

Variant: *NM_000173.7(GP1BA):c.165_168del (p.Ser55fs)*

Version: 1.0

CA658820730 [↗](#)

2736403 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 0a0dff03-9c0b-45d2-86c6-20a97a928d3c

Approved on: 2025/2/11

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HGVS expressions

NM_000173.7:c.165_168del

NM_000173.7(GP1BA):c.165_168del (p.Ser55fs)

NC_000017.11:g.4932769_4932772del

CM000679.2:g.4932769_4932772del

NC_000017.10:g.4836064_4836067del

CM000679.1:g.4836064_4836067del

NC_000017.9:g.4776844_4776847del

NG_008767.2:g.5475_5478del

ENST00000329125.6:c.165_168del

ENST00000649830.1:c.-888+1574_-888+1577del

ENST00000329125.5:c.165_168del

ENST00000611961.1:c.165_168del

NM_000173.6:c.165_168del

Likely Pathogenic

Met criteria codes **5**

PS3_Supporting

PP4

PM3_Supporting

PM2_Supporting

PVS1_Strong

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 GP1BA Version 1.0.0

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

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

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.165_168del (p.Ser55ArgfsTer12) variant in GP1BA is a frameshift variant that may cause a premature stop codon that is predicted to escape nonsense mediated decay, however it is a truncation of a functionally important region (removes the final 598 amino acids) in a gene where loss-of-function is an established disease mechanism (PVS1_Strong). At least one patient (Patient 1 in PMID: 11054083) with this variant had aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome (PP4). They also had a history of recurrent epistaxis and spontaneous skin bruises and a low platelet count ($84 \times 10^9/l$). This variant has

been detected in at least 2 probands with Bernard-Soulier syndrome. One of those individuals was compound heterozygous for this variant and the c.1601_1602del (p.Tyr534CysfsTer?) variant in GP1BA, confirmed in trans by parental testing (PMID: 11054083). This second variant was classified as Pathogenic by the VCEP. (not included here to avoid circularity). The other proband was homozygous for the c.165_168del (p.Ser55ArgfsTer12) variant (PMID: 18791947; PM3_Supporting). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). From PMID: 11054083, flow cytometric analysis was performed for GP Iba on CHO cells transiently transfected with the WT + c.165_168del (p.Ser55ArgfsTer12), which had around 60% WT expression levels above sham. They also tested c.165_168del + c.1601_1602del, which had around 5% WT expression levels above sham. Due to the methods used in this assay (where c.165_168del was not tested independently), the usual threshold of <25% WT levels to apply PS3_supporting is not the appropriate measure. The 60% expression of WT + c.165_168del is considered sufficient, particularly in light of the c.165_168del + c.1601_1602del, which had around 5% WT expression levels (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: PVS1_Strong, PP4, PM2_Supporting and PM3_Supporting, PS3_Supporting (VCEP specifications version 1).

Met criteria codes

PS3_Supporting			From PMID: 11054083, flow cytometric analysis was performed for GP Iba on CHO cells transiently transfected with the WT + c.165_168del (p.Ser55ArgfsTer12), which had around 60% WT expression levels above sham. They also tested c.165_168del + c.1601_1602del, which had around 5% WT expression levels above sham. However, c.165_168del was not tested independently. Meanwhile WT + c.1601_1602del was around 50% WT expression levels above sham. Due to the methods used in this assay, the usual threshold of <25% WT levels to apply PS3_supporting is not the appropriate measure. The 60% expression of WT + c.165_168del is considered sufficient, particularly in light of the c.165_168del + c.1601_1602del, which had around 5% WT expression levels. Flow cytometric analysis was performed on of GP Iba on CHO cells transiently transfected with the WT + c.165_168del (p.Ser55ArgfsTer12), which had around 60% WT expression levels above sham. They also tested c.165_168del + c.1601_1602del, which had around 5% WT expression levels above sham. However, c.165_168del was not tested independently. Meanwhile WT + c.1601_1602del was around 50% WT expression levels above sham. PubMed:11054083 
PP4			At least one patient (Patient 1 in PMID: 11054083) with this variant had aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome. They also had a history of recurrent epistaxis and spontaneous skin bruises and a low platelet count (84x10^9/l). Although sequencing was performed for all three BSS genes, del/dup analysis was not mentioned for this patient (PP4).
PM3_Supporting			This variant has been detected in at least 1 proband with Bernard-Soulier syndrome.This proband was homozygous for the c.165_168del (p.Ser55ArgfsTer12) variant (0.5 PM3 points, PMID: 18791947). Total points: 0.5 (PM3_Supporting).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PVS1_Strong			The c.165_168del (p.Ser55ArgfsTer12) variant in GP1BA is a frameshift variant that may cause a premature stop codon that is predicted to escape nonsense mediated decay, however it is a truncation of a functionally important region (removes the final 598 amino acids) in a gene where loss-of-function is an established disease mechanism (PVS1_Strong).



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