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Bernard Soulier Syndrome:  
A Genetic Bleeding Disorder

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1. Introduction

Platelets and other coagulation factors play an important role in the primary haemostasis mechanism, a multistep process of platelets interaction with elements of the damaged vessel wall, leading to the initial formation of a platelet plug (Ahmad et al., 2008). This mechanism requires the synergistic action of several different platelet receptors which play an essential role in each step of aggregation. Platelet adhesion, activation and aggregation are in fact regulated by specific glycoprotein on the platelet cell surface. Genetic defects in one of these glycoprotein led to bleeding symptoms due to inability of blood platelets to provide their hemostatic function in the vessel injury.

Inherited platelet defects cause bleeding symptoms of varying severity. Typically, easy bruising, epistaxis, gingival and mucocutaneous bleeding are observed in affected patients. Different diagnostic parameters have been used to classify inherited thrombocytopenia including the degree of bleeding, inheritance trait, platelet function and kinetics, and clinical abnormalities (see table 1).

The platelet defects are classified into disorders affecting either intracellular organelle of platelets, signalling pathway or surface receptors.

Currently, much effort is being put into methods to more rapidly and accurately diagnose patients with platelet disorders and to initiate appropriate therapy and prevent life threatening bleeding (Simon et al., 2008).

In this chapter, we describe many platelets disease caused by secretion defects like in Grey Platelet Syndrome (GPS), Quebec platelet disorder (QPD) or Wiscott-Aldrich syndrome (WAS), other diseases due to signal transduction shortcoming. Finally, we detail some diseases caused by deficiency of platelet complex expression in the cell surface and we develop especially Bernard Soulier syndrome (BSS).

2. Defects of secretion

Many disorders are classified in this category and are known as “storage pool disease”. This group contain several congenital diseases characterized by defects in intracellular organelle...
especially α-granule and dense granule (Simon et al., 2008). The absence of platelet granules results in a defective secretion from activated platelets as well as abnormal secretion-dependent platelet aggregation (Sandrock & Zieger, 2010). Deficiencies can alter the contents of α-granules, dense granules or both. In many patients the storage pool defect is the only abnormality detected. Nevertheless, the association with other congenital abnormalities was also shown like in Hermansky-Pudlak syndrome (HPS), Chediak-Higashi syndrome (CHS) and Wiskott-Aldrich syndrome (David et al., 2001).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Bleeding symptoms</th>
<th>Platelet count (10⁹/l)</th>
<th>Platelet aggregation</th>
<th>Inheritance</th>
<th>Gene</th>
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<tbody>
<tr>
<td>GPS</td>
<td>Mild to moderate</td>
<td>30-100</td>
<td>normal or ↓ aggregation with thrombin, collagen</td>
<td>autosomal recessive (most) or dominant</td>
<td>unknown</td>
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<tr>
<td>QPD</td>
<td>Mild to moderate</td>
<td>Normal or less</td>
<td>↓ aggregation with epinephrine</td>
<td>Autosomal dominant</td>
<td>uPA gene (PLAU)</td>
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<tr>
<td>HPS</td>
<td>Moderate to severe</td>
<td>normal</td>
<td>↓ second wave of aggregation</td>
<td>Autosomal recessive</td>
<td>HPS1-HPS8</td>
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<tr>
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</tr>
<tr>
<td>CHS</td>
<td>Moderate to severe</td>
<td>normal</td>
<td>↓ second wave of aggregation</td>
<td>Autosomal recessive</td>
<td>LYST</td>
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<tr>
<td>WAS</td>
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<td>↓ aggregation</td>
<td>X-linked recessive</td>
<td>WAS</td>
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<td>XLT</td>
<td>moderate</td>
<td>decreased</td>
<td>↓ aggregation</td>
<td>X-linked</td>
<td>WAS</td>
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<tr>
<td>GT</td>
<td>Moderate to severe</td>
<td>Normal</td>
<td>Reduced or absence of aggregation</td>
<td>Autosomal recessive</td>
<td>GPIIb and GPIIIa</td>
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<tr>
<td>BSS</td>
<td>Moderate to severe</td>
<td>10-100</td>
<td>Absence of Aggregation with ristocetin</td>
<td>Autosomal recessive (most) or dominant</td>
<td>GPIbα, GPIbβ and GPIX</td>
</tr>
</tbody>
</table>

Table 1. Clinical symptoms and candidate genes of several inherited platelet diseases

2.1 Abnormalities of α-granule
2.1.1 Grey Platelet Syndrome
The first case has been reported by Raccuglia in 1971 as a qualitative defect in platelets (Raccuglia, 1971). This rare hereditary disease is characterized by a bleeding tendency, moderate thrombocytopenia and decrease or absence of platelet α-granules and their contents probably due to the failure of maturation during megakaryocyte differentiation (White, 1979). GPS platelets are unsuitable to get and store endogenously synthesized proteins such as platelet factor-4, β-thromboglobulin, Von Willebrand Factor (vWF) as well as exogenous proteins such as fibrinogen, albumin, or factor V (Sandrock & Zieger, 2010).
Microscopic observations of patients blood smear revealed mild to moderate thrombocytopenia and enlarged (but not giant) platelets that have a gray appearance. Platelet aggregation studies are variable with no classical response pattern to ADP, epinephrine, thrombin, or collagen (Nurden, 2007). Both autosomal recessive and autosomal dominant inheritance have been reported suggesting that this syndrome is genetically heterogeneous (Mori et al, 1984) (Nurden et al., 2004). The molecular basis of GPS is unknown but could involve a “sorting” receptor for vesicles leaving the Golgi apparatus (Nurden, 2005).

2.1.2 Quebec platelet disorder
Quebec platelet disorder (QPD) is a defect in α-granule proteolysis of proteins and a deficiency of α-granule multimerin, a protein that binds factor V within the granule, thus leading to a decreased content of platelet factor V along with several other proteins like fibrinogen and vWF (Shapiro, 1999). In addition to α-granule protein degradation, this inherited bleeding disorder is associated with increased expression and storage of the fibrinolytic enzyme urokinase plasminogen activator (uPA) in platelets and intra-platelet plasmin generation (Diamandis et al., 2009). Patients showed mild thrombocytopenia, absence of aggregation with epinephrine and moderate to severe delayed bleeding following trauma or surgery that responds only to fibrinolytic inhibitor therapy (Veljkovic et al., 2009). This syndrome is inherited as an autosomal dominant manner. The genetic cause of QPD has recently been linked to inheritance of a region on chromosome 10 that contains the uPA gene (PLAU) (Diamandis et al., 2009).

2.2 Abnormalities of dense granule
Dense granule deficiency is often, but not always, associated with impaired secondary aggregation responses to some agonists (Ahmad et al., 2008).

2.2.1 Hermansky-Pudlak syndrome
Hermansky–Pudlak syndrome (HPS) is a rare autosomal recessive disorder. First HPS cases were reported on 1959 by Hermansky and Pudlak: Two unrelated patients suffered from oculocutaneous albinism, a history of frequent bruising following minimal trauma, lifelong bleeding tendency and unusual pigmented macrophages in bone marrow (Hermansky & Pudlak, 1959). This syndrome results from abnormal formation or trafficking of intracellular vesicles. The specific organelles affected in HPS are the lysosomes and lysosome-related organelles such as the melanosomes and the platelet dense granule (Cutler, 2002). Clinical manifestations showed hypopigmentation, platelet dense granule deficiency and accumulation of ceroid pigment in lysosomal organelles (Ramasamy, 2004). HPS patients have been described in different ethnic groups. However, this syndrome is frequent in Puerto Rico and in an isolated mountain village in the Swiss Alps (Schallreuter et al., 1993; Witkop et al., 1990).

Eight human HPS genes (HPS1–HPS8) have been found causing hypopigmentation and platelet storage pool deficiency. All HPS proteins are associated in multi-protein complexes essential for biogenesis and intracellular trafficking of intracellular vesicles of lysosomal lineage (Li et al., 2004). Mutations within particular HPS genes can lead to dysfunction of
the corresponding protein complex and thus to defective maturation of melanosomes and platelet dense bodies (Sandrock & Zieger, 2010).

2.2.2 Chediak-Higashi syndrome
Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disease described since 1955 by Sato (Sato, 1955). Like HPS, CHS is also characterized by oculocutaneous albinism and dense granule deficiency leading to platelet disorder and prolonged bleeding tendency. In addition, CHS patients showed severe immunologic defects and progressive neurological dysfunction making this disease lethal. If patients survive until adulthood, they develop neurological defects including neuropathies, autonomic dysfunction, atrophy, sensory deficits, seizures, and cognitive defects (Sandrock & Zieger, 2010). Only hematopoietic stem cell transplantation can improve the health status of patients (Eapen et al., 2007).

The candidate gene for this syndrome is named LYST (lysosomal trafficking regulator) (Barbosa et al., 1996; Nagle et al., 1996). The gene product is a protein which regulates the size and movement of lysosome-related organelles. LYST is predicted to be a cytosolic protein that mediates membrane interactions. Genetic defects are usually frameshift and nonsense mutations in LYST gene giving rise to truncated protein and a severe phenotype (Certain et al., 2000; Moore et al., 2002). Rarely, missense mutations are associated with a milder form of the disease.

2.3 Abnormalities of both granules
2.3.1 Wiskott-Aldrich syndrome
Wiskott–Aldrich syndrome (WAS) is a rare X-linked recessive disease. The inheritance of this syndrome explains why symptomatic individuals were all male (Aldrich et al., 1954). This syndrome has been observed first in 1939 by Alfred Wiskott. This paediatrician described three brothers who suffer from thrombocytopenia, bloody diarrhea, eczema, and recurrent ear infections; all three died early in life from intestinal bleeding and sepsis (Wiskott et al., 1939). The WAS phenotype consists of immunodeficiency, eczema, thrombocytopenia and is associated with extensive clinical heterogeneity. The immune deficiency is caused by decreased antibody production, although T cells are also affected (Vera Binder et al., 2006).

WAS is caused by mutations in WAS gene located at Xp11.22–p11.23, encoding Wiskott-Aldrich syndrome protein (WASP). This protein seems to be involved in signal transduction pathways in which tyrosine phosphorylation and adapter protein function have been suggested. Deficiency of WASP induces premature proplatelet formation in the bone marrow and cancels megakaryocytes migration (Sabri et al., 2006).

WASP is involved in innate immunity, cell motility and protection against autoimmune disease. The success of hematopoietic stem cell transplantation is related to the patient’s age, donor selection, the conditioning regimen and the extent of reconstitution. Gene therapy is expected to cure the disease because WASP is expressed exclusively in hematopoietic stem cells and it exerts a robust selective pressure (Notarangelo et al., 2008).

2.4 X-linked thrombocytopenia
X-linked thrombocytopenia (XLT) was recognized in 1960 and was suspected to be a variant of WAS. This was confirmed when XLT patients showed mutations in the WAS protein gene.
XLT patients have moderate symptoms when compared with WAS. They showed mild eczema and/or infections and they have a lower risk of cancer or autoimmunity than patients with WAS. XLT phenotype is often resulting from missense mutations given rise to defective expression of WASP (Albert et al., 2010).

3. Defects of intracellular signalling pathway

For many patients with platelet aggregation defects, the abnormalities lie in early signal transduction events. Those patients have a prolonged bleeding time on most occasions, they have an impaired dense granule secretion although their platelets have normal granule storage and generally synthesise substantial amounts of thromboxane A2 (Ramasamy, 2004). Platelet pathologies involving the signal transduction pathways mostly concern patients with mild bleeding disorders and defects of platelet aggregation which affect some stimuli more than others.

Concerned patients showed:
- Impaired Ca2+ mobilisation.
- Defective inositol-triphosphate production and a reduced phosphorylation of the protein, plekstrin, by protein kinase C.
- Deficiency of the phospholipase C-γ2 isoform,
- Specific decrease in platelet membrane Gq and decrease in platelets response to several agonists including a decreased activation of αIIbβ3.

A major effort is underway to uncover the genetic defects responsible of these phenotypes. (Nurden & Nurden, 2008)

4. Disorders of the surface membrane

Most studied disease affecting membrane receptors are Bernard Soulier syndrome which concern GPIb-IX-V complex and Glanzmann thrombasthenia with deficiency in GPIIb-IIIa complex.

4.1 Glanzmann thrombasthenia

Glanzmann thrombasthenia (GT) is the most common of the platelets diseases. It is characterized by the absence or deficiency of GPIIb-IIIa platelet complex. This complex play an essential role in platelets aggregation by fixing several ligand, like von Willebrand Factor and fibrinogen (Bellucci et al., 1983; Giltay et al., 1987). GP IIb–IIIa is one of the most abundant platelet surface receptors (about 80 000 per platelet) (Wagner et al., 1996).

The patients present normal platelet morphology, prolonged bleeding time, severe mucocutaneous diathesis and series of epistaxis, purpura or menorrhagia (Sherer & Lerner, 1999). The hallmark of this disease is a severely reduced or absent platelet aggregation in response to multiple physiological agonists such as ADP, epinephrine, thrombin and collagen. (Ahmad et al., 2008).

This disease is inherited as an autosomal recessive manner (Sherer & Lerner, 1999). Genetic defects are distributed in GPIIb or GPIIIa genes resulting in qualitative or quantitative abnormalities of the proteins. Both genes are present in our genome as single copies and are localized on chromosome 17 (table 2) (Rosenberg et al., 1997). More than 70 mutations have been described. Large deletions are very rare. Most of them are missense or nonsense mutation, insertion, small deletion and splicing defects; some of the punctual mutations
affected the mRNA production or stability (Nurden, 2005). This large number of identified mutations offers an opportunity to investigate phenotype/genotype correlations (Ramasamy, 2004).

<table>
<thead>
<tr>
<th></th>
<th>GPIIb</th>
<th>GPIIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (Kb)</td>
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<td>65</td>
</tr>
<tr>
<td>Number of exons</td>
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<td>15</td>
</tr>
<tr>
<td>Chromosome Localisation</td>
<td>17q21-23</td>
<td>17q21-23</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of GPIIb and GPIIIa genes

### 4.2 Bernard Soulier syndrome

#### 4.2.1 History

BSS was described more than 60 years ago as a severe and potentially fatal, congenital bleeding disorder. The first case was reported in 1948 by two French hematologists (Jean Bernard and Jean-Pierre Soulier) in a young male patient from a consanguineous family with severe bleeding episodes, a prolonged bleeding time, low platelet counts and very large platelets. They termed the disorder “congenital hemorrhagic parous thrombocytic dystrophy” (Bernard & Soulier, 1948). Since then, several individuals have been described with a similar disorder.

#### 4.2.2 Clinical manifestations

BSS patients present early many bleeding symptoms, most commonly epistaxis, ecchymosis, cutaneous and gingival bleeding. Some patients can show gastrointestinal haemorrhage. Severe bleeding occurred in the case of trauma, surgical intervention and in menses (Lanza, 2006). Chronic easy bruising and frequent hematomas are rarely reported (Kenny et al., 1999). Pregnancy in BSS patients may present complications of varying gravity. The severity of these bleeding symptoms is variable among patients and may range from mild to life-threatening and may become more or less severe during puberty and adulthood. Some rare BSS patients suffered fatal haemorrhage (Hadjkacem et al., 2010a). Heterozygous patients may have mild to moderate bleeding tendencies (Pham & Wang, 2007).

#### 4.2.3 Etiology

The molecular defect alters platelet complex named GPIb-IX-V. It is the surface receptor for von Willebrand factor that mediates both platelet agglutination in response to ristocetin and platelet adhesion under conditions of rapid blood flow. This complex plays an essential role in primary haemostasis ensuring platelets adhesion by its binding to von Willebrand factor, itself captured from plasma by sub-endothelial collagen (Berndt et al., 1989). GPIb-IX-V complex is composed by four glycoproteins designated GPIbα, GPIbβ, GPIX and GPV. They are expressed on the platelets surface in an apparent molar ratio of 2:2:2:1 respectively (figure 1). Approximately, 24000 copies of this complex are presents on the membrane of activated platelets (Strassel et al., 2009).

GPIbα, consists of 610 amino acids (MW 145 kDa), GPIbβ of 181 (22 kDa), GPIX of 160 (20 kDa), and GPV of 544 amino acids (82 kDa). GPIbα is disulfide linked to GPIbβ constituting GPIb dimer while GPIX and GPV bind to GPIb non-covalently (Lopez et al., 1998).
The vWF binding domain is located at the N-terminus of GPIbα. The GPIbα chain also binds a number of other ligands, including thrombin. The GPIbβ protein has N-terminal extra cellular domain that contains a cysteine knot region, which is essential for interaction with GPIX. The letter is essential for the correct assembly of the GPIb-IX-V complex on the platelet membrane. GPV is required for thrombin binding, possibly through an interaction with GPIbα. In addition, GPV binds to collagen and appears to be required for normal platelet responses to this agonist (Dong et al., 1998; Lopez et al., 1998).

Fig. 1. GPIb-IX-V complex

The GPIb-IX-V complex is formed within minutes in the endoplasmic reticulum before being transported into the Golgi cisternae to undergo post-translational modifications. Only complete complexes were expressed on the platelets membrane. The absence of one component of the complex increases the rate of degradation (Dong et al., 1998)

4.2.4 Diagnosis

The diagnosis is based on the presence of a prolonged skin bleeding time (more then 15 min), giant circulating platelets observed on a peripheral blood smear (larger than 4 µm and being able to reach 10 mm, while normal platelets are 2-3 µm) (figure 2) and thrombocytopenia (between $10^{10}$ to $10^{11}$ platelets/l compared to $1.5x10^{11}$ to $4x10^{11}$ platelets/l in healthy persons) (Hadjkacem et al., 2010a; Lanza, 2006)
BSS diagnosis is based mainly on aggregation test using an aggregometer since the platelets of patients aggregate normally in response to agonists such as adenosine diphosphate (ADP), collagen, epinephrine, arachidonic acid but they failed to aggregate in presence of ristocetin (figure 3). In addition, all BSS patients have decreased or absent expression of the GPIb-IX-V complex. For this reason, the diagnosis can be confirmed by flow cytometry using specific antibodies recognizing one or more proteins of the complex (figure 4) (Hadjkacem et al., 2010a; Ware et al., 1998).
The GPIIb-IIIa complex, normally expressed on the platelets surface of healthy persons and BSS patients, serves as a positive control. Those specialized laboratory tests are essential to avoid confusion between BSS and other similar platelet disorders (Hadjkacem et al., 2010a). Based only on clinical manifestations, many patients had been erroneously diagnosed with immune thrombocytopenia and were treated with steroids without response (Sachs et al., 2003).

Fig. 4. Flow cytometric analysis of normal and BSS platelets. (Hadjkacem et al., 2010b)

HIP8 is an antibody recognizing GPIIb-IIIa complex and serves as positive control. HIP1, MB45 and SZ2 are antibodies directed against different epitope on GPIbα. We have used simultaneously two antibodies for each platelets marking: the HIP8 and one of the GPIbα antibodies. The result is considered as double positive when the fluorescence is observed in the square 2 and it is considered as only HIP8 positive when fluorescence exist in square 1. If the fluorescence is localized in the square 3, we concluded that the GPIbα antibody failed to bind to the specific protein.

For healthy person, response is positive with all antibodies but in BSS patient, anti-GPIbα failed to bind on platelets surface because the absence of this protein.

4.2.5 Transmission mode

The BSS is an inherited disorder usually transmitted in an autosomal recessive manner and occurring in persons whose parents are close relatives. Both male and females are concerned by this disease; the male/female ratio is 1:1. An autosomal dominant with heterozygous state has also been found but rarely reported. This form was characterized by mild or no clinical symptoms and normal in vitro platelet function (Miller et al., 1992; Savoia et al., 2001).

Genetic counselling is done according to established standards for all autosomal recessive diseases.
4.2.6 Frequency
BSS is a rare disease, the frequency of homozygous has been estimated to be approximately one in one million (Lopez et al., 1998) and, according to the Hardy-Weinberg Law, the frequency of heterozygotes is 1 in 500 (Savoia et al., 2001).

4.2.7 Candidates genes
Molecular investigations of numerous BSS patients showed that only three genes are responsible of the disease: GPIbα, GPIbβ, and GPIX. No mutations have been reported in the GPV gene (Moran et al., 2000). These genes belong to the leucine-rich family of proteins and are exclusively expressed in megakaryocytes and platelets lineage. They showed common structural features except for their different chromosomal locations (Table 3). All candidate genes are present in monocopie. They are relatively poor in intron and contain their open reading frame (ORF) and the 3'UTR in a single exon except the GPIbβ where the ORF is contained in two exons (Antonucci et al., 2000; Lopez et al., 1998). GPIbα and GPIX genes shared promoter consensus sequences especially GATA and ETS sites (Mayumi et al., 1994).

<table>
<thead>
<tr>
<th></th>
<th>GPIbα</th>
<th>GPIbβ</th>
<th>GPIX</th>
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<tbody>
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<td>Chromosome localization</td>
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<td>3q-21</td>
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</tbody>
</table>

Table 3. Characteristics of BSS candidates genes

4.2.8 BSS mutations
Until now, more than fifty mutations responsible for BSS have been described: 25 mutations in the gene GPIbα, 18 mutations in GPIbβ and 11 in GPIX. These defects can be classified into three groups (table 4):
- missense mutations or short deletions, often resulting in abnormal and/or unsuitable complex with a significant reduction of protein expression on the platelets surface.
- nonsense mutations giving truncated subunits, often without the transmembrane domain.
- frameshift insertions or deletions leading to a new polypeptide with premature stop codon (Hadjkacem et al., 2010a; Lanza, 2006).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Missense mutation</th>
<th>Nonsense mutations</th>
<th>Frameshift or short deletions</th>
<th>Others</th>
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<td>GPIbβ</td>
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<td>3</td>
<td>2</td>
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<tr>
<td>GPIX</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4. Different type of mutations described in literature in each BSS candidate gene
Compound heterozygote has been also described in BSS patients. It was relatively frequent as approximately 1/5 of described BSS mutations are of this form (Hadjkacem et al., 2010a). The genetic defects observed in BSS patients affect the von Willebrand binding site on GPIbα, inhibit the association between GPIbβ and GPIX after protein synthesis, or affect post-translational modifications that may influence the function of the complex. In very few cases, a point mutation predominantly affects receptor function as some described mutations in GPIbα and GPIX (Antonucci et al., 2000).

4.2.9 BSS founder mutations
Most mutations affect only one patient or one family but few exceptions do exist, such as the Asn45Ser identified in GPIX in several families from different nations (Koskela et al., 1999), Ala156Val in GPIbα frequently observed in Italian families (Budarf et al., 1995) and a recently identified Tunisian mutation (Hadjkacem et al., 2009, 2010).

Bernard Soulier syndrome was the focus of several studies in European, Japanese and North American populations. African and Arab populations have not been studied, with few exceptions. Our laboratory studied this syndrome for the first time in Tunisia. Initially, our study concerned only one family consisting of five members: parents and three children including a boy suffering from BSS. Intermarriage increased the risk of developing the disease. We have identified a novel mutation in GPIbβ gene responsible for BSS in this family. The Ser23Stop so identified can be followed by MnlI restriction analysis of PCR amplified fragment. It is inherited as an autosomal recessive manner. Studies of protein expression of GPIb-IX-V complex showed the absence of GPIbα on the platelets surface of the patient (Hadjkacem et al., 2009).

Subsequently, our study included two other unrelated Tunisian families with BSS cases. In one of these families, we have revealed the same Ser23Stop mutation while in the second we observed compound heterozygosity including Ser23Stop in addition to two others missense mutations located in GPIbβ gene: Asp51Gly and Ala55Pro (Hadjkacem et al., 2010b).

Given that most of described BSS mutations are unique and the same Ser23Stop mutation being found in three unrelated Tunisian families, we suggested that it is an ancient mutation having a founder effect and can be used in genotyping for BSS diagnosis in further exploration of other Tunisian families. Indeed, the identification of a founder mutation can help physicians to avoid misdiagnosis.

4.2.10 Treatment
The severity of bleeding is unpredictable in the BSS, however most patients require transfusion in case of excessive bleeding (Nurden, 2005). The benefits of receiving the transfusions must be evaluated against the risks of exposure. Repeated exposure to blood products raises concern for alloimmunization and platelet refractoriness. Although some authors have suggested that patients should receive platelets from human leukocyte antigen–matched donors in order to avoid alloimmunization (Balduini et al., 2002), some patients should be warned to avoid trauma and antiplatelet drugs such as aspirin, to maintain dental hygiene and use of contraceptive devices to puberty (Lanza, 2006).

The administration of rFVIIa and Desmopressin is used to shorten the bleeding time in some patients. In rare cases of patients with serious and repetitive bleeding, bone marrow transplantation is used (Lanza, 2006).
5. Conclusion

The inherited platelet disorders are functional abnormalities of platelets due to genetic defects and lead to bleeding symptoms of varying severity. They constitute a large group of rare diseases caused by one or more mutations affecting one or more genes. These genetic defects may affect platelet granules or proteins involved in signaling pathways. Nevertheless, diseases caused by abnormalities of platelet membrane receptors are the best known platelets diseases especially the Glanzmann thrombasthenia and the Bernard Soulier syndrome. Their diagnosis is relatively easy to perform but they are manifested by severe bleeding.

Despite advances in the understanding of the etiology of these diseases, usually the underlying mechanisms remain unknown and treatment is relatively rudimentary.

6. References


Aldrich, RA.; Steinberg, AG. & Campbell, DC. (1954). Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. *Pediatrics*, vol. 13, pp. 133-139,


Barbosa, MD.; Nguyen, QA.; Tchernev, VT.; Ashley, JA.; Detter, JC.; Blaydes, SM.; Brandt, SJ.; Chotai, D.; Hodgman, C.; Solari, RC.; Lovett, M. & Kingsmore, SF. (1996). Identification of the homologous beige and Chediak-Higashi syndrome genes. *Nature*, vol. 382, pp.262–265,


Biddle, DA.; Neto, TG. & Nguyen, AND. (2001). Platelet Storage Pool Deficiency of α and δ Granules. *Archives of Pathology & Laboratory Medicine*, vol. 125, No. 8, pp. 1125-1126,
Bernard Soulier Syndrome: A Genetic Bleeding Disorder


Diamandis, M.; Paterson, AD.; Rommens, JM.; Veljkovic, DK.; Blavignac, J.; Bulman, DE.; Waye, JS.; Derome, F.; Rivard, GE & Hayward, CP. (2009). Quebec platelet disorder is linked to the urokinase plasminogen activator gene (PLAU) and increases expression of the linked allele in megakaryocytes. *Blood*, vol. 113. pp. 1543-1546.


Veljkovic, DK.; Rivard, GE.; Diamandis, M.; Blavignac, J.; Cramer-Borde, EM. & Hayward, CPM. (2009). Increased expression of urokinase plasminogen activator in Quebec platelet disorder is linked to megakaryocyte differentiation. *Blood*, vol. 113, pp. 1535-1542


The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

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