1:g.58363C>G

NG_011403.2:g.58363C>G

ENST00000360256.9:c.979C>G

ENST00000647125.1:c.*855C>G

ENST00000360256.8:c.979C>G

NM_000132.4:c.979C>G

Pathogenic

Met criteria codes 4

PM2_Supporting

PS4

PP1

PP3

Not Met criteria codes 2

PP4

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.979C>G (p.Leu327Val) variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3) meeting PM2_Supporting. This missense variant has a REVEL score of 0.657 (>0.6) and meets criteria for PP3. At least 8 probands reported with mild hemophilia A (PMID: 18691168, PMID: 11857744, PMID: 29296726, PMID: 31064749, PMID: 20860608 and internal VCEP data) meeting F8 phenotype criteria. 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 F8/F9: PS4_Very strong, PP3, PM2_Supporting.

Met criteria codes

PM2_Supporting			The c.979C>G (p.Leu327Val) variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3).
PS4			At least 8 probands reported that meet F8 phenotype criteria. PS4_Very strong is applied.
PP1			2 segregations observed in family from PMID: 20860608.
PP3			The c.979C>G (p.Leu327Val) missense variant has a REVEL score of 0.657 (>0.6) and meets criteria for PP3. Splicing prediction by HSF suggests creation of a cryptic splice acceptor site (60.89% variation). SpliceAI predicts a donor loss with delta score of 0.11, which does not meet the criteria for PP3.

Not Met criteria codes

PP4			The single MLOF proband is used for PS4_Very strong
PM5			Leu327Arg, Leu327Gln, Leu327Pro are other variants at the same residue. All three variant have been curated as VUS by the CFD-VCEP. Evidence from these variants is not considered here to avoid circularity.

Curation History

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Showing 1 to 1 of 1 rows

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