

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

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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**

PVS1_Strong

PM2_Supporting

PS3_Supporting

PP4_Moderate

PM3

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

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).
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.
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).
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).
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.

Curation History



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Showing 1 to 1 of 1 rows

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