

Variant: *NM_000407.5:c.265A>G*

Version: 1.0

CA410676935 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9b218336-0c1d-46a1-a748-0f0ef9dd921b

Approved on: 2026/4/2

Published on: 2026/4/2

HGVS expressions

NM_000407.5:c.265A>G

NC_000022.11:g.19724108A>G

CM000684.2:g.19724108A>G

NC_000022.10:g.19711631A>G

CM000684.1:g.19711631A>G

NC_000022.9:g.18091631A>G

NG_007974.1:g.5566A>G

ENST00000366425.4:c.265A>G

ENST00000366425.3:c.265A>G

ENST00000431044.5:c.*1350A>G

ENST00000455843.5:c.*1350A>G

ENST00000470814.1:n.2237A>G

NM_000407.4:c.265A>G

NR_037611.1:n.4005A>G

NR_037612.1:n.2509A>G

Likely Pathogenic

Met criteria codes **5**

PM2_Supporting

PP3_Moderate

PP4

PM3

PP1_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 1.1.0*

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

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

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.265A>G variant in GP1BB is a missense variant predicted to cause substitution of Asparagine by Aspartic acid at amino acid 89 (p.Asn89Asp). This is a well known founder variant on the French Island of Reunion. This variant has been detected in at least 5 unrelated homozygous probands with Bernard-Soulier syndrome from the this island (PMID: 31997307, 1 PM3 points, PM3). At least one patient

(Patient BSS1 in PMID: 31997307) with this variant had less than 10% expression of GPIba, GP1bb and GP9 measured by Western blot, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had excessive mucocutaneous bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome (PP4). In both Family 2 and Family 3 of PMID: 31997307, the variant was reported to segregate in the proband plus 1 additional homozygous BSS affected sibling (2 points, PP1_Moderate). The computational predictor REVEL gives a score of 0.955, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on GP1BB 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: PM3, PP1_Moderate, PP3_Moderate, PP4 and PM2_Supporting (VCEP specifications version 1.1).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP3_Moderate			The computational predictor REVEL gives a score of 0.955, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on GP1BB function (PP3_Moderate).
PP4			At least one patient (Patient BSS1 in PMID: 31997307) with this variant had less than 10% expression of GP1bb and GP9 measured by Western blot, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had excessive mucocutaneous bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome (PP4).
PM3			This variant has been detected in at least 5 unrelated homozygous probands with Bernard-Soulier syndrome from the French Island of Reunion (PMID: 31997307, 1 PM3 points).
PP1_Moderate			In both Family 2 and Family 3 of PMID: 31997307, the variant was reported to segregate in the proband plus 1 additional homozygous BSS affected sibling (2 points, PP1_Moderate).

Curation History

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