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Variant: NM_000419.4:c.1028T>C

Version: 2.0

CA399804619

953042 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 027d3ed8-b21f-44dd-bba6-8d161a3cb738
Approved on: 2023/5/16
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HGVS expressions

NM_000419.4:c.1028T>C
NC_000017.11:g.44383675A>G
CM000679.2:g.44383675A>G
NC_000017.10:g.42461043A>G
CM000679.1:g.42461043A>G
NC_000017.9:g.39816569A>G
NG_008331.1:g.10831T>C
ENST00000262407.6:c.1028T>C
ENST00000648408.1:c.459T>C
ENST00000262407.5:c.1028T>C
ENST00000592226.5:n.268T>C
NM_000419.3:c.1028T>C
NM_000419.5:c.1028T>C

Pathogenic

Met criteria codes 4

PP3 PP4_Strong PM3_Strong PM2_Supporting

Not Met criteria codes 1

BP2

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.1028T>C variant results in the missense change, Leu343Pro. The variant is absent from population databases, including gnomADv2.1.1 (PM2_supporting). It is predicted damaging by in-silico tools (REVEL score of 0.838l; PP3). It is reported in at least 4 probands (PMIDs: 36672149, 19691478, 34267460), two homozygous and two compound heterozygous individuals, one of whom the variant was seen in trans with the pathogenic variant, Leu973AlafsTer63 (PM3_strong). Patient 3 (PMID: 34267460) 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 reduced to <25%, as measured by flow cytometry(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, PP3, PM3_strong, PP4_strong (VCEP specifications version 2).

Met criteria codes

PP3	✔	REVEL score of 0.838, which is greater than or equal to 0.7; therefore, PP3 is met.
PP4_Strong	✔	At least one patient (Patient 3 in PMID: 34267460) 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 reduced to <25%, as measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. (PP4_strong)
PM3_Strong	✔	Patient GT18 from PMID: 19691478 is compound heterozygous for Leu343Pro and Leu973AlafsTer63 (classified "pathogenic" by ClinGen Platelet Disorders VCEP), confirmed in trans (1pt). Patients 2 and 3 from PMID: 34267460 are each homozygous (1pt) Total 2pt (PM3_strong).
PM2_Supporting	✔	Absent from gnomAD v2.1.1 (PM2_supporting).

Not Met criteria codes

BP2	✖	This variant (Leu343Pro) is in cis with the variant g.951G>A (PMID: 19691478); however, BP2 cannot be met because VUS g.951G>A is not known to be pathogenic.

Curation History

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