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Variant: NM_000419.5:c.571T>G

Version: 2.0

CA399805699

996171 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: afa93bc0-4563-4d08-aed9-4487bcf11f50
Approved on: 2023/11/2
Published on: 2023/11/3

HGVS expressions

NM_000419.5:c.571T>G
NC_000017.11:g.44385554A>C
CM000679.2:g.44385554A>C
NC_000017.10:g.42462922A>C
CM000679.1:g.42462922A>C
NC_000017.9:g.39818448A>C
NG_008331.1:g.8952T>G
ENST00000262407.6:c.571T>G
ENST00000262407.5:c.571T>G
ENST00000592944.1:n.256T>G
NM_000419.3:c.571T>G
NM_000419.4:c.571T>G

Likely Pathogenic

Met criteria codes 3

PP4_Strong | PM2_Supporting | PM4

Not Met criteria codes 2

BP4 | 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.571T>G (p.Phe191Val) variant has been reported in at least 1 compound heterozygous GT proband (PMID:25728920) with a phenotype highly specific to Glanzmann thrombasthenia with mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3 measured by flow cytometry (PP4_Strong). It is absent from population databases, including gnomADv2.1.1 (PM2_supporting). Splicing predictors, HSF and SpliceAI, agree that there is activation of a cryptic donor site with potential alteration of splicing. This was confirmed by minigene study in PMID: 20020534; sequencing revealed the

most common transcript contained a 4-bp deletion that introduced a frameshift and a premature stop codon in exon 7 of 30 (PM4). In summary, this variant meets criteria to be classified as likely pathogenic for GT. GT-specific criteria applied: PM2_Supporting, PM4, and PP4_Strong.

Met criteria codes

PP4_Strong	✔	GT57 of PMID:25728920 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.
PM2_Supporting	✔	This variant is absent from all population cohorts in gnomAD, ExAC, 1000 Genomes, and ESP.
PM4	✔	The c.571T>G variant causes activation of a cryptic donor site as confirmed by minigene study in PMID: 20020534. Sequencing revealed the most common transcript contained a 4-bp deletion that introduced a frameshift and a premature stop codon in exon 7 of 30.

Not Met criteria codes

BP4	✖	The variant has a low REVEL score of 0.165, however there is a predicted splice impact. HSF predicts activation of a cryptic donor site with potential alteration of splicing (55.04 > 82.18 => 49.31%) and SpliceAI agrees with a score of 0.91 for donor gain.
PM3	✖	GT57 of PMID: 25728920 is compound heterozygous for Phe191Val and Gly321Trp (classified likely pathogenic by the PD-EP). Confirmation of the trans relationship was not reported. Not considered here to avoid circularity.

Curation History

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