

Variant: NM_000419.4:c.257T>C

Version: 1.2

CA290956162 [↗](#)

953037 (ClinVar) [↗](#)

Gene: ITGA2B ([HGNC:3674](#))

Condition: Glanzmann's thrombasthenia ([MONDO:0010119](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: d20044ce-4787-4553-bd2d-0af11fd1ecb9

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HGVS expressions

NM_000419.4:c.257T>C

NC_000017.11:g.44386063A>G

CM000679.2:g.44386063A>G

NC_000017.10:g.42463431A>G

CM000679.1:g.42463431A>G

NC_000017.9:g.39818957A>G

NG_008331.1:g.8443T>C

ENST00000262407.6:c.257T>C

ENST00000262407.5:c.257T>C

NM_000419.3:c.257T>C

NM_000419.5:c.257T>C

Pathogenic

Met criteria codes **5**

PM2_Supporting

PS3_Moderate

PP4_Strong

PP3

PM3

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 ITGA2B missense variant c.257T>C (p.Leu86Pro), is demonstrated to cause reduced integrin surface expression in transfection experiments in COS7 cells (PMID: 12181054). The variant is absent from population databases. It has a REVEL score >0.7 (0.859). At least 2 compound heterozygous probands are reported in the literature (PMID: 12181054, 25728920). One proband has the pathogenic c.1440-13_1440-1del variant (assessed by Platelet Disorders VCEP) in trans (without phase confirmation). In summary, based on the available evidence at this time, the Leu86Pro variant is classified "Pathogenic". GT-specific criteria applied: PS3_Moderate, PM2_Supporting, PM3, PP3, PP4_Strong.

Met criteria codes

PM2_Supporting



The variant is absent from population databases, including gnomAD v2.1.1 and v3, meeting criteria for PM2.

PS3_Moderate			<p>In PMID12181054 transient co-expression of the Leu86Pro ITGA2B variant and wild type ITGB3 in COS7 cells and αIIbβ3 cell surface expression detection by flow cytometry demonstrated that the variant led to reduced αIIbβ3 expression levels (expression is 12.7-14.7% of control expression levels; meeting the 5-25% expression threshold for moderate evidence).</p> <hr/> <p>cDNA constructs bearing the wild-type αIIb containing Leu86 or mutants, Pro86, Gln86 and Arg86 were generated to transfect COS7 cells along with wild-type β3 constructs. Surface expression of αIIbβ3, measured by flow cytometry, was remarkably reduced in cell transfected with Pro86 (mean relative values: 12.7% & 14.7%; Figure 2) compared to wild-type αIIb. In contrast, the Gln86 and Arg86 mutants showed expression levels similar to wild type.</p> <p>PubMed:12181054 </p>
PP4_Strong			<p>Proband GT64 from PMID: 25728920 meets all requirements for PP4_Strong are met: bleeding symptoms; lack of platelet aggregation in response to various agonists; flow cytometry showed <5% expression of αIIbβ3; sequencing of coding regions and splice sites of ITGA2B and ITGB3.</p> <hr/> <p>21y/F with history of purpura and epistaxis. The authors note that flow cytometry and western blotting revealed markedly reduced expression of integrating αIIbβ3, but data is not shown. The patient was compound heterozygous for Leu86Pro (inherited from father) and Gln778Pro (inherited from mother), confirmed in trans. No information on CBC, platelet morphology, LTA analysis. PubMed:12181054 </p> <p>GT64 is a 26yo female of French ancestry, with epistaxis, mouth and tonsil bleeding, easy bruising, menorrhagia, and a bleeding score of 3. She had gingivorragia and ecchymoses as an adult and has received RBC and platelet transfusion. Platelet aggregation was absent with 3 agonists, but normal with ristocetin. αIIbβ3 expression assessed by flow cytometry was <5%. She is compound heterozygous for Leu86Pro and c.1440-13_1440-1del. Phase was not confirmed. PubMed:25728920 </p>
PP3			<p>The Leu86Pro variant has a REVEL score of 0.859 (threshold >0.7) meeting criteria for PP3.</p>
PM3			<p>GT64 from PMID: 25728920 is compound heterozygous for Leu86Pro and the c.1440-13_1440-1del variant, which is classified as pathogenic by the Platelet Disorders VCEP. Since phase is not confirmed in this proband, 0.5 pts is applied. The proband from PMID: 12181054 is compound heterozygous for Gln778Pro and Leu86Pro, confirmed in trans.1pt</p> <hr/> <p>Proband GT64 is compound heterozygous for this variant and the c.1440-13_1440-1del variant, which is classified as pathogenic by the Platelet Disorders VCEP. Since phase is not confirmed in this proband, 0.5 pts is applied towards PM3 scoring. PubMed:25728920 </p>

Curation History

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