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Variant: NM_000419.5:c.2800G>T

Version: 2.0

CA290946484

996165 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0ee33e3f-bcc1-498a-87da-e7f0c797c10b
Approved on: 2024/6/6
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HGVS expressions

NM_000419.5:c.2800G>T
NC_000017.11:g.44375039C>A
CM000679.2:g.44375039C>A
NC_000017.10:g.42452407C>A
CM000679.1:g.42452407C>A
NC_000017.9:g.39807933C>A
NG_008331.1:g.19467G>T
ENST00000262407.6:c.2800G>T
ENST00000648408.1:c.2231G>T
ENST00000262407.5:c.2800G>T
ENST00000587295.5:c.253+794G>T
ENST00000592462.5:n.2074G>T
NM_000419.3:c.2800G>T
NM_000419.4:c.2800G>T

Likely Pathogenic

Met criteria codes 4

PM3 PP4_Strong PM2_Supporting PS3_Supporting

Not Met criteria codes 1

PP3

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.2800G>T replaces the valine residue with a phenylalanine residue (p.Val934Phe). All requirements for PP4 at an upgraded strength of strong (PP4_Strong) are met by proband GT20 (PMID 25728920): epistaxis; absent platelet aggregation in response to physiologic agonists except normal response to ristocetin; flow cytometry showed 10-20% expression

of αIIbβ3; direct sequencing of all exons and splice sites of ITGA2B and ITGB3, as well as upstream regions. This variant has also been observed in a homozygous proband (PMID: 34347927) and a proband (PMID: 25728920) who also harbors a second ITGA2B variant (c.1413C>G, p.Tyr471Ter) previously classified by the VCEP as pathogenic (phase unconfirmed) (PM3). Furthermore, this variant has not been observed in population databases (absent from gnomAD v4.1.0; PM2_supporting). Finally, a functional study of this variant has been reported (PMID: 20020534; flow cytometric detection of αIIb, β3, and αIIbβ3 positive cells following transient transfection of ITGA2B cDNA carrying this variant), finding approximately 20% positive cells for the β3 subunit compared to WT (PS3_supporting). In summary, this variant meets criteria to be classified as likely pathogenic for GT. GT-specific criteria applied: PS3_supporting, PM2_supporting, PM3, and PP4_strong.

Met criteria codes

PM3	✔	One homozygous patient has been reported (PMID: 34347927) 0.5pt. This variant also has been observed in a proband harboring a second VCEP-classified pathogenic variant (c.1413C>G, p.Tyr471Ter), however the phase of the variants was unconfirmed (PMID 20020534) 0.5 points. This variant has also been observed in a proband with a second variant, p.Gly401Cys (proband GT18, PMID 25728920). However, this evidence contributed to PM3 for p.Gly401Cys and was not counted for p.Val934Phe to avoid circularity. Total 1pt (PM3)
PP4_Strong	✔	All requirements for PP4 at an upgraded strength of strong (PP4_Strong) are met by proband GT20 (PMID 25728920): epistaxis; absent platelet aggregation in response to physiologic agonists except normal response to ristocetin; flow cytometry showed 10-20% 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 v4.1.0 (PM2_supporting).
PS3_Supporting	✔	PMID: 20020534: ITGB3 cDNA carrying the c.2800G>T variant was transiently transfected into COS-7 cells. αIIb, β3, and αIIbβ3 receptor expression on the cell surface was measured by flow cytometry. The number of cells positive for αIIb, β3, and αIIbβ3 was found to be reduced. In three replicates, expression of the complex (% positive cells) was assessed by flow cytometry, using antibodies to alpha-IIb, beta-3 or the complex, finding approximately 20% positive cells for the β3 subunit compared to WT. This evidence was downgraded to PS3_Supporting because the level of αIIb, β3, and αIIbβ3 cell surface expression was not reported, only whether cells were positive or negative for surface αIIb, β3, and αIIbβ3.

Not Met criteria codes

PP3	✖	The REVEL score for this variant (0.46) does not meet the VCEP-established threshold of ≥0.7 for PP3 and the variant is not predicted to impact splicing (SpliceAI delta scores 0.00-0.01).

Curation History

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