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Variant: NM_000419.5:c.959T>C

Version: 1.1

CA399804774

2581082 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 31358f74-b374-468c-9737-c12dc8e75678
Approved on: 2026/9/3
Published on: 2026/9/4

HGVS expressions

NM_000419.5:c.959T>C
NC_000017.11:g.44383933A>G
CM000679.2:g.44383933A>G
NC_000017.10:g.42461301A>G
CM000679.1:g.42461301A>G
NC_000017.9:g.39816827A>G
NG_008331.1:g.10573T>C
ENST00000262407.6:c.959T>C
ENST00000648408.1:c.390T>C
ENST00000262407.5:c.959T>C
ENST00000589645.5:n.410T>C
ENST00000591990.5:n.504T>C
ENST00000592226.5:n.199T>C
NM_000419.3:c.959T>C
NM_000419.4:c.959T>C

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PS3 PP3 PM2_Supporting

Not Met criteria codes 1

PM3

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 Version 2.1*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000419.5(ITGA2B):c.959T>C variant in ITGA2B is a missense variant predicted to cause substitution of Phenylalanine by Serine at amino acid 320 (p.Phe320Ser). At least one patient (Patient 1 in PMID: 9722314) with this variant displayed mucocutaneous bleeding and

impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was reduced to <5% of normal, as measured by flow cytometry (PP4_Moderate). Surface expression of αIIbβ3 measured by flow cytometry in CHO cells transiently co-transfected with c.959T>C (p.Phe320Ser) variant αIIb and wild type β3 showed decreased expression at 3% WT levels, indicating that this variant impacts protein function (PMID: 9722314)(PS3). The computational predictor REVEL gives a score of 0.885, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). The highest population minor allele frequency in gnomAD v4.1 is 0.00002229 (1/44868 alleles) in the East Asian genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PS3, PP4_Moderate, PP3 and PM2_Supporting (VCEP specifications version 2).

Met criteria codes

PP4_Moderate	✔	At least one patient (Patient 1 in PMID: 9722314) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was reduced to <5% of normal, as measured by flow cytometry. However, ITGA2B and ITGB3 were not reported to be sequenced across all exons and intron/exon boundaries (PP4_Moderate).
PS3	✔	Surface expression of αIIbβ3 measured by flow cytometry in CHO cells transiently co-transfected with c.959T>C (p.Phe320Ser) variant αIIb and wild type β3 showed decreased expression at 3% WT levels, indicating that this variant impacts protein function (PMID: 9722314)(PS3).
PP3	✔	The computational predictor REVEL gives a score of 0.885, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.00002229 (1/44868 alleles) in the East Asian genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).

Not Met criteria codes

PM3	✖	Patient 1 from PMID: 9722314 is reported to be compound heterozygous for the variant with the second variant undetermined.

Curation History

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