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Variant: NM_000133.4(F9):c.1304G>A (p.Cys435Tyr)

Version: 1.0

CA414447219

811512 (ClinVar)

Gene: F9 (HGNC:2158)
Condition: hemophilia B (MONDO:0010604)
Inheritance Mode: X-linked inheritance
UUID: 34515d58-87f3-4b05-9308-5a3ca86ded96
Approved on: 2024/5/9
Published on: 2024/7/11

HGVS expressions

NM_000133.4(F9):c.1304G>A (p.Cys435Tyr)
NM_000133.4:c.1304G>A
NC_000023.11:g.139561989G>A
CM000685.2:g.139561989G>A
NC_000023.10:g.138644148G>A
CM000685.1:g.138644148G>A
NC_000023.9:g.138471814G>A
NG_007994.1:g.36254G>A
ENST00000218099.7:c.1304G>A
ENST00000643157.1:n.1723+248G>A
ENST00000218099.6:c.1304G>A
ENST00000394090.2:c.1190G>A
NM_000133.3:c.1304G>A
NM_001313913.1:c.1190G>A
NM_001313913.2:c.1190G>A

Pathogenic

Met criteria codes 5

PP1 PP3 PP4 PM2_Supporting PS4

Not Met criteria codes 1

PM1

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 F9 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Coagulation Factor Deficiency VCEP

The NM_000133.4:c.1304G>A variant in F9 is a missense variant predicted to cause substitution of Cys by Tyr at amino acid 435 (p.Cys435Tyr). This variant has been reported in 9 probands meeting F9 phenotype criteria (PS4_Very Strong, PP4; PMIDs: s: 8091381, 10698280, 29296726, 22103590, 21118338, 8217825, 7482402). The variant has been reported to segregate with hemophilia B in 2

affected family members from 1 family (PP1; PMID: 21118338). The computational predictor REVEL gives a score of 0.943, which is above the threshold of 0.6, evidence that correlates with impact to F9 function (PP3). This variant is absent from gnomAD v2, v3 and v4. In summary, this variant meets the criteria to be classified as pathogenic for hemophilia B based on the ACMG/AMP criteria applied, as specified by the ClinGen Coagulation Factor Deficiency VCEP: PS4_Very Strong, PM2_Supporting, PP4, PP3, PP1. (Version 1.0.0, 10/05/2023)

Met criteria codes

PP1	✔	Variant was identified in patient Hb7 and Hb8, who are related with severe hemophilia B, but relationship not defined so using at supporting level.
PP3	✔	REVEL score is 0.943, which is above our cutoff for PP3.
PP4	✔	At least one patient with this variant displayed severe factor IX deficiency, which is highly specific for hemophilia B (PP4, PMID: 29296726)
PM2_Supporting	✔	Variant is absent from v2.1.1 and V3.1.2.
PS4	✔	8 probands with varying severity of hemophilia B are reported across the literature (PMIDs: 8091381, 10698280, 29296726, 22103590, 21118338, 8217825, 7482402), meeting criteria for PS4_Very Strong.

Not Met criteria codes

PM1	✖	Variant is outside of exons 3, 4, and 5.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000133.4(F9):c.1304G>A (p.Cys43...	Pathogenic	Hemophilia B	2024-07-11	1.0	ClinGen Coagulation Factor Deficiency Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for F9 Version 1.0.0	F9

Showing 1 to 1 of 1 rows

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