

Variant: *NM_000174.5(GP9):c.70T>C (p.Cys24Arg)*

Version: 1.0

CA123181 [↗](#)

13533 (ClinVar) [↗](#)

Gene: GP9 ([HGNC:2815](#))

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 624db7a1-dce4-419c-9dd3-f73355aaf270

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HGVS expressions

NM_000174.5:c.70T>C

NM_000174.5(GP9):c.70T>C (p.Cys24Arg)

NC_000003.12:g.129061809T>C

CM000665.2:g.129061809T>C

NC_000003.11:g.128780652T>C

CM000665.1:g.128780652T>C

NC_000003.10:g.130263342T>C

NG_008715.1:g.6008T>C

ENST00000307395.5:c.70T>C

ENST00000307395.4:c.70T>C

NM_000174.4:c.70T>C

Likely Pathogenic

Met criteria codes **5**

PP1

PP3

PP4

PM3

PS3_Supporting

Not Met criteria codes **3**

PM2

PM5

BS1

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 GP9 Version 1.0.0

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

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

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.70T>C (p.Cys24Arg) variant in GP9 is a missense variant predicted to cause substitution of cystine by arginine at amino acid 24. This variant has been detected in at least 14 probands with Bernard-Soulier syndrome. All 14 of these individuals were homozygous for this variant at least 2 of those were confirmed in trans by parental testing (PMIDs:23402648, 21699652, 21173099, 11167791, 29119711; PM3). At least one patient (Patient BSS2.01 in PMID:23402648) with this variant had aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, the patient had macrothrombocytopenia which is consistent with Bernard-Soulier syndrome. The variant has been reported to segregate with Bernard-Soulier syndrome in the proband (meeting PP4) plus one affected family member, both with the homozygous genotype with the p.Cys24Arg variant. (PP1; PMID:21173099).

The computational predictor REVEL gives a score of 0.732, which is above the ClinGen PD VCEP threshold of >0.644 and predicts a damaging effect on function (PP3). The human copy of this variant failed to rescue thrombocytopenia when expressed in mutant thrombocytopenic zebrafish embryos. In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive Bernard-Soulier syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PM3, PP1, PP3, PP4, PS3_supporting. (VCEP specifications version 1)

Met criteria codes

PP1			The variant has been reported to segregate with Bernard-Soulier syndrome in the proband (meeting PP4) plus one affected family member, both with the homozygous genotype with the p.Cys24Arg variant. (PP1; PMID:21173099).
PP3			The computational predictor REVEL gives a score of 0.732, which is above the ClinGen PD VCEP threshold of >0.644 and predicts a damaging effect on function (PP3).
PP4			At least one patient (Patient BSS2.01 in PMID:23402648) with this variant had aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, the patient had macrothrombocytopenia which is consistent with Bernard-Soulier syndrome.
PM3			This variant has been detected in at least 14 probands with Bernard-Soulier syndrome. All 14 of these individuals were homozygous for this variant at least 2 of those were confirmed in trans by parental testing (1.0 PM3 points, PMIDs:23402648, 21699652, 21173099, 11167791, 29119711) Total points: 1.0 (PM3).
PS3_Supporting			The human copy of this variant failed to rescue thrombocytopenia when expressed in mutant thrombocytopenic zebrafish embryos (PMID: 344076040).

Not Met criteria codes

PM2			The Grpmax Filtering allele frequency in gnomAD v4.1 is 0.0005260 (based on 60/90946 alleles) in the South Asian population, which is above the ClinGen PD VCEP PM2_supporting threshold (<0.0000329) but below the BS1 threshold (>0.0007).
PM5			Another missense variant in the same codon has been reported in a patient with Bernard-Soulier syndrome [c.72T>G (p.Cys24Trp)] (PMID:21173099) However, this variant has is not considered here to avoid circularity.
BS1			The Grpmax Filtering allele frequency in gnomAD v4.1is 0.0005260 (based on 60/90946 alleles) in the South Asian population, which is above the ClinGen PD VCEP PM2_supporting threshold (<0.0000329) but below the BS1 threshold (>0.0007).

Curation History 

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