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Variant: NM_000173.7(GP1BA):c.104del (p.Lys35fs)

Version: 1.0

CA658798681

523620 (ClinVar)

Gene: GP1BA (HGNC:2811)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: d0ce6665-734a-45e8-8012-c458f57679d8
Approved on: 2025/2/11
Published on: 2025/2/17

HGVS expressions

NM_000173.7(GP1BA):c.104del (p.Lys35fs)
NM_000173.7:c.104del
NC_000017.11:g.4932708del
CM000679.2:g.4932708del
NC_000017.10:g.4836003del
CM000679.1:g.4836003del
NC_000017.9:g.4776783del
NG_008767.2:g.5414del
ENST00000329125.6:c.104del
ENST00000649830.1:c.-888+1635del
ENST00000329125.5:c.104del
ENST00000611961.1:c.104del
NM_000173.6:c.104del

Likely Pathogenic

Met criteria codes 5

PP4 PVS1_Strong PS3_Supporting PM3 PM2_Supporting

Not Met criteria codes 1

PP1

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 c.104del (p.Lys35ArgfsTer4) 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 >10% of the protein (PVS1_Strong). At least one patient (Patient GA in PMID: 8950770) 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 thrombocytopenia, giant platelets, and life-long severe bleeding, including recurrent bruising and prolonged bleeding time. This variant has been detected in at least 2 probands with Bernard-Soulier syndrome (PMID: 8950770 and

36507135). These individuals were both homozygous for the variant (PM3). Surface expression of GP1A measured by flow cytometry in mouse L cells transiently co-transfected with c.104del (p.Lys35ArgfsTer4) variant GP1A and wild type GP1B-GP9 showed undetectable expression at 0% WT levels, indicating that this variant impacts protein function (PMID: 8950770, PS3_supporting). The Grpmax Filtering allele frequency in gnomAD v4.1.0 is 3.000e-7 (based on 2/1179868 alleles) in the European non Finnish population, which is lower than the ClinGen PD VCEP threshold (<0.0001114; 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: PVS1_Strong, PP4, PM2_Supporting, PM3, and PS3_Supporting.

Met criteria codes

PP4	✔	At least one patient (Patient GA in PMID: 8950770) 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 thrombocytopenia, giant platelets, and life-long severe bleeding, including recurrent bruising and prolonged bleeding time.
PVS1_Strong	✔	The c.104del (p.Lys35ArgfsTer4) 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 >10% of the protein (PVS1_Strong).
PS3_Supporting	✔	Surface expression of GP1A measured by flow cytometry in mouse L cells transiently co-transfected with c.104del (p.Lys35ArgfsTer4) variant GP1A and wild type GP1B-GP9 showed undetectable expression at 0% WT levels, indicating that this variant impacts protein function (PMID: 8950770)(PS3_supporting).
PM3	✔	This variant has been detected in at least 2 probands with Bernard-Soulier syndrome (PMID: 8950770 and 36507135). These individuals were both homozygous for the variant (1 PM3 points, PM3).
PM2_Supporting	✔	The Grpmax Filtering allele frequency in gnomAD v4.1.0 is 3.000e-7 (based on 2/1179868 alleles) in the European non Finnish population, which is lower than the ClinGen PD VCEP threshold (<0.0001114 ; PM2_Supporting).

Not Met criteria codes

PP1	✖	The variant has been reported to segregate with Bernard-Soulier syndrome in two affected family members (PMID: 36507135). Neither patient has enough phenotypic information to meet the VCEPs PP4 criteria.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000173.7(GP1BA):c.104del (p.Lys3...	Likely Pathogenic	Bernard-Soulier Syndrome	2025-02-17	1.0	ClinGen Platelet Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GP1BA Version 1.0.0	GP1BA

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