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Variant: NM_000407.5:c.266A>C

Version: 1.0

CA410676943

Gene: GP1BB (HGNC:2812)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0fa0a643-c8f1-40a0-8416-a79ce90cb156
Approved on: 2026/4/2
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HGVS expressions

NM_000407.5:c.266A>C
NC_000022.11:g.19724109A>C
CM000684.2:g.19724109A>C
NC_000022.10:g.19711632A>C
CM000684.1:g.19711632A>C
NC_000022.9:g.18091632A>C
NG_007974.1:g.5567A>C
ENST00000366425.4:c.266A>C
ENST00000366425.3:c.266A>C
ENST00000431044.5:c.*1351A>C
ENST00000455843.5:c.*1351A>C
ENST00000470814.1:n.2238A>C
NM_000407.4:c.266A>C
NR_037611.1:n.4006A>C
NR_037612.1:n.2510A>C

Likely Pathogenic

Met criteria codes 6

PS3_Supporting PM3_Supporting PM5_Supporting PP3_Moderate PP4 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 GP1BB Version 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.266A>C variant in GP1BB is a missense variant predicted to cause substitution of Asparagine by Threonine at amino acid 89 (p.Asn89Thr). At least one patient (Patient S.B. in PMID: 12693941) 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 excessive mucocutaneous bleeding and

macrothrombocytopenia which are consistent with Bernard-Soulier syndrome (PP4). This individual was homozygous for the variant (0.5 PM3 points, PM3_Supporting). Surface expression of the GPIb-IX complex measured by flow cytometry in CHO cells transiently co-transfected with the Asn89Thr variant GP1b and wild type GP1a and GP9 showed undetectable expression, indicating that this variant impacts protein function (PMID: 12693941)(PS3_supporting). Another missense variant NM_000407.5(GP1BB):c.265A>G (p.Asn89Asp) in the same codon has been classified as Likely Pathogenic for Bernard-Soulier syndrome by the ClinGen PD VCEP (PM5_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 GP1BB function (PP3_Moderate). The highest MAF in gnomAD v4.1.0 is 0.0000009068 (based on 1/1102800 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.00006517; 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, PP3_Moderate, PM2_Supporting, PM3_Supporting, PM5_supporting and PS3_Supporting (VCEP specifications version 1.1).

Met criteria codes

PS3_Supporting ✔	Surface expression of the GPIb-IX complex measured by flow cytometry in CHO cells transiently co-transfected with the Asn89Thr variant GP1b and wild type GP1a and GP9 showed undetectable expression, indicating that this variant impacts protein function (PMID: 12693941)(PS3_supporting).
PM3_Supporting ✔	This variant has been detected in at least 1 proband with Bernard-Soulier syndrome (Proband S.B. in PMID: 12693941). This individual was homozygous for the variant (0.5 PM3 points, PM3_Supporting).
PM5_Supporting ✔	Another missense variant NM_000407.5(GP1BB):c.265A>G (p.Asn89Asp) in the same codon has been classified as Likely Pathogenic for Bernard-Soulier syndrome by the ClinGen PD VCEP (PM5).
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 GP1BB function (PP3).
PP4 ✔	At least one patient (Patient S.B. in PMID: 12693941) 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 excessive mucocutaneous bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome (PP4).
PM2_Supporting ✔	The highest MAF in gnomAD v4.1.0 is 0.0000009068 (based on 1/1102800 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.00006517 ; PM2_Supporting).

Curation History

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