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_000212.2:c.187C>T

Version: 2.0

CA8622892

631774 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 09d0fd53-4154-4560-a8c2-c5736646ca33
Approved on: 2023/8/15
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HGVS expressions

NM_000212.2:c.187C>T
NC_000017.11:g.47283375C>T
CM000679.2:g.47283375C>T
NC_000017.10:g.45360741C>T
CM000679.1:g.45360741C>T
NC_000017.9:g.42715740C>T
NG_008332.2:g.34534C>T
ENST00000696963.1:c.187C>T
ENST00000559488.7:c.187C>T
ENST00000559488.5:c.187C>T
ENST00000560629.1:c.152C>T
ENST00000571680.1:c.187C>T
NM_000212.3:c.187C>T

Likely Pathogenic

Met criteria codes 5

PM3_Supporting PS3_Moderate PP4_Strong PM2_Supporting PP3

Not Met criteria codes 1

PP1

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 missense variant, NM_000212.3(ITGB3):c.187C>T (p.Arg63Cys), has been reported in one compound heterozygous proband (PMID: 25728920) with Pathogenic variant NM_000212.2:c.505C>T Arg169Ter (PM3_supporting). The patient (GT7 in PMID: 25728920/Case 2 in PMID: 35286390) 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 15% (<25%), as measured by flow

cytometry (PP4_strong). It occurs at an extremely low frequency, with an overall allele frequency in gnomAD of 0.00002476 (MAF of 0.00005012 in the East Asian population; PM2_supporting). It is predicted damaging by in-silico tools (REVEL score of 0.98; PP3). In transiently transfected COS-7 cells expressing Arg63Cys mutant integrin FACS analysis showed 85% reduction of αIIbβ3Cys63 expression (PS3_moderate). 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: PP4_strong, PM2_supporting, PM3_supporting, PP3, PS3_moderate (VCEP specifications version 2).

Met criteria codes

PM3_Supporting ✔

This variant has been detected in at least 1 proband with Glanzmann thrombasthenia. This individual was compound heterozygous for this variant and a pathogenic variant and was not confirmed in trans. (Pathogenic variant: NM_000212.2:c.505C>T Arg169Ter [ClinVarID:953061], PMID:25728920 [Table S2]). 0.5pt (PM3_Supporting).

In patient GT7 the Arg169Ter variant was reported in trans with c.187C>T p.Arg63Cys but the phase was not confirmed. 0.5pt PubMed:25728920

PS3_Moderate ✔

Surface expression of αIIbβ3 measured by flow cytometry (FACS) in COS-7 cells transiently co-transfected with p.Arg63Cys variant β3 and wild type αIIbβ3 showed decreased expression at 15% (<25%) WT levels, indicating that this variant impacts protein function (PMID::25728920; PS3_moderate).

In transiently transfected COS-7 cells expressing Arg63Cys mutant integrin FACS analysis showed 85% reduction of αIIbβ3Cys63 expression on transfected cells compared with wild type. Disruption of protein function was not assessed. PubMed:25728920

PP4_Strong ✔

At least one patient (Patient GT7 in PMID: 25728920/Case 2 in PMID: 35286390) 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 15% (<25%), as measured by flow cytometry. (PP4_strong)

Patient GT7, compound heterozygous for Arg63Cys, had a history of mucocutaneous bleeding (easy bruising and epistaxis) and a WHO bleeding score of 1. There was absent platelet aggregation with ADP and severely reduced with at least two additional agonists but normal ristocetin-induced aggregation. There was residual (10-15%) platelet expression of alphaIIb-beta3 confirmed by flow cytometry. No mention was made of platelet count.
PubMed:25728920

PM2_Supporting ✔

The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005 (1/19954 alleles) in the East Asian population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).

PP3 ✔

There is consensus among SIFT, PolyPhen, and MutationTaster that the Arg63Cys variant is damaging/disease causing. The REVEL score of 0.98 is above the 0.7 threshold.

Not Met criteria codes

PP1 ✖

Patient GT7 of PMID: 25728920 has an affected brother however his genotype was not provided.

Patient GT7 has an affected brother however his genotype was not provided. PubMed:25728920

Curation History

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