

Variant: *NM_000174.5(GP9):c.284A>G (p.Tyr95Cys)*

Version: 1.0

CA354447931 [↗](#)

2503896 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: fc85773b-0c29-4638-9eb9-53a16007d383

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HGVS expressions

NM_000174.5(GP9):c.284A>G (p.Tyr95Cys)

NM_000174.5:c.284A>G

NC_000003.12:g.129062023A>G

CM000665.2:g.129062023A>G

NC_000003.11:g.128780866A>G

CM000665.1:g.128780866A>G

NC_000003.10:g.130263556A>G

NG_008715.1:g.6222A>G

ENST00000307395.5:c.284A>G

ENST00000307395.4:c.284A>G

NM_000174.4:c.284A>G

Likely Pathogenic

Met criteria codes **4**

PP4

PP3_Moderate

PM3

PM2_Supporting

Not Met criteria codes **1**

PM5

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.284A>G variant in GP9 is a missense variant predicted to cause substitution of Tyrosine by Cysteine at amino acid 95 (p.Tyr95Cys). At least one patient (Patient P12 in PMID: 21173099) with this variant had aggregation absent for ristocetin and present for all other agonists as well as less than 10% expression of GPIIb and GP9 as measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had excessive mucocutaneous bleeding which is consistent with Bernard-Soulier syndrome (PP4). This variant has been detected in at least two probands with Bernard-Soulier syndrome (PMIDs: 21173099, 32202057 and 29043243). Both probands were homozygous for the variant (1 PM3 point, PM3). The computational predictor REVEL gives a score of 0.814, which is above the ClinGen PD VCEP threshold of ≥ 0.773 and predicts a damaging effect on function (PP3_Moderate). This variant is absent from gnomAD

v4.1.0 (PM2_Supporting). 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: PP4, PM3, PM2_Supporting and PP3_Moderate (VCEP specifications version 1).

Met criteria codes

PP4			At least one patient (Patient P12 in PMID: 21173099) with this variant had aggregation absent for ristocetin and present for all other agonists as well as less than 10% expression of GPIIb and GP9 as measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had excessive mucocutaneous bleeding which is consistent with Bernard-Soulier syndrome (PP4).
PP3_Moderate			The computational predictor REVEL gives a score of 0.814, which is above the ClinGen PD VCEP threshold of ≥ 0.773 and predicts a damaging effect on function (PP3_Moderate).
PM3			This variant has been detected in at least two probands with Bernard-Soulier syndrome (PMIDs: 21173099, 32202057 and 29043243). Both probands were homozygous for the variant (1 PM3 point, PM3).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM5			Another missense variant in the same codon has been reported in a patient with Bernard-Soulier syndrome; NM_000174.5(GP9):c.284A>C (p.Tyr95Ser) However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen PD VCEP (PM5 not met).
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Curation History

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