When to suspect inherited platelet disorders and how to diagnose them

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Inherited platelet disorders (IPDs) are a heterogeneous group of mucocutaneous bleeding disorders of variable severity caused by genetic defects. The relevant genes encode an array of molecules of diverse function, reflecting megakaryopoiesis, platelet formation, and platelet function. Many IPD genes are widely transcribed across blood cell types and other tissues. Hence, patients with IPDs frequently present with pathologies reaching well outside the blood system.1

Accurately diagnosing IPDs is important for the appropriate clinical management of individual patients and enables a reliable estimate of their real prevalence. Glanzmann thrombasthenia (GT) and Bernard-Soulier syndrome (BSS) often present with severe bleeding symptoms early in life and are easily recognized by the platelet aggregation defect pattern.2,3) Some IPDs present with syndromic features such as hearing loss, renal impairment (GT) and Bernard-Soulier syndrome (BSS) often present with bleeding symptoms.4) If clear abnormalities emerge from the clinical assessment and/or bleeding score,6) the proband should be subjected to preliminary laboratory investigations, including full blood count, prothrombin time, activated partial thromboplastin time, and von Willebrand factor (VWF) screening tests (VWF antigen, ristocetin cofactor activity, and factor VIII coagulant activity). If these results are normal, a diagnostic work-up for IPD should be pursued. Given that several IPDs are associated with thrombocytopenia, a mildly reduced platelet count should not exclude further IPD testing.

Establishing a conclusive molecular diagnosis is the bedrock of good hematologic practice because it informs optimal treatment and can provide clarity about disease progression. For IPDs, this is particularly important in severe cases and those associated with early-onset clinical pathologies such as myelofibrosis, lung fibrosis, renal insufficiency, and malignancy.8) Thrombocytopenias caused by variants in RUNX1, ETV6, and ANKR26 are associated with increased risk of myeloid malignancy, whereas for Wiskott-Aldrich syndrome and amegakaryocytic thrombocytopenia caused by MPL variants, treatment by allogeneic hematopoietic stem cell transplantation or gene therapy may require consideration.9,10) Moreover, genetic counseling can be provided
if the diagnosis is confirmed at the DNA level.

We just started a nationwide K-PHOG survey of IPDs with next generation-sequencing. Due to clinical diversity as well as genetic heterogeneity, pediatricians must pay more attention to their diagnosis. In the genomic era, it is hoped that genetic panels for IPDs will be available soon and covered by medical insurance.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

See the article “Genetic classification and confirmation of inherited platelet disorders: current status in Korea” in Volume 63 on page 79.

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