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.1259T>C

Version: 1.1

CA399803733

1691466 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 678f59c9-6171-481a-90c0-bd5d5a13b35e
Approved on: 2024/12/17
Published on: 2024/12/17

HGVS expressions

NM_000419.5:c.1259T>C
NC_000017.11:g.44381013A>G
CM000679.2:g.44381013A>G
NC_000017.10:g.42458381A>G
CM000679.1:g.42458381A>G
NC_000017.9:g.39813907A>G
NG_008331.1:g.13493T>C
ENST00000262407.6:c.1259T>C
ENST00000648408.1:c.690T>C
ENST00000262407.5:c.1259T>C
ENST00000592226.5:n.499T>C
ENST00000592462.5:n.54T>C
NM_000419.3:c.1259T>C
NM_000419.4:c.1259T>C

Likely Pathogenic

Met criteria codes 3

PP3 PP4_Strong PM2_Supporting

Not Met criteria codes 1

PM3

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.1259T>C (p.Val420Ala) missense variant has been reported in at least one patient (GT22 in PMID: 25728920) 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 <5%, as measured by flow cytometry (PP4_strong).

This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.898, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). In summary this variant meets 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, PM2_supporting, PP3. (VCEP specifications version 2.1)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.898, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PP4_Strong	✔	At least one patient (GT22 in PMID: 25728920) 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 <5%, as measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. (PP4_strong)
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

PM3	✖	GT22 (PMID: 25728920) is compound heterozygous for Val420Ala and c.408+11C>A. Confirmation of trans phase was not reported. Not considered here to avoid cirucularity.

Curation History

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