

Variant: *NM_000174.5(GP9):c.182A>G (p.Asn61Ser)*

Version: 1.0

CA123173 [↗](#)

13529 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 6cd9eaa9-87bb-485d-8ac4-21061be1791b

Approved on: 2025/2/11

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HGVS expressions

NM_000174.5:c.182A>G

NM_000174.5(GP9):c.182A>G (p.Asn61Ser)

NC_000003.12:g.129061921A>G

CM000665.2:g.129061921A>G

NC_000003.11:g.128780764A>G

CM000665.1:g.128780764A>G

NC_000003.10:g.130263454A>G

NG_008715.1:g.6120A>G

ENST00000307395.5:c.182A>G

ENST00000307395.4:c.182A>G

NM_000174.4:c.182A>G

Pathogenic

Met criteria codes **5**

PP4_Moderate

PS3_Supporting

PP1_Strong

PP3

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 GP9 Version 1.0.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.182A>G (p.Asn61Ser) variant in GP9 is known for being frequently reported in BSS patients of European ancestry. It has been detected in at least 30 probands with Bernard-Soulier syndrome. At least 16 probands included in this curation have origin in Central or Northern Europe (France, Finland, Sweden, Germany, Belgium, Austria, and England). The literature supports the hypothesis of Koskela et al., which suggests that the c.182A>G (p.Asn61Ser) variant is an ancient founder mutation in this region (PMID:10227459). At least one patient with this variant had aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome and with full gene sequencing and del/dup analysis of all BSS genes (PP4_moderate, Department of Haematology and Transfusion Medicine, Royal North Shore Hospital, Sydney, NSW, Australia). Additionally, the patient had excessive mucocutaneous

bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome. At least 2 of the probands included in this curation were homozygous for the variant and were confirmed to have the variants in trans (PM3; PMIDs: 8049428, 14510954, 8856096, 10227459, 11297032). The variant has been reported to segregate with Bernard-Soulier syndrome in the proband (meeting PP4) plus 3 (>2) affected family members, all with the homozygous genotype. (PP1_strong; PMID:19404517). The Grp max filtering allele frequency in gnomAD v4.1 is 0.0008047 (1001/1179870 alleles) in the European (Non-Finnish) population, which is higher than the ClinGen PD VCEP threshold (>0.0007 for GP9), and therefore meets this criterion (BS1), however since this is a known founder variant BS1 will not be applied. The computational predictor REVEL gives a score of 0.721, which is above the ClinGen PD VCEP threshold of >0.644 and predicts a damaging effect on function (PP3). A zebrafish model made by deleting 17bps in exon 2 of gp9 using CRISPR-Cas9 demonstrated thrombocytopenia and abnormal bleeding. The thrombocytopenia phenotype in the zebrafish was rescued using a wild-type copy of human GP9. The human copy of GP9 containing the c.182A>G variant failed to rescue the same phenotype, indicating that this variant impacts protein function (PMID:34407604)(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: PM3, PP3, PP4_moderate, PP1_Strong, PS3_Supporting. (VCEP specifications version 1)

Met criteria codes

PP4_Moderate			At least one patient with this variant had aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome and with full gene sequencing and del/dup analysis of all BSS genes (PP4_moderate, Department of Haematology and Transfusion Medicine, Royal North Shore Hospital, Sydney, NSW, Australia). Additionally, the patient had excessive mucocutaneous bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome.
PS3_Supporting			A zebrafish model made by deleting 17bps in exon 2 of gp9 using CRISPR-Cas9 demonstrated thrombocytopenia and abnormal bleeding. The thrombocytopenia phenotype in the zebrafish was rescued using a wild-type copy of human GP9. The human copy of GP9 containing the c.182A>G variant failed to rescue the same phenotype, indicating that this variant impacts protein function (PMID:34407604)(PS3_supporting).
PP1_Strong			The variant has been reported to segregate with Bernard-Soulier syndrome in the proband (meeting PP4) plus 3 (>2) affected family members, all with the homozygous genotype. (PP1_strong; PMID:19404517).
PP3			The computational predictor REVEL gives a score of 0.721, which is above the ClinGen PD VCEP threshold of >0.644 and predicts a damaging effect on function (PP3).
PM3			At least 2 of the probands included in this curation were homozygous for the variant and were confirmed to have the variants in trans (1 PM3 point, PMIDs: 8049428, 14510954, 8856096, 10227459, 11297032). Total points: 1.0 (PM3).

Curation History 

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