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Variant: NM_000132.4(F8):c.1649G>A (p.Arg550His)

Version: 1.0

CA255115

10225 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: 2c41fca8-0d9a-4276-9f42-fc7a33592b0f
Approved on: 2024/2/2
Published on: 2024/7/11

HGVS expressions

NM_000132.4(F8):c.1649G>A (p.Arg550His)
NM_000132.4:c.1649G>A
NC_000023.11:g.154957060C>T
CM000685.2:g.154957060C>T
NC_000023.10:g.154185335C>T
CM000685.1:g.154185335C>T
NC_000023.9:g.153838529C>T
NG_011403.1:g.70664G>A
NG_011403.2:g.70664G>A
ENST00000360256.9:c.1649G>A
ENST00000647125.1:c.*1525G>A
ENST00000360256.8:c.1649G>A
NM_000132.3:c.1649G>A

Pathogenic

Met criteria codes 4

PP3 PS4 PP4_Moderate PM2_Supporting

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.1649G>A (p.Arg550His) variant is absent from males in gnomAD v2.1.1. It is reported in heterozygotes at a frequency of 0.00002442 (2/81904 alleles) in the non-Finnish European population. At least 35 male individuals with mild hemophilia A are found in the literature and internal laboratory data with the Arg550His variant. More cases are available in the literature (EAHAD reports 64 patients), however >8 probands have been counted towards PS4_VeryStrong and one for PP4_moderate. This variant is associated with discrepant factor VIII activity levels with some individuals having normal levels on one-stage assays and levels in the mild hemophilia range on a chromogenic,

or two-stage, assay (CDC Champs/EAHAD databases). Some individuals have been reported to have a history of inhibitor formation to factor replacement products (CDC Champs/EAHAD databases). The c.1649G>A (p.Arg550His) missense variant has a REVEL score of 0.78 (>0.6). Other variants at the same residue, Arg550Cys, Arg550Gly, Arg550Leu and Arg550Pro have been reported, but evidence from these variant curations has not been used in classifying the Arg550His variant. 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, PP3, PM2_Supporting.

Met criteria codes

PP3	✔	The c.1649G>A (p.Arg550His) missense variant has a REVEL score of 0.78 (>0.6).
PS4	✔	At least 35 male individuals with mild hemophilia A are found in the literature and internal laboratory data with the Arg550His variant. More cases are available in the literature (EAHAD reports 64 patients), however >8 probands have been counted towards PS4_VeryStrong.
PP4_Moderate	✔	Male with mild hemophilia A (17% factor VIII activity) in the MLOF study with full sequencing and deletion/duplication analysis of F8 and F9 genes.
PM2_Supporting	✔	The c.1649G>A (p.Arg550His) variant is absent from males in gnomAD v2.1.1. It is reported in heterozygotes at a frequency of 0.00002442 (2/81904 alleles) in the non-Finnish European population (Absent in v3.1.2).

Curation History

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