

Variant: NM_000174.5:c.404G>A

Version: 1.0

CA2602709 [↗](#)

4687494 (ClinVar) [↗](#)

Gene: GP9 ([HGNC:2815](#))

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e41b1f54-7b80-4041-a1b3-4a65b690c23a

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HGVS expressions

NM_000174.5:c.404G>A

NC_000003.12:g.129062143G>A

CM000665.2:g.129062143G>A

NC_000003.11:g.128780986G>A

CM000665.1:g.128780986G>A

NC_000003.10:g.130263676G>A

NG_008715.1:g.6342G>A

ENST00000307395.5:c.404G>A

ENST00000307395.4:c.404G>A

NM_000174.4:c.404G>A

Likely Pathogenic

Met criteria codes **3**

PM2_Supporting

PP4

PM3_Strong

Not Met criteria codes **3**

BP4

PP3

PM5

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 GP9 Version 1.1.0

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

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

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.404G>A variant in GP9 is a missense variant predicted to cause substitution of cysteine by tyrosine at amino acid 135 (p.Cys135Tyr). At least one patient (Patient BSS8.02 in PMID: 23402648) with this variant had aggregation absent for ristocetin and present for all other agonists and less than 10% expression of GPIIb/IIIa/α_{IIb}β₃ measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, the patient had macrothrombocytopenia which is consistent with Bernard-Soulier syndrome. This variant has been detected in at least 3 probands with Bernard-Soulier syndrome. Two of those individuals were compound heterozygous for this variant and the NM_000174.5(GP9):c.182A>G (p.Asn61Ser) variant which has been classified as Pathogenic by the PD VCEP. The phase of the variants was confirmed to be in trans in one of these patients (Internal from Versiti), but the phase was unknown in the other patient (PMID: 25370924). Additionally, one proband was homozygous for the variant (2 PM3 points, PM3_Strong). The Grpmax filtering allele frequency in

gnomaDv4.1 is 0.000001250 (based on 5/1170352 alleles) in the European (non-Finnish) population, which is below the <0.0000329 threshold for 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: PP4, PM2_Supporting, and PM3_Strong. (VCEP specifications version 1).			
Met criteria codes			
PM2_Supporting			The Grpmax filtering allele frequency in gnomADv4.1 is 0.000001250 (based on 5/1170352 alleles) in the European (non-Finnish) population, which is below the <0.0000329 threshold for PM2_supporting.
PP4			At least one patient (Patient BSS8.02 in PMID: 23402648; internal) with this variant had aggregation absent for ristocetin and present for all other agonists and less than 10% expression of GPIIb/IIIa measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, the patient had macrothrombocytopenia which is consistent with Bernard-Soulier syndrome. Only sequencing of GP1BA, GP1BB, and GP9 were done in this paper and the internal case.
PM3_Strong			This variant has been detected in at least 3 probands with Bernard-Soulier syndrome. Two of those individuals were compound heterozygous for this variant and the NM_000174.5(GP9):c.182A>G (p.Asn61Ser) variant which has been classified as Pathogenic by the PD VCEP. The phase of the variants was confirmed to be in trans in one of these patients (Internal from Versiti), but the phase was unknown in the other patient (PMID: 25370924). Additionally, one proband was homozygous for the variant in PMID:23402648 (2 PM3 points, PM3_Strong). Versiti 1: path variant, confirmed in trans = 1 point Versiti 2: in trans with Ib variant = 0 points Ali: 23402648 = 0.5 PMID: 25370924- path variant phase unknown = 0.5 point
Not Met criteria codes			
BP4			The computational predictor REVEL gives a score of 0.619, which is above the ClinGen PD VCEP threshold of <0.290
PP3			The computational predictor REVEL gives a score of 0.619, which is below the ClinGen PD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on GP9 function. And the computational splicing predictor SpliceAI indicated that the variant has no predicted impact on splicing.
PM5			Another variant is present at this codon, NM_000174.5(GP9):c.404G>T (p.Cys135Phe) has been classified as VUS by the PD VCEP.

Curation History [↗](#)

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