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Variant: NM_000419.5(ITGA2B):c.1361G>A (p.Gly454Asp)

Version: 2.3

CA399803524

977127 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7874e234-df85-40e5-a3db-fa1c8adbf22a
Approved on: 2025/4/15
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HGVS expressions

NM_000419.5:c.1361G>A
NM_000419.5(ITGA2B):c.1361G>A (p.Gly454Asp)
NC_000017.11:g.44380911C>T
CM000679.2:g.44380911C>T
NC_000017.10:g.42458279C>T
CM000679.1:g.42458279C>T
NC_000017.9:g.39813805C>T
NG_008331.1:g.13595G>A
ENST00000262407.6:c.1361G>A
ENST00000648408.1:c.792G>A
ENST00000262407.5:c.1361G>A
ENST00000592226.5:n.601G>A
ENST00000592462.5:n.156G>A
NM_000419.3:c.1361G>A
NM_000419.4:c.1361G>A

Likely Pathogenic

Met criteria codes 5

PP4_Strong | PM3_Supporting | PP3 | PM2_Supporting | PS3_Supporting

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(ITGA2B):c.1361G>A (p.Gly454Asp) variant has been reported, in the homozygous state, in at least one GT proband (P3 in PMID: 34275420) who 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 <5%, as measured by flow cytometry (PP4_strong). Surface expression of αIIbβ3 measured by flow cytometry in COS-7 cells transiently co-transfected with Gly454Asp variant αIIb and wild type β3 showed impaired expression levels. There is a clear decrease in percent positive cells with near absence interpreted as <25% (PMID: 34275420; PS3_supporting). The variant is predicted deleterious (REVEL score 0.812). This variant is absent from gnomAD v2.1.1 and present in gnomADv4.1 on 1 allele in the "Remaining" genetic ancestry group (PM2_supporting). In summary, this variant meets criteria to be classified as Likely Pathogenic for GT. GT-specific criteria applied: PM2_supporting, PM3_supporting, PP4_strong, PS3_supporting, and PP3.

Met criteria codes

PP4_Strong	✔	At least one patient (P3 in PMID: 34275420) 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 <5%, as measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. (PP4_strong)
PM3_Supporting	✔	P3 (PMID: 34275420) is homozygous for this variant. 0.5pt (PM3_supporting)
PP3	✔	The REVEL score for this variant is 0.812, exceeding the VCEP-established threshold of >0.7 to support a deleterious effect.
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and present in gnomADv4.1 on 1 allele in the "Remaining" genetic ancestry group.
PS3_Supporting	✔	Surface expression of αIIbβ3 measured by flow cytometry in COS-7 cells transiently co-transfected with Gly454Asp variant αIIb and wild type β3 showed impaired expression levels. There is a clear decrease in percent positive cells shown in Figure 1, with near absence interpreted as <25% (PMID: 34275420; PS3_supporting). This evidence was downgraded to PS3_Supporting because the level of αIIb, β3, and αIIbβ3 cell surface expression was not reported, only whether cells were positive or negative for surface αIIb, β3, and αIIbβ3. Surface expression of αIIbβ3 measured by flow cytometry in COS-7 cells transiently co-transfected with Gly454Asp variant αIIb and wild type β3 showed impaired expression levels. There is a clear decrease in percent positive cells shown in Figure 1, however this is not quantified (PS3_NotMet). PubMed:34275420

Curation History

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