

## Diagnostic Criteria for Inherited Platelet Function Disorders for the Canadian Rare Inherited Bleeding Disorders Registry (RIBDR)

### Glycoprotein deficiencies:

**Glanzmann thrombasthenia**: autosomal recessive; deficiency of GPIIb-IIIa; virtual absence of aggregation with all agonists except ristocetin

**Bernard-Soulier syndrome**: autosomal recessive; platelet count:  $20 \times 10^9/L$  to near normal; large platelets by light microscopy; deficiency of GPIb-IX-V; reduced aggregation with thrombin & no aggregation with ristocetin

**Collagen receptor GPVI deficiency**: deficiency of GPVI; absence of aggregation with collagen

**ADP receptor P2Y<sub>12</sub> deficiency**: absence of aggregation with ADP or slight, rapidly reversible response only & reduced aggregation with low concentrations of collagen, U46619

**Thromboxane A<sub>2</sub> receptor TP deficiency**: deficiency of TP; absence of aggregation with U46619

### Storage granule disorders:

**Gray platelet syndrome**: autosomal dominant or recessive; platelet count:  $30-100 \times 10^9/L$ ; large pale/gray platelets by light microscopy; absent/reduced  $\alpha$ -granules by electron microscopy; may show reduced aggregation with collagen, epinephrine and thrombin

**Quebec platelet disorder**: autosomal dominant; delayed onset bleeding not responsive to platelet transfusion; platelet count:  $80-200 \times 10^9/L$ ; normal platelet morphology; abnormal aggregation with epinephrine; presence of urokinase in platelet lysates using ELISA/Western blots

**Dense ( $\delta$ ) granule disorders**: autosomal dominant or recessive; platelet count normal; decreased/absent dense granules by electron microscopy; reduced/absent secretion of ATP or serotonin

*N.B.: The dense ( $\delta$ ) granule disorders are characterized by reductions in secretion-dependent aggregation (e.g. in response to high-dose ADP and to collagen and epinephrine)*

**Hermansky-Pudlak syndrome**: autosomal recessive; platelet count normal; oculocutaneous albinism; decreased/absent dense granules by electron microscopy; reduction/absence of secretion of ATP or serotonin

**Chediak-Higashi syndrome**: autosomal recessive; platelet count normal; variable oculocutaneous albinism; recurrent infections; decreased dense granules by electron microscopy; reduced secretion of ATP or serotonin; giant peroxidase positive granules in PMNs

**$\alpha\delta$  granule disorder**: autosomal dominant or recessive; platelet count normal; decreased  $\alpha$ - and dense granules by electron microscopy; reduced secretion of ATP or serotonin

### Familial thrombocytopenias: (see also table on following page for further details)

**Wiskott-Aldrich syndrome**: X-linked; platelet count:  $10-100 \times 10^9/L$ ; recurrent infections (defective cellular & humoral immunity); eczema; small platelets (MPV usually  $<6$  fl); mutation in WASP gene; milder form without immunodeficiency is *X-linked thrombocytopenia*

**MYH9-related disorders**: autosomal dominant; giant platelets; mutations in MYH9 gene

Disorder	Leukocyte inclusions	Nephritis	High tone deafness	Cataracts
<b><u>May-Hegglin anomaly</u></b>	present	none	none	none
<b><u>Sebastian syndrome</u></b>	present	none	none	none
<b><u>Fechtner syndrome</u></b>	present	present	present	present
<b><u>Epstein syndrome</u></b>	none	present	present	none

From Balduini CL et al. Inherited thrombocytopenias: a proposed diagnostic algorithm from the Italian Gruppo di Studio delle Piastrine. *Haematologica* 2003; 88:582

**Table 1. Main features of inherited thrombocytopenias classified according to platelet size. The clinical and laboratory features with the strongest diagnostic value are in bold.**

<i>Disease (abbreviation, OMIM<sup>a</sup>)</i>	<i>Inheritance<sup>b</sup></i>	<i>Gene (localization)</i>	<i>Clinical and laboratory features</i>
<b>Small platelets</b>			
*Wiskott-Aldrich syndrome (WAS, 301000)	<b>X-L</b>	WAS (Xp11)	Thrombocytopenia usually severe. <b>Severe immunodeficiency. Defective WAS protein.</b>
°X-linked thrombocytopenia (XLT, 313900)			Thrombocytopenia usually severe. Possible mild immunodeficiency. <b>Defective WAS protein.</b>
<b>Normal-sized platelets</b>			
*Familial platelet disorder and predisposition to acute myelogenous leukemia (FPD/AML, 601399)	A.D.	CBFA2 (21q22)	<b>Propensity to develop myelodysplastic syndrome or acute myelogenous leukemia.</b>
°Congenital amegakaryocytic thrombocytopenia (CAMT, 604498)	A.R.	c-mpl (1p34)	Thrombocytopenia usually severe. Hypomegakaryocytic thrombocytopenia evolving into bone marrow aplasia.
*Amegakaryocytic thrombocytopenia with radio-ulnar synostosis (CTRUS, 605432)	A.D.	HOXA11 (7p15-14)	Thrombocytopenia usually severe. <b>Reduced-absent megakaryocytes.</b> Possible aplastic anemia. <b>Radio-ulnar synostosis</b> ± other malformations. Possible sensorineural hearing loss.
*Thrombocytopenia with absent radii (TAR, 274000)	A.R.	n.d. (n.d.)	Thrombocytopenia usually severe in the first years of life. <b>Reduced megakaryocytes. Bilateral radial aplasia</b> ± other malformations.
°Autosomal dominant thrombocytopenia (THC2, 188000)	A.D.	n.d. (10p12)	None
<b>Large platelets</b>			
°Bernard-Soulier syndrome (BSS, 231200)	A.D.	GPIb $\alpha$ (17p13), GPIb $\beta$ (22q11), GPIX (3q21)	<b>Defective GPIb/IX/V. Homozygous:</b> thrombocytopenia usually severe, <b>giant platelets and defective ristocetin-induced platelet agglutination. Heterozygous:</b> mild thrombocytopenia, normal ristocetin-induced platelet agglutination.
*Velocardiofacial syndrome (VCFS, 192430)	A.D.	CGS <sup>c</sup> -GPIb $\beta$ (22q11)	<b>Cleft palate, cardiac anomalies, typical facies, learning disabilities, defective GPIb/IX/V.</b>
°Platelet-type or pseudo von Willebrand disease (PTvWD, 177820)	A.D.	GPIb $\alpha$ (17p13)	Spontaneous platelet aggregation <i>in vitro</i> and/or <b>increased platelet agglutination to low-dose ristocetin.</b> Reduction of high molecular weight vWF multimers in plasma.
°Benign Mediterranean macrothrombocytopenia (n.d., 153670)	A.D.	n.d.	None
*Dyserythropoietic anemia with thrombocytopenia (n.d., 300367)	<b>X-L</b>	GATA1 (Xp11)	Thrombocytopenia usually severe. <b>Anemia</b> from mild to severe, <b>red cell anisopoikilocytosis</b> , reduced expression of GPIb in a subpopulation of large platelets, <b>dysmegakaryocytopoiesis.</b>
*X-linked thrombocytopenia with thalassemia (XLTT, 314040)	<b>X-L</b>		Anemia from mild to nil, <b>imbalanced globin chain synthesis</b> resembling $\beta$ -thalassemia, peripheral red cell hemolysis, <b>dysmegakaryocytopoiesis</b> , splenomegaly.
*Paris-Trousseau type thrombocytopenia (TCPT, 188025/600588) Jacobsen's syndrome (JBS, 147791)	A.D.	CGS <sup>c</sup> -FL1, ETS1	<b>Cardiac and facial anomalies. Mental retardation. Giant platelet granules.</b>
*°MYH9-related disease <sup>d</sup> (n.d., n.d.) May-Hegglin anomaly (MHA, 155100) Sebastian syndrome (SBS, 605249) Fechtner syndrome (FTNS, 153640) Epstein syndrome (EPS, 153650)	A.D.	MYH9 (22q12-13)	<b>Giant platelets, neutrophil inclusions</b> ± hearing loss ± cataract ± renal defect.
°Gray platelet syndrome (GPS, 139090)	A.D.	n.d.	<b>Pale, ghost-like platelets on blood films</b> due to reduced-absent $\alpha$ -granules.
°Montreal platelet syndrome (MPS, n.d.)	A.D.	n.d.	Thrombocytopenia usually severe. <b>Spontaneous platelet aggregation <i>in vitro</i>.</b>
°Macrothrombocytopenia with platelet expression of glycoprotein A (n.d., n.d.)	A.D.	n.d.	<b>Large platelets express glycoprotein A. Defective platelet aggregation induced by arachidonic acid.</b>

\*Syndromic form °Non-syndromic form \*\*Both syndromic and non-syndromic forms exist. <sup>a</sup>On line mendelian inheritance in man; <sup>b</sup>A.D., autosomal dominant; A.R., autosomal recessive; X-L, X-linked; <sup>c</sup>Contiguous gene syndrome; <sup>d</sup>MHA, SBS, FTNS and EPS have so far been considered distinct entities, but it is now clear that they are different clinical expressions of a single disease due to MYH9 mutations.<sup>3</sup>