

Variant: *NM_000173.7:c.1454dup*

Version: 1.0

CA8315002 [↗](#)

2137887 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: f17498da-243a-4e33-ad83-e4a729eca450

Approved on: 2025/2/11

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HGVS expressions

NM_000173.7:c.1454dup

NC_000017.11:g.4934058dup

CM000679.2:g.4934058dup

NC_000017.10:g.4837353dup

CM000679.1:g.4837353dup

NC_000017.9:g.4778094dup

NG_008767.2:g.6764dup

ENST00000329125.6:c.1454dup

ENST00000649830.1:c.-888+284dup

ENST00000329125.5:c.1454dup

ENST00000611961.1:c.1376dup

NM_000173.6:c.1454dup

Pathogenic

Met criteria codes **6**

PS3_Supporting

PP1

PP4

PM2_Supporting

PVS1_Strong

PM3_Strong

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

NM_000173.7(GP1BA):c.1454dup is a frameshift variant (p.Ser486IlefsTer12), which has been reported in multiple probands with Bernard-Soulier syndrome (PMIDs:11776304, 16916536, 23402648, 24934643, 9241731). The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000004440 (based on 2/74766) in the African/African American population, which does not meet PM2_supporting or BS1. The frameshift variant may cause loss of function of the protein, however it is predicted to escape nonsense mediated decay and remove 24% of the protein (PVS1_Strong). Case 2 of PMID: 9241731 is compound heterozygous with c.1480del (classified Pathogenic by the PD-VCEP) confirmed in trans and at least two additional patients are homozygous for the variant (PM3_strong). At least one patient (Proband in

PMID:11776304) with this variant had aggregation absent for ristocetin but present for all other agonists and flow cytometry with less than 10% expression of GPIBa (PP4). The variant segregated with Bernard-Soulier syndrome in this patient plus an affected sibling, both compound heterozygous for this variant and Cys225Ser (PP1). Finally, surface expression of GP1Balpha measured by flow cytometry from transient transfection of the c.1454dup variant in CHO cells stably co-expressing the GPIbbeta and GPIX subunits showed decreased expression at 0% (<25%) WT levels, indicating that this variant impacts protein function (PMID:11776304; PS3_supporting). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive Bernard-Soulier syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PP1, PM3_strong, PS3_supporting, PVS1_strong, PP4, PM2_supporting.

Met criteria codes			
PS3_Supporting			Surface expression of GP1Balpha measured by flow cytometry from transient transfection of the c.1454dup variant in CHO cells stably co-expressing the GPIbbeta and GPIX subunits showed decreased expression at 0% (<25%) WT levels, indicating that this variant impacts protein function (PMID:11776304; PS3_supporting).
PP1			The variant has been reported to segregate with Bernard-Soulier syndrome in the proband (meeting PP4) plus one affected family member, both with the compound heterozygous genotype with c.673T>A and c.1454dup variant(s). (PP1; PMID:11776304).
PP4			At least one patient (Proband in PMID:11776304) with this variant had aggregation absent for ristocetin and present for all other agonists AND flow cytometry with less than 10% expression of GPIba, 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.
PM2_Supporting			The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000004440 (based on 2/74766) in the African/African American population, below the <0.0001114 threshold for PM2_supporting
PVS1_Strong			The c.1454dup (p.Ser486lleftsTer12) variant in GP1BA is a frameshift variant that may cause loss of function of the protein, however it is predicted to escape nonsense mediated decay and remove 24% (>10%) of the protein (PVS1_Strong).
PM3_Strong			Case 2 of PMID: 9241731 is compound heterozygous for the maternal c.1480del (classified Pathogenic by the PD-VCEP) and paternal c.1454dup. (1pt; PM3) PMID: 11776304 Patient is compound heterozygous for the maternal c.1454dupl and paternal Cys225Ser (classified Pathogenic by the PD-VCEP) variants. Not considered here to avoid circularity. BSS7.01 from PMID: 23402648: Patient is homozygous for the c.1454dup variant (.5 points). Patient from PMID:16916536: Patient is homozygous for the c.1454dup variant (.5 points).

Curation History 



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