The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000212.2:c.1594T>C

Version: 2.1

CA400029953

953010 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6f267b7c-2202-4981-a37d-6ee8ca25f48e
Approved on: 2026/3/17
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HGVS expressions

NM_000212.2:c.1594T>C
NC_000017.11:g.47292472T>C
CM000679.2:g.47292472T>C
NC_000017.10:g.45369838T>C
CM000679.1:g.45369838T>C
NC_000017.9:g.42724837T>C
NG_008332.2:g.43631T>C
ENST00000696963.1:c.1594T>C
ENST00000559488.7:c.1594T>C
ENST00000559488.5:c.1594T>C
ENST00000560629.1:c.1559T>C
NM_000212.3:c.1594T>C

Likely Pathogenic

Met criteria codes 4

PM3 PP4_Strong PM2_Supporting PP3

Not Met criteria codes 1

PM5

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.1594T>C (p.Cys532Arg) variant has been reported in the literature in at least 1 compound heterozygous proband (PMID: 25373348) in trans with the pathogenic variant c.2014+1G>A (PM3). The patient meets the criteria for PP4_strong; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3 measured by flow cytometry (PP4_strong). The highest population minor allele frequency in gnomAD v4 is 8.488e-7 (1/1178100 alleles) in the European non-Finnish genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). The

variant is predicted to have a deleterious effect (REVEL score of 0.988; PP3). In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PP4_strong, PM2_supporting, PM3, PP3 (VCEP specifications version 2).

Met criteria codes

PM3	✔	The Cys532Arg variant has been reported in the literature (PMID: 25373348) to be in trans with the Pathogenic variant c.2014+1G>A.1pt Patient GT15 has the Cys532Arg variant in trans with the Pathogenic variant c.2014+1G>A. Phase is confirmed to be in trans. PubMed:25373348
PP4_Strong	✔	The Cys532Arg variant has been described in one proband in the literature (PMID: 25373348) who meets the 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 GT15 heterozygous for Cys532Arg has severe bleeding symptoms and severely reduced platelet aggregation after stimulation with agonists such as collagen, adenosine diphosphate, arachidonic acid, adrenaline, and epinephrine. Ristocetin aggregation was almost normal. Decreased, alphaIIb-beta3 expression was determined by flow cytometry. Platelet count and size were not mentioned. PubMed:25373348
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4 is 8.488e-7 (1/1178100 alleles) in the European non-Finnish genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).
PP3	✔	SIFT, Polyphen, and MutationTaster all predict the variant to have a deleterious effect in agreement with the REVEL score of 0.988 (above the threshold of >0.7).

Not Met criteria codes

PM5	✖	Likely Pathogenic variants Cys532Tyr and Cys532Phe have also been observed at this residue however are not considered here to avoid circularity.

Curation History

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