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Variant: NM_000174.5(GP9):c.212T>C (p.Phe71Ser)

Version: 1.0

CA123177

13531 (ClinVar)

Gene: GP9 (HGNC:2815)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7f4f85a2-aada-40d5-8d5f-540a8dd10bdf
Approved on: 2026/3/17
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HGVS expressions

NM_000174.5(GP9):c.212T>C (p.Phe71Ser)
NM_000174.5:c.212T>C
NC_000003.12:g.129061951T>C
CM000665.2:g.129061951T>C
NC_000003.11:g.128780794T>C
CM000665.1:g.128780794T>C
NC_000003.10:g.130263484T>C
NG_008715.1:g.6150T>C
ENST00000307395.5:c.212T>C
ENST00000307395.4:c.212T>C
NM_000174.4:c.212T>C

Pathogenic

Met criteria codes 6

PP4 PM3_Strong PM2_Supporting PP1_Moderate PS3_Supporting PM5_Supporting

Not Met criteria codes 2

PP3 BP4

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 GP9 Version 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.212C>T variant in GP9 is a missense variant predicted to cause substitution of phenylalanine by serine at amino acid 71. This variant has been detected in at least 16 probands with Bernard-Soulier syndrome. This variant has been detected in at least 8 probands with supporting laboratory results described in the literature (PM3_Strong). Two of these probands were compound heterozygous for this variant and another variant (c.266G>A [p.Cys89Tyr], c.182A>G [p.Asn61Ser]) (PMID:24934643). Six of these probands were homozygous for the variant, with at least 3 of these confirmed using parental testing or other methods (PMIDs: 9163595, 432024, 21173099, 21699652, 25539746). At least one patient (proband in PMID: 9432024) 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).

The variant has been reported to segregate with Bernard-Soulier syndrome in the proband plus two affected family members, all with the homozygous genotype (PP1_moderate; PMID:17763149). Another missense variant in the same codon has been reported in a patient with Bernard-Soulier syndrome c.212T>G, p.Phe71Cys (PMID:21699652), classified likely pathogenic by the ClinGen PD VCEP (PM5_supporting). The highest minor allele frequency in gnomaDv4.1 is 0.00003294 (3/91084 alleles) in the South Asian genetic ancestry group, which is below the <0.0000329 threshold for PM2_supporting. Surface expression of GP1Ba measured by flow cytometry in CHO-K1 cells transiently co-transfected with the c.212T>C variant in GP9 and wild type GP1Bb showed decreased expression at ~17% (<25%) WT levels, indicating that this variant impacts protein function (PMID:10527407; 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: PP4, PM3_strong, PM2_Supporting, PS3_Supporting, PP1_Moderate, PM5_supporting (VCEP specifications version 1).

Met criteria codes

PP4	✔	At least one patient (proband in PMID:9432024) 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. Del/dup analysis was not performed.
PM3_Strong	✔	This variant has been detected in at least 8 probands with supporting laboratory results described in the literature. 2 of these probands were compound heterozygous for this variant and another pathogenic variant in trans (c.266G>A [p.Cys89Tyr], c.182A>G [p.Asn61Ser]). (2 PM3 pts, PMID:24934643). 6 of these probands were homozygous for the variant, with at least 3 of these confirmed using parental testing or other methods (1 PM3 pt PMIDs: 9163595, 432024, 21173099, 21699652, 25539746). Total points: 3 pt (PM3_Strong)
PM2_Supporting	✔	The highest minor allele frequency in gnomaDv4.1 is 0.00003294 (3/91084 alleles) in the South Asian genetic ancestry group, which is below the <0.0000329 threshold for PM2_supporting.
PP1_Moderate	✔	The variant has been reported to segregate with Bernard-Soulier syndrome in the proband (meeting PP4) plus two affected family members, all with the homozygous genotype with c.212T>C variant. (PP1_moderate; PMID:17763149).
PS3_Supporting	✔	Surface expression of GP1Ba measured by flow cytometry in CHO-K1 cells transiently co-transfected with the c.212T>C variant in GP9 and wild type GP1Bb showed decreased expression at ~17% (<25%) WT levels, indicating that this variant impacts protein function (PMID:10527407)(PS3_Supporting).
PM5_Supporting	✔	Another missense variant in the same codon has been reported in a patient with Bernard-Soulier syndrome c.212T>G, p.Phe71Cys (PMID:21699652), classified likely pathogenic by the ClinGen PD VCEP (PM5_supporting).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.638, which is below the ClinGen PD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on GP9 function and the computational splicing predictor SpliceAI indicated that the variant has no predicted impact on splicing.
BP4	✖	The computational predictor REVEL gives a score of 0.638, which is above the ClinGen PD VCEP PP3 threshold of <0.290.

Curation History

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