

Variant: NM_000407.5:c.269C>G

Version: 1.2

CA410676959 [↗](#)

Gene: GP1BB ([HGNC:2812](#))

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 25b5ead3-1e18-41ec-96a3-f00739412896

Approved on: 2025/2/18

Published on: 2025/2/18

HGVS expressions

NM_000407.5:c.269C>G

NC_000022.11:g.19724112C>G

CM000684.2:g.19724112C>G

NC_000022.10:g.19711635C>G

CM000684.1:g.19711635C>G

NC_000022.9:g.18091635C>G

NG_007974.1:g.5570C>G

ENST00000366425.4:c.269C>G

ENST00000366425.3:c.269C>G

ENST00000431044.5:c.*1354C>G

ENST00000455843.5:c.*1354C>G

ENST00000470814.1:n.2241C>G

NM_000407.4:c.269C>G

NR_037611.1:n.4009C>G

NR_037612.1:n.2513C>G

Likely Pathogenic

Met criteria codes **4**

PM2_Supporting

PP3_Moderate

PP4_Moderate

PM3_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 GP1BB Version 1.0.0*

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

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

Evidence submitted by expert panel

Platelet Disorders VCEP

NM_000407.5(GP1BB):c.269C>G (p.Pro90Arg) is a missense variant in GP1BB which has been reported in the literature in at least 1 proband in the homozygous state, BSS-15, an indian woman with mucocutaneous bleeding, normal platelet aggregation with agonists (but absent with ristocetin), and 10% platelet expression of GP1bb on flow cytometry (PMID:21699652; PP4_moderate). Additionally, the variant

is absent from gnomAD v4.1 and is predicted to have a deleterious effect (REVEL score of 0.853; PP3_Moderate). 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: PM2_Supporting, PP3_Moderate, PP4_moderate, and PM3_supporting. (VCEP specifications version 1)

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).
PP3_Moderate			The computational predictor REVEL gives a score of 0.853, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on function (PP3_Moderate).
PP4_Moderate			At least one patient (Patient BS-15 in PMID:21699652) with this variant had aggregation absent for ristocetin and present for all other agonists and 10% expression of GP1bb measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome and with full gene sequencing and del/dup analysis of all BSS genes is specific to GPIba, GP1bb, and GP9 (PP4_moderate). Additionally, the patient had excessive mucocutaneous bleeding which is consistent with Bernard-Soulier syndrome.
PM3_Supporting			This variant has been detected in at least 1 probands with Bernard-Soulier syndrome. One proband was homozygous for the variant (PMID: 21699652). Total points: .5 (PM3_supporting).

Not Met criteria codes

PM5			Another missense variant in the same codon has been reported in a patient with Bernard-Soulier syndrome c.268C>T (p.Pro90Ser) (PMID:25539746; classified Likely Pathogenic by the PD VCEP). However, this variant is not considered here to avoid circularity.
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Curation History

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