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Variant: NM_000132.4(F8):c.323A>C (p.Lys108Thr)

Version: 1.0

CA255056

10167 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: 626469c3-e7e6-43e5-b2e3-91d2f9b44e4c
Approved on: 2025/12/5
Published on: 2025/12/5

HGVS expressions

NM_000132.4:c.323A>C
NM_000132.4(F8):c.323A>C (p.Lys108Thr)
NC_000023.11:g.154997038T>G
CM000685.2:g.154997038T>G
NC_000023.10:g.154225313T>G
CM000685.1:g.154225313T>G
NC_000023.9:g.153878507T>G
NG_011403.1:g.30686A>C
NG_011403.2:g.30686A>C
ENST00000360256.9:c.323A>C
ENST00000647125.1:c.*109A>C
ENST00000360256.8:c.323A>C
ENST00000423959.5:c.218A>C
ENST00000453950.1:c.305A>C
NM_000132.3:c.323A>C

Likely Pathogenic

Met criteria codes 3

PP3 PP4_Moderate PS4

Not Met criteria codes 2

PM2 BS1

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.323A>C (p.Lys108Thr) variant is a missense variant in F8 that has been observed in at least one proband in the literature (PMID:29296726, PP4_Moderate) and four probands from an internal laboratory cohort with mild hemophilia A and type 2N von Willebrand disease ruled out (4 points PS4, PS4). This variant is predicted to have a deleterious effect (REVEL score of 0.873; PP3), which

is greater than the ClinGen CFD threshold for PP3 (>0.6). In summary, this variant meets the criteria to be classified as likely pathogenic for hemophilia A. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel (specifications version 1.0.0) for F8: PS4, PP4_Moderate, PP3.

Met criteria codes

PP3	✔	This variant is predicted to have a deleterious effect (REVEL score of 0.873; PP3), which is greater than the Clingen CFD threshold for PP3 (>0.6).
PP4_Moderate	✔	There is at least 1 proband with mild hemophilia A (mild without exclusion of type 2N von Willebrand disease), meeting phenotypic criteria for F8 (PP4_Moderate, PMID:29296726).
PS4	✔	This variant has been observed in multiple patients from internal lab data with mild hemophilia A and type 2N von Willebrand disease ruled out (4 points PS4; PS4).

Not Met criteria codes

PM2	✖	The c.323A>C (p.Lys108Thr) variant is observed in two males in population databases (gnomAD v3).
BS1	✖	The c.323A>C (p.Lys108Thr) variant is reported at an MAF of 0.00001792 (2/111637 alleles) in the general population in gnomAD v3, with 2 hemizygotes, which does not meet BS1 criteria of MAF > 0.0000333.

Curation History

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