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Variant: NM_000212.3:c.121C>T

Version: 1.0

CA400031690

1879027 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: c1b1977b-4893-41ae-be81-7bf04e7f8926
Approved on: 2022/9/20
Published on: 2022/12/7

HGVS expressions

NM_000212.3:c.121C>T
NC_000017.11:g.47274460C>T
CM000679.2:g.47274460C>T
NC_000017.10:g.45351826C>T
CM000679.1:g.45351826C>T
NC_000017.9:g.42706825C>T
NG_008332.2:g.25619C>T
ENST00000696963.1:c.121C>T
ENST00000559488.7:c.121C>T
ENST00000559488.5:c.121C>T
ENST00000560629.1:c.86C>T
ENST00000571680.1:c.121C>T
NM_000212.2:c.121C>T

Pathogenic

Met criteria codes 4

PM3_Supporting PP4_Moderate PM2_Supporting PVS1

Not Met criteria codes 1

PP1

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(ITGB3):c.121C>T (p.Gln41Ter) variant in exon 2/15 is a nonsense variant predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). It has been reported homozygous (PM3_supporting) in at least one GT proband (patient 3 in PMID: 32089034) who displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was absent, as measured

by flow cytometry (PP4_moderate). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). In summary, based on the available evidence at this time, the variant is classified as pathogenic for GT. GT-specific criteria applied: PVS1, PM2_supporting, PM3_supporting, PP4_moderate.

Met criteria codes

PM3_Supporting	✔	This variant has been detected in at least one homozygous proband with Glanzmann thrombasthenia (PM3_supporting;PMID: 32089034).
PP4_Moderate	✔	At least one patient (Patient 3 in PMID:32089034) 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 0.2-4%, as measured by flow cytometry. However, ITGA2B and ITGB3 were not reported to be sequenced across all exons and intron/exon boundaries.
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PVS1	✔	The c.121C>T p.Gln41Ter nonsense variant in exon 2 is predicted to to cause a premature stop codon in a biologically-relevant-exon and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).

Not Met criteria codes

PP1	✖	The variant has been reported to segregate with Glanzmann thrombasthenia in the proband plus one affected sibling, both with the homozygous genotype with the c.121C>T variant. However, the sibling (patient 2) only had 14% response to ristocetin and the authors defined a normal response as >60%.

Curation History

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