The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000132.3(F8):c.5217C>T (p.Asn1739=)

Version: 1.0

CA519374734

627324 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: 5c2a0d18-7d60-4a5d-807c-371e4cd3d281
Approved on: 2024/10/11
Published on: 2025/1/7

HGVS expressions

NM_000132.3(F8):c.5217C>T (p.Asn1739=)
NM_000132.3:c.5217C>T
NC_000023.11:g.154928573G>A
CM000685.2:g.154928573G>A
NC_000023.10:g.154156848G>A
CM000685.1:g.154156848G>A
NC_000023.9:g.153810042G>A
NG_011403.1:g.99151C>T
NG_011403.2:g.99151C>T
ENST00000360256.9:c.5217C>T
ENST00000360256.8:c.5217C>T
NM_000132.4:c.5217C>T

Likely Pathogenic

Met criteria codes 3

PS4 PM2_Supporting PP1

Not Met criteria codes 1

PP3

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.5217C>T (p.Asn1739=) synonymous variant is completely absent from population databases (gnomAD v2.1.1/gnomAD v3.1.1). SpliceAI predicts a score of 0.31 for the loss of the canonical donor of intron 14; however the threshold (>0.5) for SpliceAI is not met and does not meet criteria for PP3. At least 4 probands with mild hemophilia A from the literature and internal laboratory data meet F8-phenotype criteria. This variant was found to co-segregate with disease in affected family members, with two meioses observed in a family (Internal Laboratory Data), meeting criteria for PP1. In summary, this variant meets the criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel

for F8: PS4, PP1, PM2_Supporting. (ClinGen Coagulation Factor Deficiency Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for F8 Version 1.0.0., Released 10/5/2023).

Met criteria codes

PS4	✔	4 probands with mild hemophilia A are counted from the literature and internal laboratory data (PMID: 23812942, PMID: 18691168).
PM2_Supporting	✔	The variant is completely absent from population databases (gnomAD v2.1.1/gnomAD v3)
PP1	✔	This variant was found to co-segregate with disease in affected family members, with two meioses observed in a family (Internal Laboratory Data), meeting criteria for PP1.

Not Met criteria codes

PP3	✖	The c.5217C>T synonymous variant occurs as the third to last base of exon 14 and the literature indicates that a splicing impact may be predicted. SpliceAI predicts a score of 0.31 for the loss of the canonical donor of intron 14; however the threshold (>0.5) for SpliceAI is not met.

Curation History

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