

Variant: *NM_000212.2(ITGB3):c.433G>T (p.Asp145Tyr)*

Version: 1.0

CA123226 [↗](#)

13554 (ClinVar) [↗](#)

Gene: ITGB3 ([HGNC:3690](#))

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 5a88ad57-bb3d-49ef-8dd3-2e7628ef1a81

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HGVS expressions

NM_000212.2(ITGB3):c.433G>T (p.Asp145Tyr)

NM_000212.2:c.433G>T

NC_000017.11:g.47284514G>T

CM000679.2:g.47284514G>T

NC_000017.10:g.45361880G>T

CM000679.1:g.45361880G>T

NC_000017.9:g.42716879G>T

NG_008332.2:g.35673G>T

ENST00000696963.1:c.433G>T

ENST00000559488.7:c.433G>T

ENST00000559488.5:c.433G>T

ENST00000560629.1:c.398G>T

ENST00000571680.1:c.433G>T

NM_000212.3:c.433G>T

Pathogenic

Met criteria codes 6

PM2_Supporting

PP4_Moderate

PM3_Supporting

PS3

PP1

PP3

Not Met criteria codes 1

PM5

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Expert Panel

Platelet Disorders VCEP [↗](#)

Criteria Specification Information ⓘ

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000212.2(ITGB3):c.433G>T (p.Asp145Tyr) is a missense variant that is expressed normally on the platelet surface, but lacks the function of ligand binding (PMID: 2392682, PMID:15583747). It has been reported in 2 siblings with variant GT, in the homozygous state (PMIDs: 2428841, 2392682, 7520434) and a compound heterozygote (with Met150Val;PMID: 15583747). It is absent from population databases and has a REVEL score of 0.972 (threshold: >0.7). In summary, based on the available evidence at this time, the variant is classified as Pathogenic. GT-specific criteria applied: PS3, PM2_Supporting, PP1, PP3, PP4_Moderate, PM3_Supporting.

Met criteria codes

PM2_Supporting			Asp145Tyr is not reported in population databases, including gnomAD, and meets criteria for PM2.
PP4_Moderate			Proband of PMID: 15583747 had a history of mucocutaneous bleeding episodes and unprovoked bruising, prolonged bleeding time, normal platelet count and size, absent aggregation in response to ADP, adrenaline, and arachidonic acid, normal ristocetin-induced platelet agglutination. Surface expression, measured by flow cytometry and western blotting, was only reduced ~60% however binding of Fibrinogen and PAC-1 was significantly reduced. Meets the criteria for PP4_moderate; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression/dysfunction of αIIbβ3. Two male infant with sudden episode of limpness, cyanosis, and apnea, petechiae over his face and chest, nose and mouth bleeding, easy bruising. Osteopetrosis and pulmonary hemorrhage were diagnosed. Exome sequencing revealed homozygous Asp145Tyr variant. GT was not initially diagnosed in the patient. Platelet aggregation or expression studies were not done. Proband does not meet criteria for PP4. PubMed:30828542  At least 2 affected individuals (siblings of Guamanian origin) reported in this paper with epistaxis, mucus membrane bleeding, GI hemorrhage and soft-tissue bleeding since neonatal life. Bleeding episodes have been controlled with platelet transfusion. Platelet aggregation was absent in response to ADP or thrombin, but normal to ristocetin. Clot retraction was absent and bleeding times >20 minutes. Platelet size and morphology were normal. Platelets bound Fg, fibronectin, VWF negligibly when activated with thrombin. Platelet integrin content was similar to normal platelets as measured by SDS-PAGE, 2D electrophoresis and 2D tryptic peptide maps. Crossed immunoelectrophoresis revealed absence of platelet fibrinogen. At least 50% GPIIb content was estimated based on PM-1 antibody binding to platelets. The genotype of these individuals is reported in PMID: 2392682. Two siblings are reported to be homozygous for the Asp145Tyr variant. PubMed:2428841  2 siblings described in PMID: 2428841 were genotyped and found to be homozygous for the Asp145Tyr variant. PubMed:2392682 
PM3_Supporting			1 homozygous individual meets criteria for PM3_Supporting. The compound heterozygous individual (with Met150Val) was not included here to avoid circularity. 1 patient with variant GT was homozygous for Asp145Tyr PubMed:2428841  PubMed:15583747 
PS3			From PMID:15583747 expression in CHO cells found that the variant disrupts function; using flow cytometry the Asp145Tyr complex did not bind fibrinogen or PAC-1. CHO cell lines were transfected with normal αIIb and either normal β3 or the Asp145Tyr (referred to as Asp119Tyr) mutant. Cells transfected with the mutant form did not have reduced expression of the αIIbβ3 complex. However, function was disrupted as determined by functional flow cytometry; the Asp145Tyr complex did not bind fibrinogen or PAC-1. PubMed:15583747 

Asp145Tyr-bearing $\beta 3$ cDNA vector was co-transfected with wild-type $\alpha I I b$ or wild-type αv into CHO cells. Wild-type $\beta 3$ vectors were used as controls. Surface expression of integrins $\alpha I I b \beta 3$ or $\alpha v \beta 3$ with the Cam variant was found to be normal. However, the mutant $\alpha I I b \beta 3$ was found to be defective in divalent cation binding, detected by PM-1 antibody binding. Flow cytometry showed that RGD peptide ligands did not upregulate LIBS1 binding to the mutant $\alpha I I b \beta 3$. Direct interaction of RGD ligand with the receptor detected by affinity chromatography showed lack of ligand binding. [PubMed:2392682](#)

PP1

i

✓

The sibling of proband in from PMID: 2428841 (individuals of Guamanian origin) are reported homozygous for the variant, meeting criteria for PP1.

PubMed:2428841

PP3

i

✓

The variant has a REVEL score of 0.972 (threshold: >0.7) and meets criteria for PP3.

Not Met criteria codes

PM5

i

✗

This variant is evaluated as it is reported at the same residue as another likely pathogenic variant, Asp145Asn. PM5_supporting has been applied towards the classification of Asp145Asn, and is therefore not met here to avoid circularity.

Curation History

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