The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000212.3:c.1813G>A

Version: 1.1

CA291227621

1879042 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: a73bf948-5b12-4ce5-a3d0-cd83f2d51501
Approved on: 2025/3/6
Published on: 2025/3/6

HGVS expressions

NM_000212.3:c.1813G>A
NC_000017.11:g.47299430G>A
CM000679.2:g.47299430G>A
NC_000017.10:g.45376796G>A
CM000679.1:g.45376796G>A
NC_000017.9:g.42731795G>A
NG_008332.2:g.50589G>A
ENST00000696963.1:c.1813G>A
ENST00000559488.7:c.1813G>A
ENST00000559488.5:c.1813G>A
ENST00000560629.1:c.1778G>A
NM_000212.2:c.1813G>A

Likely Pathogenic

Met criteria codes 4

PM3_Supporting PP3 PP4_Strong PM2_Supporting

Not Met criteria codes 2

PM5 PS3

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_000212.3(ITGB3):c.1813G>A (p.Gly605Ser) missense variant has been reported in at least one patient (Patient GT4 in PMID:25373348) who displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was severely reduced, as measured by flow cytometry and function was pathological. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries (PP4_strong). GT4 of PMID: 25373348 is compound heterozygous for Arg242Gln (classified Pathogenic by the PD-EP) and Gly605Ser. Confirmation of trans phase was

not reported (PM3_supporting). The highest population minor allele frequency in gnomAD v4.1 is 0.00002668 (2/74954 alleles) in the African/African American genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). The computational predictor REVEL gives a score of 0.959, 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 Likely Pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PM2_supporting, PM3_supporting, PP3, PP4_strong. (VCEP specifications version 2)

Met criteria codes

PM3_Supporting	✔	GT4 of PMID: 25373348 is compound heterozygous for Arg242Gln (classified Pathogenic by the PD-EP) and Gly605Ser. Confirmation of trans phase was not reported (PM3_supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.959, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PP4_Strong	✔	At least one patient (Patient GT4 in PMID:25373348) 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 severely reduced, as measured by flow cytometry and function was pathological. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries (PP4_strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.00002668 (2/74954 alleles) in the African/African American genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).

Not Met criteria codes

PM5	✖	The additional variant Gly605Asp has also been reported but is not considered here to avoid circularity.
PS3	✖	Surface expression of αIIbβ3 measured by flow cytometry in CHO cells transiently co-transfected with Gly605Ser (here referred to as G579S) variant β3 and wild type αIIb showed decreased expression at approximately 52% of WT levels (22.2% of cells positive for the variant complex versus 42.6% of WT transfected cells) indicating that this variant may impact protein function, however it is above the <25% cutoff established by the PD-EP.
		Surface expression of αIIbβ3 measured by flow cytometry in CHO cells transiently co-transfected with Gly605Ser (here referred to as G579S) variant β3 and wild type αIIb showed decreased expression at approximately 52% of WT levels (22.2% of cells positive for the variant complex versus 42.6% of WT transfected cells) indicating that this variant may impact protein function, however it is above the <25% cutoff established by the PD-EP. PubMed:9790984

Curation History

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