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Variant: NM_000212.2(ITGB3):c.1924G>T (p.Glu642Ter)

Version: 1.0

CA123249

13565 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0f7b571b-c808-4fac-a319-7b5206f29a55
Approved on: 2021/12/21
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HGVS expressions

NM_000212.2:c.1924G>T
NM_000212.2(ITGB3):c.1924G>T (p.Glu642Ter)
NC_000017.11:g.47300488G>T
CM000679.2:g.47300488G>T
NC_000017.10:g.45377854G>T
CM000679.1:g.45377854G>T
NC_000017.9:g.42732853G>T
NG_008332.2:g.51647G>T
ENST00000696963.1:c.1924G>T
ENST00000559488.7:c.1924G>T
ENST00000559488.5:c.1924G>T
ENST00000560629.1:c.1889G>T
NM_000212.3:c.1924G>T

Pathogenic

Met criteria codes 5

PM3 PP4_Moderate PVS1_Strong PM2_Supporting PS3_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

NM_000212.2(ITGB3):c.1924G>T (p.Glu642Ter) in exon 12 of 15 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. However, RT-PCR analysis in the proband of PMID: 9845537 found that, instead, a shortened transcript was produced (in similar quantities to the normal allele) with in-frame skipping of exons 11 and 12 (reported by authors as exons 10 and 11, using alternate numbering), resulting in removal of 14% of the protein (PVS1_strong). CHO cells were transiently cotransfected with the plasmid pcDNA3-GPIIb and either WT or mutant pcDNA3-GPIIIa with this variant. To investigate the surface exposure of GPIIb-IIIa, intact cells were labeled with biotin, and the GPIIb-IIIa complexes were immunoprecipitated with anti-GPIIb (M3) or anti-GPIIIa (P37) MoAbs. No biotin-labeled products were found in cells cotransfected with normal GPIIb and mutant GPIIIa. Additionally, to examine the intracellular presence of GPIIb and/or GPIIIa as either monomers or heterodimers, total cell lysates were labeled with biotin, and GPIIb, GPIIIa, or GPIIb-IIIa

complexes were immunoprecipitated. Unlike in extracts from cells coexpressing normal subunits, heterodimers failed to immunoprecipitate using a complex-specific MoAb, suggesting that the mutant ΔGPIIIa does not complex with GPIIb. Pulse-chase experiments further verified that the mutant ΔGPIIIa does not complex to GPIIb (PMID: 9845537; PS3_supporting). This variant has been detected homozygous in at least 2 probands with Glanzmann thrombasthenia (PMIDs: 14985172, 9845537; PM3). At least one patient (Patient II.1 in PMID: 14985172) 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 <5%, as measured by flow cytometry and Western blot. 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_strong, PS3_supporting, PP4_moderate, PM3, PM2_supporitng. (VCEP specifications version 2; date of approval 12/21/21).

Met criteria codes

PM3	✔	This variant has been detected homozygous in at least 2 probands with Glanzmann thrombasthenia (PMIDs: 14985172, 9845537; PM3).
PP4_Moderate	✔	At least one patient (Patient II.1 in PMID: 14985172) 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 <5%, as measured by flow cytometry and Western blot. However, ITGA2B and ITGB3 were not sequenced across all exons and intron/exon boundaries.
PVS1_Strong	✔	NM_000212.2(ITGB3):c.1924G>T (p.Glu642Ter) in exon 12 of 15 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). However, RT-PCR analysis in the proband of PMID: 9845537 found that, instead, a shortened transcript was produced (in similar quantities to the normal allele) with in-frame skipping of exons 11 and 12 (reported by authors as exons 10 and 11, using alternate numbering), resulting in removal of 14% of the protein.
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS3_Supporting	✔	In PMID: 9845537 CHO cells were transiently cotransfected with the plasmid pcDNA3-GPIIb and either WT or mutant pcDNA3-GPIIIa. To investigate the surface exposure of GPIIb-IIIa, intact cells were labeled with biotin, and the GPIIb-IIIa complexes were immunoprecipitated with anti-GPIIb (M3) or anti-GPIIIa (P37) MoAbs. No biotin-labeled products were found in cells cotransfected with normal GPIIb and mutant GPIIIa. Additionally, to examine the intracellular presence of GPIIb and/or GPIIIa as either monomers or heterodimers, total cell lysates were labeled with biotin, and GPIIb, GPIIIa, or GPIIb-IIIa complexes were immunoprecipitated. Unlike in extracts from cells coexpressing normal subunits, heterodimers failed to immunoprecipitate using a complex-specific MoAb, suggesting that the mutant ΔGPIIIa does not complex with GPIIb. Pulse-chase experiments further verified that the mutant ΔGPIIIa does not complex to GPIIb. Downgraded to PS3_supporting because neither Western blot or flow cytometry were used to measure expression.

Curation History

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