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Variant: NM_000212.3:c.2222G>A

Version: 1.0

CA400034189

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: fc109f7d-50fd-4565-b5f2-92828c117ff9
Approved on: 2024/5/2
Published on: 2024/5/3

HGVS expressions

NM_000212.3:c.2222G>A
NC_000017.11:g.47307558G>A
CM000679.2:g.47307558G>A
NC_000017.10:g.45384924G>A
CM000679.1:g.45384924G>A
NC_000017.9:g.42739923G>A
NG_008332.2:g.58717G>A
ENST00000696963.1:c.2222G>A
ENST00000559488.7:c.2222G>A
ENST00000559488.5:c.2222G>A
ENST00000560629.1:c.2187G>A
NM_000212.2:c.2222G>A
NR_110880.1:n.363-3776C>T
NR_110881.1:n.227-3776C>T

Pathogenic

Met criteria codes 4

PVS1 PP4_Strong PM2_Supporting PS3_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.2222G>A (p.Trp741Ter) variant in exon 14 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 14 and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). Surface expression of αIIb and β3 measured by Western blot in HEK293T cells transiently co-transfected with the c.2222G>A

(p.Trp741Ter) variant β3 and wild type αIIb and β3 showed decreased expression at 0% WT levels, indicating that this variant impacts protein function (PMID: 37604334) (PS3_supporting). This variant has been detected in at least 1 proband with Glanzmann thrombasthenia (PMID: 37604334). This individual was compound heterozygous for this variant and a SINE-VNTR-Alu (SVA) retrotransposon insertion in ITGB3. This patient (Proband from PMID: 37604334) 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. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. (PP4_strong). This variant is absent from gnomAD v4.0.0 (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, PS3_supporting, PP4_Strong and PM2_Supporting (VCEP specifications version 2; date of approval 05/02/2024).

Met criteria codes

PVS1	✔	The c.2222G>A (p.Trp741Ter) variant in exon 14 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 14 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	✔	At least one patient (Proband from PMID: 37604334) 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. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. (PP4_strong).
PM2_Supporting	✔	This variant is absent from gnomAD v4.0.0 (PM2_Supporting).
PS3_Supporting	✔	Surface expression of αIIb and β3 measured by Western blot in HEK293T cells transiently co-transfected with the c.2222G>A (p.Trp741Ter) variant β3 and wild type αIIb and β3 showed decreased expression at 0% WT levels, indicating that this variant impacts protein function (PMID: 37604334) (PS3). Downgraded for a nonsense variant meeting PVS1.

Not Met criteria codes

PM3	✖	This variant has been detected in at least 1 proband with Glanzmann thrombasthenia (PMID: 37604334). This individual was compound heterozygous for this variant and a plausibly pathogenic SINE-VNTR-Alu (SVA) retrotransposon insertion in ITGB3. The variants were confirmed in trans by parental testing. The insertion has not been curated by the PD-VCEP (PM3_NotMet). SVA element was inserted in a sense orientation in intron 11 of ITGB3, resulting in aberrant splicing of ITGB3.

Curation History

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