

Variant: *NM_000407.5(GP1BB):c.268C>T (p.Pro90Ser)*

Version: 1.0

CA410676953 [↗](#)

1691254 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 0759aa21-8414-40de-a1f3-20504a07daf1

Approved on: 2025/2/18

Published on: 2025/2/18

HGVS expressions

NM_000407.5(GP1BB):c.268C>T (p.Pro90Ser)

NM_000407.5:c.268C>T

NC_000022.11:g.19724111C>T

CM000684.2:g.19724111C>T

NC_000022.10:g.19711634C>T

CM000684.1:g.19711634C>T

NC_000022.9:g.18091634C>T

NG_007974.1:g.5569C>T

ENST00000366425.4:c.268C>T

ENST00000366425.3:c.268C>T

ENST00000431044.5:c.*1353C>T

ENST00000455843.5:c.*1353C>T

ENST00000470814.1:n.2240C>T

NM_000407.4:c.268C>T

NR_037611.1:n.4008C>T

NR_037612.1:n.2512C>T

Likely Pathogenic

Met criteria codes **5**

PP3

PM3_Supporting

PM2_Supporting

PP4_Moderate

PM5_Supporting

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.268C>T is a missense variant (p.Pro90Ser), which has been reported in one homozygous proband with Bernard-Soulier syndrome. At least one patient (Patient BSS-8 in PMID:25539746) with this variant had aggregation absent for ristocetin and

present for all other agonists, and flow cytometry revealed that the GPIb α and GPIX expression was severely reduced (<10% compared to controls), which is highly specific for Bernard-Soulier syndrome and with full gene sequencing and del/dup analysis of all BSS genes is specific to GP1bb (PP4_moderate). Additionally, the patient had macrothrombocytopenia and excessive mucocutaneous bleeding which is consistent with Bernard-Soulier syndrome. The Grpmax filtering allele frequency in gnomADv4.1 is 0.000004490 (based on 2/74000 alleles) in the South Asian population, which is below the <0.0000651678 threshold for PM2_supporting. The computational predictor REVEL gives a score of 0.771, which is above the ClinGen PD VCEP PP3 threshold of >0.644 and predicts a damaging effect on GP1BB function (PP3). Another missense variant in the same codon has been reported in a patient with Bernard-Soulier syndrome c.269C>G (p.Pro90Arg) (PMID:21699652), it is classified Likely Pathogenic by the PD-VCEP (PM5_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: PP3, PP4_moderate, PM2_supporting, PM5_supporting, and PM3_supporting (VCEP specifications version 1).

Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.771, which is above the ClinGen PD VCEP threshold of >0.644 and predicts a damaging effect on function (PP3).
PM3_Supporting			This variant has been detected in at least 1 proband with Bernard-Soulier syndrome. 1 proband was homozygous for this variant (.5 points, PMID:25539746).
PM2_Supporting			The Grpmax filtering allele frequency in gnomADv4.1 is 0.000004490 (based on 2/74000 alleles) in the South Asian population, which is below the <0.0000651678 threshold for PM2_supporting.
PP4_Moderate			At least one patient (Patient BSS-8 in PMID:25539746) with this variant had aggregation absent for ristocetin and present for all other agonists, and flow cytometry revealed that the GPIb α and GPIX expression was severely reduced (<10% compared to controls), which is highly specific for Bernard-Soulier syndrome and with full gene sequencing and del/dup analysis of all BSS genes is specific to GP1bb (PP4_moderate). Additionally, the patient had macrothrombocytopenia and excessive mucocutaneous bleeding which is consistent with Bernard-Soulier syndrome.
PM5_Supporting			Another missense variant in the same codon has been reported in a patient with Bernard-Soulier syndrome c.269C>G (p.Pro90Arg) (PMID:21699652), it is classified Likely Pathogenic by the PD-VCEP (PM5_supporting).

Curation History



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