Variant: NM_000419.5:c.666C>A

Version: 1.1

CA399805465

1879011 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0d520bf1-d751-4e87-8a8c-67f33a9f90b3
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HGVS expressions

NM_000419.5:c.666C>A
NC_000017.11:g.44385168G>T
CM000679.2:g.44385168G>T
NC_000017.10:g.42462536G>T
CM000679.1:g.42462536G>T
NC_000017.9:g.39818062G>T
NG_008331.1:g.9338C>A
ENST00000262407.6:c.666C>A
ENST00000648408.1:c.97C>A
ENST00000262407.5:c.666C>A
ENST00000589645.5:n.117C>A
ENST00000591990.5:n.28C>A
ENST00000592075.5:n.35C>A
ENST00000592226.5:n.35C>A
ENST00000592253.5:n.174C>A
ENST00000592944.1:n.348C>A
NM_000419.3:c.666C>A
NM_000419.4:c.666C>A

Uncertain Significance

Met criteria codes 3

PP4_Moderate PM2_Supporting PM3_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 NM_000419.5(ITGA2B):c.666C>A (p.Phe222Leu) missense variant has been reported in at least one homozygous patient (CC in PMID: 11798398) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate; PM3_supporting). The highest population minor allele frequency in gnomAD v4.1 is 8.474e-7 (1/1180026 alleles) in the European (non-Finnish) genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). In summary, this variant meets the criteria to be classified as uncertain significance for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PM2_supporting, PM3_supporting, PP4_moderate.

Met criteria codes

PP4_Moderate	✔	At least one patient (CC in PMID: 11798398) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, αIIbβ3 surface expression was absent, as measured by flow cytometry. However, ITGA2B and ITGB3 were not sequenced across all exons and intron/exon boundaries.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 8.474e-7 (1/1180026 alleles) in the European (non-Finnish) genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).
PM3_Supporting	✔	Patient CC (PMID: 11798398) was homozygous for this variant (PM3_supporting)

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.649, which is below the ClinGen PD VCEP PP3 threshold of >0.7 and does not predict a damaging effect on ITGA2B function. And the computational splicing predictor SpliceAI indicated that the variant is not likely to have an impact on splicing.

Curation History

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