

Variant: *NM_000174.5:c.112T>C*

Version: 1.0

CA2602634 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: f26d2d30-169b-4391-8ccd-12883b994de9

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HGVS expressions

NM_000174.5:c.112T>C

NC_000003.12:g.129061851T>C

CM000665.2:g.129061851T>C

NC_000003.11:g.128780694T>C

CM000665.1:g.128780694T>C

NC_000003.10:g.130263384T>C

NG_008715.1:g.6050T>C

ENST00000307395.5:c.112T>C

ENST00000307395.4:c.112T>C

NM_000174.4:c.112T>C

Likely Pathogenic

Met criteria codes **4**

PP3_Moderate

PP4

PM3

PM2_Supporting

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.112T>C variant in GP9 is a missense variant predicted to cause substitution of Cysteine by Arginine at amino acid 38 (p.Cys38Arg). At least one patient (Patient 3 in PMID: 33553065) with this variant had less than 10% expression of GP9 measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had macrothrombocytopenia which is consistent with Bernard-Soulier syndrome (PP4). This individual, was compound heterozygous for this variant and the c.182A>G (p.Asn61Ser) variant which was classified as Pathogenic by the PD VCEP. These were confirmed in trans by family testing (1 PM3 point, PM3). The computational predictor REVEL gives a score of 0.866, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on function (PP3_Moderate). The largest MAF allele frequency in gnomAD v4.1.0 is 0.000001696 (based on 2/1179516 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: PP4, PM3, PP3 and PM3_Supporting (VCEP specifications version 1.1).

Met criteria codes

PP3_Moderate			The computational predictor REVEL gives a score of 0.866, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on function (PP3_Moderate).
PP4			At least one patient (Patient 3 in PMID: 33553065) with this variant had less than 10% expression of GP9 measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had macrothrombocytopenia which is consistent with Bernard-Soulier syndrome (PP4).
PM3			This variant has been detected in at least 1 proband with Bernard-Soulier syndrome (Patient 3 in PMID: 33553065). This individual, was compound heterozygous for this variant and the c.182A>G (p.Asn61Ser) variant which was classified as Pathogenic by the PD VCEP. These were confirmed in trans by family testing (1 PM3 point, PM3).
PM2_Supporting			The largest MAF allele frequency in gnomAD v4.1.0 is 0.000001696 (based on 2/1179516 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0000329; PM2_Supporting).

Curation History

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