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.505C>T

Version: 1.1

CA291224658

953061 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6e519b7e-edcd-4486-8716-de4b353b32ec
Approved on: 2021-02-10
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HGVS expressions

NM_000212.2:c.505C>T
NC_000017.11:g.47284586C>T
CM000679.2:g.47284586C>T
NC_000017.10:g.45361952C>T
CM000679.1:g.45361952C>T
NC_000017.9:g.42716951C>T
NG_008332.2:g.35745C>T
ENST00000696963.1:c.505C>T
ENST00000559488.7:c.505C>T
ENST00000559488.5:c.505C>T
ENST00000560629.1:c.470C>T
ENST00000571680.1:c.505C>T
NM_000212.3:c.505C>T

Pathogenic

Met criteria codes 3

PVS1 PP4_Strong PM2_Supporting

Not Met criteria codes 2

PP1 PM3

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 nonsense variant, c.505C>T (p.Arg169Ter), has been reported in one compound heterozygous proband (PMID: 25728920) and is absent from population databases. This nonsense variant occurs in exon 4 and is predicted to result in NMD. In summary, this variant meets criteria to be classified as pathogenic for GT. GT-specific criteria applied: PVS1, PP4_strong, and PM2_Supporting.

Met criteria codes

PVS1	✔	This nonsense variant occurs in exon 4 and is predicted to result in NMD.

PP4_Strong	✔	One patient has been described in PMID: 25728920 with the Arg169Ter variant 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 GT7, compound heterozygous for Arg169Ter, had a history of mucocutaneous bleeding (easy bruising and epistaxis) and a WHO bleeding score of 1. There was absent platelet aggregation with ADP and severely reduced with at least two additional agonists but normal ristocetin-induced aggregation. There was residual (10-15%) platelet expression of alphaIIb-beta3 confirmed by flow cytometry. No mention was made of platelet count. PubMed:25728920
PM2_Supporting	✔	This variant is absent from gnomAD, ExAC and 1000 Genomes.

Not Met criteria codes

PP1	✖	Patient GT7 of PMID: 25728920 has an affected brother however his genotype was not provided. Patient GT7 has an affected brother however his genotype was not provided. PubMed:25728920
PM3	✖	The Arg169Ter variant has been reported in trans with c.187C>T p.Arg63Cys, however this is was not considered here to avoid a circular argument. In patient GT7 the Arg169Ter variant was reported in trans with c.187C>T p.Arg63Cys but the phase was not confirmed. PubMed:25728920

Curation History

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