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Variant: NM_000419.5:c.1201G>T

Version: 2.0

CA399804280

996180 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: ebdb57c0-062c-474c-9608-27e62452919c
Approved on: 2023/11/2
Published on: 2023/11/3

HGVS expressions

NM_000419.5:c.1201G>T
NC_000017.11:g.44383502C>A
CM000679.2:g.44383502C>A
NC_000017.10:g.42460870C>A
CM000679.1:g.42460870C>A
NC_000017.9:g.39816396C>A
NG_008331.1:g.11004G>T
ENST00000262407.6:c.1201G>T
ENST00000648408.1:c.632G>T
ENST00000262407.5:c.1201G>T
ENST00000592226.5:n.441G>T
NM_000419.3:c.1201G>T
NM_000419.4:c.1201G>T

Likely Pathogenic

Met criteria codes 3

PP4_Strong PM2_Supporting PP3

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 ITGA2B missense variant NM_000419.5:c.1201G>T replaces the glycine residue with a cysteine residue (p.Gly401Cys). This variant has been observed in a proband (PMID 25728920) with a phenotype specific for Glanzmann's thrombasthenia (PP4_strong) who also harbors a second ITGA2B variant (c.2800G>T, p.Val934Phe) previously classified by the VCEP as likely pathogenic, however the phase of these variants is unconfirmed. This variant has not been observed in population databases (absent from gnomAD v2.1.1 and v3; PM2_supporting)

and the in silico meta-predictor REVEL score for this variant is 0.746 (above the VCEP-established threshold of 0.7; PP3). In summary, this variant is classified as likely pathogenic for GT. GT-specific criteria applied: PM2_supporting, PP3, and PP4_strong.

Met criteria codes

PP4_Strong	✔	All requirements for PP4 at an upgraded strength of strong (PP4_Strong) are met by proband GT18 (PMID 25728920): ecchymosis; residual platelet aggregation in response to physiologic agonists except normal response to ristocetin; flow cytometry showed 10% expression of αIIbβ3; direct sequencing of all exons and splice sites of ITGA2B and ITGB3, as well as upstream regions.
PM2_Supporting	✔	This variant is not observed in gnomAD v2.1.1 or v3, meeting criteria for PM2_supporting.
PP3	✔	This variant has a REVEL score of 0.944, exceeding the VCEP-established threshold of ≥0.7 and meeting the criteria for PP3. Other in silico tools also predict that this variant is "damaging" (SIFT) and "probably damaging" (PolyPhen2).

Not Met criteria codes

PM3	✖	This variant has been observed in a proband harboring a second VCEP-classified likely pathogenic variant (c.2800G>T, p.Val934Phe; PMID 25728920). However, because the phase of the variants was unconfirmed and the second variant is currently classified as likely pathogenic, this evidence scores 0.25 points and is not sufficient to apply PM3 at any strength of evidence.

Curation History

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