

Variant: *NM_000212.3:c.1388G>C*

Version: 1.1

CA400029054 [↗](#)

1691487 (ClinVar) [↗](#)

Gene: ITGB3 ([HGNC:3690](#))

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

Inheritance Mode: Autosomal recessive inheritance

UUID: dbb0136b-f516-4fb1-9771-b243432556e2

Approved on: 2025/3/6

Published on: 2025/3/6

HGVS expressions

NM_000212.3:c.1388G>C

NC_000017.11:g.47292266G>C

CM000679.2:g.47292266G>C

NC_000017.10:g.45369632G>C

CM000679.1:g.45369632G>C

NC_000017.9:g.42724631G>C

NG_008332.2:g.43425G>C

ENST00000696963.1:c.1388G>C

ENST00000559488.7:c.1388G>C

ENST00000559488.5:c.1388G>C

ENST00000560629.1:c.1353G>C

NM_000212.2:c.1388G>C

Likely Pathogenic

Met criteria codes **5**

PM3_Supporting

PP1

PP3

PP4_Strong

PM2_Supporting

Not Met criteria codes **1**

PS3

Evidence Links **1**

Expert Panel

Platelet Disorders VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000212.3(ITGB3):c.1388G>C (p.Cys463Ser) missense variant has been observed in at least one GT patient (Patient 7 in PMID: 34267460), whom displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, α IIb β 3 surface expression was reduced to 0.5-1.7%, as measured by flow cytometry (PP4_strong). The variant was been reported to segregate with Glanzmann thrombasthenia in Patient 7 plus one affected family member, both with the homozygous Cys463Ser genotype. (PM3_supporting, PP1; PMID: 34267460). The highest population minor allele frequency in gnomAD v4.1 is 0.00001098 (1/91078 alleles) in the South Asian genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). The computational predictor REVEL gives a score of 0.898, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). 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: PP4_strong, PP1, PP3, PM2_supporting, PM3_supporting. (VCEP specifications version 2.1)			
Met criteria codes			
PM3_Supporting			Patient 7 of PMID: 34267460 is homozygous for this variant (0.5pt; PM3_supporting).
PP1			The variant has been reported to segregate with Glanzmann thrombasthenia in the proband plus one affected family member, both with the homozygous Cys463Ser genotype. (PP1; PMID: 34267460).
PP3			The computational predictor REVEL gives a score of 0.898, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PP4_Strong			At least one patient (Patient 7 in PMID34267460) 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 0.5-1.7%, 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 0.00001098 (1/91078 alleles) in the South Asian genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).

Not Met criteria codes

PS3			Surface expression of αIIbβ3 measured by flow cytometry in BHK cells transiently co-transfected with Cys463Ser (here referred to as Cys437Ser) variant β3 and wild type αIIb showed decreased expression at 40% WT levels of positive cells. This modest reduction is insufficient to apply PS3 (PMID: 22308022).
			Surface expression of αIIbβ3 measured by flow cytometry in BHK cells transiently co-transfected with Cys463Ser (here referred to as Cys437Ser) variant β3 and wild type αIIb showed decreased expression at 40% WT levels of positive cells. This modest reduction is insufficient to apply PS3. PubMed:22308022 

Curation History

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