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.655G>A

Version: 1.1

CA8623016

2498348 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: b2194a84-f0e0-4aba-a7ea-46f0f3c3f5dd
Approved on: 2024/9/5
Published on: 2024/9/30

HGVS expressions

NM_000212.3:c.655G>A
NC_000017.11:g.47286300G>A
CM000679.2:g.47286300G>A
NC_000017.10:g.45363666G>A
CM000679.1:g.45363666G>A
NC_000017.9:g.42718665G>A
NG_008332.2:g.37459G>A
ENST00000696963.1:c.655G>A
ENST00000559488.7:c.655G>A
ENST00000559488.5:c.655G>A
ENST00000560629.1:c.620G>A
ENST00000571680.1:c.655G>A
NM_000212.2:c.655G>A

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PM2_Supporting PM3 PP3

Not Met criteria codes 2

BS3 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.655G>A (p.Val219Met) missense variant has been reported in at least one patient (Patient GTa, PMID:11722423) who displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). GTa is compound heterozygous for this variant and pathogenic variant c.602del (PM3). The highest population minor allele frequency in gnomAD v4.1 is 0.00001098 (1/91078 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 0.874, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). 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: PM2_supporting, PM3, PP4_moderate, and PP3.

Met criteria codes

PP4_Moderate ✔	At least one patient (Patient GTa in PMID:11722423) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). However, ITGA2B and ITGB3 were not reported to be sequenced across all exons and intron/exon boundaries.
PM2_Supporting ✔	The highest population minor allele frequency in gnomAD v4.1 is 0.00001098 (1/91078 alleles) in the South Asian population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).
PM3 ✔	This variant has been detected in at least 1 proband with Glanzmann thrombasthenia. For one of those individuals, one was compound heterozygous for this variant and a pathogenic variant c.602delA, confirmed in trans by cloning and sequencing of PCR amplified cDNA (PMID:11722423). Total points: 1 (PM3).
PP3 ✔	The computational predictor REVEL gives a score of 0.874, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).

Not Met criteria codes

BS3 ✖	Surface expression of αIIbβ3 measured by flow cytometry in HEK293T cells transiently co-transfected with Val193Met variant β3 and wild type β3 showed equal expression at 100% (>75%). Additionally, the receptor function of αIIbβ3, measured by functional flow cytometry, showed enhanced binding to 3H-SC52012 (a GPIIb/IIIa antagonist), however this assay does not meet the requirements for use by the ClinGen Platelet Disorders VCEP (PMID:11722423). Surface expression of αIIbβ3 measured by flow cytometry in HEK293T cells transiently co-transfected with Val193Met variant β3 and wild type β3 showed equal expression PubMed:11722423
PS3 ✖	Surface expression of αIIbβ3 measured by flow cytometry in HEK293T cells transiently co-transfected with Val193Met variant β3 and wild type β3 showed equal expression at 100% (>75%), (PMID:11722423). Surface expression of αIIbβ3 measured by flow cytometry in HEK293T cells transiently co-transfected with Val193Met variant β3 and wild type β3 showed equal expression PubMed:11722423

Curation History

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