Inherited Disorders of Platelets
Membrane Glycoprotein Disorders

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KEYWORDS

• Platelet glycoproteins • Bernard-Soulier syndrome • Glanzmann thrombasthenia
• Inherited bleeding tendency • Platelet disorders

KEY POINTS

- Platelet membrane glycoproteins play key roles in various aspects of platelets functions and their deficiency can produce bleeding.
- Bleeding can be severe and manifest during childhood, or mild and only manifested in adulthood after trauma or surgery.
- These disorders can mimic acquired disorders and require careful histories and detailed laboratory evaluation. Management requires both preventive measures and treatment of specific bleeding episodes according to severity.
- The study of platelet membrane disorders also has yielded important insights into the functions of affected proteins, information that has produced some of the most successful antithrombotic drugs currently in use.

Inherited platelet disorders are rare, and chiefly produce defects in primary hemostasis. The severity of symptoms primarily depends on 2 variables: (1) the identity of the deficient or defective protein, and (2) the extent of the deficiency or functional defect. Severe deficiencies manifest themselves early during childhood, with frequent episodes of mucocutaneous bleeding, such as purpura, gingival bleeding, epistaxis, menorrhagia, and prolonged bleeding after trauma or surgery. Hematuria and gastrointestinal bleeding, and rarely intracranial hemorrhage may occur spontaneously. Mild deficiencies may not be diagnosed until adulthood or until the hemostatic system is stressed by surgery or trauma. Inherited platelet disorders can also be associated with other clinical features, such as skeletal abnormalities and mental retardation in velo-cardiofacial syndrome, hearing loss, or renal disorders. In some patients, the

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presence of thrombocytopenia with large platelets may lead to the misdiagnosis of immune thrombocytopenia (ITP) and lead to unnecessary treatments. Family history, platelet aggregation tests, flow cytometric analysis of platelet surface glycoproteins, and genetic analysis discriminate inherited disorders from acquired ones, although not always with 100% certainty.

Inherited platelet disorders are a large and heterogeneous group of diseases caused by genetic mutations of a large number genes, some expressed exclusively on platelets and megakaryocytes, and some having more widespread distribution. An overview of inherited platelet function disorders and a review of disorders of platelet granules and secretion is presented elsewhere in this issue. Inherited thrombocytopenias are described in a separate review. This review primarily focuses on inherited defects of platelet membrane glycoproteins.

DISORDERS OF THE GLYCOPROTEIN IB-IX-V COMPLEX

The glycoprotein (GP) Ib-IX-V complex is constitutively expressed on platelets and megakaryocytes and mediates several important platelet interactions with other molecules. The GPIb-IX-V complex contains 4 distinct polypeptide subunits in a stoichiometry of 2 GPIbα, 4 GPIbβ, 2 GPIX, and 1 molecule of GPV.[1,2] Although this stoichiometry has been established, the exact number of subunits in a functional complex has not been. Each subunit has the structure of a type I transmembrane protein, with a single transmembrane domain separating an extracellular N-terminus from an intracellular C-terminus. Each also belongs to the leucine-rich repeat (LRR) superfamily of proteins that includes, prominently, the toll-like receptors.[3] Whether this shared ancestry implies anything about the functions of the GPIb-IX-V complex is not clear. The LRRs reside in the extracellular portion of the polypeptides, where they are flanked by disulfide loops at the N- and C-termini. In GPIbα, the polypeptide that contains the binding sites for all of the known ligands of the complex, the LRR-containing ligand-binding domain is separated from the platelet plasma membrane by a extended, highly glycosylated mucin core. Each polypeptide also has a cytoplasmic domain through which the polypeptides associate with cytoskeletal elements, such as filamin A, and adapter and signaling proteins, such as 14-3-3ζ, calmodulin, and phosphoinositide-3 kinase.[4] The 4 subunits are encoded by different genes. After transcription and translation of the polypeptides, they associate to produce the receptor complex in the endoplasmic reticulum.[5] Posttranslational modifications of the molecule are very important for the functions of the receptor and include extensive N- and O-glycosylation, palmitoylation of GPIbβ and GPIX,[6] and tyrosine sulfation.[7,8] Approximately 15,000 to 25,000 copies of GPIb-IX-V complex are expressed on human platelets.[1,9,10]

The GPIb-IX-V complex mediates several interactions of importance in thrombosis and hemostasis. GPIbα binds von Willebrand Factor (VWF),[11] thrombin,[12] P-selectin,[13] Mac-1,[14] factor XI,[15] factor XII,[16] high molecular weight kininogen,[17] thrombospondin,[18] and β-2 glycoprotein I.[19] Of these, the interaction with VWF, and possibly thrombin, appear to be the most important, as judged by the phenotype of the deficiency syndrome. Binding of GPIbα to VWF is the key event in the adhesion of platelets to the subendothelium, which is exposed with traumatic vessel injury or rupture of atherosclerotic plaques. Matrix-bound VWF, unlike VWF circulating in blood, expresses a normally cryptic GPIbα binding site, allowing platelets from the blood to adhere and spread at the site of injury, with subsequent aggregation mediated by other membrane glycoproteins. Two other circumstances in addition to being immobilized on the subendothelial surface also allow VWF to bind GPIbα: (1) exposure of plasma