The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000419.5:c.2159T>C

Version: 2.0

CA399798955

996189 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7e3fd2f9-4fdf-4e5f-90ee-eb4dec2d2fef
Approved on: 2024/3/7
Published on: 2024/3/8

HGVS expressions

NM_000419.5:c.2159T>C
NC_000017.11:g.44377726A>G
CM000679.2:g.44377726A>G
NC_000017.10:g.42455094A>G
CM000679.1:g.42455094A>G
NC_000017.9:g.39810620A>G
NG_008331.1:g.16780T>C
ENST00000262407.6:c.2159T>C
ENST00000648408.1:c.1590T>C
ENST00000262407.5:c.2159T>C
ENST00000592462.5:n.954T>C
NM_000419.3:c.2159T>C
NM_000419.4:c.2159T>C

Uncertain Significance

Met criteria codes 2

PM2_Supporting PP4_Strong

Not Met criteria codes 3

BP4 PM3 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_000419.5(ITGA2B):c.2159T>C (p.Leu720Pro) missense variant has been reported in at least three compound heterozygous GT proband (PMID: 29675921, GT database 438, and doi.org/10.1182/blood.V110.11.3921.3921). GT5 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. This variant is absent from all population cohorts in gnomADv4.0 (PM2_supporting) In summary this variant meets criteria to be classified as uncertain significance for GT. GT-specific criteria applied: PM2_Supporting and PP4_strong.

Met criteria codes

PM2_Supporting	✔	This variant is absent from all population cohorts in gnomADv4.0.
PP4_Strong	✔	GT5 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.

Not Met criteria codes

BP4	✖	The computational predictor REVEL gives a score of 0.672, which is above the ClinGen PD VCEP threshold of <0.25.
PM3	✖	Three compound heterozygous probands have been reported, which do not meet criteria for PM3. One with Pro23His (VUS without confirmation of phase), one with Ala777Asp (VUS without confirmation of phase), and one with Arg584Ter (Pathogenic but not meeting PM2).
PP3	✖	The REVEL score of 0.672 is below the threshold of >0.7 and there is no predicted impact on splicing.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000419.5:c.2159T>C	Uncertain Significance	Glanzmann Thrombasthenia	2024-03-08	2.0	ClinGen Platelet Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2.1	ITGA2B
View	NM_000419.5:c.2159T>C	Uncertain Significance	Glanzmann's Thrombasthenia	2021-01-22	1.0	-	ITGA2B

Showing 1 to 2 of 2 rows

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