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_000132.4(F8):c.5399G>A (p.Arg1800His)

Version: 1.0

CA255162

10274 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: 1098415e-d0dd-480c-8171-d26c81d47a2b
Approved on: 2024-02-02
Published on: 2024-07-11

HGVS expressions

NM_000132.4:c.5399G>A
NM_000132.4(F8):c.5399G>A (p.Arg1800His)
NC_000023.11:g.154904998C>T
CM000685.2:g.154904998C>T
NC_000023.10:g.154133273C>T
CM000685.1:g.154133273C>T
NC_000023.9:g.153786467C>T
NG_011403.1:g.122726G>A
NG_011403.2:g.122726G>A
ENST00000360256.9:c.5399G>A
ENST00000360256.8:c.5399G>A
NM_000132.3:c.5399G>A

Pathogenic

Met criteria codes 4

PP3 PP4_Moderate PM2_Supporting PS4

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.5399G>A (p.Arg1800His) variant is completely absent from gnomAD v2.1.1 and gnomAD v3.1.2, meeting the PM2_Supporting criteria. More than 17 individuals in the literature and 40 in the internal laboratory data are observed with hemophilia A ranging from mild to severe carrying the Arg1800His variant. More cases are available in the literature (EAHAD database reports 76 individuals); however, the threshold for PS4_VeryStrong (>8) and PP4_Moderate have been reached. This variant has been associated with discrepant factor VIII activity levels (PMID: 32232366). This variant has also been associated with inhibitor development to factor replacement therapy (CDC CHAMPS/EAHAD databases). The c.5399G>A (p.Arg1800His) missense variant has a REVEL score of 0.96 (>0.6),

which meets the PP3 criteria. 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: PS4_VeryStrong, PP4_Moderate, PP3, PM2_Supporting.

Met criteria codes

PP3	✔	The c.5399G>A (p.Arg1800His) missense variant has a REVEL score of 0.96 (>0.6)
PP4_Moderate	✔	Male with severe hemophilia A who had full F8 and F9 gene sequencing and deletion/duplication analysis through the MLOF study.
PM2_Supporting	✔	The c.5399G>A (p.Arg1800His) variant is completely absent from gnomAD v2.1.1 and gnomAD v3.1.2
PS4	✔	17 individuals in the literature and 40 in the internal laboratory data are observed with hemophilia A ranging from mild to severe carrying the Arg1800His variant. More cases are available in the literature (EAHAD database reports 76 individuals); however, the threshold for PS4_VeryStrong (>8) has been reached.

Curation History

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