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Variant: NM_000212.3:c.1639T>G

Version: 2.0

CA291225782

1879045 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 794bd122-d899-4bd9-8640-12b45bde13a9
Approved on: 2025/3/6
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HGVS expressions

NM_000212.3:c.1639T>G
NC_000017.11:g.47292517T>G
CM000679.2:g.47292517T>G
NC_000017.10:g.45369883T>G
CM000679.1:g.45369883T>G
NC_000017.9:g.42724882T>G
NG_008332.2:g.43676T>G
ENST00000696963.1:c.1639T>G
ENST00000559488.7:c.1639T>G
ENST00000559488.5:c.1639T>G
ENST00000560629.1:c.1604T>G
NM_000212.2:c.1639T>G

Pathogenic

Met criteria codes 5

PP3 PM3 PS3 PP4_Moderate PM2_Supporting

Not Met criteria codes 1

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_000212.3:c.1639T>G variant in ITGB3 is a missense variant predicted to cause substitution of cysteine by glycine at amino acid 547 (p.Cys547Gly). This is a critical cysteine residues for regulation of integrin alphaIIbbeta3 (PMID: 14690453). This variant has been observed in compound heterozygosity in one individual (Patient 3 in PMID: 28748566) in combination with ITGB3 variant c.1192delG (p.Ala398ProfsTer24, provisionally classified as pathogenic by the Platelet Disorders VCEP, trans phase not confirmed). This individual displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann

thrombasthenia (PP4_Moderate). An additional patient reported in DOI: 10.26502/acmcr.96550268 is compound heterozygous for this variant and the ITGB3 variant c.1552C>T (p.Gln518Ter), classified as pathogenic by the Platelet Disorders VCEP, trans phase confirmed (PM3). The highest population minor allele frequency in gnomAD v4.1 is 0.00001610 (19/1179874 alleles) in the non-Finnish European population, which is lower than the ClinGen Platelet Disorders VCEP threshold (<0.0001; PM2_Supporting). Surface expression of β3 and αIIbβ3 measured by Western blot and flow cytometry (respectively) in HEK293 cells transiently co-transfected with p.Cys547Gly variant β3 and wild type αIIb showed decreased expression at <5%, indicating that this variant impacts protein function (PMID: 25827233) (PS3). Furthermore, the computational predictor REVEL gives a score of 0.993, 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 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: PS3, PM2_Supporting, PM3, PP3, PP4_Moderate. (VCEP specifications version 2)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.993, which is above the ClinGen Platelet Disorders VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PM3	✔	Patient 3 reported in PMID: 28748566 is compound heterozygous for this variant and the ITGB3 variant c.1192delG (p.Ala398ProfsTer24, classified as pathogenic by the Platelet Disorders VCEP, trans phase not confirmed, 0.5pt) and an additional patient reported in DOI: 10.26502/acmcr.96550268 is compound heterozygous for this variant and the ITGB3 variant c.1552C>T (p.Gln518Ter), classified as pathogenic by the Platelet Disorders VCEP, trans phase confirmed, 1pt) (1.5 points; PM3).
PS3	✔	Surface expression of β3 and αIIbβ3 measured by Western blot and flow cytometry (respectively) in HEK293 cells transiently co-transfected with p.Cys547Gly variant β3 and wild type αIIb showed decreased expression at <5%, indicating that this variant impacts protein function (PMID: 25827233) (PS3).
PP4_Moderate	✔	At least one patient (Patient 3 in PMID: 28748566) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_Moderate).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.00001610 (19/1179874 alleles) in the non-Finnish European population, which is lower than the ClinGen Platelet Disorders VCEP threshold (<0.0001; PM2_Supporting).

Not Met criteria codes

PM5	✖	Two other missense variants, c.1640G>A (p.Cys547Tyr) and c.1641C>G (p.Cys547Trp), occur in the same codon, they have not been considered here to avoid circularity.

Curation History

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