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Variant: NM_000173.7(GP1BA):c.673T>A (p.Cys225Ser)

Version: 1.0

CA397318012

435347 (ClinVar)

Gene: GP1BA (HGNC:2811)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: 66f6fa49-f4ee-4cf9-ba61-10f5038d59ed
Approved on: 2025/2/11
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HGVS expressions

NM_000173.7:c.673T>A
NM_000173.7(GP1BA):c.673T>A (p.Cys225Ser)
NC_000017.11:g.4933277T>A
CM000679.2:g.4933277T>A
NC_000017.10:g.4836572T>A
CM000679.1:g.4836572T>A
NC_000017.9:g.4777352T>A
NG_008767.2:g.5983T>A
ENST00000329125.6:c.673T>A
ENST00000649830.1:c.-888+1065A>T
ENST00000329125.5:c.673T>A
ENST00000611961.1:c.673T>A
NM_000173.6:c.673T>A

Pathogenic

Met criteria codes 6

PP1 PP4 PM1 PM3_Strong PM2_Supporting PS3_Supporting

Not Met criteria codes 3

PS1 PP3 BP4

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 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

NM_000173.7(GP1BA):c.673T>A is a missense variant (p.Cys225Ser), which has been reported in at least three probands with Bernard-Soulier syndrome. Two probands are homozygous for this variant, while another proband is compound heterozygous for this variant and a pathogenic frameshift variant c.1454dup (PM3_Strong). The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000005530 (based on 2/60024 alleles) in the Admixed American population, this is below <0.0001114 the threshold for PM2_supporting. The computational predictor REVEL gives a score of 0.599, which is below the ClinGen PD VCEP PP3 threshold of >0.644 and does not predict a damaging

effect on GP1BA function. At least one patient (Patient M.L. in PMID:7819107) with this variant had aggregation absent for ristocetin but present for all other agonists and flow cytometry with less than 10% expression of GPIBa (PP4). This variant resides at a disulfide bond residue, Cys225, of GP1BA that is defined as a critical functional domain by the ClinGen PD VCEP (PM1). The variant has been reported to segregate with Bernard-Soulier syndrome in one proband (meeting PP4) plus one affected family member both with the compound heterozygous c.1454dup genotype (PMID:11776304). Finally, surface expression of GP1Ba measured by flow cytometry in CHO cells transiently co-transfected with the c.673T>A variant GP1Ba and wild type GP1Ba showed decreased expression at 0% (<25%) WT levels (PS3_supporting). 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: PP1, PM1, PS3_supporting, PM3_strong, PP4, PM2_supporting.

Met criteria codes

PP1	✔	The variant has been reported to segregate with Bernard-Soulier syndrome in the proband (meeting PP4) plus one affected family member, both with the compound heterozygous genotype with c.673T>A and c.1454dup variant(s). (PP1; PMID:11776304).
PP4	✔	At least one patient (Patient M.L. in PMID:7819107) with this variant had aggregation absent for ristocetin and present for all other agonists and flow cytometry with less than 10% expression of GPIba, 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.
PM1	✔	This variant resides at a disulfide bond residue, Cys225, of GP1BA that is defined as a critical functional domain by the ClinGen PD VCEP (PM1).
PM3_Strong	✔	This variant has been detected in at least three individuals with Bernard-Soulier syndrome. One was compound heterozygous for this variant and a pathogenic variant c.1454dup confirmed in trans by parental testing (PMID:11776304; 1pt). Two probands were homozygous for the variant (PMID:25539746, 7819107; 1pt). Total points: 2 (PM3_Strong). Found in at least two additional individuals with BSS (F2 and case 6) in the homozygous state (PMIDs:21173099, 28983057) but a maximum number of points has been given for homozygous individuals (0 points).
PM2_Supporting	✔	The Grpmax filtering allele frequency in gnomAD v4.1 is 0.000005530 (based on 2/60024 alleles) in the Admixed American population, this is below <0.0001114 the threshold for PM2_supporting
PS3_Supporting	✔	Surface expression of GP1Ba measured by flow cytometry in CHO cells transiently co-transfected with the c.673T>A variant GP1Ba and wild type GP1a showed decreased expression at 0% (<25%) WT levels, indicating that this variant impacts protein function (PMID:11776304) (PS3_supporting).

Not Met criteria codes

PS1	✖	Another variant has been reported with the same amino acid change, NM_000173.7(GP1BA):c.674G>C (p.Cys225Ser), but is not yet evaluated by the PD VCEP.
PP3	✖	The computational predictor REVEL gives a score of 0.599, which is below the ClinGen PD VCEP PP3 threshold of >0.644 and does not predict a damaging effect on GP1BA function. And the computational splicing predictor SpliceAI indicated that the variant has no predicted impact on splicing.

BP4		✖	The computational predictor REVEL gives a score of 0.599, which is above the ClinGen PD VCEP BP4 threshold of <0.290.

Curation History

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