

Variant: *NM_000419.5:c.1021G>A*

Version: 2.0

CA399804633 [↗](#)

996200 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 7fcb7f26-d6b7-44e3-93db-a7eac08f57a6

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HGVS expressions

NM_000419.5:c.1021G>A

NC_000017.11:g.44383682C>T

CM000679.2:g.44383682C>T

NC_000017.10:g.42461050C>T

CM000679.1:g.42461050C>T

NC_000017.9:g.39816576C>T

NG_008331.1:g.10824G>A

ENST00000262407.6:c.1021G>A

ENST00000648408.1:c.452G>A

ENST00000262407.5:c.1021G>A

ENST00000592226.5:n.261G>A

NM_000419.3:c.1021G>A

NM_000419.4:c.1021G>A

Likely Pathogenic

Met criteria codes **4**

PP3

PM3

PM2_Supporting

PP4_Moderate

Not Met criteria codes **1**

PM5

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.1021G>A variant in ITGA2B is a missense variant predicted to cause substitution of Alanine by Threonine at amino acid 341. At least one patient (Patient 5 in PMID:32089034) homozygous for this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). A second homozygous case has also been identified (Northern Blood Research Centre, Kolling Institute, at The University of Sydney; PM3). This

variant occurs at a MAF of 0.000002737 (3/1096028 alleles) in the European (non-Finnish) population, which is below the <0.0001 threshold for PM2_supporting. The computational predictor REVEL gives a score of 0.737, 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 likely pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PP4_moderate, PM3, PM2_supporting, PP3. (VCEP specifications version 2).

Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.737, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PM3			Case 5 of PMID: 32089034 and an additional case from Northern Blood Research Centre, Kolling Institute, at The University of Sydney are both homozygous for Ala341Thr (1pt; PM3).
PM2_Supporting			This variant occurs at a MAF of 0.000002737 (3/1096028 alleles) in the European (non-Finnish) population, which is below the <0.0001 threshold for PM2_supporting.
PP4_Moderate			One patient (Patient 5 in PMID:32089034) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). α IIb β 3 surface was above 25% as measured by flow cytometry, and patient was reported as type 3 GT, however functional flow cytometry was not reported.

Not Met criteria codes

PM5			Another missense variant in the same codon has been reported in a patient with Glanzmann thrombasthenia [c.1022C>T, p.A341V] (GT database patient 437, ClinVarID:996201 VUS). However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen PD VCEP (PM5 not met).
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Curation History

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