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Variant: NM_000419.5:c.555T>G

Version: 2.0

CA399805736

952995 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: a378c029-ae10-4b9e-9aad-49a358635fe2
Approved on: 2023/10/17
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HGVS expressions

NM_000419.5:c.555T>G
NC_000017.11:g.44385570A>C
CM000679.2:g.44385570A>C
NC_000017.10:g.42462938A>C
CM000679.1:g.42462938A>C
NC_000017.9:g.39818464A>C
NG_008331.1:g.8936T>G
ENST00000262407.6:c.555T>G
ENST00000262407.5:c.555T>G
ENST00000592944.1:n.240T>G
NM_000419.3:c.555T>G
NM_000419.4:c.555T>G

Likely Pathogenic

Met criteria codes 3

PP4_Strong PM3_Supporting PM2_Supporting

Not Met criteria codes 2

BP4 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_000419.4:c.555T>G replaces the isoleucine residue with a methionine residue (p.Ile185Met). This variant has been observed in a proband with a phenotype specific for Glanzmann's thrombasthenia (GT; PP4_Strong) who also harbors a second ITGA2B variant (c.1882C>T, p.Arg628Ter) previously classified by the VCEP as pathogenic (phase unconfirmed; PM3_supporting). Furthermore, this variant has not been observed in population databases (absent from gnomAD v2.1.1 and v3; PM2_supporting). Although the in silico meta-predictor REVEL score for this variant is 0.134 (below the VCEP-established threshold of 0.25) and multiple other in silico

tools also predict no impact on the gene product, splicing tools predict this variant creates an exonic cryptic donor site (SpliceAI delta score 0.89), potentially altering splicing. Given the conflicting in silico predictions for this variant, neither BP4 nor PP3 was applied. Experimental evidence is needed to clarify the effect of the variant on the gene product. In summary, this variant is classified as likely pathogenic for GT. GT-specific criteria applied: PM2_supporting, PP4_strong, PM3_supporting.

Met criteria codes

PP4_Strong	✔	All requirements for PP4 at an upgraded strength of moderate (PP4_Strong) are met by proband GT13 in PMID 25373348: bleeding symptoms; lack of platelet aggregation in response to various agonists except normal response to ristocetin; flow cytometry showing 5-20% expression of αIIbβ3; direct sequencing of all exons and surrounding intronic regions of ITGA2B and ITGB3.
PM3_Supporting	✔	This variant has been observed in combination with the VCEP-curated pathogenic ITGA2B variant c.1882C>T (p.Arg628Ter) in 1 proband (GT13, PMID: 25373348). However, the phase of these two variants was not confirmed. This occurrence with phase unknown scores 0.5 points, meeting PM3 at the downgraded strength level of supporting (PM3_supporting).
PM2_Supporting	✔	This variant is not observed in gnomAD v2.1.1 or v3, meeting criteria for PM2.

Not Met criteria codes

BP4	✖	This variant has a REVEL score of 0.134, meeting the criteria for BP4. Other in silico tools also predict that this variant is "tolerated" (SIFT) and "benign" (PolyPhen2). However, three splicing tools (Human Splicing Finder, MaxEntScan, and NNSPLICE) predict this variant results in the activation of an exonic cryptic donor site, potentially altering splicing.
PP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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