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_000212.3(ITGB3):c.422A>G (p.Tyr141Cys)

Version: 3.3

CA400021881

1691482 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2b7ab519-a877-44dd-bacf-01a16a1cac45
Approved on: 2025/6/17
Published on: 2025/6/27

HGVS expressions

NM_000212.3(ITGB3):c.422A>G (p.Tyr141Cys)
NM_000212.3:c.422A>G
NC_000017.11:g.47284503A>G
CM000679.2:g.47284503A>G
NC_000017.10:g.45361869A>G
CM000679.1:g.45361869A>G
NC_000017.9:g.42716868A>G
NG_008332.2:g.35662A>G
ENST00000696963.1:c.422A>G
ENST00000559488.7:c.422A>G
ENST00000559488.5:c.422A>G
ENST00000560629.1:c.387A>G
ENST00000571680.1:c.422A>G
NM_000212.2:c.422A>G

Pathogenic

Met criteria codes 5

PM2_Supporting | PP3 | PM3 | PP4_Strong | PP1_Moderate

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_000212.3:c.422A>G variant in ITGB3 is a missense variant predicted to cause substitution of tyrosine by cysteine at amino acid 141 (p.Tyr141Cys). At least one patient (Patient 12 in PMID: 36672149) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, there was absence of

GPIIbIIIa platelet surface expression by flow cytometry and ITGA2B and ITGB3 were reported to be sequenced across all exons and intron/exon boundaries (PP4_Strong). Patient GT53 reported in PMID: 19691478 is compound heterozygous for this variant and the ITGB3 variant c.415G>C (p.Asp139His, classified by the Platelet Disorders VCEP as Likely Pathogenic, trans phase confirmed - not considered here to avoid circularity). GT1-III2, of PMID: 32558238, patient No.1 of PMID: 15748237, and patients 11/12 of PMID: 36672149 are all homozygous for Tyr141Cys 1pt. Total 1pt (PM3). The variant has been reported to segregate with Glanzmann thrombasthenia (confirmed by bleeding phenotype and platelet aggregometry) in the GT1-III2 proband plus two affected family members, all homozygous for Tyr141Cys genotype. (PP1_moderate; PMID: 32558238). The highest population minor allele frequency in gnomAD v4.1 is 0.00005489 (5/91090 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 0.939, which is above the ClinGen Platelet Disorders VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). In summary, this variant meets criteria to be classified as Pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD-VCEP: PM2_Supporting, PP3, PP4_Strong, PM3, PP1_moderate. (VCEP specifications version 2)

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.00005489 (5/91090 alleles) in the South Asian genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.939, which is above the ClinGen Platelet Disorders VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PM3	✔	Patient GT53 reported in PMID: 19691478 is compound heterozygous for this variant and the ITGB3 variant c.415G>C (p.Asp139His, classified by the Platelet Disorders VCEP as Likely Pathogenic, trans phase confirmed - not considered here to avoid circularity). GT1-III2, of PMID: 32558238, patient No.1 of PMID: 15748237, and patients 11/12 of PMID: 36672149 are all homozygous for Tyr141Cys 1pt. Total 1pt (PM3)
PP4_Strong	✔	At least one patient (Patient 12 in PMID: 36672149) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, there was absence of GPIIbIIIa platelet surface expression by flow cytometry and ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries (PP4_Strong).
PP1_Moderate	✔	The variant has been reported to segregate with Glanzmann thrombasthenia (confirmed by bleeding phenotype and platelet aggregometry) in the proband plus two affected family members, all with homozygous Tyr141Cys genotype. (PP1_moderate; PMID: 32558238)

Curation History

Showing 1 to 6 of 6 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.