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Variant: NM_000419.5:c.416C>T

Version: 1.1

CA399806036

1210192 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2bebe3f2-ae3a-49e6-97f4-da340eeb4bea
Approved on: 2024/8/20
Published on: 2024/8/20

HGVS expressions

NM_000419.5:c.416C>T
NC_000017.11:g.44385709G>A
CM000679.2:g.44385709G>A
NC_000017.10:g.42463077G>A
CM000679.1:g.42463077G>A
NC_000017.9:g.39818603G>A
NG_008331.1:g.8797C>T
ENST00000262407.6:c.416C>T
ENST00000262407.5:c.416C>T
ENST00000592944.1:n.101C>T
NM_000419.3:c.416C>T
NM_000419.4:c.416C>T

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PP4_Strong 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 ITGA2B missense variant NM_000419.5:c.416C>T replaces the alanine residue with a valine residue (p.Ala139Val). This variant is absent from population databases including gnomADv4.1.0 (PM2_supporting), but has been observed in homozygosity in two individuals suspected to have Glanzmann's thrombasthenia (GT) (Patient PF in PMID: 12083483; GT22 in PMID: 16463284) (PM3). At least one of these individuals (Patient PF in PMID: 12083483) has a phenotype specific for GT (PP4_strong); bleeding phenotype strongly indicative of Glanzmann's thrombasthenia; impaired aggregation to at least two agonists, but normal or only mildly reduced agglutination with

ristocetin; <10% expression of GPIIb/IIIa; direct sequencing of all coding regions and intron/exon boundaries of ITGA2B and ITGB3. The variant is predicted by in silico tools to be damaging to protein function (REVEL score 0.794; PP3). In summary, this variant meets criteria to be classified as likely pathogenic for GT. GT-specific criteria applied: PM2_supporting, PM3, PP3, PP4_strong.

Met criteria codes

PP3	✔	The REVEL score for this variant is 0.794, exceeding the VCEP-established threshold of ≥0.7 to support a deleterious effect.
PM3	✔	This variant was reported in homozygosity in two individuals (Patient PF in PMID: 12083483; GT22 in PMID: 16463284), sufficient to apply PM3.
PP4_Strong	✔	This variant was reported in homozygosity in two individuals (Patient PF in PMID: 12083483; GT22 in PMID: 16463284). At least one of these individuals (Patient PF in PMID: 12083483) meets all requirements for PP4 at an upgraded strength of strong (PP4_strong): bleeding phenotype strongly indicative of Glanzmann's thrombasthenia; impaired aggregation to at least two agonists, but normal or only mildly reduced agglutination with ristocetin; <10% expression of GPIIb/IIIa; direct sequencing of all coding regions and intron/exon boundaries of ITGA2B and ITGB3.
PM2_Supporting	✔	This variant is absent from gnomAv4.1.0 (PM2_supporting)

Curation History

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