

Variant: *NM_000132.3(F8):c.923C>T (p.Ser308Leu)*

Version: 1.0

CA255082 [↗](#)

10195 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 1f4d95f7-0d34-4efc-abb1-889de1138193

Approved on: 2024/6/19

Published on: 2024/7/11

HGVS expressions

NM_000132.3(F8):c.923C>T (p.Ser308Leu)

NM_000132.3:c.923C>T

NC_000023.11:g.154969417G>A

CM000685.2:g.154969417G>A

NC_000023.10:g.154197692G>A

CM000685.1:g.154197692G>A

NC_000023.9:g.153850886G>A

NG_011403.1:g.58307C>T

NG_011403.2:g.58307C>T

ENST00000360256.9:c.923C>T

ENST00000647125.1:c.*799C>T

ENST00000360256.8:c.923C>T

NM_000132.4:c.923C>T

Pathogenic

Met criteria codes **5**

PP1 PP3 PM2 PS2 PS4

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>T (NM_000132.3) variant in F8 is a missense variant predicted to cause substitution of Serine by Leucine at amino acid 308 (p.Ser308Leu). This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting). This variant has been reported in at least 21 probands meeting the hemophilia A phenotype criteria specified by the Coagulation Factor Deficiency VCEP. Several probands are reported with mild hemophilia A (>4) and VWD 2N exclusion was reported in at least 2 probands (PS4_VeryStrong; PMID: 10338101, 8759905, 19448530, 8449505, 18691168, 15921397, 19719828, 16972227, 18371166, 28674365, 30046696, 31026269, 21645180, 24845853,

22958177, 17445092). This variant has been identified as a de novo occurrence with confirmed maternal relationship (X-linked condition) in 1 male patient with severe hemophilia A (2 points per the ClinGen SVI PS2/PM6 table; PS2; PMID: 1837116). The variant has been reported to segregate with mild hemophilia A in 2 affected siblings from 1 family (PP1; PMID: 19448530). This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting). The computational predictor REVEL gives a score of 0.800, which is above the threshold of 0.6, evidence that correlates with impact to F8 function (PP3). This variant has also been associated with discrepant factor VIII activity levels, with lower chromogenic factor VIII lab values (PMID: 32232366). In summary, this variant meets the criteria to be classified as pathogenic for X-linked recessive hemophilia A based on the ACMG/AMP criteria applied, as specified by the ClinGen Coagulation Factor Deficiency VCEP: PS4_VeryStrong, PS2, PP1, PP3, PM2_Supporting. (ClinGen Coagulation Factor Deficiency Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for F8 Version 1.0.0., Released 10/5/2023).

Met criteria codes

PP1			The variant has been reported to segregate with mild hemophilia A in 2 affected siblings (1 meiosis) from 1 family (PP1; PMID: 19448530).
PP3			The computational predictor REVEL gives a score of 0.800, which is above the threshold of 0.6, evidence that correlates with impact to F8 function (PP3). SpliceAI predicts no impact on splicing.
PM2			This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting).
PS2			This variant has been identified as a de novo occurrence with confirmed maternal relationship (X-linked condition) in 1 male patient with severe hemophilia A (2 points per the ClinGen SVI PS2/PM6 table; PS2; PMID: 1837116).
PS4			This variant has been reported in at least 21 probands meeting the hemophilia A phenotype criteria specified by the Coagulation Factor Deficiency VCEP. Several probands are reported with mild hemophilia A (>4) and VWD-2N exclusion was reported in at least 2 probands (PS4_VeryStrong; PMID: 10338101, 8759905, 19448530, 8449505, 18691168, 15921397, 19719828, 16972227, 18371166, 28674365, 30046696, 31026269, 21645180, 24845853, 22958177, 17445092).

Curation History

▼

▼

Showing 1 to 1 of 1 rows

--

