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:c.1372C>T

Version: 1.0

CA414914682

2775446 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: fdcc63eb-ee30-41e8-9497-98b82048ac3f
Approved on: 2024/6/20
Published on: 2024/7/11

HGVS expressions

NM_000132.4:c.1372C>T
NC_000023.11:g.154966041G>A
CM000685.2:g.154966041G>A
NC_000023.10:g.154194316G>A
CM000685.1:g.154194316G>A
NC_000023.9:g.153847510G>A
NG_011403.1:g.61683C>T
NG_011403.2:g.61683C>T
ENST00000360256.9:c.1372C>T
ENST00000647125.1:c.*1248C>T
ENST00000360256.8:c.1372C>T
ENST00000483822.2:n.192C>T
NM_000132.3:c.1372C>T

Pathogenic

Met criteria codes 4

PS4 PP1 PP3 PM2_Supporting

Not Met criteria codes 1

PP4

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.1372C>T (p.Arg458Cys) variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3) meeting PM2_Supporting. This missense variant has a REVEL score of 0.839 (>0.6), meeting criteria for PP3. At least 8 mild hemophilia A patients meeting F8-phenotype criteria are reported in the literature (PMID: 25628142, PMID: 18387975, PMID: 16173970, PMID: 17610549) and internal VCEP data. This variant was noted to segregate in a maternal uncle and nephew pair with hemophilia A (PMID: 25628142), which meets criteria for PP1. Additionally, this variant has been associated with a history of an inhibitor in at least one individual (PMID: 17610549). 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/F9: PS4_Very strong, PP1, PP3, PM2_Supporting.

Met criteria codes

PS4	✔	At least 8 mild hemophilia A patients are reported in the literature and internal laboratory data. This code is met at the PS4_Very strong level.
PP1	✔	Nephew-maternal uncle pair with mild hemophilia A confirmed by corresponding author (2 meioses).
PP3	✔	The Arg458Cys missense variant has a REVEL score of 0.839 (>0.6), meeting criteria for PP3
PM2_Supporting	✔	The c.1372C>T (p.Arg458Cys) variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3).

Not Met criteria codes

PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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