

Variant: *NM_000132.4(F8):c.409A>G (p.Thr137Ala)*

Version: 1.0

CA414919794 [↗](#)

3338831 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 13e05d71-4457-45c9-8cc3-f68feabf0137

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HGVS expressions

NM_000132.4:c.409A>G

NM_000132.4(F8):c.409A>G (p.Thr137Ala)

NC_000023.11:g.154993128T>C

CM000685.2:g.154993128T>C

NC_000023.10:g.154221403T>C

CM000685.1:g.154221403T>C

NC_000023.9:g.153874597T>C

NG_011403.1:g.34596A>G

NG_011403.2:g.34596A>G

ENST00000360256.9:c.409A>G

ENST00000647125.1:c.*195A>G

ENST00000360256.8:c.409A>G

ENST00000423959.5:c.304A>G

ENST00000453950.1:c.391A>G

NM_000132.3:c.409A>G

Likely Pathogenic

Met criteria codes **4**

PS4_Moderate

PP3

PM2_Supporting

PM5

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.409A>G (p.Thr137Ala) missense variant in F8 is absent from population databases (gnomAD v2.1.1/gnomAD v3; PM2_Supporting) and is predicted to have a deleterious effect (REVEL score of 0.907s; PP3), which is greater than the ClinGen CFD threshold for PP3 (>0.6). This variant has been observed at least three probands with mild to severe hemophilia A with type 2N von

Willebrand disease ruled out (PMID:11554935; PMID:19719828; 1 case from internal laboratory data; total 3 points, PS4_Moderate). Another missense variant (c.410C>T, p.Thr137Ile, CAID:CA255063) in the same codon has been classified as pathogenic for hemophilia A by the ClinGen Coagulation Factor Deficiency VCEP (PM5) with agreement in splicing predictors show no splicing impact. In summary, this variant meets the criteria to be classified as a 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_Moderate, PM5, PM2_Supporting, PP3.

Met criteria codes

PS4_Moderate			This variant has been observed at least three probands with mild to severe hemophilia A with type 2N von Willebrand disease ruled out (1 point PS4, PMID:11554935; 1 point PS4, PMID:19719828; 1 point PS4 Internal Laboratory Data; Total 3 points PS4, PS4_Moderate).
PP3			This variant is predicted to have a deleterious effect (REVEL score of 0.907; PP3), which is greater than the Clingen CFD threshold for PP3 (>0.6).
PM2_Supporting			This variant is absent from population databases (gnomAD v2.1.1/gnomAD v3; PM2_Supporting).
PM5			Another missense variant (c.410C>T, p.Thr137Ile, CAID:CA255063) in the same codon has been classified as pathogenic for hemophilia A by the ClinGen Coagulation Factor Deficiency VCEP (PM5) with agreement in splicing predictors show no splicing impact.

Curation History

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