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Variant: NM_000212.3:c.1495T>C

Version: 1.0

CA400029525

1330310 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 20c4f30e-4a93-4159-82da-26dde7320db5
Approved on: 2021/12/21
Published on: 2021/12/23

HGVS expressions

NM_000212.3:c.1495T>C
NC_000017.11:g.47292373T>C
CM000679.2:g.47292373T>C
NC_000017.10:g.45369739T>C
CM000679.1:g.45369739T>C
NC_000017.9:g.42724738T>C
NG_008332.2:g.43532T>C
ENST00000696963.1:c.1495T>C
ENST00000559488.7:c.1495T>C
ENST00000559488.5:c.1495T>C
ENST00000560629.1:c.1460T>C
NM_000212.2:c.1495T>C

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PP4_Strong PM2_Supporting

Evidence Links 0

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000212.3(ITGB3):c.1495T>C (p.Cys499Arg) missense variant has been reported in at least two Glanzmann thrombasthenia patients (PMIDs: 29675921, 30138987). Patient GT25 of PMID: 29675921 displayed mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3 measured by flow cytometry (PP4_strong). GT25 of PMID: 29675921 is homozygous for this variant and Case 7 of PMID: 30138987 is compound heterozygous for Cys499Arg and pathogenic variant c.1728del (PM3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.914 (PP3). 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_strong, PM3, PM2_supporitng, PP3. (VCEP specifications version 2; date of approval 12/21/2021).

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.914, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on ITGB3 function (PP3).
PM3	✔	GT 25 of PMID: 29675921 is homozygous for Cys499Arg 0.5pt and Case 7 of PMID: 30138987 is compound heterozygous for Cys499Arg and pathogenic variant c.1728del 0.5pt (PM3).
PP4_Strong	✔	GT25 of PMID: 29675921 meets the criteria for PP4_strong; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3 measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries.
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Curation History

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