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Variant: NM_000212.3:c.847_848del

Version: 1.0

CA8623068

1879015 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 907012d1-5b88-46fa-9006-b06d9f6f099a
Approved on: 2022/11/15
Published on: 2022/12/7

HGVS expressions

NM_000212.3:c.847_848del
NC_000017.11:g.47287139_47287140del
CM000679.2:g.47287139_47287140del
NC_000017.10:g.45364505_45364506del
CM000679.1:g.45364505_45364506del
NC_000017.9:g.42719504_42719505del
NG_008332.2:g.38298_38299del
ENST00000696963.1:c.847_848del
ENST00000559488.7:c.847_848del
ENST00000559488.5:c.847_848del
ENST00000560629.1:c.812_813del
ENST00000571680.1:c.847_848del
NM_000212.2:c.847_848del

Pathogenic

Met criteria codes 3

PVS1 PM2_Supporting PP4_Strong

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 NM_000212.3(ITGB3):c.847_848del (p.Ala283IlefsTer12) frameshift variant causes a premature stop codon at exon 6 and is predicted to undergo nonsense mediated decay (PVS1). This variant has been reported in one compound heterozygous individual (Patient LD in PMID:10891446 which reported the variant as c.867_868del using an alternate nucleotide numbering system, confirmed in Figure 4). One affected individual displayed abnormal bleeding and an impaired response to agonists, with a normal response to ristocetin, which is

characteristic of GT). Additionally, αIIbβ3 was found to have a surface expression of 10% (<25%), as measured by flow cytometry (Patient LD in PMID:10891446; PP4_strong). The variant was found at a very low rate (0.000008796) in the European (Non-Finnish) population in 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_strong, PM2_supporting (VCEP specifications version 2.1).

Met criteria codes

PVS1	✔	The c.847_848del (p.Ala283IlefsTer12) 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 disease mechanism (PVS1).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is [0.000008796] (1/113688 alleles) in the European (Non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001), (PM2_Supporting).
PP4_Strong	✔	At least one patient (Patient LD in PMID:10891446) 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 10% (<25%), as measured by Western blot. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries (PP4_strong).

Not Met criteria codes

PM3	✖	This variant has been detected in at least 1 probands with Glanzmann thrombasthenia. For 1 of those individuals, 1 was compound heterozygous for this variant and a likely pathogenic variant c.863T>C (p.Leu288Pro) confirmed in trans by family testing (PMID:10891446, CAID:CA400024958). However, PM3 classification was not met to avoid circularity as PM3 was already applied for the c.863T>C (p.Leu288Pro) variant (Not Met).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View		Pathogenic	Glanzmann Thrombasthenia	2022-12-07	1.0	ClinGen Platelet Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2.1	ITGB3

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