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_000419.5:c.527C>A

Version: 1.1

CA8603447

953014 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 69629f95-09fa-4449-82e5-95598024737d
Approved on: 2021/3/5
Published on: 2021/3/5

HGVS expressions

NM_000419.5:c.527C>A
NC_000017.11:g.44385598G>T
CM000679.2:g.44385598G>T
NC_000017.10:g.42462966G>T
CM000679.1:g.42462966G>T
NC_000017.9:g.39818492G>T
NG_008331.1:g.8908C>A
ENST00000262407.6:c.527C>A
ENST00000262407.5:c.527C>A
ENST00000592944.1:n.212C>A
NM_000419.3:c.527C>A
NM_000419.4:c.527C>A

Likely Pathogenic

Met criteria codes 4

PP3 PM5 PM2_Supporting PS3_Moderate

Evidence Links 1

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000419.4:c.527C>A (p.Pro176His) missense variant was identified from an individual in The National Heart, Lung and Blood Institute Exome Sequencing Project (ESP) whose full genotype and phenotype were not reported. It occurs at an extremely low frequency of 0.000008248 in the African population of gnomAD. It is predicted to have a deleterious effect (REVEL score of 0.913) which was confirmed by functional studies showing virtually no mature GPIIb protein in transfected HEK293 cells (PMID: 25827233). This variant occurs at the same residue as the pathogenic variant Pro176Ala. In summary, this variant meets criteria to be classified as Likely Pathogenic for GT. GT specific criteria used: PS3_moderate, PM2_Supporting, PM5, PP3.

Met criteria codes

PP3	ℹ	✔	SIFT (Damaging), Polyphen2-HDIV (probably Damaging), and Mutation Taster (disease causing) agree that this variant has a deleterious effect and the REVEL score is 0.913, above the >0.7 threshold.
PM5	ℹ	✔	The Pro176His variant occurs at the same residue as the previously classified Pathogenic Pro176Ala variant. The additional likely pathogenic Pro176Leu variant is not considered here.
PM2_Supporting	ℹ	✔	This variant is at an extremely low frequency (below the <1/10,000 threshold) with an overall allele frequency from gnomAD of 0.000008248 and MAF of 0.00006689 (1/14,950 alleles) in the African population.
PS3_Moderate	ℹ	✔	In PMID: 25827233 the Pro176His GPIIb was expressed in HEK293 cells which showed virtually no mature GPIIb protein by immunoblot. The Pro176His GPIIb was expressed in HEK293 cells which showed virtually no mature GPIIb protein by immunoblot or surface expression of the GPIIb/IIIa complex by flow cytometry (<5% positive cells). PubMed:25827233

Curation History

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