AUTOSOMAL DOMINANT *ITGA2B* AND *ITGB3* VARIANTS EXPAND THE PHENOTYPIC SPECTRUM OF AIIBB3-RELATED PLATELET DISORDERS

S. Ferrari, D. Regazzo, L. Onorati, A. Galbiati, L. Spiezia, A. Bertomoro, P. Simioni

Department of Medicine, University of Padova, Italy

Background and Aims. Autosomal dominant thrombocytopenias caused by heterozygous *ITGA2B* and *ITGB3* pathogenic variants are increasingly recognized as a distinct entity from classical Glanzmann thrombasthenia (GT). These disorders typically present with mild thrombocytopenia, variable platelet function defects, and heterogeneous bleeding severity. However, given their rarity, they remain poorly defined from a clinical, biochemical, and genetic perspective. We aim to describe the clinical, laboratory, and molecular features of two previously unreported heterozygous variants in *ITGA2B* and *ITGB3* genes identified in two unrelated families with autosomal dominant inheritance.

Methods. Affected individuals underwent standardized bleeding assessment using ISTH Bleeding Assessment Tool (BAT), platelet count followed by aggregation studies, performed on platelet-rich plasma using the Born method (Chronolog). Flow cytometric analysis of αIIbβ3 expression was conducted assessing CD41a expression and PAC-1 binding following ADP stimulation. Genetic analysis was performed in the proband using targeted next-generation sequencing. Identified variants were validated and tested for segregation in available family members by Sanger sequencing. Variant pathogenicity was assessed according to ACMG criteria. Reference transcripts were NM_000419.5 (*ITGA2B*) and NM_000212.3 (*ITGB3*). Structural impact was evaluated by in silico modelling.

Results. Among Family 1 carriers (5/7 individuals), the heterozygous *ITGA2B* p.Gly549Asp (c.1646G>A) (Class 4) variant co-segregated with mild thrombocytopenia and mucocutaneous bleeding. The proband showed mildly reduced platelet count (~96×10^9/L), anisocytosis, and occasional macrothrombocytes. BAT scores ranged from 1 to 7 among the carriers. Platelet aggregation was partially impaired, and above normal range in response to ADP, collagen, and epinephrine, while ristocetin-induced aggregation was preserved (Table 1). Flow cytometry revealed reduced CD41a expression and impaired PAC-1 activation after ADP stimulation. In silico structural modelling suggested destabilization of the extracellular αIIb domain (Table 1). In Family 2, the heterozygous *ITGB3* p.Arg662His (c.1985G>A)(Class 4) variant, affecting the same residue as the Sra alloantigen, previously associated with neonatal alloimmune thrombocytopenia, was identified in the proband, his sister, and father (3/4 individuals). The proband exhibited mild thrombocytopenia (~100×10^9/L), a BAT score of 1, normal platelet aggregation, and normal αIIbβ3 surface expression, consistent with a very mild or subclinical phenotype with variable expressivity.

Conclusions. These findings expand the spectrum of αIIbβ3-related autosomal dominant platelet disorders and highlight significant gene- and variant-specific phenotypic variability. Recognition of these often subtle and heterogeneous presentations is essential for accurate molecular diagnosis and appropriate genetic counselling. The contrasting phenotypes observed between the two families further suggest a continuum of disease severity ranging from functional impairment to near-normal platelet function despite thrombocytopenia depending on a variant-specific effect on αIIbβ3 expression and activation. These observations also underscore the importance of including *ITGA2B* and *ITGB3* in diagnostic workflows for inherited thrombocytopenias, particularly in cases with mild or atypical phenotypes that may be misdiagnosed as other platelet disorders.

	CLINICAL AND LABORATORY FEATURES													
	FAMILY 1	Proposita	Sister	Son	Daughter	Nephew	Niece 1	Niece 2	**FAMILY 2**	Proposita	Sister	Father	Mother
	Age	74	71	42	48	40	34	31	Age	29	31	65	65
	Platelet count (x10^9/l)	96	62	115	127	205	139	185	Platelet count (x10^9/l)	110	170	250	320
	platelet anisocytosis	yes	yes	yes	yes	yes	yes	no	platelet anisocytosis	yes	yes	no	na
	Hemorragic symptoms/ BAT score	Ecchymosis, hematoma after tooth extraction, (3)	Hemorrhoids, ecchymosis (2)	Gingival bleeding/ (1)	Gingival bleeding, ecchymosis, epistaxis, bleeding in the course of miscarriage/ (7)	0	Gingival bleeding (1)	Ecchymosis (1)	Hemorragic symptoms/ BAT score	Epistaxis (1)	0	0	0
Flow cytometry (PRP)	CD41 (GPIb-IIIa-complex)	reduced	reduced	reduced	normal	normal	reduced	normal	CD41 (GPIb-IIIa-complex)	normal	normal	normal	normal
	CD42a (GP9)	normal	normal	normal	normal	normal	normal	normal	CD42a (GP9)	normal	normal	normal	normal
	CD42b (GPIBA)	normal	normal	normal	normal	normal	normal	normal	CD42b (GPIBA)	normal	normal	normal	normal
	CD49b (GPIa-IIa)	normal	normal	normal	reduced	normal	normal	normal	CD49b (GPIa-IIa)	normal	normal	normal	normal
	PAC1 ADP (activated GpIIb-IIIa)	normal	reduced	normal	reduced	normal	normal	normal	PAC1 ADP (activated GpIIb-IIIa)	normal	normal	normal	normal
	CD62P selectin	normal	normal	normal	normal	normal	normal	normal	CD62P selectin	normal	normal	normal	normal
Aggregometry (Born Test*)	Collagen 2µg/ml (N.V. 72-98%)	33%	22%	59%	28%	71%	81%	75%	Collagen 2µg/ml (N.V. 72-98%)	83%	96%		
	Adrenaline 10 µM (N.V. 62-92%)	18%	17%	26%	17%	68%	25%	23%	Adrenaline 10 µM (N.V. 62-92%)	79%	78%		
	ADP 2 µM (N.V. 60-100%)	26%	24%	27%	26%	23%	27%	23%	ADP 2 µM (N.V. 60-100%)	20%	33%	na	na
	ADP 10 µM (N.V. 60-100%)	23%	18%	31%	41%	69%	34%	74%	ADP 10 µM (N.V. 60-100%)	83%	74%		
	Ristocetin 1.2mg/ml (N.V. 77-100%)	68%	75%	78%	68%	83%	79%	82%	Ristocetin 1.2mg/ml (N.V. 77-100%)	86%	84%		
Genetic variant	ITGA2B (NM_000419.5), p.Gly549Asp, c.1646G>A	heterozygote	heterozygote	heterozygote	heterozygote	wt	heterozygote	wt	ITGB3 (NM_000212.2) p.Arg662His, c.1985G>A	heterozygote	heterozygote	heterozygote	wt

Table 1. Clinical and laboratory characteristics of the subjects. n.a.= Not available. N.V.= Normal Value. * performed on platelet rich plasma. ^performed on whole blood, PRP= platelet rich plasma; BAT= Bleeding Assessment Tool