

Variant: *NM_000173.7(GP1BA):c.241T>C (p.Cys81Arg)*

Version: 1.0

CA287215802 [↗](#)

1677212 (ClinVar) [↗](#)

Gene: GP1BA ([HGNC:2811](#))

Condition: Bernard-Soulier syndrome ([MONDO:0009276](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: cf0c7138-8040-43a6-a6f2-a97125094a35

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HGVS expressions

NM_000173.7(GP1BA):c.241T>C (p.Cys81Arg)

NM_000173.7:c.241T>C

NC_000017.11:g.4932845T>C

CM000679.2:g.4932845T>C

NC_000017.10:g.4836140T>C

CM000679.1:g.4836140T>C

NC_000017.9:g.4776920T>C

NG_008767.2:g.5551T>C

ENST00000329125.6:c.241T>C

ENST00000649830.1:c.-888+1497A>G

ENST00000329125.5:c.241T>C

ENST00000611961.1:c.241T>C

NM_000173.6:c.241T>C

Pathogenic

Met criteria codes 4

PM2_Supporting

PP1_Strong

PP4

PM3_Strong

Not Met criteria codes 3

PS3

PP3

PM1

Evidence Links 0

Expert Panel

Platelet Disorders VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Platelet Disorders Expert

Panel Specifications to the ACMG/AMP Variant

Interpretation Guidelines for GP1BA Version 1.0.0

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

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

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000173.7:c.241T>C (p.Cys81Arg) variant in GP1BA is a missense variant predicted to cause substitution of cysteine by arginine at amino acid 81. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been detected in at least 9 individuals with Bernard-Soulier syndrome. At least one individual had aggregation absent for ristocetin and present for all other agonists and less than 10% expression of GPIba measured by flow cytometry (PP4; PMID:25370924). One proband was homozygous and two additional probands that were compound heterozygotes for this variant and a second pathogenic variant, NM_000173.7(GP1BA):c.1620G>A, p.Trp540Ter with

phase confirmed (PM3_strong; PMID:25370924). The variant was reported to segregate in the proband plus 6 additional homozygous BSS affected individuals from a small town in Iceland (PP1_strong; PMID:25370924). In summary, this variant meets the criteria to be classified as pathogenic for Bernard-Soulier syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PP4, PM2_supporting, PM3_strong, PP1_strong (Platelet VCEP GP1BA specifications version 1).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting)
PP1_Strong			The variant has been reported to segregate in the proband plus 6 additional homozygous BSS affected individuals from a small town in Iceland and 14 additional heterozygous relatives with low platelet count and larger platelet size (median 9.7 fL) compared to controls (p<0.001 for both comparisons). 9.5 pts total (PP1_strong).
PP4			At least one patient (PMID:25370924, 9639514) with this variant had aggregation absent for ristocetin and present for all other agonists and less than 10% expression of GPIba measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome (PP4).
PM3_Strong			This variant has been detected in at least 9 individuals with Bernard-Soulier syndrome. 1 proband was homozygous for the variant (0.5 points). The other homozygotes were not counted assuming there were possibly related to this individual. There were two additional probands that were compound heterozygotes for this variant and a second pathogenic variant, NM_000173.7(GP1BA):c.1620G>A (p.Trp540Ter) with phase confirmed (2 pts). Total points: 2.5.

Not Met criteria codes

PS3			This variant demonstrates increased expression of GPIba compared to controls when transfected into CHO cells. vWF binding was absent (PS3 Not Met, PMID:9639514).
PP3			The computational predictor REVEL gives a score of 0.321, which is below the ClinGen PD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on GP1BA function. And the computational splicing predictor SpliceAI indicated that the variant has no predicted impact on splicing (Splice AI score <0.5).
PM1			Not in a hotspot or critical region as determined by the PD VCEP

Curation History 

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