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Variant: NM_000132.3(F8):c.1660A>G (p.Ser554Gly)

Version: 1.0

CA255116

10226 (ClinVar)

Gene: F8 (HGNC:2157)
Condition: hemophilia A (MONDO:0010602)
Inheritance Mode: X-linked inheritance
UUID: abad070d-72d1-4e21-af79-75e18849b027
Approved on: 2024/2/2
Published on: 2024/7/11

HGVS expressions

NM_000132.3:c.1660A>G
NM_000132.3(F8):c.1660A>G (p.Ser554Gly)
NC_000023.11:g.154957049T>C
CM000685.2:g.154957049T>C
NC_000023.10:g.154185324T>C
CM000685.1:g.154185324T>C
NC_000023.9:g.153838518T>C
NG_011403.1:g.70675A>G
NG_011403.2:g.70675A>G
ENST00000360256.9:c.1660A>G
ENST00000647125.1:c.*1536A>G
ENST00000360256.8:c.1660A>G
NM_000132.4:c.1660A>G

Pathogenic

Met criteria codes 4

PP3 PP1_Strong PS4 PP4_Moderate

Not Met criteria codes 1

PM2

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.1660A>G (p.Ser554Gly) missense variant has a REVEL score of 0.938 which meets PP3 criteria (threshold >0.6). This variant is present in 1 hemizygote in gnomAD v2.1.1 and therefore, does not meet criteria for rarity in the population. Fifty-three patients are reported in Johnsen, et. al. 2107 with mild/moderate hemophilia A and the Gly554Ser variant, meeting F8 phenotype criteria for PS4_Very strong and PP4_Moderate (PMID: 29296726). The variant has been found to segregate with hemophilia A across 6 meioses among 4 different families, the PP1 criteria at the strong weight (Internal VCEP contributor). This variant has been reported in individuals who

developed an inhibitor to factor replacement therapy and discrepant chromogenic and one-stage factor VIII activity levels (CDC CHAMPS database/Internal VCEP contributor). 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, PP1_Strong, PP4_Moderate, PP3.

Met criteria codes

PP3	✔	The REVEL score is 0.938 (cutoff greater than or equal to 0.6).
PP1_Strong	✔	Variant has been seen in 6 meioses across 4 families (VCEP member clinical cohort).
PS4	✔	>8 individuals with mild/moderate hemophilia A reported in Johnsen, et al 2019 publication.
PP4_Moderate	✔	Counting 1 of numerous male probands with mild hemophilia A with full sequencing of the F8 and F9 genes with deletion and duplication analysis.

Not Met criteria codes

PM2	✖	Variant is present in one hemizygote in gnomAD v2.1.1.

Curation History

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