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Variant: NM_000419.5:c.659A>G

Version: 1.1

CA399805484

1330345 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 09887c99-a683-446b-98d1-3e37a053aab5
Approved on: 2024/10/15
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HGVS expressions

NM_000419.5:c.659A>G
NC_000017.11:g.44385175T>C
CM000679.2:g.44385175T>C
NC_000017.10:g.42462543T>C
CM000679.1:g.42462543T>C
NC_000017.9:g.39818069T>C
NG_008331.1:g.9331A>G
ENST00000262407.6:c.659A>G
ENST00000648408.1:c.90A>G
ENST00000262407.5:c.659A>G
ENST00000589645.5:n.110A>G
ENST00000591990.5:n.21A>G
ENST00000592075.5:n.28A>G
ENST00000592226.5:n.28A>G
ENST00000592253.5:n.167A>G
ENST00000592944.1:n.341A>G
NM_000419.3:c.659A>G
NM_000419.4:c.659A>G

Likely Pathogenic

Met criteria codes 3

PM3 PP4_Strong PM2_Supporting

Not Met criteria codes 2

PP3 BP4

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.659A>G (p.Tyr220Cys) has been identified in at least 2 probands, including GT35 of PMID: 29675921 meeting the criteria for PP4_strong criteria. Patient GT35 of PMID: 29675921 is compound heterozygous for Tyr220Cys and c.625-1G>A (classified Pathogenic by the PD-EP) and Patient 436 of the GT database is compound heterozygous for Tyr220Cys and Ala271Gly (classified VUS by the PD-EP), Pt 3 of PMID: 36672149 is homozygous (PM3). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003266 (1/30614alleles) in the South Asian population, which is lower than the ClinGen PD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). 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: PM2_supporting, PM3, PP4_strong. (VCEP specifications version 2)

Met criteria codes

PM3	✔	This variant has been detected in at least 3 individuals with Glanzmann thrombasthenia. Patient GT35 of PMID: 29675921 is compound heterozygous for Tyr220Cys and c.625-1G>A (classified Pathogenic by the PD-EP). Confirmation of trans phase was not reported 0.5pt Patient 436 is compound heterozygous for Tyr220Cys and Ala271Gly (classified VUS by the PD-EP). Confirmation of trans phase was not reported, not considered here to avoid circularity 0pt. Pt 3 of PMID: 36672149 is homozygous 0.5pt. Total: 1pt (PM3)
PP4_Strong	✔	GT35 of PMID: 29675921 meets the criteria for PP4_strong; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3 measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.00001098 (1/91070 alleles) in the South Asian population, which is lower than the ClinGen PD VCEP threshold (<0.0001) for PM2_Supporting.

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.604, which is below the ClinGen PD VCEP PP3 threshold of >0.7 and does not predict a damaging effect on ITGA2B/ITGB3 function. And the computational splicing predictor SpliceAI indicated that the variant has no impact on splicing.
BP4	✖	The computational predictor REVEL gives a score of 0.604, which is above the ClinGen PD VCEP BP4 threshold of <0.25.

Curation History

Showing 1 to 2 of 2 rows

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