

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

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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

PS3

PP4_Moderate

PM2_Supporting

PP3

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, α IIb β 3 surface expression was reduced to <5% of normal, as measured by flow cytometry (PP4_Moderate). Surface expression of α IIb β 3 measured by flow cytometry in CHO cells transiently co-transfected with c.959T>C (p.Phe320Ser) variant α IIb and wild type β 3 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

PS3			Surface expression of α IIb β 3 measured by flow cytometry in CHO cells transiently co-transfected with c.959T>C (p.Phe320Ser) variant α IIb and wild type β 3 showed decreased expression at 3% WT levels, indicating that this variant impacts protein function (PMID: 9722314)(PS3).
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, α IIb β 3 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).
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).
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).

Not Met criteria codes

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



 

 

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