# 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: $20x10^9$/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 $P2Y_{12}$ deficiency:** absence of aggregation with ADP or slight, rapidly reversible response only & reduced aggregation with low concentrations of collagen, U46619

**Thromboxane $A_2$ receptor TP deficiency:** deficiency of TP; absence of aggregation with U46619

## STORAGE GRANULE DISORDERS:

**Gray platelet syndrome:** autosomal dominant or recessive; platelet count: $30\text{-}100x10^9$/L; large pale/gray platelets by light microscopy; absent/reduced α-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: $80\text{-}200x10^9$/L; normal platelet morphology; abnormal aggregation with epinephrine; presence of urokinase in platelet lysates using ELISA/Western blots

**Dense (δ) 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 (δ) 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

**αδ granule disorder:** autosomal dominant or recessive; platelet count normal; decreased α- 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: $10\text{-}100x10^9$/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 disease:** autosomal dominant; giant platelets; mutations in MYH9 gene

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

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

| *Disease (abbreviation, OMIM[a])* | *Inheritance[b]* | *Gene (localization)* | *Clinical and laboratory features* |
|---|---|---|---|
| ***Small platelets*** | | | |
| *Wiskott-Aldrich syndrome (WAS, 301000) | **X-L** | *WAS* (Xp11.22-p11.23) | Thrombocytopenia usually severe. **Severe immunodeficiency. Defective WAS protein.** |
| [o]X-linked thrombocytopenia (XLT, 313900) | | | Thrombocytopenia usually severe. Possible mild immunodeficiency. **Defective WAS protein.** |
| ***Normal-sized platelets*** | | | |
| *Familial platelet disorder and predisposition to acute myelogenous leukemia (FPD/AML, 601399) | A.D. | *CBFA2* (21q22) | **Propensity to develop myelodysplastic syndrome or acute myelogenous leukemia.** |
| [o]Congenital amegakaryocytic thrombocytopenia (CAMT, 604498) | A.R. | *MPL* (1p34) | Thrombocytopenia usually severe. Hypomegakaryocytic thrombocytopenia evolving into bone marrow aplasia. |
| *Amegakaryocytic thrombocytopenia with radio-ulnar synostosis (CTRUS, 605432) | A.D. | *HOXA11* (7p15.2) | Thrombocytopenia usually severe. **Reduced-absent megakaryocytes.** Possible aplastic anemia. **Radio-ulnar synotosis** ± other malformations. Possible sensorineural hearing loss. |
| *Thrombocytopenia with absent radii (TAR, 274000) | A.R. | *RBM8A* (1q21.1) | Thrombocytopenia usually severe in the first years of life. **Reduced megakaryocytes. Bilateral radial aplasia** ± other malformations. |
| [o]Autosomal dominant thrombocytopenia (THC2, 188000) | A.D. | n.d. (10p12) | None |
| ***Large platelets*** | | | |
| [o]Bernard-Soulier syndrome (BSS, 231200) | A.D. | *GP1BA* (17p13), *GP1BB* (22q11), *GP9* (3q21) | **Defective GPIb/IX/V.** *Homozygous*: thrombocytopenia usually severe, **giant platelets and defective ristocetin-induced platelet agglutination.** *Heterozygous:* mild thrombocytopenia, normal ristocetin-induced platelet agglutination. |
| *Velocardiofacial syndrome (VCFS, 192430) | A.D. | CGS[c]-*GPIBB* (22q11.2) | **Cleft palate, cardiac anomalies, typical facies, learning disabilities, defective GPIb/IX/V.** |
| [o]Platelet-type or pseudo von Willebrand disease (PTvWD, 177820) | A.D. | *GP1BA* (17p13) | Spontaneous platelet aggregation *in vitro* and/or **increased platelet agglutination to low-dose ristocetin.** Reduction of high molecular weight VWF multimers in plasma. |
| [o]Benign Mediterranean macrothrombocytopenia (n.d., 153670) | A.D. | n.d. | None |
| *Dyserythropoietic anemia with thrombocytopenia (n.d., 300367) | **X-L** | *GATA1* (Xp11.23) | Thrombocytopenia usually severe. **Anemia** from mild to severe, **red cell anisopoikilocytosis**, reduced expression of GPIb in a subpopulation of large platelets, **dysmegakaryocytopoiesis.** |
| *[o]X-linked thrombocytopenia with thalassemia (XLTT, 314040) | **X-L** | | Anemia from mild to nil, **imbalanced globin chain synthesis** resembling β-thalassemia, peripheral red cell hemolysis, **dysmegakaryocytopoiesis,** splenomegaly. |
| * Paris-Trousseau type thrombocytopenia (TCPT, 188025/600588) Jacobsen's syndrome (JBS, 147791) | A.D. | CGS[c]-*FLI1*, *ETS1* (11q24.1-q24.3) | **Cardiac and facial anomalies. Mental retardation. Giant platelet granules.** |
| *[o]MYH9-related disease[d] (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) | **Giant platelets, neutrophil inclusions** ± hearing loss ± cataract ± renal defect. |
| [o]Gray platelet syndrome (GPS, 139090) | A.R. | *NBEAL2* (3p21.31) | **Pale, ghost-like platelets on blood films** due to reduced-absent α-granules. |
| [o]Macrothrombocytopenia with platelet expression of glycophorin A (n.d., n.d.) | A.D. | n.d. | **Large platelets express glycophorin A. Defective platelet aggregation induced by arachidonic acid.** |

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