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Variant: NM_000212.2:c.448A>G

Version: 2.1

CA8622961

953053 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 61faa416-bb84-4ca5-b091-b1cb2ab8bea3
Approved on: 2025/6/19
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HGVS expressions

NM_000212.2:c.448A>G
NC_000017.11:g.47284529A>G
CM000679.2:g.47284529A>G
NC_000017.10:g.45361895A>G
CM000679.1:g.45361895A>G
NC_000017.9:g.42716894A>G
NG_008332.2:g.35688A>G
ENST00000696963.1:c.448A>G
ENST00000559488.7:c.448A>G
ENST00000559488.5:c.448A>G
ENST00000560629.1:c.413A>G
ENST00000571680.1:c.448A>G
NM_000212.3:c.448A>G

Likely Pathogenic

Met criteria codes 4

PP3 PP4_Moderate PM3_Strong PM2_Supporting

Not Met criteria codes 2

PS3 PM5

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_000419.5:c.448A>G variant in ITGB3 is a missense variant predicted to cause substitution of methionine by valine at amino acid 150 (p.Met150Val). This variant has been detected in at least 3 probands with Glanzmann thrombasthenia. Two of these individuals were compound heterozygous for this variant and a pathogenic variant and one of those was confirmed to carry the variants in trans by parental testing (c.774_775del (phase not confirmed) and p.Asp145Tyr (phase confirmed)). An additional proband was reported to be homozygous

for the variant (personal communication with Dr. Jose Rivera (Servicio de Hematologıa y Oncologıa Medica, Hospital Universitario Morales Meseguer, Centro Regional de Hemodonacion, Universidad de Murcia)) (PM3_Strong). At least one patient (Patient GT-1, PMID: 25539746) 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 <25%), as measured by flow cytometry. However, ITGA2B and ITGB3 were not reported to be sequenced across all exons and intron/exon boundaries. The highest population minor allele frequency in gnomAD v4.1 is 0.00001098 (1/91082 alleles) in the South Asian population, which is lower than the ClinGen Platelet Disorders VCEP threshold (<0.0001; PM2_Supporting). Furthermore, the computational predictor REVEL gives a score of 0.968, 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 likely pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PM2_Supporting, PM3_Strong, PP3, PP4_Moderate. (VCEP specifications version 2)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.968, which is above the ClinGen Platelet Disorders VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PP4_Moderate	✔	At least two patients (PMID: 25539746 and Patient GT-1, PMID: 15583747) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate).
PM3_Strong	✔	This variant has been detected in at least 3 probands with Glanzmann thrombasthenia. Two of these individuals were compound heterozygous for this variant and a pathogenic variant and one of those was confirmed to carry the variants in trans by parental testing (c.774_775del, GT-1 in PMID: 25539746, phase not confirmed, 0.5 points) and p.Asp145Tyr (PMID: 15583747, phase confirmed, 1.0 point). An additional proband was reported to be homozygous for the variant (personal communication with Dr. Jose Rivera (Servicio de Hematologıa y Oncologıa Medica, Hospital Universitario Morales Meseguer, Centro Regional de Hemodonacion, Universidad de Murcia), 0.5 points). Total points: 2.0 (PM3_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.00001098 (1/91082 alleles) in the South Asian population, which is lower than the ClinGen Platelet Disorders VCEP threshold (<0.0001; PM2_Supporting).

Not Met criteria codes

PS3	✖	CHO cell lines were transfected with normal αIIb and either normal β3 or the Met150Val mutant. Cells transfected with the mutant form had a reduced amount of the αIIbβ3 complex, however the reduction was not quantified from the Western blot. Binding to Fibrinogen and PAC-1 were not disrupted.
PM5	✖	NM_000212.3(ITGB3):c.450G>A (p.Met150Ile) is not considered here to avoid circularity.

Curation History

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