The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000407.5(GP1BB):c.443G>A (p.Trp148Ter)

Version: 1.0

CA410677524

1691232 (ClinVar)

Gene: GP1BB (HGNC:2812)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: 231fb197-4be4-4ed0-b749-985409b65e2c
Approved on: 2025/2/11
Published on: 2025/2/13

HGVS expressions

NM_000407.5:c.443G>A
NM_000407.5(GP1BB):c.443G>A (p.Trp148Ter)
NC_000022.11:g.19724286G>A
CM000684.2:g.19724286G>A
NC_000022.10:g.19711809G>A
CM000684.1:g.19711809G>A
NC_000022.9:g.18091809G>A
NG_007974.1:g.5744G>A
ENST00000366425.4:c.443G>A
ENST00000366425.3:c.443G>A
ENST00000431044.5:c.*1528G>A
NM_000407.4:c.443G>A
NR_037611.1:n.4183G>A
NR_037612.1:n.2687G>A

Pathogenic

Met criteria codes 5

PP4_Moderate | PM2_Supporting | PM3 | PS3_Supporting | PVS1_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 GP1BB Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.443G>A (p.Trp148Ter) variant in GP1BB is a nonsense variant that may cause loss of function of the protein, however, it is predicted to escape nonsense mediated decay and remove 28% of the protein (PVS1_Strong). This variant has been detected in at least 2 unrelated probands with Bernard-Soulier syndrome. One proband was homozygous for the variant (0.5 points, PMID: 12447957). The second proband was compound heterozygous for this variant and a pathogenic or likely pathogenic variant that was confirmed in trans by parental testing

(22q11.2 deletion including GP1BB, 1 point, PMID: 23566026, PM3). At least one patient (Patient 1 in PMID: 23566026) with this variant had less than 10% expression of GPIba and GP9 compared to controls. The patient also had excessive mucocutaneous bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome. Full gene sequencing of GP1BA, GP1BB, and GP9 were performed as well as del/dup analysis (PP4_Moderate). The Grpmax filtering allele frequency in gnomaDThe Grpmax filtering allele frequency in gnomaDv4.1 is 7.700e-7 (based on 3/1034782 alleles) in the European (non-Finnish) population, which is below the <0.0000651678 threshold for PM2_supporting. Surface expression of GP1BB and GP9 measured by flow cytometry and Western blot in HEK293T cells transiently co-transfected with the NM_000407.5:c.443G>A variant GP1BB and wild type GP1BA/GP9 showed decreased expression at 0% WT levels, indicating that this variant impacts protein function (PMID: 12447957)(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: PVS1_Strong, PP4_Moderate, PM3, PM2_Supporting and PS3_Supporting (VCEP specifications version PILOT).

Met criteria codes

PP4_Moderate	✔	At least one patient (Patient 1 in PMID: 23566026) with this variant had less than 10% expression of GPIba and GP9 compared to controls. The patient also had excessive mucocutaneous bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome. Full gene sequencing of GP1BA, GP1BB, and GP9 were performed as well as del/dup analysis (PP4_Moderate).
PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomaDv4.1 is 7.700e-7 (based on 3/1034782 alleles) in the European (non-Finnish) population, which is below the <0.0000651678 threshold for PM2_supporting.
PM3	✔	This variant has been detected in at least 2 unrelated probands with Bernard-Soulier syndrome. One proband was homozygous for the variant (0.5 points, PMID: 12447957). The second proband was compound heterozygous for this variant and a pathogenic or likely pathogenic variant that was confirmed in trans by parental testing (22q11.2 deletion of GP1BB, 1 point, PMID: 23566026). PM3_Moderate. NM_000407.5(GP1BB):c.443G>A (p.Trp148Ter) was found on maternal allele, 22q11.2 deletion found on paternal allele.
PS3_Supporting	✔	Surface expression of GP1b and GP9 measured by flow cytometry and Western blot in HEK293T cells transiently co-transfected with the NM_000407.5:c.443G>A variant GP1b and wild type GP1b showed decreased expression at 0% WT levels, indicating that this variant impacts protein function (PMID: 12447957)(PS3_supporting).
PVS1_Strong	✔	The c.443G>A (p.Trp148Ter) variant in GP1BB is a nonsense variant that may cause loss of function of the protein, however, it is predicted to escape nonsense mediated decay and remove > 10% (28%) of the protein (PVS1_Strong).

Curation History

Showing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000407.5(GP1BB):c.443G>A (p.Trp...	Pathogenic	Bernard-Soulier Syndrome	2025-02-13	1.0	ClinGen Platelet Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GP1BB Version 1.0.0	GP1BB

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.