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Variant: NM_000132.4(F8):c.5303G>A (p.Arg1768His)

Version: 1.0

CA10568007

627328 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: 4f3c8b67-eb47-4289-b4da-2951df274143
Approved on: 2024/2/9
Published on: 2024/7/11

HGVS expressions

NM_000132.4:c.5303G>A
NM_000132.4(F8):c.5303G>A (p.Arg1768His)
NC_000023.11:g.154906490C>T
CM000685.2:g.154906490C>T
NC_000023.10:g.154134765C>T
CM000685.1:g.154134765C>T
NC_000023.9:g.153787959C>T
NG_011403.1:g.121234G>A
NG_011403.2:g.121234G>A
ENST00000360256.9:c.5303G>A
ENST00000360256.8:c.5303G>A
NM_000132.3:c.5303G>A

Pathogenic

Met criteria codes 5

PP4_Moderate PM2_Supporting PS3 PS4 PP3

Not Met criteria codes 1

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.5303G>A (p.Arg1768His) variant is completely absent from gnomAD v2.1.1 and v3.1.1, which meets PM2_Supporting. This missense variant has a REVEL score of 0.819 and meets PP3 criteria (threshold >0.6). At least 7 patients are reported in the literature with mild hemophilia A, meeting F8 phenotype criteria for PP4_Moderate and PS4 (PMID: 29296726, 17222201, 12871415, 21166991, 16972227, 24452774). This variant is known to have discrepant factor VIII levels, with chromogenic (two-stage) being 2-fold lower than one-stage assay levels (EAHAD database, PMID: 32232366). Finally, a COS-1 cell line was used to demonstrate decreased factor VIII activity and

antigen levels (PMID: 30997536). In summary, this variant meets criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F8: PS3, PS4, PM2_Supporting, PP3, PP4_Moderate.

Met criteria codes

PP4_Moderate	✔	Male with mild hemophilia A with 47% one-stage factor VIII activity level. Chromogenic factor VIII level not provided. Variant is known to be discrepant.
PM2_Supporting	✔	Variant only seen in 1 female in gnomAD v2.1.1 and v3.1.
PS3	✔	Evidence of decreased F8 antigen and activity in a COS-1 cell line.
PS4	✔	Variant report in at least 6 published probands with mild hemophilia A. MLOF case counted towards for PP4.
PP3	✔	REVEL score is 0.819, which is above the cutoff of 0.6.

Not Met criteria codes

PM5	✖	Arg1768Cys has also been reported in at least two individuals with mild hemophilia A; however, there is not enough evidence to reach a likely pathogenic classification at this time.

Curation History

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