

Variant: NM_000174.5:c.266G>A

Version: 1.0

CA354447789 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 41ba4c10-055f-4122-a444-abd8a5e0815e

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HGVS expressions

NM_000174.5:c.266G>A

NC_000003.12:g.129062005G>A

CM000665.2:g.129062005G>A

NC_000003.11:g.128780848G>A

CM000665.1:g.128780848G>A

NC_000003.10:g.130263538G>A

NG_008715.1:g.6204G>A

ENST00000307395.5:c.266G>A

ENST00000307395.4:c.266G>A

NM_000174.4:c.266G>A

Pathogenic

Met criteria codes **5**

PP4_Moderate

PS3_Supporting

PM3_Strong

PP3_Moderate

PP1

Not Met criteria codes **2**

BS1

PM2

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 NM_000174.5(GP9):c.266G>A variant in GPIX is a missense variant predicted to cause substitution of cysteine by tyrosine at amino acid 89 (p.Cys89Tyr). This variant has been detected in at least 7 probands with Bernard-Soulier syndrome (PM3_Strong). Of those individuals, 2 (PMIDs: 24934643, 28765788) were compound heterozygous for this variant and a pathogenic or likely pathogenic variant and both of those were confirmed in trans by family testing or other methods (c. 212T>C [p.Phe71Ser], c.182A>G [p.Asn61Ser]. The other 5 probands were homozygous for the variant, with at least 2 of these confirmed in trans (PMIDs: 24934643, 16916536, 8972003). All seven probands are reported to have Japanese ancestry, which points to the likelihood that this variant originated in a common ancestor. At least one patient (Case 1 in PMID:8972003) with this variant had less than 10% expression of GPIIb measured by Western blot, which is highly specific for Bernard-Soulier syndrome, in addition to macrothrombocytopenia. This proband received full gene sequencing and del/dup

analysis of all BSS genes (PMID: 1577776). The variant has been reported to segregate with Bernard-Soulier syndrome in the proband (meeting PP4) plus one affected family member (sister in family 1), both with the homozygous genotype with the c.266G>A variant (PP1; PMID:8972003). Surface expression of GP1a and GP9 measured by flow cytometry in CHO DUK- cells transiently co-transfected with the c.266G>A variant in GP9 and wild type GP1a and GP1b showed absent expression (<25%) WT levels, indicating that this variant impacts protein function (PMID:8972003)(PS3_Supporting). The computational predictor REVEL gives a score of 0.926, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on function (PP3_Moderate). 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_Strong, PP4_Moderate, PP1, PP3_Moderate, PS3_Supporting. (VCEP specifications version 1)

Met criteria codes

PP4_Moderate			At least one patient (Case 1 in PMID:8972003) with this variant had less than 10% expression of GPIba measured by Western blot, which is highly specific for Bernard-Soulier syndrome, in addition to macrothrombocytopenia. This proband received full gene sequencing and del/dup analysis of all BSS genes, with the only abnormality being "two or three tandem repeats of a 13-amino acid sequence in the mucin-like macroglycopeptide region in GPIBa." In one study of this region in 206 individuals, it was reported that the triple repeat variant had an allele frequency of 7% in the Japanese population and 1% in the caucasian population. The double repeat of the 13 amino acid sequence was found at 1% in the Japanese population and 11% in individuals of caucasian ancestry (PMID: 1577776).
PS3_Supporting			Surface expression of GP1a and GP9 measured by flow cytometry in CHO DUK- cells transiently co-transfected with the c.266G>A variant in GP9 and wild type GP1a and GP1b showed absent expression (<25%) WT levels, indicating that this variant impacts protein function (PMID:8972003)(PS3_supporting).
PM3_Strong			This variant has been detected in at least 7 probands with Bernard-Soulier syndrome. Of those individuals, 2 were compound heterozygous for this variant and a pathogenic or likely pathogenic variant and both of those were confirmed in trans by family testing or other methods (c. 212T>C [p.Phe71Ser], c.182A>G [p.Asn61Ser]. The proband compound heterozygous for the p.Phe71Ser variant was already scored in the p.Phe71Ser curation, so it was not awarded points. 1.0 PM3 points, PMIDs: 24934643, 28765788). The other 5 probands were homozygous for the variant, with at least 2 of these confirmed in trans (1.0 PM3 points, PMIDs: 24934643, 16916536, 8972003). Total points: 2.0 (PM3_Strong).
PP3_Moderate			The computational predictor REVEL gives a score of 0.926, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on function (PP3_Moderate).
PP1			The variant has been reported to segregate with Bernard-Soulier syndrome in the proband (meeting PP4) plus one affected family member (sister in family 1), both with the homozygous genotype with the c.266G>A variant. In the same paper, the variant was reported to segregate with BSS in the proband and one affected member of family 2. Both family members were homozygous. (PP1; PMID:8972003).

Not Met criteria codes

BS1			The Grpmax filtering allele frequency in gnomADv4.0.0 is 0.00007155 (based on 6/36062 alleles) in the East Asian population, which is above the ClinGen PD VCEP PM2_supporting threshold (<0.0000329) but below the BS1 threshold (>0.0007).
PM2			The Grpmax filtering allele frequency in gnomADv4.1 is 0.00005788 (based on 6/44880 alleles) in the East Asian population, which is above the ClinGen PD VCEP PM2_supporting threshold (<0.0000329) but below the BS1

threshold (>0.0007).

Curation History

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