Inherited platelet disorders (IPDs) are a heterogeneous group of diseases affecting platelet production, morphology, and function. The degree of thrombocytopenia and functional abnormality of platelets determines the clinical manifestations. Although severe deficiencies may cause excessive bleeding beginning in early childhood, most of IPDs have mild bleeding tendencies and therefore are not always easy to distinguish from acquired platelet disorders. The diagnosis of IPD may require extensive laboratory investigation, because current routine laboratory tests are not satisfactory for differential diagnosis in some cases, and most of the specific tests are not readily available in many countries. This review summarizes the classification and clinical and molecular characteristics of known IPDs, including Bernard-Soulier syndrome and Glanzmann thrombasthenia, with a focus on current challenges in the laboratory diagnosis and management of bleeding in these patients.

Introduction
Platelets, the smallest cells in the blood, are involved in hemostasis, inflammation, tissue remodeling, and wound healing. They play a crucial role in hemostasis: adhesion and aggregation of the platelets lead to the formation of a “hemostatic plug.” Subsequent activation of the coagulation system induces fibrin generation on the surface of activated platelets. Either acquired or inherited thrombocytopenia and/or platelet function defect will cause bleeding. In clinical practice, most of the platelet disorders are due to acquired problems including drugs and metabolic diseases. Since Dr Eduard Glanzmann’s description of “thrombasthenia” a century ago, several inherited platelet disorders (IPDs) have been identified. Numerous classifications have been proposed based on platelet count, size, function, or underlying genetic abnormality (Table 1). Although IPDs are rare, studies to elucidate their pathogenesis have contributed enormously to current knowledge. The identification of molecular pathology in patients with IPD has improved our understanding of normal megakaryocyte and platelet physiology, as well as the mechanisms of hemostasis and thrombosis. These investigations also gave very important insight into the development of platelet- and megakaryocyte-directed therapies in patients with thrombosis and thrombocytopenia.

Clinical findings, laboratory evaluation, and management of IPDs
The degree of thrombocytopenia and functional abnormalities of platelets determines the severity of bleeding symptoms. IPD patients usually present with mucocutaneous bleeding such as easy bruising, purpura, gingival bleeding, and epistaxis beginning in early childhood. Spontaneous life-threatening bleeding (intracranial hemorrhage, massive gastrointestinal or genitourinary bleeding) is rare.1-4 Menorrhagia and bleeding during pregnancy and labor are of special concern in female patients.5,6 Unexpected excessive bleeding after trauma or surgery may be the first symptom in milder cases.1,9 Rarely, IPD is a component of a complex of multisystem disorder such as Fanconi anemia, Chediak-Higashi syndrome, or May-Hegglin anomaly (Table 2). The presence of skeletal, facial, ocular, audiological, neurological, renal, cardiac, and immune problems associated with bleeding is suggestive of the existence of such disorders.2,3 IPD patients with isolated macrothrombocytopenia share common clinical and basic laboratory features of other acquired platelet disorders and are sometimes misdiagnosed as immune thrombocytopenia. It is important to distinguish patients with IPD from those with acquired platelet disorders to avoid unnecessary or potentially harmful treatments.2 A blood smear is helpful for patients with myosin heavy chain 9 (MYH9)-related diseases (giant platelets and Döhle-like inclusion bodies within leukocytes) and Gray platelet syndrome (pale platelets); a smear also gives information about the platelet count because automated cell counters may not recognize giant platelets. Optical platelet counters or flow cytometric analysis may help with platelet counting.1,2,7 Bone marrow biopsy is required if the IPD patient has pancytopenia as in Fanconi anemia or severe thrombocytopenia as in congenital amegakaryocytic thrombocytopenia. Coagulation tests should be normal.1,7 Skin bleeding time (Ivy, template) is prolonged, but is not recommended as a screening test for investigation of patients with IPD because it is invasive and poorly reproducible.1 A platelet function analyzer (PFA) assay simulates a damaged vessel wall using collagen + ADP- and collagen + epinephrine–embedded cartridges. Citrated whole blood passes through these cartridges at high shear stress and platelets bind to the membrane of the cartridge, blocking the system, and generating the “closure time.” PFA is very sensitive in detecting Bernard-Soulier syndrome (BSS), platelet-type von Willebrand disease (VWD), and Glanzmann thrombasthenia (GT), but may be normal in patients with storage pool deficiencies and platelet membrane phospholipid disorders.1,3,7 The basic investigation of IPD should include light transmission aggregometry (LTA) using ADP, collagen, ristocetin, epinephrine, and arachidonic acid at different concentrations.8 LTA shows characteristic patterns in patients with BSS, platelet-type VWD, and GT. Although LTA is accepted as the gold standard for diagnosing IPD, it is difficult to obtain platelet-rich plasma in pediatric cases and in patients with thrombocytopenia.7,8 LTA may be normal in some patients with storage pool diseases, so the measurement of platelet nucleotide
Desmopressin (DDAVP, 1-amo-8-D-arginine vasopressin) stimulates the release of VWF from endothelial cells and increases factor VIII levels in plasma. It is indicated for the prevention or treatment of bleeding episodes in patients with type-1 VWD and in patients with hemophilia A with factor VIII levels > 2% to 5%. The data on the efficacy and safety of desmopressin in the treatment of IPD patients are limited because the literature includes only small case series with different results. Although desmopressin has no direct effect on platelets, the ultra-large von Willebrand Factor (VWF) released by desmopressin may facilitate platelet adhesion and decrease the bleeding time in some patients with IPD, such as those with BSS, storage pool diseases, and MYH9-related disorders. Desmopressin has no effect on bleeding in patients with GT. It can be given as IV infusion over 30 minutes, subcutaneous injection, or intranasal spray. A major side effect of desmopressin is water retention and hyponatremia. Desmopressin also may bind to the vasopressin receptors of blood vessels and uterus. It should be used cautiously for pregnant women due to potential risk of preterm labor.

Management of menorrhagia in patients with IPD involves both gynecologic and hematologic treatments. Oral contraceptives or hormonal intrauterine devices together with tranexamic acid may reduce bleeding during menses. Patients with severe bleeding after trauma, surgery, or delivery may require platelet and RBC transfusions. HLA-compatible platelet concentrates are recommended to avoid alloimmunization if possible. Recombinant factor VIIa can be used in patients with life-threatening bleeding who are unresponsive to platelet transfusions and in patients with alloantibodies. Thrombopoietin (TPO)–mimetic drugs have been shown to increase platelet counts in some patients with MYH9-related disorders, but the efficacy and safety of these drugs should be carefully investigated. Hematopoietic stem cell transplantation is used only in IPD patients with BM failure or megakaryocytic aplasia (see below).

Decreased production of platelets
Megakaryocytic commitment of hematopoietic stem cells is the first step for platelet production. Several transcription factors, including GATA-1, FLI-1, and FOG-1, are involved in this process. The differentiation of the megakaryoblast to megakaryocyte and production of platelets is primarily regulated by TPO. TPO binds to the c-Mpl receptor and mediates the growth and maturation of megakaryocytes. TPO/cMPL signaling has been shown to be crucial, not only for normal thrombopoiesis, but also for the maintenance of stem cells. Several mutations on TPO, cMPL, and some other cytokines have been reported in patients with inherited thrombocytopenia and BM failure.

Congenital amegakaryocytic thrombocytopenia
Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare, autosomal-recessive disorder presented at birth with isolated severe thrombocytopenia (platelet counts usually < 50 × 10^9/L). Although no other skeletal or mental abnormalities are expected in

Table 1. Classification of inherited platelet disorders

1. Decreased production of platelets
   a. CAMT
   b. Congenital hypo/amegakaryocytic thrombocytopenia with skeletal abnormalities
      i. TAR syndrome
      ii. ATRUS
      iii. Fanconi anemia
2. MYH9-related diseases:
   a. May-Hegglin anomaly
   b. Epstein syndrome
   c. Fechtner syndrome
   d. Sebastian syndrome
3. Platelet membrane phospholipid abnormalities:
   a. Scott syndrome
   b. Stormorken syndrome
4. Platelet granule deficiencies (storage pool disease)
   a. α-granule defects
      i. Gray platelet syndrome
      ii. Paris-Trousseau syndrome
      iii. Quebec platelet syndrome
      iv. ARC syndrome
   b. Dense granule defects
      i. Hermansky-Pudlak syndrome
      ii. Chediak-Higashi syndrome
      iii. Griscelli syndrome
   c. α- and dense granule defects
5. Disorders of platelet surface receptors
   a. GP Ib/IX-V defects
      i. Bernard-Soulier syndrome
      ii. Platelet-type VWD
   b. Vascular occlusive syndrome
   c. GPVI defects
   d. Integrin αβ3 (GP Ib/IIa) defects: Glanzmann thrombasthenia
   e. Integrin αβ1 (VLA-5) defects
   f. Integrin αβ1 (VLA-6) defects
   g. Integrin αβ3 defects
6. Miscellaneous: GATA-1 related thrombocytopenia, Wiskott-Aldrich syndrome, Mediterranean macrothrombocytopenia, Montreal platelet syndrome, familial platelet disorder with propensity to myelodysplasia (FDP/AML)
<table>
<thead>
<tr>
<th>Storage pool diseases</th>
<th>Inheritance, locus, and gene(s)</th>
<th>Platelets</th>
<th>Bleeding diathesis</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha (α) storage pool diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray platelet syndrome</td>
<td>AR, AD? 3p21.31 NBEAL2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild to moderate MPV</td>
<td>Mild to moderate</td>
<td>Splenomegaly, Bone marrow fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased MPV</td>
<td>Prolonged bleeding time</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absent or decreased α-granules</td>
<td>Variable aggregation responses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild thrombocytopenia</td>
<td>Mild bleeding tendency</td>
<td>Dysmegakaryopoiesis, Facial, cardiac, mental abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal and giant α-granules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paris-Trousseau syndrome</td>
<td>AD 11q23 FLI1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild thrombocytopenia</td>
<td>Mild bleeding tendency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased MPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prolonged bleeding time</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone marrow fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quebec platelet disorder</td>
<td>AD 10q22.2 FLAUI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal count or mild thrombocytopenia</td>
<td>Mild to moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased α-granule proteins</td>
<td>Delayed bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Over-expression of urokinase-type plasminogen activator</td>
<td>Decreased aggregation with epinephrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild bleeding tendency</td>
<td></td>
<td>Facial, cardiac, mental abnormalities</td>
</tr>
<tr>
<td>Arthrogryposis, renal dysfunction and cholestasis (ARC) syndrome</td>
<td>AR 15q26.1 VPS33B, VIPAR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal count or mild thrombocytopenia</td>
<td>Mild bleeding tendency</td>
<td>Joint contractions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large and pale platelets</td>
<td>Decreased aggregation with ADP and arachidonic acid</td>
<td>Facial abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased α-granule proteins</td>
<td></td>
<td>Cholestasis, Renal tubular acidosis</td>
</tr>
<tr>
<td>Hermansky-Pudlak syndrome</td>
<td>AR Multiple</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Platelet count normal</td>
<td>Mild to severe bleeding</td>
<td>Oculocutaneous albinism, nystagmus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased δ-granule proteins</td>
<td>Prolonged bleeding time</td>
<td>Lysoosomal deposition of ceroid lipofuscin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Granulomatous colitis, Pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neutropenia, Albinism with silvery gray hair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neurological abnormalities, Immunodeficiency</td>
</tr>
<tr>
<td>Chediak-Higashi syndrome</td>
<td>AR 1q42.3 CHS1/LYST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Platelet count normal</td>
<td>Mild to moderate bleeding tendency</td>
<td>Oculocutaneous albinism, Severe immunoedeficiency, pancytopenia, organomegaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Giant inclusions in platelets and leukocytes</td>
<td></td>
<td>Neurological abnormalities</td>
</tr>
<tr>
<td>Griscelli syndrome (type 1-3)</td>
<td>AR 15q21.2, 15q21.3, 2q37.3 MYO5A, RAB27A, MLPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal count or mild thrombocytopenia</td>
<td>Mild to moderate bleeding</td>
<td>Albinism with silvery gray hair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impaired secretion-dependent platelet aggregation</td>
<td>Neurological abnormalities</td>
</tr>
</tbody>
</table>

**Table 2. Storage pool diseases**
Hematology 2013 271

Proximal deletions of 1q21.1 are found to be associated with TAR null mutation in RNA binding motif protein 8a gene (RBM8a). Frequency noncoding single nucleotide polymorphism and a rare TAR syndrome is caused by compound inheritance of a low frequency noncoding single nucleotide polymorphism and a rare null mutation in RNA binding motif protein 8a gene (RBM8a). Proximal deletions of 1q21.1 are found to be associated with TAR syndrome, whereas distal deletions or duplications are found to be associated with skeletal and neuropsychiatric abnormalities. Another interesting feature of TAR syndrome is the increasing platelet count as the patient ages. The investigation of cytokine profiles in TAR patients of different ages should provide important information about the differences in megakaryopoiesis/thrombopoiesis between neonates and adults.

Amegakaryocytic thrombocytopenia with radioulnar synostosis
Amegakaryocytic thrombocytopenia with radioulnar synostosis (ATRUS) is a very rare cause of inherited thrombocytopenia characterized by fusion of the radius and ulna near the elbow, resulting in limited pronation and supination of the forearm. So far, fewer than 10 families with ATRUS are reported in the existing literature. Recently, a homeobox transcription factor (HOXA11) gene mutation was described in patients with ATRUS.

Fanconi anemia
Fanconi anemia is an autosomal-recessive disorder characterized by progressive BM failure, multiple congenital abnormalities, and predisposition to malignancy. Fanconi anemia cells have chromosomal instability and hypersensitivity to DNA interstrand cross-linking agents such as mitomycin C and diepoxybutane. Although abnormalities concerning the radius may be associated with Fanconi anemia, hypoplasia or aplasia of thumbs with development of BM failure distinguishes it from TAR syndrome.

MYH9-related diseases
The MYH9 gene encodes nonmuscle myosin IIA heavy chain, a protein involved in cell motility and maintenance of cell shape. Mutations of the MYH9 gene were found to be associated with macrothrombocytopenia, nephritis, hearing loss, and inclusion bodies in leukocytes (Döhle-like bodies) and are classified as “MYH9-related diseases.” The localization of the MYH9 gene distinguishes the clinical phenotype: mutations in the motor domain are associated with more severe defects such as lower platelet counts and early onset of hearing loss and nephritis compared with the milder phenotype seen in tail-domain mutations. The molecular mechanisms causing hematological, renal, and ophthalmological abnormalities are unknown. The majority of patients with MYH9-related disorders have mild to moderate bleeding tendencies. BM megakaryocyte number and morphology is normal. Platelet counts are variable, but lifespan of platelets is normal. Döhle-like inclusion bodies, which are clusters of ribosomes and nonmuscle myosin IIA heavy chain microfilaments, may be seen within granulocytes, eosinophils, and monocytes on a peripheral blood smear or with immunostaining using specific antibodies. Platelet aggregation studies reveal minor abnormalities concerning the radius may be associated with Fanconi anemia, hypoplasia or aplasia of thumbs with development of BM failure distinguishes it from TAR syndrome.

Platelet membrane phospholipid abnormalities
In resting platelets, the outer layer of the platelet membrane contains phosphatidylcholine, which carries a neutral charge, whereas the inner layer is rich in negatively charged phospholipids such as phosphatidylserine. After activation of the platelets, negatively charged phospholipids are exposed on the outer layer and provide a surface for activation of coagulation factors. Externalization of inner phospholipids also mediates apoptosis, cell clearance, and

Figure 1. Arthrogryposis (persistent joint contractures), renal dysfunction, and cholestasis (ARC) syndrome is a very rare multisystem disorder. The degeneration of the anterior motor neuron cells causes multiple joint contractures, muscle weakness, and fibrosis. Decreased alpha granule proteins in ARC syndrome leads to platelet aggregation defects and bleeding tendency.

Thrombocytopenia with absent radii syndrome
Thrombocytopenia with absent radii (TAR) syndrome is characterized by thrombocytopenia with the absence of a radius in each forearm (Figure 1). Other skeletal abnormalities are bone defects in the lower and upper extremities, short stature, and facial abnormalities. Renal and cardiac abnormalities may also be present. Inheritance of TAR syndrome is complex: an autosomal-recessive pattern is described in most cases. Affected children born with severe thrombocytopenia usually require platelet transusions. Allergic reactions to cow's milk may be seen in half of the patients and this may worsen the thrombocytopenia. The platelet counts recover during childhood and may even be normal in adult patients with TAR syndrome. BM biopsy shows isolated megakaryocytic hypoplasia with normal myeloid and erythroid progenitors. Serum TPO level is high and TPO signaling is found to be defective. The genetic background of TAR syndrome is unknown. Investigations showed no abnormality on the cMPL gene. A microdeletion on chromosome 1q21.1 has been identified in patients with TAR syndrome with unknown significance and has been also found in their unaffected relatives. Recently, Albers et al demonstrated that TAR syndrome is caused by compound inheritance of a low-frequency noncoding single nucleotide polymorphism and a rare null mutation in RNA binding motif protein 8a gene (RBM8a).
complement binding. Scott syndrome is an inherited bleeding disorder characterized by the loss of the capacity of platelets to externalize phosphatidylserine. Platelet count, size, adhesion, and aggregation activities are normal. The impaired binding of activated factor V and factor VIII results in diminished thrombin generation. 

Platelet granule deficiencies (storage pool diseases)

Three types of granules are present in platelets. Dense (β) granules contain nonprotein molecules such as ADP, ATP, calcium, magnesium, and serotonin. α-granules store proteins either produced by megakaryocytes or acquired from the blood by endocytosis. These proteins include VWF, fibrinogen, thrombospondin, factor V, fibronectin, and platelet-derived growth factor. Lysosomes contain hydrolases able to eliminate circulating platelet aggregates. Deficiencies of α- and/or dense granules (storage pool diseases) may cause bleeding diathesis (Table 2). α-granule disorders (Gray platelet syndrome, Paris-Trousseau syndrome, Quebec platelet disorder, ARC-arthrogryposis, renal dysfunction, and cholestasis syndrome) usually present with mild to moderate bleeding tendencies with unknown reasons. Asplenia, neurological symptoms, and ichthyosis were also reported in patients with Stormorken syndrome.

Disorders of platelet surface receptors

Platelets express different molecules on their surface, including leucin-rich-repeat receptors such as GPIb-IX-V complex; integrins such as αIbβ3 (GPIb-IIIa); proteins of the Ig superfamily such as GPIV; G-protein-coupled receptors such as PAR1, PAR4, and ADP receptors; and C-type lectin receptors such as P-selectin. Expression and activity of these receptors are dependent on the activation status of platelets. Platelet surface receptors and their signaling processes are very important for hemostasis. Two inherited platelet surface receptor disorders, BSS and GT, clearly show that even genetic deficiency of a single platelet receptor may cause bleeding tendency.

Bernard Soulier syndrome

The GPIb-IX-V complex is expressed on platelets and megakaryocytes. The receptor consists of 4 distinct polypeptide subunits that are encoded by different genes: GPIbα, GPIbβ, GPIX, and GPV. The major component of this complex, GPIbα, binds to VWF and several other molecules involved in hemostasis, thrombosis, and inflammation, such as thrombin, P-selectin, factor XI, factor XII, high-molecular-weight kininogen, thrombospondin, and β-2 GPI. After endothelial damage, GPIbα binds to collagen-bound VWF, which expresses a normally cryptic binding site for GPIbα. GPIbα also may bind VWF in plasma under high shear conditions or when defective VWF cleavage occurs, such as in thrombotic microangiopathies.

BSS is an inherited bleeding disorder characterized by macrothrombocytopenia and an absence of ristocetin-induced platelet aggregation. The prevalence of the syndrome is estimated at less than 1 in 1 000 000. The majority of BSS cases are inherited in an autosomal-recessive pattern. Mutations responsible for BSS are heterogeneous: nonsense and missense mutations and frameshift insertions or deletions may be found in genes encoding GPIbα, GPIbβ, or GPI. These mutations inhibit expression of the GP Ib-IX-V receptor on the surface of platelets. There is no reported case of an isolated GPV gene mutation. Rarely, mutation may only impair VWF binding with normal expression of the receptor (Bolzano variant).

As in other IPDs, BSS manifests itself by a bleeding tendency in early childhood. Easy bruising, purpura, epistaxis, gingival bleeding, menorrhagia, and excessive bleeding after surgery or trauma are common signs. Although the severity of bleeding is associated with a genetic defect affecting receptor functions and platelet counts, it is quite variable in patients who have the same mutations. Other genetic differences and acquired conditions affecting hemostasis may influence bleeding severity in these patients. Heterozygotes may not have any bleeding symptoms, but giant platelets may be seen on a peripheral blood smear.

Platelet counts are variable mostly due to the presence of giant platelets and usually range from 20 to 140 × 10^9 in BSS patients. The association between macrothrombocytopenia and GP Ib-IX-V mutations is not known. Decreased platelet lifespan, impaired megakaryopoiesis, and defective interaction of GP Ib-IX-V complex with cytoskeleton have been hypothesized. Leukocyte...
counts and morphology should be examined carefully for the differential diagnosis of other giant platelet syndromes. Skin bleeding time and PFA-100 closure time are prolonged. Routine coagulation tests should be normal. Prothrombin consumption and thrombin generation tests are markedly decreased because of the defective binding of FXI and thrombin. Results of platelet aggregation studies are pathognomonic for BSS: normal aggregation responses with ADP, arachidonic acid, collagen, and epinephrine with the absence of an aggregation curve with ristocetin. Impaired aggregation response may be seen at low concentrations of thrombin. Flow cytometric analysis of platelets is also characteristic for BSS: normal binding with CD41 (GP IIb) and CD61 (GPIIIa) antibodies, but defective binding with CD42a (GPIX), CD42b (GP Ib), CD42c (GP Ibβ), and CD42d (GPV) antibodies suggest BSS. Immunoblotting after separating components of the GP Ib-IX-V complex with sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) may describe the defective fragments but needs specialized interpretation.

Platelet-type (or pseudo) VWD

Platelet-type (or pseudo) VWD is an autosomal-dominant disorder characterized by mild thrombocytopenia, large platelets, and a mild-to-moderate bleeding diathesis. GP Ibα gene mutations (a 27-bp deletion and 4 point mutations) that cause increased binding state may increase the bleeding risk.VCFS may require major surgery for their anomalies and this carrier state may be consistent with a diagnosis of GT. Flow cytometry, however, may not recognize variant cases expressing functionally abnormal αIIbβ3. Platelet aggregation studies and genetic analysis are preferred for these patients.

Velocardiofacial syndrome

Velocardiofacial syndrome (VCFS) is an inherited disorder characterized by abnormal pharyngeal arch development. VCFS can present in numerous ways, as more than 180 clinical features have been described. Palatal abnormalities, craniofacial defects, cardiac abnormalities, hypotonia, defective thymic development, and immune deficiency are common features of the syndrome. VCFS is caused by a microdeletion located on chromosome 22q11.2. The platelet receptor GPIIbβ3 gene is located in the same chromosome and microdeletion may also cause GPIIbβ3 deficiency. These patients may have macrothrombocytopenia and decreased aggregation with ristocetin, as seen in heterozygous BSS carriers. Children with VCFS may require major surgery for their anomalies and this carrier state may increase the bleeding risk.

Glanzmann thrombasthenia

GT is an autosomal-recessive bleeding disorder characterized by a defective platelet integrin αIIbβ3 receptor. The integrin αIIbβ3 (GP IIb-IIIa) receptor is abundantly expressed on platelets: ~ 80 000 copies are found on the surface of each platelet. The receptor is a heterodimer consisting of αIIb and β3 subunits found in an inactive state in resting platelets. After platelet activation, inside-out signal-

Although the exact prevalence of the GT is unknown, it is estimated to be ~1 in 1 000 000. A slight female predominance (58% vs 42%) is reported. Similar to other IPDs, mucocutaneous bleeding starting in childhood is the major clinical finding. Bleeding severity is quite variable in patients with GT. The presence of thrombophilic mutations such as the FV Leiden mutation and prothrombin gene mutation may change bleeding patterns in these patients.

Platelet counts are normal in GT except for the variant forms with activating mutations of αIIbβ3. Skin bleeding time and PFA-100 closure times are both prolonged. Aggregation studies with LTA show no platelet aggregation in response to collagen, ADP, epinephrine, and arachidonic acid. The aggregation response to high-dose ristocetin is usually normal, but may be reversible in some cases. In flow cytometric analysis, absence or greatly decreased levels of CD41 and CD61 and normal levels of CD42 are consistent with a diagnosis of GT. Flow cytometry, however, may not recognize variant cases expressing functionally abnormal αIIbβ3. Platelet aggregation studies and genetic analysis are preferred for these patients.

Other platelet surface receptor deficiencies are very rare, and majority of these defects have no significant hemostasis in humans. GPVII (collagen receptor) deficiency is reported only in patients with bleeding diathesis (2 with compound heterozygous mutations, 4 with homozygous mutations).

Miscellaneous

GATA-1 related thrombocytopenia. The GATA-1 gene is located on the X-chromosome and encodes GATA-1 protein, which belongs to the GATA family of transcription factors. GATA-1 plays an important role in the development erythroid and megakaryocytic cells. Several mutations have been described in GATA-1, resulting in platelet abnormalities (dysmegakaryopoiesis, thrombocytopenia, large or small platelets, α-granule deficiency) and dyserythropoietic anemia with different clinical severity. Increased hemoglobin A2, persistence of hemoglobin F, and unbalanced production of α- and β-globulin synthesis may cause a “beta-thalassemia-like phenotype” in some patients. The same phenotype was also described in
a child with congenital erythropoietic porphyria caused by a R216W mutation of the GATA-1 gene. GATA-1s is a shorter isoform of GATA-1 with loss of the N-terminal transcription activation domain. It has been shown to be associated with the development of acute megakaryoblastic leukemia and transient myeloproliferative disorder in patients with Down syndrome.

Familial platelet disorder with propensity to myeloid malignancy. Familial platelet disorder with propensity to myeloid malignancy is an autosomal-dominant disorder characterized by thrombocytopenia and a genetic predisposition to the myeloid malignancies. Germline RUNX1 mutations have been described in these families. Hematopoietic stem cell transplantation using a sibling known to be negative for RUNX1 mutations is the only curative option.

Wiskott-Aldrich syndrome. Wiskott-Aldrich syndrome (WAS) is an X-linked recessive immunodeficiency syndrome caused by WAS protein gene (WASP) mutations. WAS protein regulates actin filament reorganization in hematopoietic cells and regulates lymphocyte and platelet functions. The different WASp mutations generate different phenotypes: WAS, X-linked thrombocytopenia, and X-linked neutropenia. The classic or severe WAS is characterized by microthrombocytopenia, eczema, and susceptibilities to infections, autoimmune diseases, and malignancies. These patients have a very poor prognosis. Currently, the only curative therapy is the allogeneic hematopoietic stem cell transplantation if a matched donor is available. Genetically modified autologous hematopoietic stem cell transplantation may represent an alternative form of therapy in these patients.

Disclosures
Conflict-of-interest disclosure: The author declares no competing financial interests. Off-label drug use: None disclosed.

Correspondence
Reyhan Diz-Küçükkaya, MD, Istanbul Bilim University, Avrupa Florence Nightingale Hospital, Hematology-Oncology Clinic, Bedrettin mahallesi, Bedii Gorbun sokak, No. 1, 34420, Şişhane-Beşöglu, İstanbul, Turkey; Phone: +90 212 224 4950; Fax: +90 212 315 3640; e-mail: rkucukkaya@hotmail.com.

References
25. Clark SR, Thomas CP, Hammond VJ, et al. Characterization of platelet aminophospholipid externalization reveals fatty acids...


