

Variant: *NM_000132.3(F8):c.1094A>G (p.Tyr365Cys)*

Version: 1.0

CA10568501 [↗](#)

618104 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 97530a61-603a-4523-afe2-1c7c833609ed

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HGVS expressions

NM_000132.3(F8):c.1094A>G (p.Tyr365Cys)

NM_000132.3:c.1094A>G

NC_000023.11:g.154966603T>C

CM000685.2:g.154966603T>C

NC_000023.10:g.154194878T>C

CM000685.1:g.154194878T>C

NC_000023.9:g.153848072T>C

NG_011403.1:g.61121A>G

NG_011403.2:g.61121A>G

ENST00000360256.9:c.1094A>G

ENST00000647125.1:c.*970A>G

ENST00000360256.8:c.1094A>G

NM_000132.4:c.1094A>G

Pathogenic

Met criteria codes 4

PP4_Moderate PP3 PM1 PS4

Not Met criteria codes 3

BS1 PP1 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 NM_000132.3(F8):c.1094A>G variant predicts a missense change, Tyr365Cys, in the a1 interdomain of FVIII protein, reported to impair activation and deactivation of the protein meeting PM1 criteria (PMID: 12139751). This variant does not meet the rarity population criteria. It is reported in multiple individuals (>32) in the literature (PMID: 29296726, PMID: 12139751, PMID: 21645180, PMID: 17445092, PMID: 21751985, PMID: 18691168, PMID: 18034822, PMID: 19456877, PMID: 15810915, PMID: 11857744). Of note, this variant is associated with discrepant factor VIII activity levels between the one-stage and two-stage, or chromogenic, assay, and individuals with

factor VIII levels measured on a two-stage assay may be within the normal range (EAHAD/CDC Champs databases). Additionally, individuals with this variant may have a mild to no bleeding history. The variant has a REVEL score of 0.756 (threshold >0.6) meeting PP3 criteria. In summary, the variant meets criteria to be classified as pathogenic causing decreased factor VIII activity levels, but may have a lower penetrant bleeding phenotype. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Expert Panel for F8: PS4_Very Strong, PM1, PP4_Moderate, PP3.

Met criteria codes

PP4_Moderate			Male with mild hemophilia A with 11% factor VIII activity level who underwent full gene sequencing of F8 and F9 with deletion/duplication analysis.
PP3			Tyr365Cys has a REVEL score of 0.756, meeting the threshold for PP3 for F8 (>= 0.6). CADD score of 22.3 (threshold >= 21) also meets PP3.
PM1			Data from Mumford et al, 2002; PMID: 12139751 suggests that the Tyr365Cys variant results in impaired activation of the FVIII zymogen and faster decay compared to WT of the activated heterotrimer due to its location in the acidic a1 interdomain region and proximity to thrombin, FIXa, FXa, and APC cleavage sites. "The Tyr365Cys variant is shown to result in impaired activation of the FVIII zymogen and faster decay compared to WT of the activated heterotrimer. The Tyr365 residue occurs in the acidic a1 interdomain, which is reported to minimize FVIIIa dissociation by stabilizing the A2 domain. Tyr365 is one of the tyrosine residues that is shown to be sulfated during post-translational modification (PMID: 1554716). Variants at this residue may be less efficiently cleaved by thrombin at Arg373 (PMID: 8051097). Arg336 is noted to be a cleavage site for FIXa, FXa and APC (PMID: 3082357). The a1 region is thought to be a key regulator in the inactivation of FVIIIa heterotrimer (PMID: 8349670) and to comprise a binding site for FXa (PMID: 8999906)." Evidence is applied towards PM1, pending expert review.
PS4			More than 8 patients reported in the literature with the variant and inverse discrepant FVIII:C measured lower by OSA and in the normal range by TSA or CSA, meet F8 phenotype criteria. VWD was ruled out in proband from PMID: 19456877. Patients reported with this variant across the literature are noted to have mild HA based on FVIII:C1I; however, no significant bleeding abnormalities are noted. PS4_Very Strong is applied based on low factor VIII levels; however, it is noted that individuals may not be symptomatic.

Not Met criteria codes

BS1			The variant is reported in gnomAD v2.1.1 at a frequency of 0.0001466 (12/81864 alleles with 6 hemizygotes) and in gnomAD v3 at a frequency of 0.0001388 (7/50445 alleles with 1 hemizygote) in the non-Finnish European population. The MAFs do not meet the BS1 threshold for F8 (>= 0.000167).
PP1			Potentially PP1_Strong based on the report of at least 2 male relatives of unrelated probands seen in PMID: 21751985. However, PP1 is not applied since pedigrees/exact relationships are not available.
PM2			Tyr365Cys is reported in gnomAD with hemizygotes. 6 hemizygotes are noted in the NFE population in gnomAD v2.1.1. PM2 not met. However, PS4 is counted upon expert review.

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