

Variant: NM_000132.4:c.1899G>T

Version: 1.0

CA414910251 [↗](#)

2775444 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: bc8dc28d-54fd-4af4-95fd-9e395c0344e4

Approved on: 2024/2/2

Published on: 2024/7/11

HGVS expressions

NM_000132.4:c.1899G>T

NC_000023.11:g.154953896C>A

CM000685.2:g.154953896C>A

NC_000023.10:g.154182171C>A

CM000685.1:g.154182171C>A

NC_000023.9:g.153835365C>A

NG_011403.1:g.73828G>T

NG_011403.2:g.73828G>T

ENST00000360256.9:c.1899G>T

ENST00000647125.1:c.*1775G>T

ENST00000360256.8:c.1899G>T

NM_000132.3:c.1899G>T

Pathogenic

Met criteria codes **5**

PS4

PP1

PP3

PM2_Supporting

PP4_Moderate

Not Met criteria codes **1**

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 NM_000132.4(F8):c.1899G>T (p.Met633Ile) variant is completely absent from population databases (gnomAD v2.1.1/gnomAD v3) meeting PM2_Supporting. This missense variant has a REVEL score of 0.88 (>0.6) meeting PP3. At least 9 individuals with hemophilia A (mix of severities from severe to mild reported) from the literature are reported with the Met633Ile variant (PMID: 29296726, PMID: 19369668, PMID: 9886318 and PMID: 18691168) meeting PS4_Very strong and PP4_Moderate. 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, PP4_Moderate, PP3, PM2_Supporting.

Met criteria codes

PS4			At least 8 individuals from the literature and internal laboratory data are reported with mild hemophilia A and the Met633Ile variant.
PP1			Two members of a family were genotyped. The degree of relationship was unknown, so the code is applied at the supporting level.
PP3			The c.1899G>T (p.Met633Ile) missense variant has a REVEL score of 0.88 (>0.6)
PM2_Supporting			This missense variant is completely absent from population databases (gnomAD v2.1.1/gnomAD v3)
PP4_Moderate			Male with mild hemophilia A with 11% factor VIII activity level who had full gene sequencing for F8 and F9 with deletion/duplication analysis.

Not Met criteria codes

PM5			2 variants at the same residue, Met633Val and Met633Thr, are reported in the EAHAD database. PM5 is not considered as the two variants have not yet been evaluated by the CFD-VCEP.
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Curation History

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