

Variant: NM_000407.5(GP1BB):c.397G>C (p.Ala133Pro)

Version: 1.0

CA126156 [↗](#)

16039 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e065f435-9da7-4596-bfe9-5e3f8f1846a0

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HGVS expressions

NM_000407.5:c.397G>C

NM_000407.5(GP1BB):c.397G>C (p.Ala133Pro)

NC_000022.11:g.19724240G>C

CM000684.2:g.19724240G>C

NC_000022.10:g.19711763G>C

CM000684.1:g.19711763G>C

NC_000022.9:g.18091763G>C

NG_007974.1:g.5698G>C

ENST00000366425.4:c.397G>C

ENST00000366425.3:c.397G>C

ENST00000431044.5:c.*1482G>C

NM_000407.4:c.397G>C

NR_037611.1:n.4137G>C

NR_037612.1:n.2641G>C

Likely Pathogenic

Met criteria codes **5**

PS3_Supporting

PP1

PP4

PM3

PM2_Supporting

Not Met criteria codes **2**

BP4

PP3

Evidence Links **1**

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

The missense variant NM_000407.5(GP1BB):c.397G>C (p.Ala133Pro) has a Grpmax Filtering allele frequency in gnomAD v4.1 is 0.00002722 (based on 3/29196 alleles) in the East Asian population, which is lower than the ClinGen PD VCEP threshold (<0.00006517;

PM2_Supporting). At least one patient (Patient A.K. in PMID: 9116284) with this variant had aggregation absent for ristocetin and present for all other agonists and flow cytometry found the expression of GPIb α , the GPIb/IX complex, and GPIX were remarkably lower than the

normal control. 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. The patient is compound heterozygote has been reported with Tyr113Cys (provisionally classified Likely Pathogenic by PD VCEP) and Ala133Pro confirmed in trans from heterozygous parents (PMID: 9116284; PM3). There is segregation of this variant in 1 additional compound heterozygous BSS family member (PMID: 9116284; total 1pt, PP1). In transiently transfected CHO cells HA-GPIbβ was present on the cell surface but GPIX was not (PMID: 21908432). In transiently transfected CHO cells HA-GPIbβ was present on the cell surface around 20% but GPIX was absent (PMID: 21908432; PS3_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: PS3_supporting, PM3, PM2_supporting, PP1, PP4.

Met criteria codes

PS3_Supporting			In transiently transfected CHO cells HA-GPIbβ was present on the cell surface around 20% but GPIX was absent (PMID: 21908432).
transfected CHO cells HA-GPIbβ was present on the cell surface around 5% but GPIX was absent			
	PubMed:21908432 		
PP1			Segregation of this variant in 1 additional compound heterozygous BSS family member (PMID: 9116284; total 1pt, PP1)
PP4			At least one patient (Patient A.K. in PMID: 9116284) with this variant had aggregation absent for ristocetin and present for all other agonists and flow cytometry found the expression of GPIbα, the GPIb/IX complex, and GPIX were remarkably lower than the normal control. 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.
PM3			One compound heterozygote has been reported with Tyr113Cys (classified Likely Pathogenic by PD VCEP) and Ala133Pro confirmed in trans from heterozygous parents (PMID: 9116284; PM3)
PM2_Supporting			The Grpmax Filtering allele frequency in gnomAD v4.1 is 0.00002722 (based on 3/29196 alleles) in the East Asian population, which is lower than the ClinGen PD VCEP threshold (<0.00006517; PM2_Supporting).

Not Met criteria codes

BP4			The computational predictor REVEL gives a score of 0.496, which is above the ClinGen PD VCEP threshold of <0.290.
PP3			The computational predictor REVEL gives a score of 0.496, which is below the ClinGen PD VCEP PP3 threshold of >0.7 and does not predict a damaging effect on GP1BB function. And the computational splicing predictor SpliceAI indicated that the variant has no predicted impact on splicing.

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