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Variant: NM_000212.3:c.863T>C

Version: 1.0

CA400024958

1879009 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2a3b6394-60d8-451f-a60f-882a76f81607
Approved on: 2022/11/15
Published on: 2022/12/7

HGVS expressions

NM_000212.3:c.863T>C
NC_000017.11:g.47287155T>C
CM000679.2:g.47287155T>C
NC_000017.10:g.45364521T>C
CM000679.1:g.45364521T>C
NC_000017.9:g.42719520T>C
NG_008332.2:g.38314T>C
ENST00000696963.1:c.863T>C
ENST00000559488.7:c.863T>C
ENST00000559488.5:c.863T>C
ENST00000560629.1:c.828T>C
ENST00000571680.1:c.863T>C
NM_000212.2:c.863T>C

Pathogenic

Met criteria codes 5

PP4_Strong PM2_Supporting PS3 PM3 PP3

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.863T>C (p.Leu288Pro) missense variant has been identified in one compound heterozygous individual (Patient LD in PMID:10891446 which reported the variant as c.883T>C using an alternate nucleotide numbering system, confirmed in Figure 4). This patient had mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann Thrombasthenia. Additionally, αIIbβ3 surface expression was reduced to 10% (<25%), as measured by Western blot (PP4_strong). This

variant was confirmed in trans with c.847_848del (classified Pathogenic by the PD VCEP; PM3) in Patient LD in PMID:10891446. A functional impact of this variant was reported in PMID: 10891446; Leu288Proβ3 cDNA was constructed and cotransfected with wild-type αIIb into COS-7 cells. Biotin surface labeling of these transiently transfected cells showed that the complex-specific antibody AP2 immunoprecipitated only trace amounts of αIIbLeu262Proβ3. Furthermore, Leu288Pro cDNA was transfected into 293 cells and showed 40-50% expression of αv-Leu288Proβ3 compared to wild type as measured by flow cytometry and transfected 293 cells with the variant were unable to interact with immobilized fibrinogen, unlike WT transfected cells which demonstrated significant adhesion and spreading to immobilized fibrinogen (PMID: 10891446: PS3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). In silico predictor revealed a REVEL score of 0.99, predicting a deleterious effect (PP3). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive Glanzmann thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PP4_strong, PP3, PM2_supporting, PM3, and PS3.

Met criteria codes

PP4_Strong	✔	At least one patient (Patient LD in PMID:10891446) 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 10% (<25%), as measured by Western blot. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries (PP4_strong).
PM2_Supporting	✔	This variant is absent from gnomAD v[2.1.1] (PM2_Supporting).
PS3	✔	Leu288Proβ3 (referred to here as Leu262Pro) cDNA was constructed and cotransfected with wild-type αIIb into COS-7 cells. Biotin surface labeling of these transiently transfected cells showed that the mutant complex was poorly expressed and less stable than the wild type: from a detergent lysate, the complex-specific antibody AP2 immunoprecipitated only trace amounts of αIIbLeu262Proβ3. This does not meet PS3 requirements based on use of immunoprecipitation rather than Western blot or flow cytometry. Additionally, metabolic labeling of transfected COS-7 cells with35S-methionine was used to assess the biosynthesis of αIIbLeu262Proβ3, finding the maturation of the mutant complex was markedly delayed. This is not an approved functional assay for PS3. Furthermore Leu288Pro cDNA was transfected into 293 cells and showed 40-50% expression of αv-Leu288Proβ3 compared to wild type as measured by flow cytometry. Additionally, transfected 293 cells with the variant were unable to interact with immobilized fibrinogen on a 96 well microliter plate, unlike WT transfected cells which demonstrated significant adhesion and spreading to immobilized fibrinogen. In light of additional supportive evidence, lack of fibrinogen binding was considered sufficient for application of PS3, despite testing in complex with αv rather than αIIb. Leu288Proβ3 (referred to here as Leu262Pro) cDNA was constructed and cotransfected with wild-type αIIb into COS-7 cells. Biotin surface labeling of these transiently transfected cells showed that the mutant complex was poorly expressed and less stable than the wild type: from a detergent lysate, the complex-specific antibody AP2 immunoprecipitated only trace amounts of αIIbLeu262Proβ3. This does not meet PS3 requirements based on use of immunoprecipitation rather than Western blot or flow cytometry. Additionally, metabolic labeling of transfected COS-7 cells with35S-methionine was used to assess the biosynthesis of αIIbLeu262Proβ3, finding the maturation of the mutant complex was markedly delayed. This is not an approved functional assay for PS3. Furthermore Leu288Pro cDNA was transfected into 293 cells and showed 40-50% expression of αv-Leu288Proβ3 compared to wild type as measured by flow cytometry. Additionally, transfected 293 cells with the variant were unable to interact with immobilized fibrinogen on a 96 well microliter plate, unlike WT transfected cells which demonstrated significant adhesion and spreading to immobilized fibrinogen. In light of additional supportive evidence, lack of fibrinogen binding was considered sufficient for application of PS3, despite testing in complex with αv rather than αIIb. **PubMed:10891446**
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.847_848del (p.Ala283IlefsTer12), confirmed in trans by family testing, (CAID:CA8623068, PMID:10891446).

PP3		✔	The computational predictor REVEL gives a score of .99, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).

Curation History

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