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Variant: NM_000173.7(GP1BA):c.92T>C (p.Val31Ala)

Version: 1.0

CA8314693

585094 (ClinVar)

Gene: GP1BA (HGNC:2811)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: 143c642a-230a-4e13-8e33-dd5498edc2b7
Approved on: 2025/2/11
Published on: 2025/2/12

HGVS expressions

NM_000173.7(GP1BA):c.92T>C (p.Val31Ala)
NM_000173.7:c.92T>C
NC_000017.11:g.4932696T>C
CM000679.2:g.4932696T>C
NC_000017.10:g.4835991T>C
CM000679.1:g.4835991T>C
NC_000017.9:g.4776771T>C
NG_008767.2:g.5402T>C
ENST00000329125.6:c.92T>C
ENST00000649830.1:c.-888+1646A>G
ENST00000329125.5:c.92T>C
ENST00000611961.1:c.92T>C
NM_000173.6:c.92T>C

Uncertain Significance

Met criteria codes 1

BS1

Not Met criteria codes 5

PP3 PP4 PM5 BS2 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

The missense variant NM_000173.7(GP1BA):c.92T>C (p.Val31Ala) has been reported in one macrothrombocytopenia patient heterozygous for this variant (PMID: 34400424) however the same variant was detected in the mother with normal laboratory parameters. No BSS patients have been reported to our knowledge. The Grpmax Filtering allele frequency in gnomAD v4.1 is 0.0006253 (based on 784/1179792 alleles) in the European (non-Finnish) population, which is higher than the ClinGen PD VCEP threshold (>0.0005; BS1). In summary, this

variant meets the criteria to be classified as uncertain significance for autosomal recessive Bernard-Soulier syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: BS1 (ClinGen Platelet Disorders VCEP specifications version 1).

Met criteria codes

BS1	✔	The Grpmax Filtering allele frequency in gnomAD v4.1 is 0.0006253 (based on 784/1179792 alleles) in the European (non-Finnish) population, which is higher than the ClinGen PD VCEP threshold (>0.0005), and therefore meets this criterion (BS1). Of note, the highest MAF is in the Ashkenazi Jewish population at 0.01591 including 4 homozygote, but as a bottle-necked population it is not considered for BA1.

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.452, 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 (score 0.00).
PP4	✖	One patient has been reported heterozygous for this variant (PMID: 34400424). Although giant platelets and decreased ristocetin- induced platelet aggregation in the patient made the authors consider Bernard-Soulier syndrome, flow cytometry (CD41a 86.2%, CD42a 92.9%, CD42b 92.5%, and CD61 87.8%) and gene analysis did not support the diagnosis of Bernard- Soulier syndrome.
PM5	✖	NM_000173.7:c.91G>T (p.Val31Leu) has been observed at the same amino acid residue, however it has only been reported with dominant isolated giant platelet disorder (PMID: 26849716) and has not been assessed as Pathogenic for BSS.
BS2	✖	PMID: 34400424 Detected same heterozygous mutation in patient and her mother. Laboratory parameters and flow cytometry of mother did not support diagnosis of Bernard–Soulier syndrome but insufficient information is available for BS2.
BP4	✖	The computational predictor REVEL gives a score of 0.452, which is above the ClinGen PD VCEP BP4 threshold of <0.290.

Curation History

Showing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000173.7(GP1BA):c.92T>C (p.Val3...	Uncertain Significance	Bernard-Soulier Syndrome	2025-02-12	1.0	ClinGen Platelet Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GP1BA Version 1.0.0	GP1BA

Showing 1 to 1 of 1 rows

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