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.601G>A

Version: 2.0

CA399805612

996156 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7cc1a3c4-475e-4230-a075-72db8b006f19
Approved on: 2024/2/20
Published on: 2024/2/20

HGVS expressions

NM_000419.5:c.601G>A
NC_000017.11:g.44385309C>T
CM000679.2:g.44385309C>T
NC_000017.10:g.42462677C>T
CM000679.1:g.42462677C>T
NC_000017.9:g.39818203C>T
NG_008331.1:g.9197G>A
ENST00000262407.6:c.601G>A
ENST00000648408.1:c.32G>A
ENST00000262407.5:c.601G>A
ENST00000589645.5:n.55G>A
ENST00000592253.5:n.33G>A
ENST00000592944.1:n.286G>A
NM_000419.3:c.601G>A
NM_000419.4:c.601G>A

Likely Pathogenic

Met criteria codes 4

PM3 PP4_Strong PP3 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 c.601G>A (p.Gly201Ser) variant on the ITGA2B gene is a missense variant which is absent from large population cohorts, including gnomADv4.0 (PM2_supporting). This variant has been reported in at least 2 unrelated probands in the homozygous state (PM3), who meet

the diagnostic criteria for GT. Both probands meet criteria for PP4_Strong which includes a history of significant mucocutaneous bleeding, absent platelet aggregation with three physiological agonists (and normal with ristocetin). Flow cytometry demonstrated reduced (<5%) surface expression of αIIbβ3. In silico tools (REVEL score = 0.899) predict a deleterious effect on gene function (PP3). In summary, this variant meets criteria for PP4_strong, PM3, PM2_supporting and PP3; and is therefore classified as likely pathogenic for GT.

Met criteria codes

PM3	✔	The p.Gly201Ser variant has been reported in homozygous state in two unrelated individuals by PMID: 25728920 [0.5+0.5 = 1 point] ; PM3 applied.
PP4_Strong	✔	This variant has been reported in two unrelated individuals by PMID:25728920. Both probands meet criteria for PP4_Strong which includes a history of significant mucocutaneous bleeding, absent platelet aggregation with three physiological agonists (and normal with ristocetin). Flow cytometry demonstrated reduced (<5%) surface expression of αIIbβ3. Sanger sequencing of all exons and UTRs of ITGA2B and ITGB3 genes was performed.
PP3	✔	REVEL score = 0.899, which is above the threshold of >0.70; PP3 applied.
PM2_Supporting	✔	The p.Gly201Ser variant is absent from all large population databases, including gnomADv4.0 (PM2_supporting).

Curation History

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