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Variant: NM_000212.3:c.665T>C

Version: 1.0

CA291224887

996163 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: a7348126-93c5-4b00-af91-024cf35b361f
Approved on: 2020/11/10
Published on: 2021/1/22

HGVS expressions

NM_000212.3:c.665T>C
NC_000017.11:g.47286310T>C
CM000679.2:g.47286310T>C
NC_000017.10:g.45363676T>C
CM000679.1:g.45363676T>C
NC_000017.9:g.42718675T>C
NG_008332.2:g.37469T>C
ENST00000696963.1:c.665T>C
ENST00000559488.7:c.665T>C
ENST00000559488.5:c.665T>C
ENST00000560629.1:c.630T>C
ENST00000571680.1:c.665T>C
NM_000212.2:c.665T>C

Pathogenic

Met criteria codes 5

PM3_Supporting PP4_Strong PS3 PM2_Supporting PP3

Evidence Links 2

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

NM_000212.3(ITGB3):c.665T>C (p.Leu222Pro) is a missense variant which has been previously reported in at least two symptomatic individuals who meet the diagnostic criteria for the GT phenotype (PMIDs:25728920, 11897046). This variant is present at an extremely low MAF of 0.000064 in the Non-Finnish European subpopulation in gnomAD. This variant has been predicted to be deleterious by multiple in silico tools (REVEL score = 0.97). This variant has been reported to occur in the homozygous state in one proband as well as in heterozygous state with another pathogenic variant (p.Cys624Tyr) in a non related proband. Functional studies have demonstrated a deleterious effect on the gene product, preventing the binding of soluble fibrinogen and fibrinogen mimetic antibodies (PMID: 11776310). This variant meets GT specific criteria for PS3, PP4_strong, PM2_supporting, PP3 and PM3_supporting and is therefore classified as Pathogenic.

Met criteria codes

PM3_Supporting ✔

This variant has been reported to occur homozygously in a proband by Morel-Kopp et al, 2001 (PMID: 11776310). 0.5 points. This variant has also been reported to occur in compound heterozygous state with another variant p.Cys624Tyr by PMID: 25728920. However this evidence is not considered here to avoid circularity. With 0.5 points, PM3_Supporting criteria is met.

PubMed:11776310

PP4_Strong ✔

Proband (GT9) had a history of moderate mucocutaneous bleeding, lack of platelet aggregation with three physiological agonists (but normal aggregation with ristocetin) and reduced (10-20%) surface expression of αIIbβ3 demonstrated by flow cytometry. Sanger sequencing ensured coverage of exons and splice sites of the ITGA2B and ITGB3 genes as well as untranslated regions. PMID: 25728920 PP4_strong applied

PubMed:25728920

PS3 ✔

Morel-Kopp et al performed functional studies using CHO transfected cell. Expression of the mutant beta3Pro196 (Leu222Pro) subunit in CHO cells resulted in normal biosynthesis of beta3 but selectively interfered with alphaIIbbeta3 maturation and transport to the cell surface. Functional analysis of the beta3 mutant receptors revealed that this mutation prevented the binding of macromolecules, soluble fibrinogen and fibrinogen mimetic antibodies (ex. PAC-1), following antibody activation. (PMID: 11776310). PS3 applied.

Morel-Kopp et al performed functional studies using CHO transfected cell. expression of the mutant beta3Pro196 subunit in CHO cells, either associated with recombinant human alphaIIb or alphav, resulted in normal biosynthesis of beta3 and heterodimerization with alphav or alphaIIb, but selectively interfered with alphaIIbbeta3 maturation and transport to the cell surface. Functional analysis of the beta3 mutant receptors revealed that this mutation prevented the binding of macromolecules, soluble fibrinogen or the fibrinogen mimetic MoAb PAC-1, following antibody activation or DTT treatment of the cells. Thus, L196 motif is located in a 3 subunit domain identified by Tuckwell and Humphries that is structurally important for allowing the conformational switch necessary for the exposure of the RGD-ligand contact site in the MIDAS-like domain of the 3 subunit. PubMed:11776310

PM2_Supporting ✔

The overall AF in gnomAD(v2.1.1) is 0.00003 (1/31396) and the European (Non-Finnish) subpopulation has a MAF of 0.000064 (1/15425 alleles) which is < 0.01%. Therefore PM2_supporting applied.

PP3 ✔

REVEL score = 0.97 which is above the threshold recommended (0.70) for PP3.

Curation History

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