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Variant: NM_000212.3:c.1646G>C

Version: 2.0

CA400030198

996174 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: fb8a77c7-778b-45b9-b85e-90b1dc27f737
Approved on: 2024/3/7
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HGVS expressions

NM_000212.3:c.1646G>C
NC_000017.11:g.47292524G>C
CM000679.2:g.47292524G>C
NC_000017.10:g.45369890G>C
CM000679.1:g.45369890G>C
NC_000017.9:g.42724889G>C
NG_008332.2:g.43683G>C
ENST00000696963.1:c.1646G>C
ENST00000559488.7:c.1646G>C
ENST00000559488.5:c.1646G>C
ENST00000560629.1:c.1611G>C
NM_000212.2:c.1646G>C

Likely Pathogenic

Met criteria codes 5

PM3 PM2_Supporting PP4_Moderate PP1 PP3

Not Met criteria codes 1

PS3

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.1646G>C (p.Cys549Ser) missense variant is reported in at least 2 compound heterozygous GT probands confirmed in trans with Pathogenic variant c.2113del and Likely Pathogenic variant Gln254Lys respectively (PM3). Both probands of PMID: 31088191 meet the criteria for PP4_Moderate; including mucocutaneous bleeding, and impaired aggregation with all agonists except ristocetin. Additionally, reduced surface expression of β3 was measured by flow cytometry at ~13% compared to normal. Co-segregation of compound heterozygous genotype Cys549Ser/Gln254Lys with disease was observed in the proband and one affected sibling (PMID:

31088191; PP1). It is found at an extremely low frequency with a MAF of 0.00005453 in the East Asian gnomADv2.1.1 population (PM2_Supporting) and it is predicted damaging by in-silico tools (REVEL score of 0.885; PP3). In summary, this variant meets criteria to be classified as Likely Pathogenic for GT. GT-specific criteria applied: PM2_Supporting, PM3, PP1, PP3, and PP4_Moderate.

Met criteria codes

PM3	✔	At least 2 compound heterozygous individuals have been reported with this variant in PMID: 31088191 confirmed in trans with c.2113del (Pathogenic, 1pt) and Gln254Lys (Likely Pathogenic; not included here to avoid circularity) respectively.
PM2_Supporting	✔	This variant is at an extremely low frequency (below the <1/10,000 threshold) MAF of 0.00007557 (3/ 39696 alleles) in the gnomADv4.0 East Asian population.
PP4_Moderate	✔	Both probands of PMID: 31088191 meet the criteria for PP4_Moderate; including mucocutaneous bleeding, and impaired aggregation with all agonists except ristocetin. Additionally, reduced surface expression of β3 was measured by flow cytometry at ~13% compared to normal.
PP1	✔	Co-segregation of compound heterozygous genotype Cys549Ser and Gln254Lys with disease was observed in the proband and one affected sibling (PMID: 31088191).
PP3	✔	REVEL score of 0.885 is above the >.0.7 threshold in support of a deleterious effect.

Not Met criteria codes

PS3	✖	Surface expression of αIIbβ3 measured by flow cytometry in BHK cells transiently co-transfected with Cys549Ser (here referred to as Cys523Ser) variant β3 and wild type αIIb showed decreased expression at 55% WT levels of positive cells. This modest reduction is insufficient to apply PS3 (PMID: 22308022). Similar results with 37% WT levels of positive cells were reported in PMID: 26514956, which also suggests this variant causes constitutive activation. Surface expression of αIIbβ3 measured by flow cytometry in BHK cells transiently co-transfected with Cys549Ser (here referred to as Cys523Ser) variant β3 and wild type αIIb showed decreased expression at 56% WT levels of positive cells. This modest reduction is insufficient to apply PS3 (PMID: 22308022). PubMed:22308022

Curation History

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