

Variant: NM_000419.5(ITGA2B):c.1772A>C (p.Asp591Ala)

Version: 1.0

CA8602942 [↗](#)

627020 (ClinVar) [↗](#)

Gene: ITGA2B ([HGNC:3674](#))

Condition: Glanzmann thrombasthenia ([MONDO:0100326](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 0573a051-dc7f-431c-a4f5-8d38b0d16bb5

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HGVS expressions

NM_000419.5(ITGA2B):c.1772A>C (p.Asp591Ala)

NM_000419.5:c.1772A>C

NC_000017.11:g.44379795T>G

CM000679.2:g.44379795T>G

NC_000017.10:g.42457163T>G

CM000679.1:g.42457163T>G

NC_000017.9:g.39812689T>G

NG_008331.1:g.14711A>C

ENST00000262407.6:c.1772A>C

ENST00000648408.1:c.1203A>C

ENST00000262407.5:c.1772A>C

ENST00000592462.5:n.567A>C

NM_000419.3:c.1772A>C

NM_000419.4:c.1772A>C

Pathogenic

Met criteria codes 4

PP4_Strong

PM3_Strong

PP3

PM2_Supporting

Not Met criteria codes 1

PS3

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.1772A>C (p.Asp591Ala) missense variant has been reported in at least six patients, including at least one patient (P13 in PMID: 34275420) who displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, α IIb β 3 surface expression was reduced to <5%, as measured by flow

cytometry (PP4_strong). At least four patients have been reported homozygous for this variant (PMIDs: 34275420, 29385657, ClinVar SCV004013075.1). Two additional compound heterozygous patients have been reported (PMID: 34355501), the first patient had Pro176Ala confirmed in trans (classified Pathogenic by the PD-EP, score 1pt) and the second patient had c.1440-13_1440-1del assumed in trans (PM3_strong).The highest population minor allele frequency in gnomAD v4.0.0 is 0.000005932 (7/1180006 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). The computational predictor REVEL gives a score of 0.755, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). In summary, this variant meets criteria to be classified as Pathogenic for autosomal recessive Glanzmann thrombasthenia. GT-specific criteria applied: PM2_supporting, PM3_strong, PP4_strong and PP3.

Met criteria codes

PP4_Strong			At least one patient (P13 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_Strong			At least four patients have been reported homozygous for this variant (PMIDs: 34275420, 29385657, ClinVar SCV004013075.1). Two additional compound heterozygous patients have been reported (PMID: 34355501), the first patient had Pro176Ala confirmed in trans (classified Pathogenic by the PD-EP, score 1pt) and the second patient had c.1440-13_1440-1del assumed in trans Total 2.5pt (PM3_Strong)
PP3			The computational predictor REVEL gives a score of 0.755, 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 v4.0.0 is 0.000005932 (7/1180006 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).

Not Met criteria codes

PS3			Surface expression of αIIbβ3 measured by flow cytometry in HEK-293 cells transiently co-transfected with Asp591Ala variant αIIb and wild type β3 showed strongly reduced expression levels. There is a clear decrease in percent positive cells shown in Figure 1, however this is not quantified. As the αIIb:p.Ala591 αIIbβ3 expression was faint but significant, its functions was studied in transiently transfected HEK-293 cells expressing either the WT or the variant form of αIIbβ3 were incubated with fibrinogen conjugated to FITC and analyzed by flow cytometry. The αIIb:p. Ala560 αIIbβ3 behaved similarly to WT with activation occurring with 1 mM DTT and 2 mM calcium to bind fibrinogen (PMID: 34275420; PS3_NotMet).
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Curation History 

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