Variant: NM_000132.3:c.1244C>A

Version: 1.0

CA414915809

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: 1eeea77a-9f96-4436-83f8-8780f845c2d2
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HGVS expressions

NM_000132.3:c.1244C>A
NC_000023.11:g.154966453G>T
CM000685.2:g.154966453G>T
NC_000023.10:g.154194728G>T
CM000685.1:g.154194728G>T
NC_000023.9:g.153847922G>T
NG_011403.1:g.61271C>A
NG_011403.2:g.61271C>A
ENST00000360256.9:c.1244C>A
ENST00000647125.1:c.*1120C>A
ENST00000360256.8:c.1244C>A
ENST00000483822.2:n.64C>A
NM_000132.4:c.1244C>A

Likely Pathogenic

Met criteria codes 5

PS4_Moderate PM2_Supporting PP4_Moderate PP3 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 c.1244C>A (p.Ala415Asp) variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3/gnomAD v4). The missense variant has a REVEL score of 0.922 (PP3, >0.6). This variant has been reported in three probands with mild and moderate hemophilia A, meeting phenotypic criteria for F8 (PP4, PS4_Moderate, PMID: 16786531). Ala415Val is a pathogenic variant at the same residue (PM5). In summary, this variant meets criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8/F9: PM5, PS4_Moderate, PP4_Moderate, PP3, PM2_Supporting.

Met criteria codes

PS4_Moderate	✔	2 individuals with moderate hemophilia A reported in PMID: 29296726 and 16786531 meet F8 phenotype criteria to apply PS4_Moderate.
PM2_Supporting	✔	The c.1244C>A (p.Ala415Asp) variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3/gnomAD v4).
PP4_Moderate	✔	1 individual with moderate hemophilia A reported in PMID: 29296726 (deletion/duplication analyses confirmed) meets the F8 phenotype criteria.
PP3	✔	The c.1244C>A (p.Ala415Asp) missense variant has a REVEL score of 0.922 (>0.6). No splicing impact is predicted by spliceAI.
PM5	✔	Ala415Thr and Ala415Val are variants at the same residue. Ala415Thr is a VUS while Ala415Val is a pathogenic variant. PM5 met based on Ala415Val being a pathogenic variant.

Curation History

Showing 1 to 1 of 1 rows