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Variant: NM_000212.3:c.563C>T

Version: 1.0

CA8622981

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 60cdaca0-307b-44cc-95e8-23a459a8381e
Approved on: 2024/6/6
Published on: 2024/6/7

HGVS expressions

NM_000212.3:c.563C>T
NC_000017.11:g.47284644C>T
CM000679.2:g.47284644C>T
NC_000017.10:g.45362010C>T
CM000679.1:g.45362010C>T
NC_000017.9:g.42717009C>T
NG_008332.2:g.35803C>T
ENST00000696963.1:c.563C>T
ENST00000559488.7:c.563C>T
ENST00000559488.5:c.563C>T
ENST00000560629.1:c.528C>T
ENST00000571680.1:c.563C>T
NM_000212.2:c.563C>T

Likely Pathogenic

Met criteria codes 5

PM3_Supporting PP3 PS3 PP4_Moderate PM2_Supporting

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 563C>T variant in ITGB3 is a missense variant predicted to cause substitution of Serine by Leucine at amino acid 188 (p.Ser188Leu). Surface expression of αIIbβ3 measured by Western blot in COS-7 cells transiently co-transfected with Ser188 β3 (wild type) and Leu188 β3 (mutant) showed absent immunoprecipitation, indicating that this variant impacts protein function (PMID: 9684783)(PS3). At least one patient (Patient BL in PMID: 9684783) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists

except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_Moderate). The GT patient from PMID: 9684783 was homozygous for this variant (0.5 PM3 points, PM3_Supporting). The computational predictor REVEL gives a score of 0.771, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). The highest population minor allele frequency in gnomAD v4.1.0 is 0.000001695 (2/1180026 alleles) in the European (Non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). 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: PS3, PP3, PP4_Moderate, PM2_Supporting and PM3_Supporting (VCEP specifications version 2; date of approval 06/06/2024).

Met criteria codes

PM3_Supporting ✔	This variant has been detected in at least 1 proband with Glanzmann thrombasthenia (PMID: 9684783). This individual was homozygous for the variant (0.5 PM3 points, PM3_Supporting).
PP3 ✔	The computational predictor REVEL gives a score of 0.771, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).
PS3 ✔	Surface expression of αIIbβ3 measured by Western blot in COS-7 cells transiently co-transfected with Ser188 β3 (wild type) and Leu188 β3 (mutant) showed absent immunoprecipitation, indicating that this variant impacts protein function (PMID: 9684783)(PS3). reduced ligand binding **PubMed:11806996**
PP4_Moderate ✔	At least one patient (Patient BL in PMID: 9684783) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate).
PM2_Supporting ✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.000001695 (2/1180026 alleles) in the European (Non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).

Curation History

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