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Variant: NM_000132.3(F8):c.5822A>G (p.Asn1941Ser)

Version: 1.0

CA255184

10294 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: a2b52c30-02cc-49a6-9a79-849230686deb
Approved on: 2024/2/2
Published on: 2024/7/11

HGVS expressions

NM_000132.3:c.5822A>G
NM_000132.3(F8):c.5822A>G (p.Asn1941Ser)
NC_000023.11:g.154904082T>C
CM000685.2:g.154904082T>C
NC_000023.10:g.154132357T>C
CM000685.1:g.154132357T>C
NC_000023.9:g.153785551T>C
NG_011403.1:g.123642A>G
NG_011403.2:g.123642A>G
ENST00000360256.9:c.5822A>G
ENST00000360256.8:c.5822A>G
NM_000132.4:c.5822A>G

Pathogenic

Met criteria codes 6

PS3 PS4 PP1 PP3 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.5822A>G (p.Asn1941Ser) 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 0.943 (>0.6) and meets criteria for PP3. At least 80 probands have been reported in the literature and from internal laboratory data who meet the F8 phenotype criteria meeting thresholds for PS4_Very strong (>8 probands) and PP4_Moderate. Two brothers have been reported with severe hemophilia A, which meets the PP1 criteria (PMID: 15996930). Functional evidence from PMID: 21217077 shows that the variant results in a secretory defect based on barely detectable levels of antigen and activity when expressed in BHK cells, which meets PS3 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_Very strong, PS3, PM2_Supporting, PP1, PP3.

Met criteria codes

PS3	✔	Functional evidence from PMID: 21217077: The Asn1941Ser variant was expressed in BHK-M cells resulted in barely detectable levels of FVIII activity (measured by OSA) and FVIII antigen (measured by ELISA) levels. In addition, authors show that the variant results in stalling of FVIII folding in the ER, preventing or delaying its transport to the Golgi, and therefore limiting the secretion of the protein. The intracellularly retained FVIII is shown to be functionally normal or near normal. Patients with this variant are reported with inhibitors, which may be due to the inability to produce sufficient amounts of FVIII antigen to generate immunologic tolerance.
PS4	✔	At least 80 probands have been reported in the literature and from internal laboratory data who meet the F8 phenotype criteria. The threshold for PS4_VeryStrong is met (>8 probands)
PP1	✔	At least two siblings have been reported with the variant and severe hemophilia A.
PP3	✔	This missense variant has a REVEL score of 0.943 (>0.6) and meets criteria for PP3
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.5822A>G (p.Asn1941Ser) variant is completely absent from gnomAD v2.1.1 and v3.1.1

Curation History

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