

Variant: NM_000419.5:c.800G>A

Version: 2.0

CA399805147 [↗](#)

953015 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9dbbf079-8500-47e8-9f60-62847fdfe25e

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HGVS expressions

NM_000419.5:c.800G>A

NC_000017.11:g.44384585C>T

CM000679.2:g.44384585C>T

NC_000017.10:g.42461953C>T

CM000679.1:g.42461953C>T

NC_000017.9:g.39817479C>T

NG_008331.1:g.9921G>A

ENST00000262407.6:c.800G>A

ENST00000648408.1:c.231G>A

ENST00000262407.5:c.800G>A

ENST00000589645.5:n.251G>A

ENST00000591990.5:n.162G>A

ENST00000592075.5:n.169G>A

ENST00000592226.5:n.40G>A

ENST00000592253.5:n.308G>A

ENST00000592944.1:n.482G>A

NM_000419.3:c.800G>A

NM_000419.4:c.800G>A

Likely Pathogenic

Met criteria codes 4

PP4_Strong

PM3_Supporting

PP3

PM2_Supporting

Not Met criteria codes 2

PM5

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 NM_000419.5:c.800G>A (p.Gly267Glu) missense variant has been reported in at least one compound heterozygous patient (PMID: 12083483) with a phenotype highly specific to GT. Patient DRP of PMID: 12083483 meets the criteria for PP4_Strong; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of α IIb β 3 measured by flow cytometry (PP4_Strong). This patient is compound heterozygous for the variants c.2930del (classified Pathogenic by the Platelet Disorders VCEP) and Gly267Glu (PM3_supporting). It is absent from population databases, including gnomADv4.0.0 (PM2_supporting) and predicted to have a deleterious effect (REVEL score 0.838; PP3). In summary this variant meets criteria to be classified as Likely Pathogenic for GT. GT-specific criteria applied: PM2_Supporting, PM3_Supporting, PP3, and PP4_Strong.

Met criteria codes

PP4_Strong			Patient DRP of PMID: 12083483 meets the criteria for PP4_Strong; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of α IIb β 3 measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. Mild bleeding severity (defined by authors as bleeding only after trauma or surgery or minor symptoms, such as epistaxis). Platelets failed to aggregate in response to ADP, epinephrine, collagen,and thrombin and normally agglutinated in response to ristocetin. Surface expression measured by flow cytometry found 1.3% GPIIb and 0.9% GPIIIa compared to wildtype.
PM3_Supporting			Patient DRP of PMID: 12083483 is compound heterozygous for ariant c.2930del (classified Pathogenic by the Platelet Disorders VCEP) and Gly267Glu (confirmation of trans phase not reported). 0.5pt
PP3			The REVEL score is 0.838 predicting a damaging effect, above the >0.7 threshold for PP3.
PM2_Supporting			This variant is absent from gnomADv4.0.0.

Not Met criteria codes

PM5			The Gly267Ala variant (ClinVar 890601, VUS) was observed by Illumina as part of a predisposition screen in an ostensibly healthy population but has not been reported in a GT patient and is not considered here to avoid circularity.
PS3			In PMID: 18791937 HEK cells were transfected with the Gly267Glu variant of GPIIb and WT GPIIIa. Surface expression measured by flow cytometry found 9 +/- 5% positive cells (compared to 30 +/- 14% in control cells). This evidence was considered at PS3_supporting 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, however at ~30% WT expression levels this is above the <25% threshold for PS3 at any strength.

Curation History 

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