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Variant: NM_000212.3:c.225_226del

Version: 1.0

CA626684825

1330313 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 549f1ce3-ed8e-471a-b899-8e5e43282d09
Approved on: 2021/11/9
Published on: 2021/12/23

HGVS expressions

NM_000212.3:c.225_226del
NC_000017.11:g.47283413_47283414del
CM000679.2:g.47283413_47283414del
NC_000017.10:g.45360779_45360780del
CM000679.1:g.45360779_45360780del
NC_000017.9:g.42715778_42715779del
NG_008332.2:g.34572_34573del
ENST00000696963.1:c.225_226del
ENST00000559488.7:c.225_226del
ENST00000559488.5:c.225_226del
ENST00000560629.1:c.190_191del
ENST00000571680.1:c.225_226del
NM_000212.2:c.225_226del

Pathogenic

Met criteria codes 4

PM3_Supporting PP4_Moderate PM2_Supporting PVS1

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_000212.3(ITGB3):c.225_226del (p.Ala76ProfsTer10) in exon 3 of ITGB3 is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 3/15 and is predicted to lead to nonsense mediated decay (PVS1). GT7 of PMID: 32237906 displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, β3 surface expression was reduced to 0.3%, as measured by flow cytometry. GT7 (PMID: 32237906) is compound heterozygous for c.225_226del and Arg242Ter (classified Pathogenic by the PD-VCEP; PM3_supporting). The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001087 (2/18394 alleles) in the East Asian population, which is lower than the ClinGen PD VCEP threshold (<0.0001; 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_moderate, PM2_supporting, PM3_supporting. (VCEP specifications version 2; date of approval 11/04/2021)

Met criteria codes

PM3_Supporting	✔	GT7 (PMID: 32237906) is compound heterozygous for c.225_226del and Arg242Ter (classified Pathogenic by the PD-VCEP). Confirmation of trans phase was not reported.
PP4_Moderate	✔	GT7 (PMID: 32237906) displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, β3 surface expression was reduced to 0.3%, as measured by flow cytometry. However, ITGA2B and ITGB3 were not reported to be sequenced across all exons and intron/exon boundaries.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001087 (2/18394 alleles) in the East Asian population, an additional 2820 alleles in gnomAD v3.1.1 did not have the variant for a total of 2/21214 alleles or 0.000942, which is below the ClinGen PD VCEP threshold (<0.0001).
PVS1	✔	The c.225_226del (p.Ala76ProfsTer10) variant in exon 3 of ITGB3 is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 3/15 and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).

Curation History

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