

## Review Article

# Inherited Platelet Disorders

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## Abstract

The inherited platelet disorders are heterogenous and rare diseases. These disorders are normally associated with bleeding diathesis due to either a platelet functional abnormality or haemostatic procoagulant defect. They can be classified into molecular abnormalities that give rise to dysfunctional platelet receptors, alpha or dense granule deficiencies, platelet signaling pathway disorders or altered platelet coagulant function. This review will examine each of the mechanisms associated with inherited platelet disorders.

## ABBREVIATIONS

ADP: Adenosine Diphosphate; ATP: Adenosine Triphosphate; BSS: Bernard-Soulier Syndrome; GP: Glycoprotein; GT: Glanzmann Thrombasthenia; HLA: Human Leukocyte Antigen; ITAM: Immunoreceptor Tyrosine-Based Activation Motif; MHA: May-Hegglin Anomaly; MYH9: Myosin Heavy Chain 9; NBEAL2: Neurobeachin-Like 2; PARs: Protease Activated Receptors; PS: Phosphatidyl Serine; SPD: Storage Pool Diseases; VWF: von Willebrand Factor

## INTRODUCTION

Inherited platelet disorders are rare bleeding diseases. They can be classified as hereditary macrothrombocytopenias/ micro thrombocytopenia, and disorders of platelet signaling defects, platelet granules, platelet membrane, and defective platelet coagulant function [1].

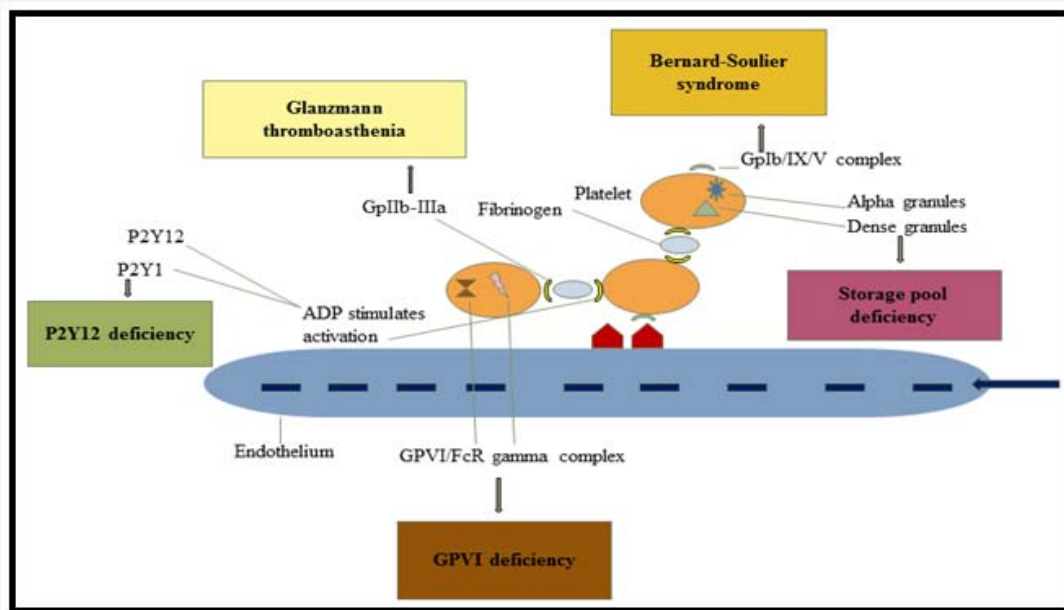
## Role of platelets in haemostasis and thrombosis

The main role of platelets is to maintain vascular system integrity and normal haemostasis. These functions rely on the ability of the platelets to provide particular receptors to interact with the exposed extracellular matrix such as type 1 collagen and von Willebrand Factor (VWF) in order to activate signaling pathways. It has been shown that VWF, fibronectin, fibrinogen and collagen are capable of stimulating platelet adhesion and aggregation. Platelets are generated and activated by locally-produced agonists to induce a change in their shape from discs to tiny spheres with reorganised cytoskeleton and filopodia [2]. These activated platelets release their alpha and dense granule contents such as P-selectin and adenosine diphosphate (ADP). P-selectin is expressed on the surface of activated platelets where it basically mediates the rolling and tethering of leukocytes that are needed for strong extravasation and adhesion. Upon the release of ADP and thromboxane A<sub>2</sub>, further platelet activation is stimulated and results in the aggregation of platelets that eventually form platelet plugs at injury sites to arrest bleeding

[3]. These platelet agonists bind to their respective receptors such as G-protein coupled receptor in a manner that modulates intracellular mechanisms. Thrombin plays an important role in platelet activation via GPIIb/IIIa binding of thrombin to position it for efficient cleavage of the N-terminal end of protease activated receptor (PARs) molecules particularly PAR-1 in humans. This induces G-protein coupled receptor signaling pathways that are essential in platelet activation [4]. In contrast, ADP is largely kept at high concentrations in dense granules. It is released in reaction to ADP purinergic receptors; P<sub>2</sub>Y<sub>1</sub> and P<sub>2</sub>Y<sub>12</sub> to mediate platelet activation. In addition, platelet procoagulant activity is activated by these two receptors [5]. This review aims to provide an overview of inherited platelet disorders that are caused by heritable gene mutations and/or defective platelet function and signaling pathways.

## Platelet membrane disorders

**Bernard-Soulier Syndrome (BSS):** Although being rare, this autosomal recessive disorder causes a lifelong bleeding tendency. The condition manifests itself by damaging the platelet aggregation through a defect in glycoprotein Ib/IX protein complex that associates with endothelial VWF [6]. When this protein complex is absent, platelets are unable to adhere to the damaged area of vascular endothelium. In this case, bleeding may occur, and the platelets are seen to be abnormally large when viewed under the microscope. The condition can be controlled through platelet transfusion [7]. Some of the defects manifest in the form of abnormal production of platelets by the demarcation membrane system of the megakaryocytes. BSS is one of the best exemplary conditions demonstrating such defects. Patients that suffer from this condition carry mutations in the GPIIb/IIIa, GPIX or GPIIb/IIIa genes (Figure 1) [8]. In addition, heat shock protein gp96/grp94 plays an essential role as a chaperone for trafficking of GPIIb/IIIa-V complex to the platelet surface [9]. Consequently,



**Figure 1.** Sites of molecular abnormalities that give rise to inherited platelet disorders. Green line represents GPIb/IX/V complex, gray sphere represents fibrinogen, yellow line represents GPIIb/IIIa protein, light green triangle represents dense granules, blue star represents alpha granules, brown diamond & light pink represent GPVI/FcR gamma complex.

these individuals often have insufficient platelet glycoprotein (GP) Iba/Ib $\beta$ /IX/V receptors that are essential in binding of VWF. Patients often report severe bleeding with large platelets and moderate thrombocytopenia. The usual laboratory test for this condition is carried out by exposure of the platelets to collagen, ADP, epinephrine or arachidonic acid [10]. Nonetheless, platelets do not aggregate with ristocetin, but will only aggregate in the presence of collagen or epinephrine. In BSS, the giant platelets arise due to a defective interaction between actin binding protein in the platelet cytoskeleton and the cytoplasmic domain of the GPIIb $\alpha$  polypeptide [11].

**Glanzmann Thrombasthenia (GT):** Glanzmann thrombasthenia was first described in 1918. It is a rare autosomal recessive bleeding syndrome affecting the megakaryocyte lineage and characterized by lack of platelet aggregation to a range of agonists except ristocetin. It is characterised by a platelet abnormality where the platelets contain defective or low levels of integrin  $\alpha_{IIb}\beta_3$  which is the receptor for fibrinogen [12]. As a result, no fibrinogen bridging of platelets to other platelets can occur, and the bleeding time is significantly prolonged. Thus, the human bleeding disorder GT results from defects in the genes for either the integrin  $\alpha_{IIb}$  or the  $\beta_3$  subunit. The molecular basis is linked to either quantitative and/or qualitative abnormalities of integrin  $\alpha_{IIb}\beta_3$  [13]. This receptor mediates the binding of adhesive proteins that attach aggregating platelets and ensure stable thrombus formation at sites of vessel injury. GT is associated with clinical variability with some patients having only minimal bruising while others have frequent, severe and potentially fatal hemorrhages [14]. However, GT can be divided into three types I, II, and III. Patients with less than 5% of normal integrin  $\alpha_{IIb}\beta_3$  are classified as type I (severely quantitative) and 5% to 20% as type II (mildly quantitative). Type III variants (qualitative)

usually have dysfunctional receptors with near-normal integrin  $\alpha_{IIb}\beta_3$  levels. Variability exists in the subtypes found in various ethnic groups. Many GT mutations affect functionally important sites on integrin  $\alpha_{IIb}$  or integrin  $\beta_3$  subunit which affects either ligand binding, complex stability, signaling and/or trafficking of integrin  $\alpha_{IIb}\beta_3$  complex to platelet surface. In addition, type I GT is frequently related to Iraqi-Jews and Arabs residing in Israel because of a truncated integrin  $\beta_3$  as a result of an 11-bp deletion within the integrin  $\beta_3$  gene or due to a 13-bp deletion in the integrin  $\alpha_{IIb}$  gene. On the other hand, type II GT is more often found in the Japanese population [15]. Transfusion of HLA-compatible platelet concentrates may be necessary to prevent bleeding during surgery. GT can be a severe hemorrhagic disease, however the prognosis is excellent with careful supportive care [16].

### Hereditary macrothrombocytopenias

**May-Hegglin anomaly (MHA), Sebastian, Fechtner and Epstein syndromes:** The hereditary macrothrombocytopenias include May-Hegglin anomaly, Sebastian, Fechtner and Epstein syndromes. These are rare autosomal dominant disorders characterized by macro thrombocytopenia with granulocyte blue body inclusions known as Dohle-like bodies. The unique cytoplasmic inclusion bodies are aggregates of nonmuscle myosin heavy chain IIA and are only present in granulocytes. It is not been clarified yet why inclusion bodies are not present in platelets, monocytes, and lymphocytes, or how giant platelets are formed. The platelets are abnormally large defined by an increased mean platelet volume and an additional peak in the white blood cell analysis. Some of these syndromes also have symptoms of nephritis or sensory problem of deafness. *MYH9* gene mutations are also known to play a role in the pathogenesis of several

related disorders involving macro thrombocytopenia and leukocyte inclusions, including Sebastian, Fechtner, and Epstein syndromes [17,18].

### Hereditary micro thrombocytopenia

**Wiskott-Aldrich syndrome:** Thrombocytopenia with small platelets can be observed in patients who suffer from Wiskott-Aldrich syndrome. A recessive X-linked disorder is characterized by immunologically related inflammatory skin disorder, eczema, and recurrent infections. Laboratory analysis reveals small platelets that are half the size of normal platelets. This condition is severe in the sense that the platelets do not aggregate. Instead, they form a pool-like pattern seen under the microscope [19].

### Platelet granule disorders

**Dense Granule storage pool deficiency:** Platelet storage pool diseases (SPD) are a heterogeneous group of disorders associated with an abnormal presence or contents of intracytoplasmic platelet granules, causing a mild to moderate bleeding [20]. Two common platelet granules are called dense granules and alpha granules. Human platelets contain three to eight dense granules per platelet, each measuring 100 to 300 nm in diameter. Dense granule or  $\delta$ -storage pool diseases ( $\delta$ -SPD) encompasses a rare and heterogeneous group of conditions characterized by defects in the number or content of platelet  $\delta$ -granules. The causes of  $\delta$ -SPD are multiple and variable and can be classified into congenital diseases including Hermansky-Pudlak and Chediak-Higashi syndromes, nonsyndromic inherited platelet disorders, or acquired forms, most often associated with hematologic malignancies such as myeloproliferative syndrome, acute leukemia, or myelodysplastic syndromes [21]. Decreased dense granule secretion leads to a defective hemostatic response to vascular injury and patients suffer from mild to moderate hemorrhagic diathesis mainly characterized by mucocutaneous bleedings. Thus, rapid and accurate diagnosis is crucial to initiate appropriate therapy that in turn prevents bleeding. Granules are storage spaces inside each platelet. During the process of making a platelet plug, the platelets change shape and contents inside the granules are pushed out into the bloodstream [22]. This stimulates platelets to mediate primary arrest of bleeding is due to the formation of platelet aggregates, secreted contents include ADP, released from the platelets after their contact with collagen. The mechanism by which ADP, as well as adenosine triphosphate (ATP) and serotonin, are specifically extruded from the platelets before inducing aggregation has been termed the release reaction and has been likened to the secretory mechanism found in other cells [23]. Therefore, individuals with insufficient number of platelet granules or dysfunctional granules with abnormally low concentrations of platelet agonists can have significant effects on coagulation pathways during a vascular event.

**Gray platelet syndrome:** In Gray platelet syndrome, platelets lack alpha granules and the contents in them due to mutations in Neurobeachin-like 2 (NBEAL2) genes that affect alpha granule development. Platelets with this mutation are not able to stick to the injured blood vessel wall, or repair the injured blood vessel. Microscopically, platelets in patients with alpha SPD look gray which give rise to the name of Gray platelet syndrome [24]. When platelets are not able to store contents

or secrete them when needed, the platelets are ineffective in forming a plug. Alpha SPD usually results in mild to moderate bleeding symptoms. Bleeding lasts longer than normal which requires careful clinical management. Patients with alpha SPD rarely requires treatment unless prior to undergoing surgery or following a severe physical injury [25,26].

### Platelet coagulant function disorders

**Scott syndrome:** This rare congenital bleeding disorder is linked to a defect in membrane lipid assembly with lack of expression of phosphatidyl serine (PS) to the external cell membrane of platelets. This forms a critical component of the platelet procoagulant response involving calcium dependent membrane catalytic tenase activity (complex of coagulation factors VIIIa and IXa) and prothrombinase activity (complex of coagulation factors Va and Xa) [27]. Several studies on patients with Scott phenotype have revealed novel missense mutations in the ATP-binding cassette transporters that may provide the link between phospholipid transport and membrane asymmetry with the bleeding phenotype. However, the translocation of PS in Scott syndrome is thought to affect multiple haematological lineages due to a stem cell mutation [28].

### Platelet signaling disorders

**$P_2Y_{12}$  deficiency:** This rare condition is a haemorrhagic disorder that is characterised by mild to moderate bleeding due to platelet  $P_2Y_{12}$  receptor deficiency resulting in selective impairment of platelet responses to ADP [29].  $P_2Y_{12}$  deficiency results from mutations in the  $P_2RY_{12}$  gene (3q24-q25), subsequently triggering the premature truncation of the  $P_2Y_{12}$  receptor or the synthesis of a dysfunctional  $P_2Y_{12}$  receptor. ADP activates platelets through its interaction with two purinergic G protein-coupled receptors,  $P_2Y_1$  and  $P_2Y_{12}$ . The  $P_2Y_1$  receptor mediates mobilization of ionized calcium and is responsible for ADP-induced shape change and weak and transient aggregation [30]. However, the  $P_2Y_{12}$  receptor is responsible for the completion and amplification of the response to ADP and to all platelet agonists including thromboxane  $A_2$ , thrombin, and collagen. In addition,  $P_2Y_{12}$  receptor plays a main role in the formation and stabilisation of a thrombus particularly at high shear [31].

**GPVI deficiency:** Patients with GPVI deficiency often suffers from mild bleeding. GPVI-related defects are due to an acquired deficiency resulting from the presence of anti-GPVI autoantibodies or a congenital deficiency where GPVI is not expressed at a functional level causing defective signalling to integrin  $\alpha_{IIb}\beta_3$  [32]. In addition, GPVI-related defects can result from defective platelet aggregation in response to collagen or other GPVI agonists such as collagen related peptide (CRP) or convulxin but in some instances, normal  $\alpha_{IIb}\beta_3$ -dependent aggregation to other platelet agonists, such as ristocetin/von Willebrand factor (acting *via* platelet GPIb-IX-V) or ADP (acting *via*  $P_2Y_1$  and  $P_2Y_{12}$ ) can still occur [32]. The initiation of GPVI/FcR gamma chain-mediated activation signal is triggered by tyrosine phosphorylation of the immune receptor tyrosine-based activation motif (ITAM) signaling pathway within the FcR gamma-chain, which leads to the binding of tyrosine kinase Syk to ITAM. Consequently, this stimulates the activation of the downstream effector molecules including phospholipase  $Cy2$  and phosphoinositide-3 kinase [33].

## DISCUSSION & CONCLUSION

Platelets are fundamental for primary haemostasis to arrest bleeding and for wound repair. However, in inherited platelet disorders abnormalities of platelet membrane receptors, alpha or dense granules, platelet coagulant function or platelet signaling disorders, bleeding complications occur. Inherited platelet disorders are a heterogeneous group of abnormal hematological conditions and are often responsible for bleeding diatheses with various severities; ranging from mild to chronic mucocutaneous haemorrhage. The most serious forms of these ailments are associated with deficiencies in the number and distribution of secretory granules as well as platelet membrane receptors. Most of these ailments share common therapy approaches although some therapies may show greater efficacy in certain patients as opposed to others. In this regard, adjunctive treatment, like platelet transfusion and fibrin glue during surgery, remain the main therapies available currently.

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