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Variant: NM_000419.5:c.620C>T

Version: 1.0

CA399805570

1330317 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: ba684d4a-1d07-4cd5-8cc1-3bf4a36d6616
Approved on: 2021/11/4
Published on: 2021/12/23

HGVS expressions

NM_000419.5:c.620C>T
NC_000017.11:g.44385290G>A
CM000679.2:g.44385290G>A
NC_000017.10:g.42462658G>A
CM000679.1:g.42462658G>A
NC_000017.9:g.39818184G>A
NG_008331.1:g.9216C>T
ENST00000262407.6:c.620C>T
ENST00000648408.1:c.51C>T
ENST00000262407.5:c.620C>T
ENST00000589645.5:n.74C>T
ENST00000592253.5:n.52C>T
ENST00000592944.1:n.305C>T
NM_000419.3:c.620C>T
NM_000419.4:c.620C>T

Likely Pathogenic

Met criteria codes 4

PM3_Supporting PP3 PP4_Strong PM2_Supporting

Not Met criteria codes 1

PS3

Evidence Links 1

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000419.5(ITGA2B):c.620C>T (p.Thr207Ile) missense variant has been reported in at least one Glanzmann thrombasthenia patient (PMIDs: 21113249, 15543332). Patient OK displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia . Additionally, αIIbβ3 surface expression was reduced to 4%, as measured by flow cytometry, and there was<1% binding to PAC-1. (PP4_strong). Patient OK is homozygous for this variant (PM3_Supporting). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.729 (PP3). In summary, this variant

meets the criteria to be classified as Likely Pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PP4_strong, PM3_supporting, PM2_supporitng, PP3. (VCEP specifications version 2; date of approval 11/04/2021)

Met criteria codes

PM3_Supporting	✔	One homozygous patient (OK) has been reported in PMID: 21113249. 0.5pt (PM3_supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.729, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on ITGA2B function (PP3).
PP4_Strong	✔	Patient OK displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was reduced to 4%, as measured by flow cytometry, and there was <1% binding to PAC-1. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries (PP4_strong;PMID: 21113249) .
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PS3	✖	COS-7 cells were transiently transfected with Thr207Ile αIIb and wildtype β3 and showed marked reduction in surface expression measured by immunoprecipitation. CHO cells were stably transfected with Thr207Ile αIIb and wildtype β3 and flow cytometry analysis showed a decreased surface expression (~30%, which is above the <25% required to meet PS3) and functional analysis showed αIIbβ3 receptor expression on the platelet surface is able to bind to immobilized fibrinogen and siliconized glass (PS3 not met; PMID: 15543332).

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Curation History

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