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_000132.4:c.923C>G

Version: 1.1

CA414917900

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: 65178e0c-0443-451f-95b7-660dec0f7b08
Approved on: 2024/12/6
Published on: 2024/12/6

HGVS expressions

NM_000132.4:c.923C>G
NC_000023.11:g.154969417G>C
CM000685.2:g.154969417G>C
NC_000023.10:g.154197692G>C
CM000685.1:g.154197692G>C
NC_000023.9:g.153850886G>C
NG_011403.1:g.58307C>G
NG_011403.2:g.58307C>G
ENST00000360256.9:c.923C>G
ENST00000647125.1:c.*799C>G
ENST00000360256.8:c.923C>G
NM_000132.3:c.923C>G

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PP3 PM5 PS4_Supporting PM2_Supporting

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.923C>G (p.Ser308Trp) variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3 - PM2_Supporting). This missense variant has a REVEL score of 0.857 (>0.6), meeting criteria for PP3. This variant has been reported in one individual with mild hemophilia A (PMID: 29296726 - PP4_Moderate). Additionally, there is one patient with mild hemophilia A (FVIII:C of 6%) is noted in the internal VCEP data who also has a family history of hemophilia A (PS4_Supporting). Ser308Leu, a variant at the same residue, has been classified as pathogenic by the CFD-VCEP, meeting criteria for 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/F9: PM5, PS4_Supporting, PP4_Moderate, PP3, PM2_Supporting.

Met criteria codes

PP4_Moderate	✔	One proband from MLOF with mild hemophilia A, which was deletion and duplication analysis was performed.
PP3	✔	This missense variant has a REVEL score of 0.857 (>0.6), meeting criteria for PP3. SpliceAI predicts no impact on splicing.
PM5	✔	PM5 is met as Ser308Leu, a variant at the same residue has been provisionally classified as pathogenic by the CFD-VCEP.
PS4_Supporting	✔	1 proband with mild hemophilia A - baseline FVIII:C = 6% and most recent FVIII:C of 10%.
PM2_Supporting	✔	The c.923C>G (p.Ser308Trp) variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3.1.1).

Curation History

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