

Variant: *NM_000407.5(GP1BB):c.47T>C (p.Leu16Pro)*

Version: 1.0

CA410676273 [↗](#)

627320 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: bd7b0fd0-8404-4a5a-bbdd-d3baf91f527e

Approved on: 2025/2/18

Published on: 2025/2/18

HGVS expressions

NM_000407.5:c.47T>C

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NC_000022.11:g.19723890T>C

CM000684.2:g.19723890T>C

NC_000022.10:g.19711413T>C

CM000684.1:g.19711413T>C

NC_000022.9:g.18091413T>C

NG_007974.1:g.5348T>C

ENST00000366425.4:c.47T>C

ENST00000366425.3:c.47T>C

ENST00000431044.5:c.*1132T>C

ENST00000455843.5:c.*1132T>C

ENST00000470814.1:n.2019T>C

NM_000407.4:c.47T>C

NR_037611.1:n.3787T>C

NR_037612.1:n.2291T>C

Likely Pathogenic

Met criteria codes **5**

PP4

PP3_Moderate

PM3

PS4_Supporting

PM2_Supporting

Not Met criteria codes **1**

PP1

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.47T>C (p.Leu16Pro) is a missense variant in **GP1BB** that has been reported in the literature in at least two probands diagnosed with Bernard-Soulier syndrome in the homozygous state (PM3, PMIDs:32419170, 24934643). One of those patients

displayed absent expression of GP1bb (CD42) in addition to excessive mucocutaneous bleeding and macrothrombocytopenia (PP4). At least 5 unrelated individuals heterozygous for this variant have been reported with macrothrombocytopenia (<150x10⁹ platelets/l and MPV >12) in four publications (PMIDs: 28064200, 36173017, 31793234, 30609015; PS4_supporting). The Grpmax filtering allele frequency in gnomADv4.1 is 8.200e-7 (based on 4/1141542 alleles) in the European (non-Finnish) population, which is below the <0.0000651678 threshold for PM2_supporting. Additionally, the variant is predicted to have a deleterious effect (REVEL score of 0.886; 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: PS4_Supporting, PM2_Supporting, PP3_Moderate, PP4, and PM3 (VCEP specifications version 1).

Met criteria codes

PP4			At least one patient (Patient from PMID:32419170) with this variant had absent expression of GP1bb, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, the patient had excessive mucocutaneous bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome.
PP3_Moderate			The computational predictor REVEL gives a score of 0.886, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on function (PP3_Moderate).
PM3			The variant has been reported in at least two homozygous individual with Bernard-Soulier syndrome (PMIDs: 32419170, 24934643, PM3).
PS4_Supporting			At least 5 unrelated individuals heterozygous for this variant have been reported with macrothrombocytopenia (<150x10 ⁹ platelets/l and MPV >12) in four publications (PMIDs: 28064200, 36173017, 31793234, 30609015) for 1.25pt total (PS4_supporting).
PM2_Supporting			The Grpmax filtering allele frequency in gnomADv4.1 is 8.200e-7 (based on 4/1141542 alleles) in the European (non-Finnish) population, which is below the <0.0000651678 threshold for PM2_supporting.

Not Met criteria codes

PP1			PMID: 36173017 reports a heterozygous sibling with macrothrombocytopenia (108x10 ⁹ platelets/l and MPV 14.3 fl) 0.25pt. PMID: 30609015 reports a son who is also heterozygous with 108x10 ⁹ platelet/l and 14.3 fl MPV 0.25pt and 41% GP1b-V-IX expression measured by flow cytometry 0.5pt total 0.75pt (PP1_NotMet)
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Curation History 

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