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Variant: NM_000173.7:c.667T>G

Version: 1.0

CA8314813

Gene: GP1BA (HGNC:2811)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2b735a0b-196c-4f09-9382-c45ed3ab5c39
Approved on: 2025/11/6
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HGVS expressions

NM_000173.7:c.667T>G
NC_000017.11:g.4933271T>G
CM000679.2:g.4933271T>G
NC_000017.10:g.4836566T>G
CM000679.1:g.4836566T>G
NC_000017.9:g.4777346T>G
NG_008767.2:g.5977T>G
ENST00000329125.6:c.667T>G
ENST00000649830.1:c.-888+1071A>C
ENST00000329125.5:c.667T>G
ENST00000611961.1:c.667T>G
NM_000173.6:c.667T>G

Likely Pathogenic

Met criteria codes 5

PM3 PS3_Supporting PM2_Supporting PP1 PP4

Not Met criteria codes 1

PP3

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 GP1BA Version 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.667T>G variant in GP1BA is a missense variant predicted to cause substitution of Tryptophan by Glycine at amino acid 223 (p.Trp223Gly). At least one patient (Patient 2 in PMID:17083647) with this variant had aggregation absent for ristocetin and present for all other agonists as well as absent expression of GPIba measured by Western blot, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had excessive mucocutaneous bleeding which is consistent with Bernard-Soulier syndrome (PP4). The variant has been reported to segregate in this proband plus 1 additional homozygous BSS affected family members (1 point, PP1, PMID: 17083647). This variant has been detected in at least 2 probands with Bernard-Soulier syndrome (PMID: 17083647 and internal lab contributor). These

two individuals were both homozygous for the variant (1 point, PM3). Surface expression of GP1ba measured by flow cytometry in BHK cells transiently co-transfected with c.667T>G (p.Trp223Gly) variant GP1BA, and wild type GP1BB and GP9 showed decreased expression at trace WT levels, indicating that this variant impacts protein function (PMID: 17083647)(PS3_supporting). The Grpmax Filtering allele frequency in gnomAD v4.1.0 is 7.900e-7 (based on 4/1179888 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001114; 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: PM3, PP1, PP4, PM2_Supporting and PS3_Supporting (VCEP specifications version 1).

Met criteria codes

PM3	✔	This variant has been detected in at least 2 probands with Bernard-Soulier syndrome (PMID: 17083647 and internal lab contributor). These two individuals were both homozygous for the variant (1 point, PM3).
PS3_Supporting	✔	Surface expression of GP1ba measured by flow cytometry in BHK cells transiently co-transfected with c.667T>G (p.Trp223Gly) variant GP1BA, and wild type GP1BB and GP9 showed decreased expression at trace WT levels, indicating that this variant impacts protein function (PMID: 17083647)(PS3_supporting).
PM2_Supporting	✔	The Grpmax Filtering allele frequency in gnomAD v4.1.0 is 7.900e-7 (based on 4/1179888 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001114; PM2_Supporting).
PP1	✔	The variant has been reported to segregate in the proband plus 1 additional homozygous BSS affected family members (1 point, PP1, PMID: 17083647).
PP4	✔	At least one patient (Patient 2 in PMID:17083647) with this variant had aggregation absent for ristocetin and present for all other agonists as well as absent expression of GPIba measured by Western blot, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had excessive mucocutaneous bleeding which is consistent with Bernard-Soulier syndrome (PP4).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.562, which is below the ClinGen PD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on GP1BA function. The computational splicing predictor SpliceAI indicated that the variant has no predicted impact on splicing (Splice AI score <0.5).

Curation History

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