

Variant: *NM_000419.5:c.2063C>T*

Version: 2.0

CA399799766 [↗](#)

1210185 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 08d0d385-0175-4f6f-b39b-c1f635eba146

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HGVS expressions

NM_000419.5:c.2063C>T

NC_000017.11:g.44378393G>A

CM000679.2:g.44378393G>A

NC_000017.10:g.42455761G>A

CM000679.1:g.42455761G>A

NC_000017.9:g.39811287G>A

NG_008331.1:g.16113C>T

ENST00000262407.6:c.2063C>T

ENST00000648408.1:c.1494C>T

ENST00000262407.5:c.2063C>T

ENST00000592462.5:n.858C>T

NM_000419.3:c.2063C>T

NM_000419.4:c.2063C>T

Likely Pathogenic

Met criteria codes **3**

PM2_Supporting

PP4_Strong

PM3_Supporting

Not Met criteria codes **2**

BP4

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 ITGA2B missense variant NM_000419.5:c.2063C>T replaces the alanine residue with a valine residue (p.Ala688Val). This variant is very rare in control population databases; the highest population minor allele frequency in gnomAD v4.1.0 is 0.00003332 (2/60020 alleles) in the Admixed American population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). It has been observed in homozygosity in one individual (Case 36 in PMID: 28983057; PM3_supporting) with a phenotype specific for Glanzmann's thrombasthenia

(GT). Case 36 (in PMID: 28983057) meets all requirements for PP4 at an upgraded strength of strong (PP4_strong): bleeding phenotype strongly indicative of Glanzmann's thrombasthenia; impaired aggregation to at least two agonists, but normal or only mildly reduced agglutination with ristocetin; markedly reduced expression of GPIIb/IIIa (confirmed to be <20% by personal communication with author); direct sequencing of all exons, untranslated regions, and flanking regions of ITGA2B and ITGB3. In summary, this variant meets criteria to be classified as likely pathogenic for GT. GT-specific criteria applied: PM2_supporting, PM3_supporting, PP4_strong.

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0 is 0.00003332 (2/60020 alleles) in the Admixed American population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).
PP4_Strong			This variant was reported in homozygosity in one individual (Case 36 in PMID: 28983057) who meets all requirements for PP4 at an upgraded strength of strong (PP4_strong): bleeding phenotype strongly indicative of Glanzmann's thrombasthenia; impaired aggregation to at least two agonists, but normal or only mildly reduced agglutination with ristocetin; markedly reduced expression of GPIIb/IIIa (confirmed to be <20% compared to controls by personal communication with author Dr. Jose Rivera); direct sequencing of all exons, untranslated regions, and flanking regions of ITGA2B and ITGB3.
PM3_Supporting			This variant was observed in homozygosity in one individual (Case 36 in PMID: 28983057), earning 0.5 points and sufficient to apply PM3_supporting.

Not Met criteria codes

BP4			See explanation for PP3.
PP3			The REVEL score for this variant is 0.394, below the VCEP-established threshold of ≥0.7 to apply PP3 and above the VCEP-established threshold of <0.25 to apply BP4. Additionally, splice predictors (SpliceAI and MaxEntScan) do not predict a damaging effect on splicing.

Curation History

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