

Variant: *NM_000173.7(GP1BA):c.434T>C (p.Leu145Pro)*

Version: 1.0

CA8314774 [↗](#)

1684365 (ClinVar) [↗](#)

Gene: GP1BA ([HGNC:2811](#))

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9f80c092-c2c7-40c2-9f9e-f5b43af9c95b

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HGVS expressions

NM_000173.7:c.434T>C

NM_000173.7(GP1BA):c.434T>C (p.Leu145Pro)

NC_000017.11:g.4933038T>C

CM000679.2:g.4933038T>C

NC_000017.10:g.4836333T>C

CM000679.1:g.4836333T>C

NC_000017.9:g.4777113T>C

NG_008767.2:g.5744T>C

ENST00000329125.6:c.434T>C

ENST00000649830.1:c.-888+1304A>G

ENST00000329125.5:c.434T>C

ENST00000611961.1:c.434T>C

NM_000173.6:c.434T>C

Likely Pathogenic

Met criteria codes **5**

PP1

PP4

PP3_Moderate

PM3

PS3_Supporting

Not Met criteria codes **2**

BS1

PM2

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 GP1BA Version 1.0.0

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

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

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000173.7(GP1BA):c.434T>C (p.Leu145Pro) missense variant occurs in the first amino acid of the fifth leucine-rich repeat of the GPIb α polypeptide and the computational predictor REVEL gives a score of 0.862, which is above the ClinGen PD VCEP threshold of >0.773 to predict a damaging effect on function (PP3_Moderate). At least three BSS patients have been reported with this variant, including 2 homozygotes (PMID: 10996832 and PMID: 7579348; PM3) and one compound heterozygote (PMID: 10089893) in trans with c.1601_1602del. At least one patient (Patient 1 in PMID: 7579348) with this variant had aggregation absent for ristocetin and present for all other agonists,

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. Patient 1 and their affected cousin are both homozygous for the variant (PMID: 7579348; PP1). Functional analysis was performed with both wild-type and mutant GPIb α cDNAs transiently transfected into L cells that had been previously transformed with stable constructs expressing GPIb β and IX. Measured by flow cytometry, 43% of cells expressed GPIb α protein on their surface when transfected with normal GPIb α cDNA under the described conditions. However, no GPIb α expression could be appreciated on the surface of the cells transfected with the mutant GPIb α cDNA (PMID: 7579348; 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: PM3, PP1, PP3_Moderate, and PP4.

Met criteria codes

PP1			Both affected cousins are homozygous (PMID: 7579348; PP1)
PP4			At least one patient (Patient 1 in PMID: 7579348) with this variant had aggregation absent for ristocetin and present for all other agonists, 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 0.862, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on function (PP3_Moderate).
PM3			At least three BSS patients have been reported with this variant, including 2 homozygotes (1pt; PMID: 10996832 and PMID: 7579348) and one compound heterozygote (PMID: 10089893) in trans with c.1601_1602del (does not affect this classification and not yet curated by the PD VCEP). Total 1pt (PM3)
PS3_Supporting			Both wild-type and mutant GPIb α cDNAs were transiently transfected into L cells that had been previously transformed with stable constructs expressing GPIb β and IX. Measured by flow cytometry, 43% of cells expressed GPIb α protein on their surface when transfected with normal GPIb α cDNA under the described conditions. However, no GPIb α expression could be appreciated on the surface of the cells transfected with the mutant GPIb α cDNA (PMID: 7579348; PS3_supporting)

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			The Grpmax filtering AF in gnomADv4.1 is 0.00001746 (based on 4/74920 alleles) in the African/African American population, below the threshold of 0.0001114 for PM2_supporting. However, the highest population minor allele frequency in gnomAD v4.1 is 0.001031 (34/25018 alleles) in the Finnish population (not considered for the Grpmax FAF) which is higher than the ClinGen PD VCEP BA1 threshold (>0.001 for GP1BA) but bottlenecked populations are not considered for BA1. Given this conflicting information no population criteria are included.

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