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Variant: NM_000419.4(ITGA2B):c.641T>C (p.Leu214Pro)

Version: 1.0

CA115848

2901 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 99e33fc5-37e3-4481-a9c5-52cd04f26ea6
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HGVS expressions

NM_000419.4:c.641T>C
NM_000419.4(ITGA2B):c.641T>C (p.Leu214Pro)
NM_000419.3:c.641T>C
NM_000419.5:c.641T>C
ENST00000262407.5:c.641T>C
ENST00000589645.5:n.92T>C
ENST00000591990.5:n.3T>C
ENST00000592075.5:n.10T>C
ENST00000592226.5:n.10T>C
ENST00000592253.5:n.149T>C
ENST00000592944.1:n.323T>C
NC_000017.11:g.44385193A>G
CM000679.2:g.44385193A>G
NC_000017.10:g.42462561A>G
CM000679.1:g.42462561A>G
NC_000017.9:g.39818087A>G
NG_008331.1:g.9313T>C

Pathogenic

Met criteria codes 5

PM2_Supporting PS3 PP3 PM3 PP4_Moderate

Evidence Links 5

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.641T>C variant that results in the Leu214Pro amino acid change is reported in five homozygous individuals in the literature (PMID: 19691478, 9473221, 21113249). It is absent in population databases and is predicted damaging by in-silico tools. Experimental evidence shows moderate levels of surface expression of the GPIIb-IIIa complex, but impaired fibrinogen and PAC-1 binding. In summary, based on available evidence at this time, the Leu214Pro variant is classified as pathogenic. GT-specific criteria applied: PS3, PM2_supporting, PM3, PP3, PP4_moderate.

Met criteria codes

PM2_Supporting	✔	Leu214Pro is not reported in gnomAD or other population databases and meets PM2.
PS3	✔	Evidence from PMID: 9473221 meets criteria for PS3. Transfection in CHO cells revealed ~60% expression of the αIIbβ3 complex but PAC-1 and fibrinogen binding were similar to background levels. Patient-derived mutant cDNA construct was expressed in CHO cells with normal β3. Flow cytometry revealed ~60% expression of the αIIbβ3 complex. PAC-1 binding measured by flow cytometry showed mutant-expressing cells were similar to mock-transfected cells in PAC-1 binding. Similarly, fibrinogen binding of mutant-expressing cells was similar to the background binding levels observed in mock-transfected cells. PubMed:9473221
PP3	✔	The variant has a REVEL score of 0.798 (recommended threshold >0.7) and meets PP3
PM3	✔	3 homozygous individuals from PMID: 19691478 contribute to an overall score of 1 pt towards PM3. The compound heterozygous proband GT-2 of The compound heterozygotes PMID: 25539746 harbors pathogenic variant c.2473_2481delinsTCACCTGGTC. 0.5pt (PMIDs: 27696190, 27607598) with c.2602-3C>G and Gly412Arg were not counted to avoid circularity. Patient was a compound heterozygote for c.641T>C (p.Leu214Pro) and pathogenic variant c.1234G>A (p.Gly412Arg). The variants were confirmed to be in trans by parental testing. However, to avoid circularity the proband was counted only towards the classification Gly412Arg not Leu214Pro. PubMed:27607598 The proband in this paper is a compound heterozygote with this c.2602-3C>G splice variant and c.641T>C (Leu214Pro). To avoid circularity the proband was counted only towards the classification c.2602-3C>G not Leu214Pro. PubMed:27696190 3 homozygous individuals, GT12, GT26 and GT68 meet criteria for PM3. PubMed:19691478
PP4_Moderate	✔	3 individuals with Type III GT from PMID: 19691478 meet criteria for PP4_moderate; including mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin. 3 homozygous individuals with normal platelet count and size. Patients had a history of mucocutaneous bleeding, showed absent or reduced platelet aggregation with ADP, adrenaline, arachidonic acid, and collagen, but normal aggregation to ristocetin. αIIbβ3 expression was between 20% and normal and western blot analysis showed reduced αIIbβ3. PubMed:19691478 55yo male with repeated episodes of epistaxis, excessive bleeding after dental extractions and lacerations, and pharyngeal and gastric bleeding. Several of these episodes required platelet transfusion. The proband's parents were non-consanguineous. Platelet aggregation in response to ADP was absent, but normal to ristocetin. Clot retraction was absent in 1hr and partial in 24hrs. GPIIIa level in the patient's platelets was determined to be ≈35% of normal while total of proGPIIb and mature GPIIb was estimated to be ≈30% of normal, by Western blotting. Platelet fibrinogen levels were ~5% of normal, evaluated by scanning densitometry of SDS-PAGE gels. This proband does not meet criteria for PP4 due to the absence of platelet count information and aggregometry data on at least 2 agonists other than ristocetin. PubMed:9473221 Male proband with a history of spontaneous or life-threatening hemorrhages, including gastrointestinal bleeding. The authors note that he may have had repeated episodes requiring platelet transfusion. Flow cytometry showed <1% αIIb expression and <1% PAC-1 binding. Platelet aggregation in response to ADP and collagen was reduced, while that to ristocetin was slightly inhibited. This proband does not meet criteria for PP4 due to the absence of platelet count information as well as the slightly inhibited platelet aggregation in response to ristocetin, which is expected to be normal in GT patients. PubMed:21113249

Curation History

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