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Variant: NM_000419.5:c.647C>T

Version: 1.1

CA399805506

1210176 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 42979f22-3724-4b1f-8245-4e2216c55d02
Approved on: 2024/9/5
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HGVS expressions

NM_000419.5:c.647C>T
NC_000017.11:g.44385187G>A
CM000679.2:g.44385187G>A
NC_000017.10:g.42462555G>A
CM000679.1:g.42462555G>A
NC_000017.9:g.39818081G>A
NG_008331.1:g.9319C>T
ENST00000262407.6:c.647C>T
ENST00000648408.1:c.78C>T
ENST00000262407.5:c.647C>T
ENST00000589645.5:n.98C>T
ENST00000591990.5:n.9C>T
ENST00000592075.5:n.16C>T
ENST00000592226.5:n.16C>T
ENST00000592253.5:n.155C>T
ENST00000592944.1:n.329C>T
NM_000419.3:c.647C>T
NM_000419.4:c.647C>T

Likely Pathogenic

Met criteria codes 4

PP4_Strong | PM3_Supporting | PP3 | PM2_Supporting

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(ITGA2B):c.647C>T (p.Ala216Val) missense variant has been previously reported in the context of Glanzmann thrombasthenia. One individual (GT55) with the p.Ala216Val missense variant in homozygous state (PM3_supporting) presented with significant mucocutaneous bleeding. Platelet aggregometry demonstrated absence of platelet aggregation with 3 platelet agonists and normal aggregation with ristocetin. Surface expression of αIIbβ3 was demonstrated to be reduced (11-22%) by flowcytometry. Sanger sequencing ensured coverage of exons and splice sites of the ITGA2B and ITGB3 genes as well as untranslated regions (PMID:25728920; PP4_strong). This variant is absent from all continental populations in gnomAD v4.1.0 (PM2_Supporting). Multiple in silico tools predict this variant to be deleterious (REVEL score = 0.85; PP3). This variant meets criteria for PP4_strong, PM2_supporting, PM3_supporting and PP3 and is classified as Likely pathogenic.

Met criteria codes

PP4_Strong	✔	One individual (GT55) with the p.Ala216Val missense variant in homozygous state presented with significant mucocutaneous bleeding. Platelet aggregometry demonstrated absence of platelet aggregation with 3 platelet agonists and normal aggregation with ristocetin. Surface expression of αIIbβ3 was demonstrated to be reduced (11-22%) by flowcytometry. Sanger sequencing ensured coverage of exons and splice sites of the ITGA2B and ITGB3 genes as well as untranslated regions (UTR). PMID:25728920 PP4_strong applied.
PM3_Supporting	✔	The p.Ala216Val variant has been reported to occur in homozygosity in one proband (PMID:25728920) 0.5 points.
PP3	✔	REVEL score for this variant is 0.85 which is above the threshold of >0.70
PM2_Supporting	✔	This variant is absent from all continental populations in gnomAD v4.1.0 (PM2_Supporting). The highest population minor allele frequency is 0.00001600 (1/62510alleles) in the remaining population, which is lower than the ClinGen PD VCEP threshold (<0.0001).

Curation History

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