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Variant: NM_000212.3:c.812dup

Version: 1.0

CA915940807

2498362 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 07a52271-ea0f-4cb7-99fc-7026ad53f54b
Approved on: 2023/3/21
Published on: 2023/3/21

HGVS expressions

NM_000212.3:c.812dup
NC_000017.11:g.47287104dup
CM000679.2:g.47287104dup
NC_000017.10:g.45364470dup
CM000679.1:g.45364470dup
NC_000017.9:g.42719469dup
NG_008332.2:g.38263dup
ENST00000696963.1:c.812dup
ENST00000559488.7:c.812dup
ENST00000559488.5:c.812dup
ENST00000560629.1:c.777dup
ENST00000571680.1:c.812dup
NM_000212.2:c.812dup

Pathogenic

Met criteria codes 4

PM2_Supporting PVS1 PP4_Moderate PM3_Supporting

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 NM_000212.3(ITGB3):c.812dup variant is a frameshift variant in exon 6 predicted to cause a premature stop codon in exon 6/15 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). At least one patient (Patient 12 in PMID:15748237) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, αIIbβ3 surface expression was reduced to

0%, as measured by flow cytometry. Patient 12 (PMID:15748237) is homozygous for this variant (0.5pt; PM3_Supporting). The variant is absent from gnomAD, 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, PM3_Supporting (VCEP specifications version 2.1).

Met criteria codes

PM2_Supporting	✔	Variant is absent from gnomAD.
PVS1	✔	The c.812dup (p.Leu271PhefsTer7) variant in exon 6 is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 6/15 and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established mechanism (PVS1).
PP4_Moderate	✔	At least one patient (Patient 12 in PMID: 15748237) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, αIIbβ3 surface expression was reduced to 0% (<25%), as measured by flow cytometry. However, ITGA2B and ITGB3 were not reported to be sequenced across all exons and intron/exon boundaries.
PM3_Supporting	✔	This variant has been detected in at least 1 proband with Glanzmann thrombasthenia. One proband was homozygous for the variant (PMID:15748237). Total points: .5 (PM3_Supporting).

Curation History

Showing 1 to 1 of 1 rows

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