

Variant: *NM_000174.5(GP9):c.442dup (p.Val148fs)*

Version: 1.0

CA546416976 [↗](#)

3588372 (ClinVar) [↗](#)

Gene: GP9 ([HGNC:2815](#))

Condition: Bernard-Soulier syndrome ([MONDO:0009276](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: f9c5f81c-73bb-4057-bf35-96b12274fe74

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HGVS expressions

NM_000174.5(GP9):c.442dup (p.Val148fs)

NM_000174.5:c.442dup

NC_000003.12:g.129062181dup

CM000665.2:g.129062181dup

NC_000003.11:g.128781024dup

CM000665.1:g.128781024dup

NC_000003.10:g.130263714dup

NG_008715.1:g.6380dup

ENST00000307395.5:c.442dup

ENST00000307395.4:c.442dup

NM_000174.4:c.442dup

Likely Pathogenic

Met criteria codes **4**

PM3_Supporting

PM2_Supporting

PVS1_Strong

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.442dup (p.Val148GlyfsTer67) variant in GP9 is a frameshift variant that may cause a premature stop codon that is predicted to escape nonsense mediated decay, however the truncation includes the functionally important transmembrane domain (alters amino acids 148-169) in a gene where loss-of-function is an established disease mechanism (PVS1_Strong). At least one patient (Patient P13 in PMID: 21173099) with this variant had aggregation absent for ristocetin and present for all other agonists as well as less than 10% expression of GPIIb and GP9 measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had excessive mucocutaneous bleeding is consistent with Bernard-Soulier syndrome (PP4). This individual was homozygous for the variant (0.5 PM3 points, PM3_Supporting). The Grpmax Filtering allele frequency in gnomAD v4.1.0 is 0.0000003000 (based on 2/1165574 alleles) in the

European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0000329; 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, PP4, PM3_Supporting and PM2_Supporting (VCEP specifications version 1).

Met criteria codes

PM3_Supporting			This variant has been detected in at least 1 proband with Bernard-Soulier syndrome (PMID: 21173099). This individual was homozygous for the variant (0.5 PM3 points, PM3_Supporting).
PM2_Supporting			The Grpmax Filtering allele frequency in gnomAD v4.1.0 is 0.0000003000 (based on 2/1165574 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0000329; PM2_Supporting).
PVS1_Strong			The c.442dup (p.Val148GlyfsTer67) variant in GP9 is a frameshift variant that may cause a premature stop codon that is predicted to escape nonsense mediated decay, however the truncation includes the functionally important transmembrane domain (alters amino acids 148-169) in a gene where loss-of-function is an established disease mechanism (PVS1_Strong).
PP4			At least one patient (Patient P13 in PMID: 21173099) with this variant had aggregation absent for ristocetin and present for all other agonists as well as less than 10% expression of GPIIb and GP9 measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had excessive mucocutaneous bleeding is consistent with Bernard-Soulier syndrome (PP4).

Curation History



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