

Variant: NM_000419.5:c.399C>G

Version: 1.0

CA399806084 [↗](#)

2506415 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 1a545608-ad8b-46a0-a00f-e2c0198826a0

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HGVS expressions

NM_000419.5:c.399C>G

NC_000017.11:g.44385833G>C

CM000679.2:g.44385833G>C

NC_000017.10:g.42463201G>C

CM000679.1:g.42463201G>C

NC_000017.9:g.39818727G>C

NG_008331.1:g.8673C>G

ENST00000262407.6:c.399C>G

ENST00000262407.5:c.399C>G

NM_000419.3:c.399C>G

NM_000419.4:c.399C>G

Pathogenic

Met criteria codes **6**

PM2_Supporting

PP4_Moderate

PM3_Supporting

PS3

PP3

PM4

Evidence Links **1**

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.399C>G (p.Asp133Glu) missense variant was reported in a patient with type 1 GT (PMID 15717695). This variant is absent from the gnomAD database v2.1.1 (PM2_Supporting). It has a REVEL score of 0.288 which does not meet the threshold established by the PD EP, however, SpliceAI predicts the gain of a donor splice site (0.83) at this location (PP3_Met). Patient RNA confirmed that the c.399C>G variant creates a new donor splice site at this location, resulting in a 9-base pair deletion (c.400-408) that would result in an amino acid substitution Asp133Glu and an in-frame deletion of 3 amino acid residues (PM4). This variant was identified in a patient with GT type 1 (PMID 15717695) with severe intestinal bleeding. The patient's platelet aggregation study showed no response to ADP or

collagen but did show a normal response to ristocetin. GPIIb was completely absent with a faint amount of GPIIIa when analyzed using immunoblot (PP4_Moderate). This variant was found to be homozygous in the patient in which it was identified (PM3_Supporting). 293-Tcells were transfected with mutant GPIIb cDNA of this missense variant constructed using PCR mutagenesis. The construct was cotransfected into 293-T cells with wild-type GPIIIa cDNA Flow cytometry demonstrated no detectable amounts of GPIIbIIIIa complexes or GPIIb on the surface of transfected 293-T cells, but normal expression was observed with the wildtype GPIIb (PS3). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PM2_supporting, PP3, PM3_Supporting, PP4_Moderate, PS3, PM4 (VCEP specifications version 2.1).

Met criteria codes

PM2_Supporting			This variant is absent from the gnomAD database v2.1.1 (PM2_Supporting).
PP4_Moderate			This variant was identified in a patient with GT type 1 (PMID 15717695) with severe intestinal bleeding. The patient's platelet aggregation study showed no response to ADP or collagen but did show a normal response to ristocetin. GPIIb was completely absent with a faint amount of GPIIIa when analyzed using immunoblot. ITGB3 was not sequenced as part of this study.
PM3_Supporting			This variant was found to be homozygous in the patient in which it was identified (PMID 15717695).
PS3			<p>293-Tcells were transfected with mutant GPIIb cDNA of this missense variant constructed using PCR mutagenesis. The construct was cotransfected into 293-T cells with wild-type GPIIIa cDNA Flow cytometry demonstrated no detectable amounts of GPIIbIIIIa complexes or GPIIb on the surface of transfected 293-T cells, but normal expression was observed with the wildtype GPIIb.</p> <p>Flow cytometry demonstrated no detectable amounts of GPIIbIIIIa complexes or GPIIb on the surface of transfected 293-T cells, whereas normal expression was observed with the wildtype GPIIb. GPIIIa was detected, although the expression level was low, probably because GPIIIa formed complexes with an intrinsic integrin subunit. Transfection efficiency and the expression of GPIIb mRNA were confirmed by RTPCR analyses of these cells. Immunoblotting analysis of whole cell lysates with an anti-GPIIb MoAb demonstrated that both pro-GPIIb and mature GPIIb were detected in cells transfected with wild-type GPIIb. However, neither band was detected in cells with mutant GPIIb cDNA, even after immunoprecipitation with anticomplex or antiGPIIb antibodies. The results suggested that the mutant GPIIb was rapidly degraded after protein synthesis. Previous reports have shown that mutations of the -propeller domain of GPIIb, a main interface with GPIIIa, were associated with rapid degradation of uncomplexed GPIIb. The amino acid alteration reported here, although located away from the interface with GPIIIa [10], may have caused a significant shape change in the beta-propeller domain. PubMed:15717695 </p>
PP3			This variant has a REVEL score of 0.288 that does not meet the threshold established by the PD EP. Although, this variant is predicted to impact splicing. SpliceAI predicts the gain of a donor splice site (0.83) at this location. VarSeak calls this a class 3 variant with a MaxEntScan of 6.52 (PP3_Met).
PM4			Patient RNA confirmed that the c.399C>G variant creates a new donor splice site at this location, resulting in a 9-base pair deletion (nt 400-408) that would result in an amino acid substitution Asp133Glu and an in-frame deletion of 3 amino acid residues (Val134-Ile-Val).

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