

Variant: NM_000419.5:c.605T>G

Version: 1.1

CA399805605 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: d0ec0d32-e549-4ba4-97cb-8de97b73ac2d

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HGVS expressions

NM_000419.5:c.605T>G

NC_000017.11:g.44385305A>C

CM000679.2:g.44385305A>C

NC_000017.10:g.42462673A>C

CM000679.1:g.42462673A>C

NC_000017.9:g.39818199A>C

NG_008331.1:g.9201T>G

ENST00000262407.6:c.605T>G

ENST00000648408.1:c.36T>G

ENST00000262407.5:c.605T>G

ENST00000589645.5:n.59T>G

ENST00000592253.5:n.37T>G

ENST00000592944.1:n.290T>G

NM_000419.3:c.605T>G

NM_000419.4:c.605T>G

Pathogenic

Met criteria codes **5**

PP1_Moderate

PM2_Supporting

PP4_Moderate

PS3

PP3

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 c.605T>G variant in ITGA2B is a missense variant predicted to cause substitution of phenylalanine by cystine at amino acid 202. At least one patient (Proband in PMID:15219201) with this variant displayed mucocutaneous bleeding and impaired aggregation with all

agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). The variant has been reported to segregate with Glanzmann thrombasthenia in the proband (confirmed by bleeding phenotype and platelet aggregometry) plus two affected family members, all with the homozygous genotype with the c.605T>G variant. (PP1_moderate; PMID:15219201). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). Surface expression of α IIb β 3 measured by flow cytometry in CHO cells transiently co-transfected with p.Phe202Cys α IIb and wild type β 3 showed absent expression (<5%) WT levels, indicating that this variant impacts protein function (PMID:15219201)(PS3). The computational predictor REVEL gives a score of 0.781, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). 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: PS3, PP1_moderate, PP4_moderate, PP3, PM2_supporting. (VCEP specifications version 2; date of approval 03/07/2024)

Met criteria codes

PP1_Moderate			The variant has been reported to segregate with Glanzmann thrombasthenia in the proband (confirmed by bleeding phenotype and platelet aggregometry) plus two affected family members, all with the homozygous genotype with the c.605T>G variant. (PP1_moderate; PMID:c.605T>G).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP4_Moderate			At least one patient (Proband in PMID:15219201) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate).
PS3			Surface expression of αIIbβ3 measured by flow cytometry in CHO cells transiently co-transfected with p.Phe202Cys αIIb and wild type β3 showed decreased expression at absent (<5%) WT levels, indicating that this variant impacts protein function (PMID:15219201)(PS3). Surface expression of αIIbβ3 measured by flow cytometry in CHO cells transiently co-transfected with p.Phe202Cys αIIb and wild type β3 showed decreased expression at absent (<5%) WT levels, indicating that this variant impacts protein function (PMID:15219201)(PS3). PubMed:15219201 
PP3			The computational predictor REVEL gives a score of 0.781, 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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Showing 1 to 2 of 2 rows

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