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Variant: NM_000212.3:c.1641C>G

Version: 2.0

CA400030171

1691476 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 88f958b5-fd37-421f-8386-032781178629
Approved on: 2025/3/6
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HGVS expressions

NM_000212.3:c.1641C>G
NC_000017.11:g.47292519C>G
CM000679.2:g.47292519C>G
NC_000017.10:g.45369885C>G
CM000679.1:g.45369885C>G
NC_000017.9:g.42724884C>G
NG_008332.2:g.43678C>G
ENST00000696963.1:c.1641C>G
ENST00000559488.7:c.1641C>G
ENST00000559488.5:c.1641C>G
ENST00000560629.1:c.1606C>G
NM_000212.2:c.1641C>G

Pathogenic

Met criteria codes 5

PP4_Strong PM2_Supporting PM3 PM5 PP3

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.1641C>G variant in ITGB3 is a missense variant predicted to cause substitution of cysteine by tryptophan at amino acid 547 (p.Cys547Trp). This is a critical cysteine residues for regulation of integrin alphaIIbbeta3 (PMID: 14690453). This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.891, which is above the ClinGen Platelet Disorders VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). Another missense variant (c.1639T>G (p.Cys547Gly)) in the same codon has been provisionally classified as pathogenic for Glanzmann thrombasthenia by the ClinGen Platelet Disorders VCEP

(PM5). Splicing prediction using SpliceAI revealed no expected effects on splicing due to either of these variants. There are at least four homozygous (reported unrelated) GT patients (PMID: 32558238, 19691478; PM3). At least one patient (Patient GT4 in PMID: 32558238) 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 absent, as measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. (PP4_strong) In summary, this variant meets the 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, PM3, PM5, PP3, PP4_Strong. (VCEP specifications version 2)

Met criteria codes

PP4_Strong	✔	At least one patient (Patient GT4 in PMID: 32558238) 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 absent, as measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. (PP4_strong)
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PM3	✔	There are at least four homozygous (reported unrelated) GT patients (PMID: 32558238, 19691478).
PM5	✔	Another missense variant (c.1639T>G (p.Cys547Gly)) in the same codon has been provisionally classified as pathogenic for Glanzmann thrombasthenia by the ClinGen Platelet Disorders VCEP (PM5). Splicing prediction using SpliceAI revealed no expected effects on splicing due to either of these variants.
PP3	✔	The computational predictor REVEL gives a score of 0.891, which is above the ClinGen Platelet Disorders VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).

Curation History

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