The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000419.5(ITGA2B):c.476G>T (p.Gly159Val)

Version: 1.1

CA399805900

977126 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3cba4d4c-64ad-4e93-a2f6-e178841f7086
Approved on: 2025/5/1
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HGVS expressions

NM_000419.5(ITGA2B):c.476G>T (p.Gly159Val)
NM_000419.5:c.476G>T
NC_000017.11:g.44385649C>A
CM000679.2:g.44385649C>A
NC_000017.10:g.42463017C>A
CM000679.1:g.42463017C>A
NC_000017.9:g.39818543C>A
NG_008331.1:g.8857G>T
ENST00000262407.6:c.476G>T
ENST00000262407.5:c.476G>T
ENST00000592944.1:n.161G>T
NM_000419.3:c.476G>T
NM_000419.4:c.476G>T

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PP4_Moderate PM5_Supporting PM3_Supporting

Not Met criteria codes 1

PS3

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 missense variant NM_000419.5(ITGA2B):c.476G>T (p.Gly159Val) has been reported in at least one patient (P2 in PMID: 34275420) with mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). The patient is homozygous for Gly159Val (PM3_supporting). This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.751, which is above the ClinGen PD VCEP threshold of >0.7 and

predicts a damaging effect on function (PP3) and is is absent from gnomAD v2.1.1 (PM2_Supporting). Another missense variant c.475G>A (p.Gly159Ser) [PMID: 16359515] in the same codon has been classified Likely Pathogenic for Glanzmann thrombasthenia by the ClinGen PD VCEP (PM5_supporting). In summary this variant meets 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: PP3, PP4_moderate, PM2_supporting, PM3_supporting, PM5_supporting (VCEP specifications version 2.1).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.751, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on ITGB3 function (PP3).
PP4_Moderate	✔	At least one patient (Patient 1 in PMID: 34275420) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Platelet surface expression of the αIIbβ3 complex was not tested by these authors though the patient was reported as type I GT from local lab in Turkey by flow cytometry analysis.
PM5_Supporting	✔	Another missense variant c.475G>A (p.Gly159Ser) [PMID: 16359515] in the same codon has been classified Likely Pathogenic for Glanzmann thrombasthenia by the ClinGen PD VCEP.
PM3_Supporting	✔	P2 (PMID: 34275420) is homozygous for this variant (PM3_supporting).

Not Met criteria codes

PS3	✖	Surface expression of αIIbβ3 measured by flow cytometry in COS-7 cells transiently co-transfected with Gly159Val variant αIIb and wild type β3 showed normal expression levels (PMID: 34275420; PS3_NotMet). Testing of fibrinogen binding function of the expressed protein was not reported. Surface expression of αIIbβ3 measured by flow cytometry in COS-7 cells transiently co-transfected with Gly159Val variant αIIb and wild type β3 showed normal expression levels (PS3_NotMet). Testing of fibrinogen binding function of the expressed protein was not reported. The authors suggest that the c.476G>T variant may instead affect splicing; and report that the Human Splice Finder tool predicted that the αIIb:c.476 G > T SNV might create a cryptic donor splicing site in exon 4 leading to a frame shift (αIIb:p.Gly159Alafs). This splice impact is not predicted by SpliceAI and was not confirmed in patient cDNA or mini-gene assay. PubMed:34275420

Curation History

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