

SUPPLEMENTARY MATERIAL**Inherited platelet function disorders: a comprehensive narrative review focusing on diagnostic and management aspects**

Antonietta Ferretti,¹ Nicola Portesi,² Chiara Gorio,³ Marzia Leotta,⁴ Alessandra Strangio,⁴ Antonella Ierardi,⁴ Bianca Maria Roccon,⁵ Giulia Albrici,³ Giulia Carracchia,³ Marta Mattana,⁶ Chiara Biasoli,⁷ Cristina Santoro,⁸ Tiziano Martini,⁹ Rita Carlotta Santoro,⁴ on behalf of AICE

¹Department of Hemorrhagic and Thrombotic Diseases, "A. Gemelli" University Polyclinic Foundation IRCCS, Rome; ²Clinical Chemistry Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia; ³Pediatric Onco-Hematology Unit, Children's Hospital, ASST Spedali Civili di Brescia; ⁴Hemostasis and Thrombosis Unit, Renato Dulbecco University Hospital, Catanzaro; ⁵Regional Hub Center for Hemophilia and Congenital Bleeding Disorders, University Hospital of Parma; ⁶Hematology and Rare Diseases Unit, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo; ⁷Hemophilia and Transfusion Center, "Bufalini" Hospital, Cesena; ⁸Department of Hematology, Policlinico Umberto I, Rome; ⁹Regional Reference Centre for Inherited Bleeding and Thrombotic Disorders, Transfusion Medicine, Città della Salute e della Scienza University Hospital, Turin, Italy

Corresponding author: Nicola Portesi, Clinical Chemistry Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia, 25123 Brescia, Italy.
E-mail: nicola.portesi@asst-spedalicivili.it

Bleeding, Thrombosis and Vascular Biology 2026; 5:581
doi:10.4081/btvb.2026.581

Supplementary Table S1. IPFDs clinical, genetic and laboratory features for defect type (adapted from^{7;15;19}).

Defect Class / Target		Disorder	Main genes	Syndromic manifestations	Blood Smear	LTA	Granule Content	Granule Release	Flow Cytometry	Other Studies
Adhesive proteins receptor defects	<i>αIIbβ3</i>	<u>Glanzmann Thrombasthenia</u>	<i>ITGA2B</i> , <i>ITGB3</i> <i>AR inheritance</i>	-	Normal. Macrothrombocytopenia in autosomal dominant GT-variant	Absent aggregation to all agonists except ristocetin	Normal	Normal	GP IIb–IIIa complex absent or reduced and defective in activation (PAC-1)	Impaired clot retraction; impaired spreading on fibrinogen; SDS page of platelet GPs
	<i>GPIb/IX/V</i>	<u>Bernard Soulier Syndrome</u>	<i>GPIBA</i> ; <i>GPIBB</i> ; <i>GP9</i> <i>AR inheritance</i>	-	Macrothrombocytopenia	Ristocetin agglutination absent; normal aggregation to other agonists	Normal	Normal	GP Ib/IX/V complex absent or severely reduced	SDS page of platelet GPs
		<u>Platelet-type VWD</u>	<i>GPIBA</i> <i>AD inheritance</i>	-	Mild Macrothrombocytopenia	Ristocetin response increased	Normal	Normal	Increased binding of the Willebrand factor to the GP Ib–IX–V complex	Mixing tests showing the platelet origin of ristocetin hyper reactivity. HMW-VWF multimers reduced
		<u>22q11.2 deletion syndrome</u>	<i>GPIBB</i> <i>AD inheritance</i>	-	Macrothrombocytopenia	Ristocetin agglutination absent or severely reduced (30% of cases)	Normal	Normal	GP Ib–IX–V complex reduced	
	<i>GPIa/IIa</i> ; <i>GPVI</i>	<u>Defects of collagen receptors</u>	<i>GP6</i>	-	Normal or mild Macrothrombocytopenia	Collagen (or CRP) and convulxin aggregation defective	Normal	Normal	GP Ia–IIa complex or GP VI absent or reduced	SDS page of platelet GPs
	<i>CD36</i>	<u>Defect of GPIV</u>	<i>CD36</i>	-	Normal	Normal	Normal	Normal	CD36 expression	Reduced adhesion of

									reduced	platelets to collagen under flow conditions
G-protein coupled receptor defects	<i>α2-adrenoreceptor</i>	<u>Defect of α2-adrenoreceptor</u>		-	Normal	Epinephrine aggregation absent	Normal	Reduced	No uniform pattern	
	<i>TP</i>	<u>Defect of the TxA2 receptor</u>	<i>TBXA2R</i>	-	Normal	AA and TxA2 analogs aggregation absent or severely impaired; collagen aggregation reduced; ADP and epinephrine secondary wave absent	Normal	Impaired secretion to the same agonists of LTA	No uniform pattern	
	<i>P2Y12</i>	<u>Defect of ADP receptor</u>	<i>P2RY12</i>	-	Normal	ADP aggregation severely defective	Normal	Normal	No uniform pattern	Impaired inhibition of adenylyl cyclase by ADP
Granule defects	<i>Alpha-granule</i>	<u>Gray platelet syndrome</u>	<i>NBEAL2, GFI1B</i>	Bone marrow fibrosis (not always)	Macro-thrombocytopenia; Gray or pale platelets; Dyserythropoiesis	Thrombin and TRAP6 aggregation reduced	Alpha-granules absence	Alpha-granule release absence	Reduced expression of CD62P (P-selectine) after activation, variable phenotype	Increased B12 plasmatic levels. WB and ELISA: reduced alpha-granule proteins
		<u>ARC syndrome</u>	<i>VPS33B, VIPAS39</i>	Arthrogryposis, renal dysfunction, cholestasis, cerebral malformations, deafness, congenital heart disease, diabetes	Macro-thrombocytopenia; Gray or pale platelets	Epinephrine, ADP, collagen and arachidonic acid aggregation impaired; variable phenotype	Alpha-granules absence	Alpha-granule release absence	Reduced expression of CD62P (P-selectine) after activation, variable phenotype	
		<u>Paris-Trousseau</u>	<i>del11q23</i>	Facial and skull	Macro-	Epinephrine,	Normal	Defective	Reduced	Giant alpha-

		<u>syndrome</u>		dysmorphisms, mental retardation, congenital heart defects	thrombocytopenia	ADP, collagen and arachidonic acid aggregation impaired; variable phenotype		upon stimulation with thrombin	expression of CD62P (P-selectin) after activation, variable phenotype	granules. MYH10 expression in platelets
	<i>Delta-granule</i>	<u>Hermansky-Pudlak syndrome</u>	<i>HPS1, AP32B1, HPS3, HPS4, HPS5, HPS6, DTNBP1, BLOC1S3, BLOC1S5, AP3B1, PLDN</i>	Oculocutaneous albinism, nystagmus and visual acuity loss; pulmonary fibrosis, granulomatous colitis, or immunodeficiency depending on subtype	Normal	Secondary wave aggregation absent	Decrease in platelet nucleotide (or 5HT) content and increased ATP/ADP ratio	Delta-granule secretion defect	Reduced expression of CD63 after activation	
		<u>Chediak-Higashi syndrome</u>	<i>LYST</i>	Oculocutaneous albinism, recurrent infections, severe immunological deficiency, neurological problems	Normal number; Inclusion granules in white blood cells	Secondary aggregation defective	Decrease in platelet nucleotide (or 5HT) content and increased ATP/ADP ratio	Delta-granule secretion defect	Reduced expression of CD63 after activation	TEM: enlarged platelet delta-granules
		<u>Isolated delta-storage pool deficiency</u>		-	Normal	Secondary wave aggregation absent	Decrease in platelet nucleotide (or 5HT) content and increased ATP/ADP ratio	Delta-granule secretion defect	Normal	
		<u>SLFN14 related thrombocytopenia</u>	<i>SLFN14</i>	-	Thrombocytopenia	Normal	Delta-granule deficiency	Decreased ATP secretion in response to ADP, collagen and TRAP-6	Reduced expression of CD63 and CD62P after activation, no uniform pattern	
		<u>Autism with</u>	<i>NBEA</i>	Autism	Normal	Normal	Normal	Reduced	Normal	Platelet ATP

		<u>platelet dense granule defect</u>								secretion reduced. TEM: delta-granules reduced
	<i>Alpha-Delta granule</i>	<u>alpha/delta storage pool deficiency</u>		-	Normal	Normal	Alpha / delta-granule deficiency	Alpha / delta-granule secretion defect	Normal	
Signal transduction defects	<i>Gai1</i>	- - - - <u>G-proteins defects</u>		-	Normal	ADP and epinephrine aggregation impaired	Normal	No uniform pattern	No uniform pattern	absent inhibition of forskolin-stimulated cAMP increase by ADP, thrombin, or epinephrine; diminished <i>Gai1</i>
	<i>Gaq</i>		<i>GNAQ promoter</i>	-	Normal	ADP, epinephrine, collagen, U46619, PAF aggregation impaired	Normal	Impaired secretion to the same agonists of LTA	No uniform pattern	defective TxA2 production in response to ADP and thrombin; defective Ca ²⁺ mobilization in response to ADP and Thrombin; impaired GTPase activity; diminished <i>Gaq</i>
	<i>Gas gain of function</i>		<i>GNAS1</i>	-	Normal	Normal	Normal	No uniform pattern	No uniform pattern	enhanced cAMP generation upon stimulation; sensitivity to inhibition by agents that elevate cAMP. WB: higher membrane-associated <i>Gas</i>
	<i>Gas loss of function</i>			-	Normal	Normal	Normal	No uniform pattern	No uniform pattern	reduced cAMP production after stimulation of Gs-coupled receptors; impaired platelet

										shape change
	<i>cPLA2α</i>	<u>Cytosolic phospholipase A2 defect</u>	<i>PLA2G4A</i>	Bleeding from gastrointestinal ulcer	Normal	ADP and collagen aggregation impaired; AA aggregation normal	Normal	Reduced	No uniform pattern	reduction of urinary metabolites of PGE2, PGD2, PGI2 and TxA2; decreased serum TxB2; decreased cPLA2
	<i>PLC</i>	<u>Phospholipase C defect</u>		-	Normal	ADP, PAF, U46619, collagen, and thrombin aggregation impaired	Normal	Reduced	No uniform pattern	diminished formation of IP3 and DAG by thrombin and PAF; impaired Ca ⁺⁺ mobilization. WB: decreased expression of PLC-β2
	<i>COX pathway</i>	<u>COX-1 defect</u>	<i>PTGS1</i>	-	Normal	ADP, collagen, epinephrine and AA aggregation impaired	Normal	Reduced	Normal	reduced platelet TXA2 production in response to AA but normal in response to PGH2
		<u>Thromboxane synthase defect</u>	<i>TBXAS1</i>	Ghosal syndrome (increased bone density with predominant diaphyseal involvement, corticosteroid-sensitive anemia) in some patients	Normal	AA aggregation absent or severely impaired; TxA2 analogs aggregation normal. ADP and epinephrine aggregation impaired	Normal	Reduced	Normal	Serum TXB2 reduced. WB: thromboxane synthase absent
	<i>Kindlin-3</i>	<u>Leukocyte adhesion deficiency-III (LAD-III)</u>	<i>FERMT3</i>	Predisposition to recurrent infections		GT-like platelet phenotype	Normal	Normal	No uniform pattern	leukocyte function defect

	<i>CalDAG-GEFI</i>	<u>CalDAG-GEFI defect</u>	<i>RASGRP2</i>	-		GT-like platelet phenotype	Normal	Normal	No uniform pattern	
	<i>Src</i>	<u>Src defect</u>	<i>SRC</i>		Platelet cytoplasmic vacuoles	No uniform pattern	Normal	Defective	No uniform pattern	
	<i>PKA</i>	<u>PKA defect</u>	<i>PRKACG</i>	-	Macro-thrombocytopenia	No uniform pattern	Normal	Normal	No uniform pattern	defective α IIB β 3 activation, P-selectin exposure and Ca ²⁺ mobilization; defective phosphorylation of filamin A
Transcription factor defects		<u>Familial platelet disorder with associated myeloid malignancy (FPD/AML)</u>	<i>RUNX1</i>	Increased risk of developing myeloid hematological malignancies	Mild thrombocytopenia	ADP and AA aggregation impaired	Delta-granule defective (occasionally alpha)	Delta-granule secretion defect (occasionally alpha)	Normal	MYH10 expression in platelets
		<u>FLI1-related delta granule defect</u>	<i>FLI1 (11q23)</i>	Alopecia, eczema, recurrent viral infections, psoriasis	Mild thrombocytopenia	Collagen and PAR-1 agonist aggregation reduced	Delta-granule defective	Delta-granule secretion defect	Normal	MYH10 expression in platelets
		<u>GATA1-defect</u>	<i>GATA</i>	Dyserythropoiesis, anemia, beta-thalassemia, congenital erythropoietic porphyria	Macro-thrombocytopenia	Collagen and ristocetin aggregation reduced	Alpha-granule count reduced	Alpha-granule release reduced	Diminished expression of GPIb-alpha	
		<u>GF11B-related defect</u>	<i>GF1B</i>	-	Macro-thrombocytopenia. Dyserythropoiesis	Normal	Alpha / delta-granule deficiency	Alpha / delta-granule secretion defect	No uniform pattern	
Cytoskeleton defects		<u>Wiskott-Aldrich Syndrome/XLTH</u>	<i>WAS (Xp11.23)</i>	Eczema, immune dysfunction, enhanced susceptibility to infections, autoimmune	Micro-thrombocytopenia	delta-SPD phenotype	delta-SPD phenotype	delta-SPD phenotype	GPIb, GPIa, GPIIb-IIIa reduction; GPIb-IIIa activation impaired; P-	Impaired clot retraction

			diseases, malignancy (only in WAS)					selectin expression and activation impaired	
	<u>ADAP defect</u>	<i>FYB</i>	-	Micro- thrombocytopenia	Normal	Normal	Normal	Increased expression of P-selectin and PAC-1 but impaired expression upon activation	Mildly reduced platelet adhesion to fibrinogen and VWF
	<u>Filamin A defects</u>	<i>FLNA</i>	-	Macro- thrombocytopenia	Collagen aggregation impaired	Normal	Collagen granule release impaired	Normal	heterogeneous distribution of α - granules; abnormal distribution of FLNa in platelets
Membrane phospholipid defect	<u>Scott syndrome</u>	<i>TMEM16F</i>	-	Normal	Normal	Normal	Normal	Impaired annexin V binding	impaired platelet procoagulant activity
	<u>Stormorken syndrome</u>	<i>STIM1, ORAI1</i>	Miosis, muscle weakness, dyslexia, ichthyosis, asplenia	Normal number; Howell-Jolly bodies in red blood cells	Normal	Normal	Normal	Enhanced annexin V binding and defective GPIIb-IIIa activation (PAC-1)	Impaired clot retraction. Increased platelet procoagulant activity
Enhanced fibrinolytic activity	<u>Quebec platelet disorder</u>	<i>PLAU</i>	-	Normal	Epinephrine aggregation absent	Alpha- granule content defective	Alpha- granule release defective	Normal	low levels of platelet factor V
Unclassified (exocytosis defect?)	<u>Primary secretion defect</u>	?	-	Normal	Normal	Normal	Impaired	Normal	not well-defined platelet function abnormality