

Variant: *NM_000212.3:c.728A>T*

Version: 1.0

CA400023604 [↗](#)

1210177 (ClinVar) [↗](#)

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

Condition: Glanzmann's thrombasthenia ([MONDO:0010119](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 0346dbad-e2e5-4e6a-b339-8f1710ebf6a9

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HGVS expressions

NM_000212.3:c.728A>T

NC_000017.11:g.47286373A>T

CM000679.2:g.47286373A>T

NC_000017.10:g.45363739A>T

CM000679.1:g.45363739A>T

NC_000017.9:g.42718738A>T

NG_008332.2:g.37532A>T

ENST00000696963.1:c.728A>T

ENST00000559488.7:c.728A>T

ENST00000559488.5:c.728A>T

ENST00000560629.1:c.693A>T

ENST00000571680.1:c.728A>T

NM_000212.2:c.728A>T

Pathogenic

Met criteria codes **6**

PM3_Supporting

PM2_Supporting

PP3

PP4_Moderate

PM5_Supporting

PS3

Evidence Links **1**

Expert Panel

Platelet Disorders VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The ITGB3 missense variant NM_000212.3:c.728A>T replaces the aspartic acid residue with a valine residue (p.Asp243Val). This variant has been observed in homozygosity in an individual with a phenotype specific for Glanzmann's thrombasthenia (GT) (PMID: 18832906). In silico tools predict the variant is damaging to protein function and are supported by in vitro studies in CHO cells suggesting the expression of ITGB3 cDNA leads to reduced binding to soluble fibrinogen (25%) and reduced adhesion to immobilized fibrinogen (10%) compared to cells expressing wild type ITGB3 cDNA, despite normal levels of protein on the cell surface (PMID: 18832906). A different missense change at this amino acid residue (c.727G>C, p.Asp243His) has been reported and is provisionally classified by the Platelet Disorders VCEP as likely

pathogenic. Furthermore, this variant is absent from control population databases. In summary, this variant meets criteria to be classified as pathogenic for GT. GT-specific criteria applied: PS3, PP4_moderate, PP3, PM2_supporting, PM3_supporting, PM5_supporting.			
Met criteria codes			
PM3_Supporting			This variant has been observed in homozygosity in one proband (PMID: 18832906), sufficient to apply PM3_supporting.
PM2_Supporting			This variant is absent from all population cohorts in gnomAD, ExAC, 1000 Genomes, and ESP.
PP3			REVEL score of 0.985 is above the >.0.7 threshold to support a deleterious effect.
PP4_Moderate			All requirements for PP4_moderate are met (PMID: 18832906): history of mucocutaneous bleeding and impaired aggregation to at least two agonists, but normal or only mildly reduced agglutination with ristocetin. Although flow cytometry showed a normal level of α IIb β 3 on the surface of patient platelets, the authors suggest a conformational change of the heterodimer near a ligand-binding site leads to defective fibrinogen binding based on reduced (60%) binding to an antibody recognizing an epitope located in a Ca2+-dependent region of the α IIb β 3 complex. However, functional flow cytometry of patient cells to demonstrate the inability of platelet binding to activated GPIIb/IIIa was not reported.
PM5_Supporting			A different missense change at this amino acid residue (c.727G>C, p.Asp243His) has been observed and is provisionally classified by the Platelet Disorders VCEP as likely pathogenic.
PS3			PMID: 18832906: Expression of ITGB3 cDNA carrying the c.728A>T (p.Asp243Val) variant in CHO cells led to a significant reduction in soluble fibrinogen binding (25%; demonstrated by flow cytometry) and immobilized fibrinogen adhesion (10%; demonstrated by light microscopy) compared to cells expressing wild type ITGB3. CHO cells stably transfected with wild type ITGB3 cDNA or ITGB3 cDNA carrying the c.728A>T (p.Asp243Val) variant were treated with dithiothreitol to induce a high-affinity state, allowing for fibrinogen binding, and binding to soluble fibrinogen was measured by flow cytometry. Cells expressing ITGB3 cDNA carrying the c.728A>T (p.Asp243Val) variant bound reduced amounts (25%) of soluble fibrinogen compared to cells expressing wild type ITGB3 cDNA. Similarly, when exposed to immobilized fibrinogen, adherence of cells expressing ITGB3 cDNA carrying the c.728A>T (p.Asp243Val) variant was reduced by 90% compared to cells expressing wild type ITGB3 cDNA. PubMed:18832906 

Curation History 

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Showing 1 to 1 of 1 rows

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