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# *Variant: NM_000212.2:c.31T>C*

Version: 2.0

*CA291240306*

*953028 (ClinVar)*

**Gene**: ITGB3 (HGNC:3690)
**Condition**: Glanzmann thrombasthenia (MONDO:0100326)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 07621490-1d19-4752-8280-1009a61df585
**Approved on**: 2023/11/2
**Published on**: 2023/12/13

## *HGVS expressions*

**NM_000212.2:c.31T>C**
NC_000017.11:g.47253892T>C
CM000679.2:g.47253892T>C
NC_000017.10:g.45331258T>C
CM000679.1:g.45331258T>C
NC_000017.9:g.42686257T>C
NG_008332.2:g.5051T>C
ENST00000696963.1:c.31T>C
ENST00000559488.7:c.31T>C
ENST00000559488.5:c.31T>C
ENST00000571680.1:c.31T>C
NM_000212.3:c.31T>C

**Pathogenic**

**Met criteria codes** 4

PP4_Strong PM2_Supporting PS3 PM3

**Not Met criteria codes** 2

PP1 PP3

Evidence Links 4

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 c.31T>C (p.Trp11Arg) missense variant has been reported in at least 3 probands (PMIDs: 25728920, 28748566, 25373348), at least one of whom (PMID: 25728920) meets criteria for PP4_Strong; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3 measured by flow cytometry. Two homozygotes (PM3) and one compound heterozygote (with Likely Pathogenic Cys486Trp variant) has been observed. It is absent from controls in gnomADv2.1.1 (PM2_supporting. The expression of αIIbβ3 on the surface of HEK cells was evaluated by flow cytometry and showed no detectable αIIbβ3 protein (PMID:**

**36122578; PS3). In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive Glanzmann thrombasthenia. GT-specific criteria applied: PS3, PM2_supporting, PM3, and PP4_strong.**

**Met criteria codes**

**PP4_Strong** ✔

The Trp11Arg variant has been described in 3 probands in the literature, at least one of whom (PMID: 25728920) meets criteria for PP4_Strong; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3 measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries.

Patient 1, homozygous for the Trp11Arg variant, had mild thrombocytopenia and absent aggregation with all agonists employed (which agonists were used was not specified). No mention was made of mucocutaneous bleeding, platelet size, or protein expression. PubMed:28748566

Patient GT62, homozygous for Trp11Arg, had a history of mucocutaneous bleeding (esophageal bleeding, easy bruising, gingivorrhagia, menorrhagia) and a WHO bleeding score of 3. There was absent platelet aggregation with at least three agonists but normal ristocetin-induced aggregation. Severely reduced (<5%) platelet expression of alphaIIb-beta3 was confirmed by flow cytometry. No mention was made of platelet count or size. PubMed:25728920

Patient GT2 heterozygous for Trp11Arg has severe bleeding symptoms and severely reduced platelet aggregation after stimulation with agonists such as collagen, adenosine diphosphate, arachidonic acid, adrenaline, and epinephrine. Patient specific ristocetin agglutination not noted. Decreased, <5% alphaIIb-beta3 expression was determined by flow cytometry. Platelet count and size were not mentioned. PubMed:25373348

**PM2_Supporting** ✔

Absent from controls in population databases including gnomAD and ExAC.

**PS3** ✔

The authors used site-directed mutagenesis to induce the mutated 31C in wild-type ITGB3 cDNA. HEK cells were transfected with the respective wild-type (31T) or mutant (31C) expression vectors, cultured, and lysed. Cell lysates were analyzed by western blot using monoclonal antibodies against β3 (CD61, clone AP3) or αIIb (CD41, clone Gi16). Presence of GAPDH was evaluated as an internal reference. In wild-type and mutant lysates, a band of 87 kDa was detected by AP3, indicating presence of β3 protein in both cells. Despite equal concentration of GAPDH, analysis showed a significant decrease in β3 protein in transfected HEK cells expressing 31C when compared with the wild-type. Integrin αIIb was expressed in comparable amounts by both, mutant and wild-type cells. However, the pattern was different, and the main band was slightly lighter for the mutant form. The expression of αIIbβ3 on the surface of HEK cells was evaluated by flow cytometry. Wild-type αIIb and β3 proteins were detectable in cytoplasm as well as on the surface of transfected cells, HEK cells. In contrast, analysis of αIIbβ3 protein on the cell surface of transfected cells showed no detectable αIIbβ3 protein on mutant-transfected cells. These observations indicated that despite cytoplasmic presence of both β3 (c.31C variant) and αIIb, no mutant αIIbβ3 integrin was transported to the cell surface (PMID: 36122578).

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cytoplasmic presence of both β3 (c.31C variant) and αIIb, no mutant αIIbβ3 integrin was transported to the cell surface. PubMed:36122578

**PM3** ✔

This Trp11Arg variant has been observed twice in homozygous cases in the literature (PMIDs: 25728920, 28748566). 1pt And confirmed in trans with Likely Pathogenic variant Cys486Trp (PMID: 25373348), not considered here to avoid circularity.

Patient 1 is homozygous for the Trp11Arg variant. PubMed:28748566
Patient GT62 is homozygous for Trp11Arg, family is reported as not consanguineous. PubMed:25728920
Patient GT2 has the Trp11Arg variant in trans with Cys486Trp (Likely Pathogenic). Phase is confirmed to be in trans. In order to avoid a circular argument, this in trans variant is not counted toward PM3 for Trp11Arg as Trp11Arg is counted toward Cys486Trp. PubMed:25373348

**Not Met criteria codes**

**PP1** ✖

Patient GT62 (PMID: 25728920), homozygous for Trp11Arg, has an affected sister however her genotype was not reported.

Patient GT62, homozygous for Trp11Arg, has an affected sister however her genotype was not reported. PubMed:25728920

**PP3** ✖

There are conflicting interpretations from pathogenicity predictors, SIFT predicts damaging, PolyPhen benign, and MutationTaster neutral with a REVEL score of 0.675 (below the 0.7 cutoff).

## Curation History

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