Variant: NM_000212.2(ITGB3):c.176T>C (p.Leu59Pro)

Version: 1.0

CA123235

13558 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 55e31015-4a08-43d4-8768-dba28433a961
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HGVS expressions

NM_000212.2:c.176T>C
NM_000212.2(ITGB3):c.176T>C (p.Leu59Pro)
NC_000017.11:g.47283364T>C
CM000679.2:g.47283364T>C
NC_000017.10:g.45360730T>C
CM000679.1:g.45360730T>C
NC_000017.9:g.42715729T>C
NG_008332.2:g.34523T>C
ENST00000696963.1:c.176T>C
ENST00000559488.7:c.176T>C
ENST00000559488.5:c.176T>C
ENST00000560629.1:c.141T>C
ENST00000571680.1:c.176T>C
NM_000212.3:c.176T>C

Benign

Met criteria codes 4

BA1 BS3 BP4 BP2

Not Met criteria codes 2

BS2 PM5

Evidence Links 2

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The ITGB3 c.176T>C (p.Leu59Pro) missense variant has been reported many times in the literature as an alloantigenic site. This variant has been observed in cis with several other Glanzmann thrombasthenia variants, including the pathogenic c.224del frameshift variant (PMID: 25728920). It is present in gnomAD at an overall allele frequency of 0.1223 (and 0.1550 in the non-Finnish European population). Computational evidence suggest no impact on the gene/gene product, with a REVEL score of 0.217. Functional studies in CHO cells have shown no deleterious effect on surface expression or fibrinogen binding (PMID: 10727448). In summary, this variant meets criteria to be classified as benign for GT. GT-specific criteria applied: BA1, BS3, BP2, BP4.

Met criteria codes

BA1	✔	The overall allele frequency reported in gnomAD is 0.1223. The highest allele frequency in a major continental population is 0.1550 in the non-Finnish European population (19,976/128,876 alleles). This is above the >0.24% threshold.
BS3	✔	PMID: 10727448: Stable CHO cell lines were established expressing either the WT Leu59 or Pro59 variant ITGB3 with the WT ITGA2B. Surface expression (examined by flow cytometry), adhesive properties (by measurement of the binding of the LIBS antibody), and binding to soluble fibrinogen, were all normal. Stable CHO cell lines were established expressing either the WT Leu59 or Pro59 variant ITGB3 with the WT ITGA2B. Surface expression (examined by flow cytometry), adhesive properties (by measurement of the binding of the LIBS antibody), and binding to soluble fibrinogen, were all normal. Significantly greater cell adhesion was observed over a range of immobilized fibrinogen concentrations for the Leu59Pro variant. A small but consistent increase in pp125FAK phosphorylation was observed in the Leu59Pro cells compared with the WT cells that had adhered to fibrinogen. Similar results were observed in 293 cells, which also displayed normal surface expression. PubMed:10727448
BP4	✔	The REVEL score of 0.217 is below the <0.25 threshold.
BP2	✔	This variant has been observed in cis with several other variants, including c.224del frameshift variant (PMID: 27469266 and PMID: 25728920), classified as pathogenic by the Platelet Disorders VCEP. The Leu59Pro variant was observed in cis with ITGB3 variants c.565C>T (p.Pro189Ser) in patient GT12 and c.224del (p.Cys75Leufs) in patient GT61. As well as in cis with ITGA2B variants c.3148dup (p.Leu717Alafs) in patient GT42, and c.1544+1G>A (p.Val513Leufs) in patients GT19 and GT24. Each of these patients are homozygous for Leu59Pro as reported in PMID: 27469266. PubMed:25728920

Not Met criteria codes

BS2	✖	Although homozygosity has been reported in population databases (2419 individuals in the gnomAD cohort) of reportedly healthy individuals, phenotypic data is not available.
PM5	✖	Additional alloantigenic variant Leu59Val has also been observed at this residue. The ClinGen Platelet Disorders VCEP has classified Leu59Val as Likely Benign.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000212.2(ITGB3):c.176T>C (p.Leu...	Benign	Glanzmann's Thrombasthenia	2021-01-22	1.0	-	ITGB3

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