The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000419.3(ITGA2B):c.1787T>C

Version: 1.2

CA115846

2900 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: c6b42f33-92f7-4a71-822b-932469bd66ae
Approved on: 2023/11/17
Published on: 2023/11/3

HGVS expressions

NM_000419.3(ITGA2B):c.1787T>C
NC_000017.11:g.44379780A>G
CM000679.2:g.44379780A>G
NC_000017.10:g.42457148A>G
CM000679.1:g.42457148A>G
NC_000017.9:g.39812674A>G
NG_008331.1:g.14726T>C
ENST00000262407.6:c.1787T>C
ENST00000648408.1:c.1218T>C
ENST00000262407.5:c.1787T>C
ENST00000592462.5:n.582T>C
NM_000419.3:c.1787T>C
NM_000419.4:c.1787T>C
NM_000419.5:c.1787T>C

Pathogenic

Met criteria codes 4

PP4_Strong PM2_Supporting PM3_Strong PP1

Not Met criteria codes 1

PP3

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 NM_000419.5(ITGA2B):c.1787T>C (p.Ile596Thr) missense variant has been reported in the homozygous state in at least 2 apparently unrelated individuals (PMID: 22513797, 20020534) and in the compound heterozygous state in 4 individuals (PMID: 9215749, 9734640, 34552732, 25373348). The second variants in these patients are c.3060+2T>C (classified Pathogenic by the PD-VCEP; without confirmation

of trans phase), Glu355Lys (classified Pathogenic by the PD-VCEP; with confirmation of trans phase), c.2841+1G>T, and c.408G>C (latter two not considered here to avoid circularity) respectively (PM3_Strong). The proband from PMID: 22513797 meets criteria for PP4_Strong including mucocutaneous bleeding; abnormal platelet aggregometry in response to at least 2 agonist and normal response to ristocetin; absent surface expression of GPIIb-IIIa on flow cytometry; and full sequencing of ITGA2B and ITGB3. It was found to co-segregate with disease in 1 additional family member (PP1). Ile596Thr is reported in gnomAD v4.0.0 at a frequency of 0.00008305 (98/1179968 alleles) in the non-Finnish European population, below the PM2_supporting threshold of <0.0001. In summary, this variant is classified Pathogenic for autosomal recessive Glanzmann thrombasthenia. GT-specific codes applied: PP4_Strong, PM2_Supporting, PM3_Strong, PP1. (PD-VCEP specifications version 2)

Met criteria codes

PP4_Strong	✔	Proband from PMID: 22513797 meet criteria for PP4_Strong including mucocutaneous bleeding; abnormal platelet aggregometry in response to at least 2 agonist and normal response to ristocetin; absent surface expression of GPIIb-IIIa on flow cytometry; and full sequencing of ITGA2B and ITGB3.
PM2_Supporting	✔	Ile596Thr is reported in gnomAD v4.0.0 at a frequency of 0.00008305 (98/1179968 alleles) in the non-Finnish European population, below the PM2_supporting threshold of <0.0001.
PM3_Strong	✔	The variant has been observed in the homozygous state in at least 2 apparently unrelated individuals (PMID: 22513797, 20020534; 1pt) and in the compound heterozygous state in 4 individuals (PMID: 9215749, 9734640, 34552732, 25373348). The second variants in these patients are c.3060+2T>C (classified Pathogenic by the PD-VCEP without confirmation of trans phase 0.5pt), Glu355Lys (classified Pathogenic by the PD-VCEP with confirmation of trans phase 1pt), c.2841+1G>T, and c.408G>C (latter two not considered here to avoid circularity) respectively. Total 2.5pt; PM3_Strong
PP1	✔	Patient 3 is the 16yo sister of the proband, Patient 4. Both siblings are diagnosed with GT, homozygous for the variant and meet phenotype criteria, thus meeting PP1

Not Met criteria codes

PP3	✖	In-silico evidence is available from PMID: 29385657: the authors suggest that Ile596 is a likely mutational hot spot; it is relatively well conserved both between species and within human α-subunits. They report that the Thr introduces an -OH alcoholic function close to Arg551, which competes for H-bonds with residues Asp542, Ser594 and Asp591 changing interatom distances and creating an additional H-bond within connecting loops extending from the lower region of the thigh. However, the Ile596Thr variant has a REVEL score <0.7: 0.628.

Curation History

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