

Variant: NM_000419.5:c.97A>G

Version: 1.0

CA399806951 [↗](#)

1879065 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 14f93a2b-ecb8-40b1-a935-12924abccee

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HGVS expressions

NM_000419.5:c.97A>G

NC_000017.11:g.44389377T>C

CM000679.2:g.44389377T>C

NC_000017.10:g.42466745T>C

CM000679.1:g.42466745T>C

NC_000017.9:g.39822271T>C

NG_008331.1:g.5129A>G

ENST00000262407.6:c.97A>G

ENST00000262407.5:c.97A>G

NM_000419.3:c.97A>G

NM_000419.4:c.97A>G

Pathogenic

Met criteria codes **6**

PM2_Supporting

PP4_Strong

PM3_Supporting

PS3

PP1_Strong

PP3

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.97A>G (p.Asn33Asp) missense variant has been reported in four homozygous siblings (patients 2, 4, 6, and 9 PMID:21029361; PM3_supporting). All siblings displayed abnormal bleeding and one sibling tested for platelet aggregation demonstrated impaired response to agonists, with a normal response to ristocetin, which is characteristic of GT. Three of the siblings, including the proband, demonstrated absent platelet α IIb β 3 surface expression measured by flow cytometry (PP4_strong, PP1_strong). In Silico predictor revealed a REVEL score of 0.773, predicting a pathogenic effect (PP3). The variant is not found in gnomAD v2.1.1 (PM2_supporting). In BHK cells transfected with the p.Asn33Asp variant, surface expression of α IIb β 3 was absent (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: PP4_strong, PP1_strong, PP3, PS3, PM2_supporting, and PM3_supporting.

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v[2.1.1] (PM2_Supporting).
PP4_Strong			At least one patient (Patient-III2 in PMID:21029361) 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 not found (<25%), as measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries.
PM3_Supporting			This variant has been detected in at least 1 proband with Glanzmann thrombasthenia. One proband was homozygous for the variant (PMID:21029361). Total points: .5 (PM3_Supporting).
PS3			Surface expression of α IIb and α IIb β 3 measured by flow cytometry in BHK cells transiently co-transfected with Asn2Asp variant α IIb and wild type β 3 showed decreased expression at 0% (<5%) WT levels, indicating that this variant impacts protein function (PMID:21029361) (PS3).
PP1_Strong			The variant has been reported to segregate with Glanzmann Thrombasthenia in the proband (confirmed by bleeding phenotype and platelet aggregometry) plus three affected siblings with the same homozygous genotype. (PP1_strong, PMID: 21029361).
PP3			The computational predictor REVEL gives a score of [.773], which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).

Curation History



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