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.647A>G

Version: 2.0

CA400023432

996202 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: fdb42228-059f-4071-9acb-241f8f10568a
Approved on: 2023/11/2
Published on: 2023/11/3

HGVS expressions

NM_000212.3:c.647A>G
NC_000017.11:g.47286292A>G
CM000679.2:g.47286292A>G
NC_000017.10:g.45363658A>G
CM000679.1:g.45363658A>G
NC_000017.9:g.42718657A>G
NG_008332.2:g.37451A>G
ENST00000696963.1:c.647A>G
ENST00000559488.7:c.647A>G
ENST00000559488.5:c.647A>G
ENST00000560629.1:c.612A>G
ENST00000571680.1:c.647A>G
NM_000212.2:c.647A>G

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PM3 PP4_Moderate

Not Met criteria codes 1

PM5

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 ITGB3 missense variant NM_000212.3:c.647A>G replaces the tyrosine residue with a cysteine residue (p.Tyr216Cys). This variant has been observed in homozygosity in a proband (GT-4, PMID: 25539746) with a phenotype specific for Glanzmann's thrombasthenia (PP4_moderate) and in heterozygosity in an individual with a second pathogenic ITGB3 variant in trans (GT-11, PMID: 25539746; PM3). This variant has not been reported in population databases (PM2_supporting) and is predicted to be damaging by in silico tools (REVEL 0.953;

PP3). In summary, this variant meets criteria to be classified as likely pathogenic for GT. GT-specific criteria applied: PM3, PP4_moderate, PM2_supporting, PP3.

Met criteria codes

PM2_Supporting	✔	This is a rare variant not reported in control population databases, including gnomAD v2.1.1, gnomAD v3, PAGE, 1000 Genomes, and ESP, meeting the criterion to apply PM2_supporting.
PP3	✔	The REVEL score for this variant is 0.953, exceeding the VCEP-established threshold of ≥ 0.7 to apply PP3.
PM3	✔	This variant has been observed in homozygosity in one individual (GT-4, PMID: 25539746) and in a second individual (GT-11, PMID: 25539746) in trans with ITGB3 variant NM_000212.3:c.665T>C (p.Leu222Pro) classified as pathogenic. These occurrences are sufficient to apply PM3.
PP4_Moderate	✔	All requirements for PP4_moderate are met (GT-4, PMID: 25539746): history of bleeding; impaired aggregation to at least two agonists, but normal or only mildly reduced agglutination with ristocetin; flow cytometry showed <5% expression of αIIbβ3.

Not Met criteria codes

PM5	✖	Another missense variant NM_000212.3(ITGB3):c.646T>C (p.Tyr216His) variant in the same codon has been classified as likely pathogenic for Glanzmann thrombasthenia by the ClinGen PD VCEP. It is not considered here to avoid circularity.

Curation History

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