

Variant: *NM_000132.3(F8):c.6046C>T (p.Arg2016Trp)*

Version: 1.0

CA255197 [↗](#)

10304 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 3d921025-1d2e-41c3-9200-a2d11c4ad044

Approved on: 2024/2/2

Published on: 2024/7/11

HGVS expressions

NM_000132.3(F8):c.6046C>T (p.Arg2016Trp)

NM_000132.3:c.6046C>T

NC_000023.11:g.154902120G>A

CM000685.2:g.154902120G>A

NC_000023.10:g.154130395G>A

CM000685.1:g.154130395G>A

NC_000023.9:g.153783589G>A

NG_011403.1:g.125604C>T

NG_011403.2:g.125604C>T

ENST00000360256.9:c.6046C>T

ENST00000360256.8:c.6046C>T

NM_000132.4:c.6046C>T

Pathogenic

Met criteria codes **4**

PP4_Moderate

PM2_Supporting

PP3

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.6046C>T (p.Arg2016Trp) variant is completely absent from gnomAD v2.1.1 and gnomAD v3 meeting PM2_Supporting. This missense variant has a REVEL score of 0.822 (>0.6) meeting PP3 criteria. More than 46 probands are reported with the variant and moderate-severe hemophilia A in the literature and internal laboratory data (PMID: 29296726, 20102490, 18387975), meeting F8 phenotype criteria. This variant has been associated with discrepant factor VIII activity levels (PMID: 32232366). This variant has also been reported in individuals with a history of inhibitor development to factor replacement therapy (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: PS4_Very Strong, PP4_Moderate, PP3, PM2_Supporting.

Met criteria codes

PP4_Moderate			Male with severe hemophilia A who had full F8 and F9 gene sequencing and deletion/duplication analysis.
PM2_Supporting			The c.6046C>T (p.Arg2016Trp) variant is completely absent from gnomAD v2.1.1 and gnomAD v3.
PP3			This missense variant has a REVEL score of 0.822 (>0.6) and meets criteria for PP3.
PS4			More than 46 probands are reported with the variant and moderate-severe hemophilia A in the literature and internal laboratory data (PMID: 29296726, 20102490, 18387975), meeting F8 phenotype criteria. The threshold for PS4_Very Strong is met (>8).

Curation History



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