

Variant: *NM_000132.3(F8):c.1063C>T (p.Arg355Ter)*

Version: 1.0

CA255031 [↗](#)

10139 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: ecf66ee1-bbaa-44e7-ba8d-3ac575927b66

Approved on: 2024/2/2

Published on: 2024/7/11

HGVS expressions

NM_000132.3(F8):c.1063C>T (p.Arg355Ter)

NM_000132.3:c.1063C>T

NC_000023.11:g.154966634G>A

CM000685.2:g.154966634G>A

NC_000023.10:g.154194909G>A

CM000685.1:g.154194909G>A

NC_000023.9:g.153848103G>A

NG_011403.1:g.61090C>T

NG_011403.2:g.61090C>T

ENST00000360256.9:c.1063C>T

ENST00000647125.1:c.*939C>T

ENST00000360256.8:c.1063C>T

NM_000132.4:c.1063C>T

Pathogenic

Met criteria codes 6

PP4_Moderate

PS2_Moderate

PP1

PS4

PM2_Supporting

PVS1

Not Met criteria codes 1

PS3

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.1063C>T (p.Arg355Ter) variant is a nonsense variant that is predicted to introduce a premature stop codon in exon 8/26 and expected to result in nonsense-mediated mRNA decay, which meets PVS1 criteria. At least 20 probands from the literature reviewed below are reported to be hemizygous for the Arg355Ter variant, with severe Hemophilia A (FVIII:C <1%), which meets the PP4_Moderate and PS4_Very strong criteria. Inhibitors are reported in a few of these patients. One de novo occurrence without confirmation of maternity or paternity and an expected severe phenotype is reported in PMID: 29381227, which meets the PS2_Moderate criteria. Two siblings in one

family in PMID: 15996930 are noted to have severe HA and the Arg355Ter variant, which meets PP1 criteria. 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: PVS1, PS4_Very Strong, PP4_Moderate, PS2_Moderate, PP1, PM2_Supporting.

Met criteria codes

PP4_Moderate			Male with severe hemophilia A who had full F8 and F9 gene sequencing and deletion/duplication analysis through the MLOF study.
PS2_Moderate			1 de novo occurrence without confirmation of maternity or paternity and an expected severe phenotype is reported in PMID: 29381227 (1 point for de novo evidence = moderate).
PP1			Two siblings in one family in PMID: 15996930 are noted to have severe HA and the Arg355Ter variant.
PS4			At least 20 probands from the literature reviewed below are reported to be hemizygous for the Arg355Ter variant, with severe Hemophilia A (FVIII:C <1%). Inhibitors are reported in a few of these patients. Probands meet F8 phenotype criteria to apply PS4_Very Strong.
PM2_Supporting			The c.1063C>T (p.Arg355Ter) variant is absent from males in population databases; but it is reported at a frequency of 0.00001224 (1/81723 non-Finnish European alleles) in gnomAD v2.1.1.
PVS1			The c.1063C>T (p.Arg355Ter) variant is a nonsense variant that is predicted to introduce a premature stop codon in exon 8/26 and expected to result in nonsense-mediated mRNA decay.

Not Met criteria codes

PS3			PMID: 26915717 describes characterization of FVIII B domain variants by evaluating FVIII:C and FVIII:Ag levels in the conditioned medium following transient transfection in COS-1 cells. Arg355Ter was used as a pathogenic control. It is noted that neither FVIII:C nor FVIII:Ag were detectable for this nonsense variant. The evidence is noted for information; however, PS3 is not applied when NMD is predicted and PVS1 is met.
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Curation History

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