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_000174.5(GP9):c.368C>T (p.Pro123Leu)

Version: 1.0

CA2602698

343220 (ClinVar)

Gene: GP9 (HGNC:2815)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: f7b48811-99dd-4607-bc7c-cff00d6c20db
Approved on: 2025-03-06
Published on: 2025-03-06

HGVS expressions

NM_000174.5:c.368C>T
NM_000174.5(GP9):c.368C>T (p.Pro123Leu)
NC_000003.12:g.129062107C>T
CM000665.2:g.129062107C>T
NC_000003.11:g.128780950C>T
CM000665.1:g.128780950C>T
NC_000003.10:g.130263640C>T
NG_008715.1:g.6306C>T
ENST00000307395.5:c.368C>T
ENST00000307395.4:c.368C>T
NM_000174.4:c.368C>T

Benign

Met criteria codes 1

BA1

Not Met criteria codes 3

BP4 PS4 PP4

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 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.368C>T variant in GP9 is a missense variant predicted to cause substitution of proline by leucine at amino acid 123 (p.Pro123Leu). The Grpmax Filtering allele frequency in gnomAD v4.1 is 0.001561 (based on 1906/1175218 alleles) in the European (non-Finnish) population, which is higher than the ClinGen PD VCEP threshold (>0.001), and therefore meets this criterion (BA1). The computational predictor REVEL gives a score of 0.196, which is below the ClinGen PD VCEP threshold of <0.290 and predicts no damaging effect on GP9 function and the computational splicing predictor SpliceAI reported a delta score 0.01 for acceptor gain (BP4_NotMet). In summary, this variant meets the criteria to be classified as benign for autosomal recessive Bernard-Soulier syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: BA1.

Met criteria codes

BA1	✔	The Grpmax Filtering allele frequency in gnomAD v4.1 is 0.001561 (based on 1906/1175218 alleles) in the European (non-Finnish) population, which is higher than the ClinGen PD VCEP threshold (>0.001), and therefore meets this criterion (BA1).

Not Met criteria codes

BP4	✖	The computational predictor REVEL gives a score of 0.196, which is below the ClinGen PD VCEP threshold of <0.290 and predicts no damaging effect on GP9 function and the computational splicing predictor SpliceAI reported a delta score 0.01 for acceptor gain (BP4_NotMet)
PS4	✖	Internal cases: found this variant in heterozygosis in four cases in IPD series. All four have moderate macrothrombocytopenia not considered due to high allele frequency and no PP4 meeting BSS patient
PP4	✖	PMID: 28561420. Report of two neonates heterozygous for the variant with severe neonatal thrombocytopenia and life-threatening intra-cranial hemorrhage. This was attributed to the variant causing a new alloantigen that was incompatible with their mother. Mother was homozygous for the wild-type allele and father was heterozygous for the variant. Does not meet PP4. PMID: 28748566. Variant found in patient #24 (see table S2). Does not meet PP4, more details/specifics needed about clinical phenotype of patient. Internal cases: found this variant in heterozygosis in four cases in IPD series. All four have moderate macrotrombocytopenia

Curation History

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