

Variant: NM_000407.5:c.89G>A

Version: 1.0

CA410676362 [↗](#)

Gene: GP1BB ([HGNC:2812](#))

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

Inheritance Mode: Autosomal recessive inheritance

UUID: ed97a76c-9ca5-415e-802b-2c766926b351

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HGVS expressions

NM_000407.5:c.89G>A

NC_000022.11:g.19723932G>A

CM000684.2:g.19723932G>A

NC_000022.10:g.19711455G>A

CM000684.1:g.19711455G>A

NC_000022.9:g.18091455G>A

NG_007974.1:g.5390G>A

ENST00000366425.4:c.89G>A

ENST00000366425.3:c.89G>A

ENST00000431044.5:c.*1174G>A

ENST00000455843.5:c.*1174G>A

ENST00000470814.1:n.2061G>A

NM_000407.4:c.89G>A

NR_037611.1:n.3829G>A

NR_037612.1:n.2333G>A

Likely Pathogenic

Met criteria codes **6**

PM2_Supporting

PS3_Supporting

PP3_Moderate

PP1

PP4

PM3_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.89G>A (p.Cys30Tyr) variant in GP1BB is a missense variant predicted to cause substitution of Cysteine by Tyrosine at amino acid 30 (p.Cys30Tyr). At least one patient (Proband PMID: 12958615) with this variant had aggregation absent for ristocetin and present for all other agonists as well as less than 10% expression of GPIba and GP1bb measured by Western blot, 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 points, PM3_Supporting). The variant has been reported to segregate in the proband plus 1 additional homozygous BSS affected sibling (1 point, PP1). Surface expression of the GPIba measured by flow cytometry in CHO cells transiently co-transfected with p.Cys30Tyr variant GP1b and wild type GP1a and GP9 showed absent expression, indicating that this variant impacts protein function (PMID: 12958615)(PS3_supporting). The computational predictor REVEL gives a score of 0.792, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on GP1BB function (PP3_Moderate). This variant is absent from gnomAD v4.1.0 (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: PP3_Moderate, PP1, PP4, PM2_Supporting, PM3_Supporting and PS3_Supporting (VCEP specifications version 1.1).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS3_Supporting			Surface expression of the GPIba measured by flow cytometry in CHO cells transiently co-transfected with p.Cys30Tyr variant GP1bb and wild type GP1a and GP9 showed absent expression, indicating that this variant impacts protein function (PMID: 12958615)(PS3_supporting).
PP3_Moderate			The computational predictor REVEL gives a score of 0.792, which is above the ClinGen PD VCEP threshold of >0.773 and predicts a damaging effect on GP1BB function (PP3_Moderate).
PP1			The variant has been reported to segregate in the proband plus 1 additional homozygous BSS affected sibling (1 point, PP1).
PP4			At least one patient (Proband PMID: 12958615) with this variant had aggregation absent for ristocetin and present for all other agonists as well as less than 10% expression of GPIba and GP1bb measured by Western blot, 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).
PM3_Supporting			This variant has been detected in at least 1 proband with Bernard-Soulier syndrome (PMID: 12958615). This individual was homozygous for the variant (0.5 points, PM3_Supporting).

Curation History



 

 

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