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.2444A>G (p.Tyr815Cys)

Version: 2.3

CA399795789

977129 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: f8c8505a-d4b4-4c99-8662-1730f2636de5
Approved on: 2025/4/15
Published on: 2025/5/13

HGVS expressions

NM_000419.5(ITGA2B):c.2444A>G (p.Tyr815Cys)
NM_000419.5:c.2444A>G
NC_000017.11:g.44376089T>C
CM000679.2:g.44376089T>C
NC_000017.10:g.42453457T>C
CM000679.1:g.42453457T>C
NC_000017.9:g.39808983T>C
NG_008331.1:g.18417A>G
ENST00000262407.6:c.2444A>G
ENST00000648408.1:c.1875A>G
ENST00000262407.5:c.2444A>G
ENST00000587295.5:c.96A>G
ENST00000592462.5:n.1239A>G
NM_000419.3:c.2444A>G
NM_000419.4:c.2444A>G

Likely Pathogenic

Met criteria codes 4

PM3_Supporting PP4_Strong PM2_Supporting PS3_Supporting

Not Met criteria codes 1

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 missense variant NM_000419.5(ITGA2B):c.2444A>G (p.Tyr815Cys) has been reported, in the homozygous state (PM3_supporting), in at least one GT proband (P15 in PMID: 34275420) who displayed mucocutaneous bleeding and impaired aggregation with all agonists except

ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was reduced to <5%, as measured by flow cytometry (PP4_strong). The highest population minor allele frequency in gnomAD v4.1 is 0.00001333 (1/75002 alleles) in the African/African-American genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). 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

PM3_Supporting	✔	P15 is homozygous for this variant (PMID: 34275420; PM3_supporting)
PP4_Strong	✔	At least one patient (P15 in PMID: 34275420) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was reduced to <5%, as measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. (PP4_strong)
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.00001333 (1/75002 alleles) in the African/African-American genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).
PS3_Supporting	✔	Surface expression of αIIbβ3 measured by flow cytometry in COS-7 cells transiently co-transfected with Gly454Asp variant αIIb and wild type β3 showed impaired expression levels. There is a clear decrease in percent positive cells shown in Figure 1, interpreted as <25% (PMID: 34275420; PS3_supporting). This evidence was downgraded to PS3_Supporting because the level of αIIb, β3, and αIIbβ3 cell surface expression was not reported, only whether cells were positive or negative for surface αIIb, β3, and αIIbβ3.
		Surface expression of αIIbβ3 measured by flow cytometry in HEK-293 cells transiently co-transfected with Tyr815Cys variant αIIb and wild type β3 showed impaired expression levels. There is a clear decrease in percent positive cells shown in Figure 1, however this is not quantified (PS3_NotMet). PubMed:34275420

Not Met criteria codes

PP3	✖	The REVEL score of 0.516 is intermediate between the >0.7 threshold for PP3 and the <0.25 threshold for BP4. No impact on splicing is predicted by SpliceAI or MaxEntScan.

Curation History

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