

Variant: *NM_000132.4(F8):c.1834C>T (p.Arg612Cys)*

Version: 1.0

CA255129 [↗](#)

10236 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: be2964af-17d7-41a7-9c33-7afda47fa9fa

Approved on: 2024/6/19

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HGVS expressions

NM_000132.4:c.1834C>T

NM_000132.4(F8):c.1834C>T (p.Arg612Cys)

NC_000023.11:g.154953961G>A

CM000685.2:g.154953961G>A

NC_000023.10:g.154182236G>A

CM000685.1:g.154182236G>A

NC_000023.9:g.153835430G>A

NG_011403.1:g.73763C>T

NG_011403.2:g.73763C>T

ENST00000360256.9:c.1834C>T

ENST00000647125.1:c.*1710C>T

ENST00000360256.8:c.1834C>T

NM_000132.3:c.1834C>T

Pathogenic

Met criteria codes **5**

PP4_Moderate

PP3

PP1_Strong

PS2

PS4

Not Met criteria codes **1**

PM2

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.1834C>T (p.Arg612Cys) variant is present in 3 hemizygotes in gnomAD v2.1.1, so PM2_Supporting is not met. The REVEL score of 0.88 which meets PP3 criteria (threshold >0.6). Thirty-two patients were reported with mild-moderate hemophilia A in a single publication and over 100 individuals were identified in the My Life Our Future Cohort, meeting F8 phenotype criteria for PP4_Moderate and PS4_Very strong (PMID: 18691168, 29296726). This variant has been associated with mostly mild, but also moderate and severe, hemophilia A with and without inhibitors to factor replacement therapies. This may be in part because the variant has also been associated with discrepant

factor VIII activity levels, with chromogenic assays (two-stage) being 2-fold lower than one stage assays (EAHAD database; PMID: 32232366). The variant has been reported to segregate with hemophilia A in greater than 6 meioses across two families (PP1_Strong; PMID: 9292523). This variant has also been found to have at least one de novo occurrence in the mother of a proband, where the proband was found to have the unaffected maternal grandfather's allele via haplotype analysis (PS2; PMID: 9292523). Additionally, this variant has been reported in patients with and without a history of inhibitors to factor replacement products (EAHAD database). 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: PS2, PS4_Very strong, PP1_Strong, PP3 and PP4_Moderate.

Met criteria codes

PP4_Moderate			Male with mild hemophilia A with 6% factor VIII activity level and no history of inhibitor.
PP3			REVEL score is 0.808 according to MyVariant.Info, which is above the cutoff of 0.6.
PP1_Strong			Variant segregates in greater than 6 meioses in at least two separate families in Thompson, et al. 1997.
PS2			Variant was found to be de novo in proband's mother by testing maternal grandparents for the variant and performing a haplotype analysis showing the proband inherited his unaffected maternal grandfather's allele. This family was assigned 2 points which is consistent with a strong weight of evidence.
PS4			>100 males with mild to severe hemophilia reported in literature. This meets criteria for PS4_Very strong (PS4_VS is greater than 8 probands).

Not Met criteria codes

PM2		This variant is present in three hemizygotes in gnomAD v2.1.1.
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Curation History

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