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Variant: NM_000212.3:c.450G>A

Version: 1.0

CA400022022

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: b9e0d7cc-ceef-4377-bd01-0cd0e9afc627
Approved on: 2025/6/19
Published on: 2025/6/19

HGVS expressions

NM_000212.3:c.450G>A
NC_000017.11:g.47284531G>A
CM000679.2:g.47284531G>A
NC_000017.10:g.45361897G>A
CM000679.1:g.45361897G>A
NC_000017.9:g.42716896G>A
NG_008332.2:g.35690G>A
ENST00000696963.1:c.450G>A
ENST00000559488.7:c.450G>A
ENST00000559488.5:c.450G>A
ENST00000560629.1:c.415G>A
ENST00000571680.1:c.450G>A
NM_000212.2:c.450G>A

Likely Pathogenic

Met criteria codes 5

PM3_Supporting PP3 PP4_Moderate PM2_Supporting PM5_Supporting

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

NM_000212.3(ITGB3):c.450G>A (p.Met150Ile) has a computational predictor REVEL gives a score of 0.908, which is above the ClinGen Platelet Disorders VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). Another missense variant NM_000212.3(ITGB3):c.448A>G (p.Met150Val) in the same codon has been classified as likely pathogenic for Glanzmann thrombasthenia by the ClinGen PD VCEP (PM5_supporting). The highest population minor allele frequency in gnomAD v4.1 is 8.474e-7 (1/1180040 alleles) in

the European (non-Finnish) population, which is lower than the ClinGen Platelet Disorders VCEP threshold (<0.0001; PM2_Supporting). At least one homozygous (PM3_supporting) patient (Patient 6 in PMID: 40239810) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, αIIbβ3 surface expression was reduced to 2.7% (<25%), as measured by flow cytometry (PP4_Moderate). In summary, this variant meets the 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_moderate, PM3_supporting, PM2_supporting, PP3, PM5_supporting. (VCEP specifications version 2).

Met criteria codes

PM3_Supporting	✔	Patient 6 in PMID: 40239810 is compound heterozygous for p.Arg88X (classified pathogenic by the PD VCEP) and p.Met150Ile, confirmation of trans phase not reported (0.5pt)
PP3	✔	The computational predictor REVEL gives a score of 0.908, which is above the ClinGen Platelet Disorders VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PP4_Moderate	✔	At least one patient (Patient 6 in PMID: 40239810) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, αIIbβ3 surface expression was reduced to 2.7% (<25%), as measured by flow cytometry (PP4_Moderate). However, ITGA2B and ITGB3 were not reported to be sequenced across all exons and intron/exon boundaries.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 8.474e-7 (1/1180040 alleles) in the Eupropean (non-Finnish) population, which is lower than the ClinGen Platelet Disorders VCEP threshold (<0.0001; PM2_Supporting).
PM5_Supporting	✔	Another missense variant NM_000212.3(ITGB3):c.448A>G (p.Met150Val) in the same codon has been classified as likely pathogenic for Glanzmann thrombasthenia by the ClinGen PD VCEP (PM5_supporting).

Curation History

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