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Variant: NM_000419.5:c.475G>A

Version: 1.1

CA8603454

1879033 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: daebdb43-1899-46c5-a4ad-83767a0c3af3
Approved on: 2025/5/1
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HGVS expressions

NM_000419.5:c.475G>A
NC_000017.11:g.44385650C>T
CM000679.2:g.44385650C>T
NC_000017.10:g.42463018C>T
CM000679.1:g.42463018C>T
NC_000017.9:g.39818544C>T
NG_008331.1:g.8856G>A
ENST00000262407.6:c.475G>A
ENST00000262407.5:c.475G>A
ENST00000592944.1:n.160G>A
NM_000419.3:c.475G>A
NM_000419.4:c.475G>A

Likely Pathogenic

Met criteria codes 4

PM3_Supporting PS3 PP3 PM2_Supporting

Not Met criteria codes 1

PP4

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 missense variant NM_000419.5(ITGA2B):c.475G>A (p.Gly159Ser has been identified in at least one patient UPN 2 (PMID: 16359515; PMID: 16359515) reported to have GT. The patient is homozygous for Gly159Ser (PM3_supporting). The highest population minor allele frequency in gnomAD v4.1 is 0.00001098 (1/91082 alleles) in the South Asian population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). The computational predictor REVEL gives a score of 0.735, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).The highest population minor allele frequency in gnomAD v2.1.1 is

0.00003267 (1/30606 alleles) in the South Asian population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). In HEK 293 cells there was expression on 52% of cells transfected with normal αIIb and β3 and 0% of cells with Gly159Ser were positive. Furthermore, immunoblotting from cell lysates found mature αIIb was seen in the normal αIIbβ3 cells, but there was no detectable mature αIIb in the G159S mutant (PMID: 16359515; PS3). In summary this variant meets 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: PP3, PM2_supporting, PM3_supporting, PS3 (VCEP specifications version 2.1).

Met criteria codes

PM3_Supporting	✔	UPN 2 (PMID: 16879215) is homozygous for this variant (PM3_supporting).
PS3	✔	in PMID: 16359515, HEK 293 cells were transfected with Gly159Ser αIIb and wildtype β3. Compared to expression on 52% of cells transfected with normal αIIb and β3, 0% of cells with Gly159Ser were positive. Furthermore, immunoblotting from cell lysates found mature αIIb was seen in the normal αIIbβ3 cells, but there was no detectable mature αIIb in the G159S mutant. Pulse-chase analysis further found that pro-αIIb molecules were also synthesized at the normal rate but there was no progression to mature αIIb in the G159S mutant. The G159S mutation completely prevents the transport of the pro-αIIbβ3 complex from the ER to the Golgi.
PP3	✔	The computational predictor REVEL gives a score of 0.735, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.00001098 (1/91082 alleles) in the South Asian population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).

Not Met criteria codes

PP4	✖	UPN 2 (PMID: 16359515; PMID: 16359515) has a history of mucocutaneous bleeding, including epistaxis, ecchymosis, GI bleeding, and gingival bleeding. There was absent in vitro platelet aggregation in response to ADP, epinephrine, and collagen. Platelet surface expression of αIIbβ3 was measured at 16.4% of wildtype levels by flow cytometry and absent by Western blot. PP4 not met because ristocetin induced agglutination was not done. DNA sequencing was performed on amplicons that showed mobility shifts by SSCP analysis.

Curation History

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