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Variant: NM_000419.5:c.1642C>T

Version: 1.0

CA399802364

2506417 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: bdc06307-e375-4cad-a8a9-98626be2be20
Approved on: 2023/6/1
Published on: 2023/6/2

HGVS expressions

NM_000419.5:c.1642C>T
NC_000017.11:g.44380112G>A
CM000679.2:g.44380112G>A
NC_000017.10:g.42457480G>A
CM000679.1:g.42457480G>A
NC_000017.9:g.39813006G>A
NG_008331.1:g.14394C>T
ENST00000262407.6:c.1642C>T
ENST00000648408.1:c.1073C>T
ENST00000262407.5:c.1642C>T
ENST00000592226.5:n.1115C>T
ENST00000592462.5:n.437C>T
NM_000419.3:c.1642C>T
NM_000419.4:c.1642C>T

Pathogenic

Met criteria codes 3

PP4_Moderate PVS1 PM2_Supporting

Not Met criteria codes 1

PM3

Evidence Links 0

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.1642C>T (p.Gln548Ter) variant in exon 17 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 17 and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). At least one patient (Patient 1 in PMID: 23624894) with this variant displayed mucocutaneous bleeding and impaired aggregation

with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was reduced to 0% (<25%), as measured by flow cytometry. Molecular genetic analysis was performed for the ITGA2B, but no genotyping was performed for ITGB3 (PP4_moderate). This variant has been detected in at least 1 proband with Glanzmann thrombasthenia (PMID:23624894). This individual was compound heterozygous for this variant and the NM_000419.3:c.1750C>T (Arg584Ter) variant, which was classified as Pathogenic by the PD VCEP (but occurs at too high a frequency to consider for PM3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PVS1, PP4_Moderate, PM2_Supporting (VCEP specifications version 2).

Met criteria codes

PP4_Moderate	✔	At least one patient (Patient 1 in PMID: 23624894) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was reduced to 0% (<25%), as measured by flow cytometry. Molecular genetic analysis was performed for the ITGA2B, but no genotyping was performed for ITGB3 (PP4_moderate).
PVS1	✔	The c.1642C>T (p.Gln548Ter) variant in exon 17 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 17 and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PM3	✖	This variant has been detected in at least 1 proband with Glanzmann thrombasthenia (PMID:23624894). This individual was compound heterozygous for this variant and the NM_000419.3:c.1750C>T (Arg584Ter) variant, which was classified as Pathogenic by the PD VCEP. These variants were confirmed in trans by parental testing. NM_000419.3:c.1750C>T (Arg584Ter) does not meet PM2 so is not considered here.

Curation History

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