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_000419.5:c.1771dup

Version: 1.0

CA915940334

1879036 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 59b6d07d-2891-455f-864a-b6ecdc0e1550
Approved on: 2022/8/5
Published on: 2022/12/7

HGVS expressions

NM_000419.5:c.1771dup
NC_000017.11:g.44379798dup
CM000679.2:g.44379798dup
NC_000017.10:g.42457166dup
CM000679.1:g.42457166dup
NC_000017.9:g.39812692dup
NG_008331.1:g.14710dup
ENST00000262407.6:c.1771dup
ENST00000648408.1:c.1202dup
ENST00000262407.5:c.1771dup
ENST00000592462.5:n.566dup
NM_000419.3:c.1771dup
NM_000419.4:c.1771dup

Pathogenic

Met criteria codes 3

PP4_Strong | 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

NM_000419.5(ITGA2B):c.1771dup in exon 18 is a frameshift variant predicted to cause p.(p.Asp591GlyfsTer47), with a premature stop codon in exon 19/30 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). At least two patient (GT31 in PMID: 25728920 and the patient in PMID: 17488698) 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 <5%, as measured by flow cytometry (PP4_strong). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). In summary this variant meets 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_strong, PM2_supporting. (VCEP specifications version 2.1).

Met criteria codes

PP4_Strong	✔	At least two patient (GT31 in PMID: 25728920 and the patient in PMID: 17488698) 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 <5%, as measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. (PP4_strong)
PVS1	✔	NM_000419.5(ITGA2B):c.1771dup in exon 18 is a frameshift variant predicted to cause p.(p.Asp591GlyfsTer47), with a premature stop codon in exon 19/30 leading 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	✖	GT31 (PMID: 25728920) is compound heterozygous for c.1771dup and c.3061-1G>A. Confirmation of trans phase was not reported. The patient reported in PMID: 17488698 is compound heterozygous for c.1771dup and His813Asn. Variants are confirmed in trans by independent segregation in patient's daughters. Not considered here to avoid circularity.

Curation History

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