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Variant: NM_000419.5:c.470C>A

Version: 1.2

CA399805912

2498354 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: de63d0f9-0c54-4db7-bb9c-646cd7f71b5e
Approved on: 2023/2/2
Published on: 2023/2/23

HGVS expressions

NM_000419.5:c.470C>A
NC_000017.11:g.44385655G>T
CM000679.2:g.44385655G>T
NC_000017.10:g.42463023G>T
CM000679.1:g.42463023G>T
NC_000017.9:g.39818549G>T
NG_008331.1:g.8851C>A
ENST00000262407.6:c.470C>A
ENST00000262407.5:c.470C>A
ENST00000592944.1:n.155C>A
NM_000419.3:c.470C>A
NM_000419.4:c.470C>A

Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PP4_Strong PS3 PM3_Supporting

Not Met criteria codes 1

PP1

Evidence Links 1

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 NM_000419.5:c.470C>A variant in ITGA2B is a missense variant predicted to cause substitution of Proline by Histidine at amino acid 157 (p.Pro157His). At least one patient (Patient 1 in PMID: 18976939) with this variant 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 0%, as measured by flow cytometry and Western blot. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries (PP4_Strong). Surface expression of αIIbβ3 measured by flow cytometry in CHO cells transiently co-transfected

with the NM_000419.5:c.470C>A (p.Pro157His) variant αIIb and wild type αIIb showed decreased expression at 0% of WT levels, indicating that this variant impacts protein function (PMID: 18976939)(PS3). The computational predictor REVEL gives a score of 0.782, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). This variant has been detected in at least 1 probands with Glanzmann thrombasthenia. This individual was homozygous for the variant (PMID: 18976939, 0.5 PM3 points) Total points: 0.5 (PM3_Supporting). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PP4_Strong, PS3, PP3, PM2_Supporting and PM3_Supporting (VCEP specifications version 2).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.782, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PP4_Strong	✔	At least one patient (Patient 1 in PMID: 18976939) with this variant 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 0%, as measured by flow cytometry and Western blot. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries (PP4_Strong).
PS3	✔	Surface expression of αIIbβ3 measured by flow cytometry in CHO cells transiently co-transfected with the NM_000419.5:c.470C>A (p.Pro157His) variant αIIb and wild type αIIb showed decreased expression at 0% of WT levels, indicating that this variant impacts protein function (PMID: 18976939)(PS3). Variant is reported as c.470 C>A (p.Pro126His) PubMed:18976939
PM3_Supporting	✔	This variant has been detected in at least 1 probands with Glanzmann thrombasthenia. This individuals was homozygous for the variant (PMID: 18976939, 0.5 PM3 points) Total points: 0.5 (PM3_Supporting).

Not Met criteria codes

PP1	✖	Unaffected parents were both heterozygous for the variant.

Curation History

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