

Variant: *NM_000419.5:c.985G>T*

Version: 2.0

CA399804719 [↗](#)

1030781 (ClinVar) [↗](#)

Gene: ITGA2B ([HGNC:3674](#))

Condition: Glanzmann thrombasthenia ([MONDO:0100326](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: b2c81f25-21e7-45e9-a5e8-ee5e5513cbf4

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HGVS expressions

NM_000419.5:c.985G>T

NC_000017.11:g.44383907C>A

CM000679.2:g.44383907C>A

NC_000017.10:g.42461275C>A

CM000679.1:g.42461275C>A

NC_000017.9:g.39816801C>A

NG_008331.1:g.10599G>T

ENST00000262407.6:c.985G>T

ENST00000648408.1:c.416G>T

ENST00000262407.5:c.985G>T

ENST00000589645.5:n.436G>T

ENST00000591990.5:n.530G>T

ENST00000592226.5:n.225G>T

NM_000419.3:c.985G>T

NM_000419.4:c.985G>T

Likely Pathogenic

Met criteria codes **3**

PP4_Moderate

PM3_Strong

PM2_Supporting

Not Met criteria codes **3**

BP4

PP3

PS3

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 ITGA2B missense variant NM_000419.5:c.985G>T replaces the valine residue with a phenylalanine residue (p.Val329Phe) and is absent from control population databases. This variant has been observed in four individuals (in homozygosity in GT-56, PMID: 30792900 and

<https://doi.org/10.24911/IJMDC.51-1568613172>; in compound heterozygosity in Patient M, PMID: 12424194 (in trans with ITGA2B variant c.1232dup (p.Tyr411Ter), provisionally classified as pathogenic by the Platelet Disorders VCEP) and in heterozygosity in GT-62, PMID: 30792900 (second ITGA2B variant not identified)) suspected to have Glanzmann's thrombasthenia (GT). At least one of these individuals was reported to have a bleeding and laboratory phenotype specific for GT (<https://doi.org/10.24911/IJMDC.51-1568613172>). Although functional studies of this variant have been reported (PMID: 12424194; flow cytometric detection of α IIb β 3 positive cells following transient transfection of ITGA2B cDNA carrying this variant, immunoprecipitation of α IIb in lysates of transiently transfected cells, and pulse-chase analysis), these experiments did not meet the requirements for PS3. In summary, this variant meets criteria to be classified as likely pathogenic for GT. GT-specific criteria applied: PM2_supporting, PM3_strong, PP4_moderate.

Met criteria codes

PP4_Moderate			All requirements for PP4_moderate are met (https://doi.org/10.24911/IJMDC.51-1568613172): history of bleeding and impaired aggregation to at least two agonists, but normal or only mildly reduced agglutination with ristocetin.
PM3_Strong			This variant has been observed in one individual (Patient M, PMID: 12424194) in trans with ITGA2B variant c.1232dup (p.Tyr411Ter), classified as pathogenic by the Platelet Disorders VCEP (1pt) and in homozygosity in two individuals (GT-56, PMID: 30792900 and https://doi.org/10.24911/IJMDC.51-1568613172 ; 1pt). These occurrences are sufficient to apply PM3_strong (2pt). This variant was also identified in heterozygosity (GT-62, PMID: 30792900) with no second ITGA2B variant identified (although ITGB3 variant c.1265G>A (p.Ser422Asn) was also observed in this proband in heterozygosity).
PM2_Supporting			This variant is absent from gnomAD v4.0.0 (PM2_Supporting).

Not Met criteria codes

BP4			See explanation for PP3.
PP3			The REVEL score for this variant is 0.469, below the VCEP-established threshold of ≥ 0.7 to apply PP3 and above the VCEP-established threshold of < 0.25 to apply BP4. Additionally, splice predictors (SpliceAI and MaxEntScan) do not predict a damaging effect on splicing.
PS3			PMID: 12424194: ITGA2B cDNA carrying the c.985G>T variant was transiently transfected into 293T cells. α IIb β 3 receptor expression on the cell surface was measured by flow cytometry and shown to be reduced to approximately 28% compared to wild type (13% $\pm$ 5% of cells were positive for the α IIb β 3 receptor compared to 46% $\pm$ 12% of cells transiently transfected with wild type cDNA). However, this evidence was not used to support PS3 at any level of strength because the level of α IIb β 3 cell surface expression was not measured, only whether cells were positive or negative for surface α IIb β 3. Other experiments reported in this publication (immunoprecipitation of α IIb in lysates from the transfected cells and pulse-chase analyses) also did not meet the requirements to apply PS3 at any level of strength.

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