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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 PM5_Supporting PM3_Supporting PM2_Supporting PP4_Moderate

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 GPIbα 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).
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).
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 GPIbα 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.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000407.5(GP1BB):c.268C>T (p.Pro...	Likely Pathogenic	Bernard-Soulier Syndrome	2025-02-18	1.0	ClinGen Platelet Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GP1BB Version 1.0.0	GP1BB

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