

Variant: NM_001313913.2:c.1232G>A

Version: 1.0

CA10529891 [↗](#)

1685804 (ClinVar) [↗](#)

Gene: F9 ([HGNC:2158](#))

Condition: hemophilia B ([MONDO:0010604](#))

Inheritance Mode: X-linked inheritance

UUID: 48a2df65-8924-479f-bdf7-b364a056c79a

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HGVS expressions

NM_001313913.2:c.1232G>A

NC_000023.11:g.139562031G>A

CM000685.2:g.139562031G>A

NC_000023.10:g.138644190G>A

CM000685.1:g.138644190G>A

NC_000023.9:g.138471856G>A

NG_007994.1:g.36296G>A

ENST00000218099.7:c.1346G>A

ENST00000643157.1:n.1723+290G>A

ENST00000218099.6:c.1346G>A

ENST00000394090.2:c.1232G>A

NM_000133.3:c.1346G>A

NM_001313913.1:c.1232G>A

NM_000133.4:c.1346G>A

Uncertain Significance

Met criteria codes **1**

PS4

Not Met criteria codes **4**

BA1

PP3

PM5

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 F9 Version 1.0.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Coagulation Factor Deficiency VCEP

The c.1346G>A, p.Arg449Gln variant is reported with a Grpmax of 0.0001042 in gnomAD v2.1.1 with 7 hemizygotes meets the BA1 threshold of 0.0000556. However, this code was not applied due to the number of reported very mild hemophilia B cases being similar to the number of hemizygotes in gnomAD. There are at least 6 published cases in the literature and >1 unpublished case in the EAHAD Database with this variant and very mild hemophilia B meeting PS4 (PMID: 31267011, 31272859, 8091381, 10739381, 8076946, 8320491).

Typically, the PS4 code would not be applied when criteria for BA1 is met, but an exception was made for this variant given the number of known cases of very mild hemophilia B, which could lead to affected or undiagnosed individuals in control populations. In summary, this variant meets criteria to be classified as variant of uncertain significance. ACMG/AMP criteria applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F9: PS4.

Met criteria codes

PS4			There are at least 6 published cases in the literature (PMID: 31267011, 31272859, 8091381, 10739381, 8076946, 8320491) with this variant and mild hemophilia B and two unpublished cases in the EAHAD Database (only 1 unpublished case was included due to limited information).
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Not Met criteria codes

BA1			The c.1346G>A (p.Arg449Gln) variant is reported with a Grpmax of 0.0001042 in gnomAD v2.1.1 with 7 hemizygotes meets the BA1 threshold of 0.0000556 (or 0.00556%). However, this code was not applied due to the number of reported very mild hemophilia B cases being similar to the number of hemizygotes in gnomAD.
PP3			The Arg449Gln missense variant has a REVEL score of 0.588 which is below the threshold of 0.6 set by the CFD VCEP for PP3. SpliceAI score is 0.02, which is the below the cutoff of 0.5.
PM5			There is another variant c.1345C>T (p.Arg449Trp) at the same residue that has been curated by the CFD VCEP to be a VUS.
PM2			There are 7 hemizygotes in gnomAD v2.1.1.

Curation History



 

 

Showing 1 to 1 of 1 rows

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