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Variant: NM_000133.3(F9):c.572G>A (p.Arg191His)

Version: 1.0

CA255342

10585 (ClinVar)

Gene: F9 (HGNC:2158)
Condition: hemophilia B (MONDO:0010604)
Inheritance Mode: X-linked inheritance
UUID: 36190763-aaae-49d3-a95b-1e8f8f6199ab
Approved on: 2024/2/9
Published on: 2024/7/11

HGVS expressions

NM_000133.3:c.572G>A
NM_000133.3(F9):c.572G>A (p.Arg191His)
NC_000023.11:g.139551113G>A
CM000685.2:g.139551113G>A
NC_000023.10:g.138633272G>A
CM000685.1:g.138633272G>A
NC_000023.9:g.138460938G>A
NG_007994.1:g.25378G>A
ENST00000218099.7:c.572G>A
ENST00000643157.1:n.1239G>A
ENST00000218099.6:c.572G>A
ENST00000394090.2:c.458G>A
NM_001313913.1:c.458G>A
NM_000133.4:c.572G>A
NM_001313913.2:c.458G>A

Pathogenic

Met criteria codes 4

PP3 PM1_Strong PS4 PP4_Moderate

Not Met criteria codes 4

PP1 PM5 PM2 PS3_Supporting

Evidence Links 2

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_000133.3(F9):c.572G>A predicts a missense change, Arg191His, at the activation residue. This residue is a site for cleavage by FXIa in order to activate FIX and therefore critical for protein function, which meets criteria for PM1_Strong. Over 100 patients meet the F9 phenotype criteria have been reported in the literature (selected PMIDs: 7873393,1972560, 26782891, 27865967, 24375831), meeting

PS4_Very strong and PP4_Moderate. The variant has a REVEL score of 0.73 (threshold >0.6), meeting PP3. In summary, the variant meets criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency VCEP for F9: PS4_Very Strong, PM1_Strong, PP4_Moderate, PP3.

Met criteria codes

PP3	✔	Arg191His has a REVEL score of 0.73 (threshold >0.6) and a CADD score of 22 (threshold >21) meet criteria for PP3.
PM1_Strong	✔	The Arg191 residue is a site for cleavage by FXIa in order to activate FIX. The CFD-VCEP determines this residue as critical for protein function warranting application of PM1_Strong The Arg191 residue forms the N-terminal cleavage site for FXIa. Upon cleavage at this site alone, it is shown that FIX zymogen is converted to FIXaα, an enzyme lacking proteolytic activity; and fully exposes the binding site for FVIII light chain, enabling assembly of FIX-FVIII complex. PubMed:7797466 Article outlines mechanism for FIX activation. Arg191 cleavage by FXIa facilitates subsequent cleavage at Arg226 at ~7-fold higher rate to limit accumulation of FIXaα. PubMed:24759143
PS4	✔	More than 100 individuals meet phenotype criteria for F9 and are counted towards PS4_Very Strong (threshold >=8 probands). (Note, the VCI does not allow selection of PS4_Very Strong, therefore PS4 is selected.)
PP4_Moderate	✔	Male with moderate hemophilia B with a factor IX level of 5% who had F8 and F9 full gene sequencing with deletion/duplication analysis.

Not Met criteria codes

PP1	✖	Although relatives/Family members with similarly low FIX levels of probands with Hemophilia B are reported in the literature, it is not sufficient to apply PP1 based on the number of informative meioses.
PM5	✖	At least 4 other missense variants at the same residue have been reported. c.571C>T (Arg191Cys), c.571C>A (Arg191Ser); c.572G>T (Arf191Leu) and c.572G>C (Arg191Pro). These variants have not been evaluated by the CFD-VCEP and are not considered here towards PM5.
PM2	✖	Arg191His is reported at a frequency of 0.00001221 (1/81909 alleles with 1 hemizygote) in the NFE population in gnomAD v2.1.1 and reports 1 hemizygous allele in the NFE population in gnomAD v3. PM2 is not met, but upon expert review, PS4 is counted.
PS3_Supporting	✖	In PMID: 31537632, FIX cDNA with the Arg191His missense variant was expressed in the HEK293 VKOR cell line. FIX-R191H is noted to yield FIXaα, which would remain in an unactivated form, while wild-type FIX yields FIXaβ. Chromogenic assay with small molecule chromogenic substrate, Pefachrome IXa, revealed similar kcat/KM values as WT, while 1.6+-0.2% coagulant activity of WT was determined by measuring aPTT in FIX immunodepleted plasma. This information is noted, but PS3 is not applied since experts opined that there's overlap in the reasoning for this code and PM1_Strong.

Curation History

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