

Variant: *NM_000407.5(GP1BB):c.338A>G (p.Tyr113Cys)*

Version: 1.0

CA126154 [↗](#)

16038 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 79f71b78-4613-46b3-af36-3a2a756781e9

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HGVS expressions

NM_000407.5:c.338A>G

NM_000407.5(GP1BB):c.338A>G (p.Tyr113Cys)

NC_000022.11:g.19724181A>G

CM000684.2:g.19724181A>G

NC_000022.10:g.19711704A>G

CM000684.1:g.19711704A>G

NC_000022.9:g.18091704A>G

NG_007974.1:g.5639A>G

ENST00000366425.4:c.338A>G

ENST00000366425.3:c.338A>G

ENST00000431044.5:c.*1423A>G

ENST00000455843.5:c.*1423A>G

ENST00000470814.1:n.2310A>G

NM_000407.4:c.338A>G

NR_037611.1:n.4078A>G

NR_037612.1:n.2582A>G

Likely Pathogenic

Met criteria codes **7**

PS3_Supporting

PM3_Supporting

PS4_Moderate

PP3

PP4

PM2_Supporting

PP1_Moderate

Not Met criteria codes **1**

PM5

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 1.0.0*

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

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

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000407.5(GP1BB):c.338A>G (p.Tyr113Cys) is a rare missense variant with a Grpmax Filtering allele frequency in gnomAD v4.1 is 0.00004600 (based on 4/29100 alleles in the East Asian population), which is lower than the ClinGen PD VCEP threshold (<0.00006517;

PM2_Supporting). The computational predictor REVEL gives a score of 0.748, which is above the ClinGen PD VCEP threshold of >0.644 and predicts a damaging effect on function (PP3). Plasmids encoding GPIb, GPIb and GPIX were transiently transfected into 293T cells, and this variant suppressed the expression of GPIb/IX complexes (PMID: 11816714; PS3_supporting). This variant has been reported in one homozygous BSS patient (PMID: 11816714; PM3_supporting) and one compound heterozygous BSS patient (PMID: 24051937) with in trans variant Arg82Cys (classified VUS by the PD VCEP). At least one patient (PMID: 11816714) with this variant had aggregation absent for ristocetin and present for all other agonists and GPIb was detectable in reduced amounts on platelet surfaces by flow cytometry, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, the patient had excessive mucocutaneous bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome. Seven individuals heterozygous for the variant are considered informative due to measurable, quantitative abnormalities relevant to the disease (i.e. significantly reduced platelet surface expression of GP1b, giant platelets, and macrothrombocytopenia) in PMIDs: 11816714 and 28064200 (PS4_moderate). Plus there was segregation of this variant in 5 additional informative heterozygous family members (PMID: 28064200 and PMID: 11816714; PP1). In summary this variant is classified as Likely Pathogenic using the ACMG criteria specified by the PD VCEP: PS4_Moderate, PS3_supporting, PM2_supporting, PM3_supporting, PP1, PP3, and PP4.

Met criteria codes

PS3_Supporting			Plasmids encoding GPIb, GPIb and GPIX were transiently transfected into 293T cells. This variant suppressed the expression of GPIb/IX complexes, GPIX was not expressed but GPIba was detectable on the cell surface though in a lesser amounts as compared to when transfected with three wild-type subunits (PMID: 11816714; PS3_supporting).
PM3_Supporting			This variant has been reported in one homozygous BSS patient (PMID: 11816714; PM3_supporting) and two compound heterozygous BSS patients (PMID: 24051937 and PMID: 9116284) with in trans variant Arg82Cys and Ala133Pro (not yet classified by the PD VCEP).
PS4_Moderate			Seven individuals heterozygous for the variant are considered informative due to measurable, quantitative abnormalities relevant to the disease (i.e. significantly reduced platelet surface expression of GP1b, giant platelets, and macrothrombocytopenia). Total 2.25pt (PS4_moderate)
PP3			The computational predictor REVEL gives a score of 0.748, which is above the ClinGen PD VCEP threshold of >0.644 and predicts a damaging effect on function (PP3).
PP4			At least one patient (PMID: 11816714) with this variant had aggregation absent for ristocetin and present for all other agonists and GPIb was detectable in reduced amounts on platelet surfaces by flow cytometry, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, the patient had excessive mucocutaneous bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome.
PM2_Supporting			The Grpmax Filtering allele frequency in gnomAD v4.1 is 0.00004600 (based on 4/29100 alleles in the East Asian population), which is lower than the ClinGen PD VCEP threshold (<0.00006517; PM2_Supporting).
PP1_Moderate			Segregation of this variant in 5 additional heterozygous family members and 1 additional compound heterozygous BSS family member (PMID: 28064200, PMID: 9116284, and PMID: 11816714; total 2.5pt, PP1_Moderate)

Not Met criteria codes

PM5			Another variant has been reported at this amino acid residue, however Tyr113Phe has only been reported (PMID: 27291889) in a heterozygous macrothrombocytopenia patient (no BSS patients) so is not considered here.
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Curation History [↗](#)

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