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Variant: NM_000419.5:c.812C>G

Version: 1.1

CA399805123

1330344 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3af1a58d-a1fd-4e71-b04f-5632eb56efb0
Approved on: 2024/10/15
Published on: 2024/10/16

HGVS expressions

NM_000419.5:c.812C>G
NC_000017.11:g.44384573G>C
CM000679.2:g.44384573G>C
NC_000017.10:g.42461941G>C
CM000679.1:g.42461941G>C
NC_000017.9:g.39817467G>C
NG_008331.1:g.9933C>G
ENST00000262407.6:c.812C>G
ENST00000648408.1:c.243C>G
ENST00000262407.5:c.812C>G
ENST00000589645.5:n.263C>G
ENST00000591990.5:n.174C>G
ENST00000592075.5:n.181C>G
ENST00000592226.5:n.52C>G
ENST00000592253.5:n.320C>G
ENST00000592944.1:n.494C>G
NM_000419.3:c.812C>G
NM_000419.4:c.812C>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

Missense variant NM_000419.5(ITGA2B):c.812C>G (p.Ala271Gly) has been identified in at least 2 probands, including GT6 of PMID: 29675921 meeting the criteria for PP4_strong criteria. Patient GT6 of PMID: 29675921 is compound heterozygous for Ala271Gly and Met724Ile (classified Likely Pathogenic) by the PD VCEP) and Patient 436 of the GT database is compound heterozygous for Ala271Gly and Tyr220Cys (classified Likely Pathogenic by the PD VCEP) (PM3_supporting). This variant is absent from gnomAD v4.1 (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: PM3_supporting, PM2_supporting, PP4_strong. (VCEP specifications version 2)

Met criteria codes

PP4_Strong	✔	GT6 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.
PM3_Supporting	✔	This variant has been detected in at least 2 individuals with Glanzmann thrombasthenia. Patient GT6 of PMID: 29675921 is compound heterozygous for Ala271Gly and Met724Ile (classified Likely Pathogenic) by the PD VCEP). Confirmation of trans phase was not reported 0.25pt Patient 436 of the GT database is compound heterozygous for Ala271Gly and Tyr220Cys (classified Likely Pathogenic by the PD VCEP). Confirmation of trans phase was not reported 0.25pt Total: 0.5pt (PM3_supporting)
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

BP4	✖	The computational predictor REVEL gives a score of 0.579, which is above the ClinGen PD VCEP BP4 threshold of <0.25.
PP3	✖	The computational predictor REVEL gives a score of 0.579, 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 suggests a possible splice acceptor site loss 12bp downstream, however the score of 0.3 is below the recommended threshold of >0.5.

Curation History

Showing 1 to 2 of 2 rows

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