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Variant: NM_000132.3(F8):c.1214T>G (p.Ile405Ser)

Version: 1.0

CA255098

10208 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: 09c5f952-1d82-42e6-b221-8818af0dd1db
Approved on: 2024/6/19
Published on: 2024/7/11

HGVS expressions

NM_000132.3:c.1214T>G
NM_000132.3(F8):c.1214T>G (p.Ile405Ser)
NC_000023.11:g.154966483A>C
CM000685.2:g.154966483A>C
NC_000023.10:g.154194758A>C
CM000685.1:g.154194758A>C
NC_000023.9:g.153847952A>C
NG_011403.1:g.61241T>G
NG_011403.2:g.61241T>G
ENST00000360256.9:c.1214T>G
ENST00000647125.1:c.*1090T>G
ENST00000360256.8:c.1214T>G
ENST00000483822.2:n.34T>G
NM_000132.4:c.1214T>G

Likely Pathogenic

Met criteria codes 5

PS4_Moderate PM5_Supporting PM2_Supporting PP3 PP4_Moderate

Not Met criteria codes 1

PM1

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 variant, NM_000132.3(F8):c.1214T>G causes a missense change, Ile405Ser, which is not reported in gnomAD v2.1.1 or v3 or v4. This variant has been reported in at least three patients with Hemophilia A in the literature (PS4_Moderate, PP4_Moderate, PMIDs: 8307558). The variant has a REVEL score of 0.985 (PP3 threshold >0.6). Another variant at the same codon, Ile405Thr, is curated by the Coagulation Factor Deficiency Variant Curation Expert Panel as likely pathogenic (PM5_Supporting). In summary, the clinical significance of this variant

is likely pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8: PS4_Moderate, PP4_Moderate, PP3, PM2_Supporting, PM5_Supporting.

Met criteria codes

PS4_Moderate	✔	This variant has been reported in 2 probands meeting F8 phenotype criteria (PS4_Moderate; PMID: 8307558 and CHAMP US database).
PM5_Supporting	✔	c.1214T>C (p.Ile405Thr) is a variant at the same codon and is curated by the Coagulation Factor Deficiency VCEP to be likely pathogenic, meeting criteria for PM5_Supporting.
PM2_Supporting	✔	Ile405Ser is absent from gnomAD v2 and v3.
PP3	✔	REVEL score of 0.985 (threshold >0.6) and CADD score of 26.3 (threshold >21) meet criteria for PP3.
PP4_Moderate	✔	One patient with this variant displayed FVIII:C <1%, and deletion/duplication analysis was performed, which is highly specific for Hemophilia A (PP4, PMID: 29296726).

Not Met criteria codes

PM1	✖	Ile405Ser occurs in the A2 domain. PM1 is not applied at this time.

Curation History

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