

Variant: NM_000212.2:c.629G>C

Version: 2.0

CA400023389 [↗](#)

953047 (ClinVar) [↗](#)

Gene: ITGB3 ([HGNC:3690](#))

Condition: Glanzmann thrombasthenia ([MONDO:0100326](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 4a2ca60f-e835-4227-b8e2-93600aff608f

Approved on: 2023/11/2

Published on: 2023/11/3

HGVS expressions

NM_000212.2:c.629G>C

NC_000017.11:g.47286274G>C

CM000679.2:g.47286274G>C

NC_000017.10:g.45363640G>C

CM000679.1:g.45363640G>C

NC_000017.9:g.42718639G>C

NG_008332.2:g.37433G>C

ENST00000696963.1:c.629G>C

ENST00000559488.7:c.629G>C

ENST00000559488.5:c.629G>C

ENST00000560629.1:c.594G>C

ENST00000571680.1:c.629G>C

NM_000212.3:c.629G>C

Pathogenic

Met criteria codes **6**

PP4_Moderate

PP1

PP3

PM3

PS3

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 NM_000212.2:c.628T>A (p.Cys210Ser) missense variant has been reported in the compound heterozygous state (in trans with Pathogenic variant Pro189Ser) in one proband and his brother (PMID: 31565851) with a phenotype highly specific to GT (PM3, PP4_moderate). Multiple lines of computational evidence support a deleterious effect with a REVEL score of 0.963 (PP3). The variant is absent from population databases, including gnomADv2.1.1 (PM2_supporting). Functional studies show reduced binding to fibrinogen

when expressed in CHO cells (PMID: 14690453; PS3). In summary this variant meets criteria to be classified as Pathogenic for autosomal recessive Glanzmann thrombasthenia. GT-specific criteria applied: PP4_moderate, PP3, PP1, PM2_supporting, PM3, PS3.

Met criteria codes

PP4_Moderate			The proband of PMID: 31565851 meets the criteria for PP4; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of α IIb β 3.
PP1			The proband and brother of PMID: 31565851 share the compound heterozygous genotype of Pro189Ser and Cys210Ser. Both are diagnosed with both GT and macrothrombocytopenia.
PP3			SIFT (Damaging), Polyphen2-HDIV 1 (probably Damaging), and Mutation Taster (disease causing) agree that this variant has a deleterious effect and the REVEL score is 0.936, above the >0.7 threshold.
PM3			The patient is compound heterozygous for Pro189Ser (classified as Pathogenic by the ClinGen Platelet Disorders VCEP) and Cys210Ser . The variants are in trans as confirmed by independent segregation in the next generation (PM3; PMID: 31565851).
PS3			In PMID: 14690453 the authors transiently expressed the Cy210Ser (referred to as Cys184Ser) mutant together with WT GPIIb in CHO cells and tested their ability to bind to soluble fibrinogen by flow cytometry. The Cys210Ser mutant was expressed but did not bind to fibrinogen even when activated with mAb PT25-2. Transiently expressed the Cy210Ser (referred to as Cys184Ser) mutant together with WT GPIIb in CHO cells and tested their ability to bind to soluble fibrinogen by flow cytometry. The Cys210Ser mutant was expressed but did not bind to fibrinogen even when activated with mAb PT25-2. PubMed:14690453 
PM2_Supporting			This variant is absent from all population cohorts in gnomAD, ExAC, 1000 Genomes, and ESP.

Curation History

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