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Variant: NM_000407.5(GP1BB):c.448del (p.Ala150fs)

Version: 1.0

CA638504295

627075 (ClinVar)

Gene: GP1BB (HGNC:2812)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: affdd230-5d28-41fd-b2b3-098410612dc1
Approved on: 2025/2/11
Published on: 2025/2/17

HGVS expressions

NM_000407.5:c.448del
NM_000407.5(GP1BB):c.448del (p.Ala150fs)
NC_000022.11:g.19724291del
CM000684.2:g.19724291del
NC_000022.10:g.19711814del
CM000684.1:g.19711814del
NC_000022.9:g.18091814del
NG_007974.1:g.5749del
ENST00000366425.4:c.448del
ENST00000366425.3:c.448del
ENST00000431044.5:c.*1533del
NM_000407.4:c.448del
NR_037611.1:n.4188del
NR_037612.1:n.2692del

Likely Pathogenic

Met criteria codes 4

PP4 PVS1_Strong PM2_Supporting PS3_Supporting

Not Met criteria codes 2

PS4 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 variant NM_000407.5(GP1BB):c.448del (p.Ala150ArgfsTer?) has been reported in at least one individual with Bernard Soulier Syndrome. At least one patient compound heterozygous for this variant had macrothrombocytopenia and aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, surface expression of GP1ba, GP1bb, and GP9 measured by flow cytometry in 293T cells transiently co-transfected with the c.448del variant and wild type GP1ba and

GP9 showed decreased expression at 0% (<25%) WT levels, indicating that this variant impacts protein function (PMID:16978236) (PS3_supporting). Finally, the variant is a frameshift variant which may cause loss of function of the protein, however it is predicted to escape nonsense mediated decay and remove <10% of the protein, affecting the critical transmembrane domain (PVS1_strong). The Grpmax filtering allele frequency in gnomaDv4.1 is 0.00001079 (based on 2/30690 alleles) in the East Asian population, which is below the <0.0000651678 threshold for 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, PM2_supporting, PP4, PS3_supporting.

Met criteria codes

PP4	✔	At least one patient (Proband in PMID:16978236) with this variant had aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, the patient had macrothrombocytopenia which is consistent with Bernard-Soulier syndrome.
PVS1_Strong	✔	The c.448del (p.Ala150ArgfsTer?) variant in GP1BB 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%, affecting the critical transmembrane domain (PVS1_Strong).
PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomaDv4.1 is 0.00001079 (based on 2/30690 alleles) in the East Asian population, which is below the <0.0000651678 threshold for PM2_supporting.
PS3_Supporting	✔	Surface expression of GP1a and GP1b and GP9 measured by flow cytometry in 293T cells transiently co-transfected with the GP1b c.448del variant and wild type GP1a and GP9 showed decreased expression at 0% (<25%) WT levels, indicating that this variant impacts protein function (PMID:16978236)(PS3_supporting).

Not Met criteria codes

PS4	✖	Heterozygous L-5 is reported with macrothrombocytopenia (47x10^9 platelets/l; MPV not provided) 0pt; H-7 macrothrombocytopenia (120x10^9 platelets/l; MPV not provided) 0pt PS4_NotMet due to missing MPV information
PM3	✖	The c.448del variant has been found in at least one individual with BSS, compound heterozygous for this variant and the Likely Pathogenic p.Cys147Ser, not considered here to avoid circularity.

Curation History

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