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Variant: NM_000212.3:c.892C>T

Version: 1.0

CA400025098

1330332 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: b69cc91a-b563-41d5-a9a7-da4f9b6f7e07
Approved on: 2021/6/30
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HGVS expressions

NM_000212.3:c.892C>T
NC_000017.11:g.47287184C>T
CM000679.2:g.47287184C>T
NC_000017.10:g.45364550C>T
CM000679.1:g.45364550C>T
NC_000017.9:g.42719549C>T
NG_008332.2:g.38343C>T
ENST00000696963.1:c.892C>T
ENST00000559488.7:c.892C>T
ENST00000559488.5:c.892C>T
ENST00000560629.1:c.857C>T
ENST00000571680.1:c.892C>T
NM_000212.2:c.892C>T

Pathogenic

Met criteria codes 4

PM2_Supporting PVS1 PP4_Strong PM3_Supporting

Evidence Links 0

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000212.3(ITGB3):c.892C>T (p.Gln298Ter) nonsense variant creates 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 two probands has been reported with this variant, including GT28 of PMID: 29675921 who meets the criteria for PP4_strong. A second patient in PMID: 21136216 is homozygous for Gln298Ter (PM3_supporting). 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, PM2_supporting, PM3_supporting, PP4_strong. (VCEP specifications version 2; date of approval xx/xx/xxxx)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PVS1	✔	The NM_000212.3(ITGB3):c.892C>T (p.Gln298Ter) is a nonsense 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).
PP4_Strong	✔	GT28 of PMID: 29675921 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.
PM3_Supporting	✔	PMID: 21136216 Patient is homozygous for Gln298Ter (reported as 892C>T Arg272Ter but sequence trace in Figure 1 confirms it is Gln272Ter, legacy for Gln298Ter). 0.5pt (PM3_supporting). GT28 is compound heterozygous for Gln298Ter and c.1728del (Classified Pathogenic by the PD-VCEP). Confirmation of trans phase was not reported. Not considered here to avoid circularity.

Curation History

Showing 1 to 1 of 1 rows

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