Title: Genetic classification and confirmation of inherited platelet disorders and current status in Korea

Running title: Inherited platelet disorders

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Abstract

Inherited platelet disorders (IPDs), which manifest as primary hemostasis defects, often underlie abnormal bleeding and a family history of thrombocytopenia, bone marrow failure, hematologic malignancies, undefined mucocutaneous bleeding disorder, or congenital bony defects. A wide heterogeneity in IPD types, in regard to the presence or absence of thrombocytopenia, platelet dysfunction, bone marrow failure, and dysmegakaryopoiesis, is observed in patients. The individual processes involved in platelet production and hemostasis are genetically controlled: to date, mutations more than 50 genes involved in various steps of platelet biogenesis have been implicated in IPDs. Representative IPDs resulting from defects in specific pathways, such as THPO/MPL signaling; transcriptional regulation; granule formation, trafficking, and secretion; proplatelet formation; cytoskeleton regulation; and transmembrane GP signaling, are reviewed, and the underlying gene mutations discussed based on the NCBI database and Online Mendelian Inheritance in Man accession number (OMIM). Further, the status and prevalence of genetically confirmed IPDs in Korea are explored based on the literature searches of PubMed and KoreaMed database. IPDs are congenital bleeding disorders that can be dangerous due to unexpected bleeding and also requires genetic counseling for family members and descendants. Therefore, the pediatrician should be suspicious and aware of IPDs and able to carry out appropriate tests if the patient has an unexpected bleeding. However, each disease of IPDs are extremely rare, thus the domestic incidence of IPDs are unclear and it is difficult to diagnose IPDs. Diagnostic confirmation or differential diagnoses of IPDs are challenging, time-consuming, and expensive, and patients are frequently misdiagnosed. Comprehensive molecular characterization and classification for these disorders should enable accurate and precise diagnosis and facilitate improved patient management.

Keywords: Congenital Platelet Function Disorder, Glanzmann Thrombasthenia, Bernard–Soulier syndrome, Giant Platelet Syndrome, Storage Pool Disease, Von Willebrand Disease

Introduction

There are two important components of hemostasis: primary hemostasis (platelet response to vessel injury and platelet-plug formation) and secondary hemostasis (generation of fibrin deposition by the coagulation cascade).[1)] In particular, platelets play a key role in adequate primary hemostasis through four fundamental mechanisms: adhesion, aggregation, secretion, and procoagulant activity.[2, 3)] Normal platelet adhesion requires the presence of von Willebrand factor (vWF), glycoprotein (GP) receptors on platelets, and adequate release of platelet granular contents, such as adenosine diphosphate (ADP), serotonin, and thromboxane A2.[1)] Thus, familial inherited thrombocytopenia, platelet function disorders due to defects in GP receptors or storage pool diseases, von Willebrand's disease (vWD), or immune thrombocytopenia (ITP) can show similar primary hemostatic problems.[4)] Symptoms/signs include mucocutaneous bleeding, easy bruising, frequent or persistent nosebleeds, persistent oozing after abrasions or dental treatment, and massive bleeding during menstruation or after delivery.[4)] Accordingly, inherited platelet disorders (IPDs) should be suspected when patients have the following characteristics: 1) bleeding out of proportion to platelet count; 2) family history of thrombocytopenia, bone marrow failure, or leukemia; 3) family history of undefined mucocutaneous bleeding disorder regardless of the platelet count; and 4) whenever vWD is being considered as the cause of bleeding.[4)]

However, diagnostic confirmation and differential diagnosis of IPDs are complicated, time consuming, and expensive; thus, many patients with IPD are not appropriately diagnosed.[4, 5)] Notably, IPDs are typically quite heterogeneous; patients often present with or without thrombocytopenia, with or without platelet dysfunction, with or without bone marrow failure, and with or without dysmegakaryopoiesis.[6)] In most cases, individual megakaryopoiesis, platelet formation, and platelet function are genetically controlled, and

more than 50 genes associated with IPDs have been identified in recent studies by genome-wide association study and next-generation sequencing.[7] These genes can be classified according to the specific pathway that is disrupted in platelet formation, e.g., the thrombopoietin (THPO)/THPO receptor (MPL) signaling pathway, transcriptional regulation, granule formation/trafficking/secretion, cytoskeleton regulation, and transmembrane protein signaling pathway (Fig. 1, adapted from Lentaigne, *et al.*[7]).

Therefore, in this review, representative IPDs based on genetic classification and the current status of these diseases in Korea will be discussed based on the NCBI database, Online Mendelian Inheritance in Man accession number (OMIM) database, the literature searches of PubMed and KoreaMed database. In particular, this review focuses on IPDs with thrombocytopenia or thrombocytopathy. The characteristics of the respective IPDs are described in Table 1, and the diagnostic sequence and flow in IPD is described in Fig. 2.[4, 8] Further, the reported data about genetically confirmed Korean IPD patients are summarized in Table 2.

Defects in the THPO/MPL signaling pathway

Congenital amegakaryocytic thrombocytopenia (CAMT)

CAMT (OMIM #604498) is a rare autosomal recessive IPD with severe thrombocytopenia from infancy due to *MPL* gene mutation and high levels of serum THPO.[9)] Recently, a genetically confirmed Korean patient with CAMT harboring a novel mutation in the *MPL* gene was reported.[10)] CAMT is characterized by megakaryocytopenia in the bone marrow, thrombocytopenia with normal platelet size, and progressive bone marrow failure to aplastic anemia.[9)] A classification (types I–III) according to the disease severity and outcome was proposed in 2005.[11)] Approximately 10–30% of patients with CAMT have orthopedic/neurological abnormalities or intracranial hemorrhage.[6)] The THPO receptor, encoded by the *MPL* gene, promotes the growth and proliferation of megakaryocytes and may play a role in the maintenance of hematopoietic stem cells.[9, 11)] CAMT with bone marrow failure to aplastic anemia is best managed by hematopoietic stem cell transplantation (HSCT).[12)]

Defects in transcriptional regulation

X-linked thrombocytopenia with or without dyserythropoietic anemia (XLTDA)

XLTDA (OMIM #300367) is a rare X-linked recessive IPD with unknown prevalence; only a few cases have been reported worldwide.[13-16)] No Korean cases of XLTDA associated with *GATA1* have been reported to date. The *GATA1* gene encodes a crucial transcription factor, GATA-binding factor 1, involved in the development of erythrocytes and megakaryocytes at early-stage hematopoietic stem cells.[14)] Depending on the specific mutation in *GATA1*, macrothrombocytopenia, variable severity of anemia, hemolysis, and hypercellular marrow with erythroid dysplasia can occur.[2)]

Jacobsen syndrome and Paris-Trousseau syndrome

Jacobsen syndrome (OMIM #147791) and Paris-Trousseau syndrome (OMIM #188025) are rare autosomal-dominant IPDs associated with deletion of chromosome 11q.[17, 18] A few Korean cases have been reported.[19-21] These diseases share several similar phenotypes (dysmorphic features and intellectual disabilities) and macrothrombocytopenia with giant α-granules due to the fusion of smaller organelles.[17, 22] Chromosome 11q23.3 includes the *FLI1* gene, which encodes an essential transcription factor for megakarypoiesis.[23] Hemizygous deletion of *FLI1* prevents progenitor cells from undergoing the normal differentiation process, thereby generating a large population of small immature megakaryocytes that undergo lysis.[23]

Radioulnar synostosis with amegakaryocytic thrombocytopenia (RUSAT)

RUSAT1 (OMIM #605432) and RUSAT2 (OMIM #616738) are recently introduced and identified autosomal-dominant IPDs with progressive bone marrow failure and pancytopenia, necessitating HSCT.[24, 25] Only a few families with these conditions have been reported worldwide,[2] and no Korean cases have been described in the literature. These syndromes involve amegakaryocytic thrombocytopenia and skeletal defects (limited pronation/supination of the forearm due to proximal fusion of the radius-ulna).[24, 25] RUSAT1 and RUSAT2 are caused by variants in the homeobox A11 (*HOXA11*) and EVI1 complex locus (*MECOM*) genes, respectively.[24, 25] The protein encoded by the *HOXA11* gene is a DNA-binding transcription factor that regulates gene expression, morphogenesis, and differentiation.[24] The oncoprotein EVI1, encoded by the *MECOM* gene, is also a transcriptional regulator involved in hematopoiesis and stem cell self-renewal in human cells.[26] In mice, MECOM is expressed at high levels in the limb bud of embryos, suggesting that this gene is also involved in limb development.[27]

Thrombocytopenia-absent radius (TAR) syndrome

TAR syndrome (OMIM #274000), also known as chromosome 1q21.1 deletion syndrome, is a rare autosomal-recessive IPD with congenital hypomegakaryocytic thrombocytopenia and bilateral radial aplasia.[28] A few Korean cases have been reported to date.[29, 30] Recently, a mutation in the RNA-binding motif protein 8A (*RBM8A*) gene was shown to cause TAR syndrome.[31] RBM8A has several important cellular functions in the production of other proteins by facilitating the transport of mRNA.[31] In TAR syndrome, thrombocytopenia becomes less severe over time; the platelet levels have even been reported to become normal in some cases.[2, 6, 28] Some patients also have other congenital anomalies, e.g., lower limb anomalies, cow milk intolerance, renal anomalies, cardiac anomalies, intracranial vascular malformation, facial hemangioma, sensorineural hearing loss, and scoliosis.[28] Skeletal evaluation and bone marrow study are important in thrombocytopenia, such as RUSAT or TAR. Two diseases can emphasize that thorough orthopedic examination is necessary for the patients with thrombocytopenia.

Defects in granule formation, trafficking, or secretion

Hermansky-Pudlak syndrome (HPS) (dense granule disorder)

HPS is a rare heterogeneous autosomal recessive IPD group with several genetic defects, including mutations in *HPS1* (OMIM #203300), *AP3B1* (HPS2, OMIM #608233), *HPS3* (OMIM #614072), *HPS4* (OMIM #614073), *HPS5* (OMIM #614074), *HPS6* (OMIM #614075), *DTNBP1* (HPS7; OMIM #614076), *BLOC1S3* (OMIM #614077), and *BLOC1S6* (OMIM #614171).[7, 32] HPS is a disease group of defects in lysosomes, melanosomes, and granule biogenesis.[33] These conditions share features such as oculocutaneous albinism and bleeding symptoms due to normal platelet counts but platelet dysfunction associated with dense-granule defects.[2, 6, 32] Owing to the presence of dense-granule defects, HPS platelets

result in defects in aggregation with the absence of second wave aggregation in response to adrenaline.[2)] Proteins encoded by the *HPS* gene are involved in intracellular vesicle transport, protein sorting, and vesicle docking/fusion.[2, 33)] Additional manifestations, including pulmonary fibrosis, granulomatous colitis, neutropenia, or immunodeficiency, can occur according to the type of mutation.[2, 6, 32)] No Korean cases of HPS have been reported; however, HPS is a common genetic disorder in Puerto Rico, affecting 1 in 800 individuals, with more than 500 reported cases.[34)]

Chediak-Higashi syndrome (CHS) (dense granule disorder)

CHS (OMIM #214500) is a rare autosomal recessive IPD characterized by ocular cutaneous hypopigmentation, platelet dysfunction, immunodeficiency due to abnormal natural killer cell function, and peripheral neuropathy associated with mutations in the lysosomal trafficking regulator (*LYST*) gene.[35, 36)] Thus, CHS results in disruption of the structure and function of lysosomes and related structures in cells. For example, enlarged lysosomes in immune system cells cannot respond appropriately to foreign invaders. HPS and CHS share common clinical manifestations (oculocutaneous albinism and platelet dysfunction due to dense granule defect), but can be differentially diagnosed by large peroxidase-positive cytoplasmic granules in neutrophils and more severe symptoms at earlier age in case of CHS.[35)] Few Korean CHS cases have been reported to date.[37)]

Defects in proplatelet formation and cytoskeleton regulation

MYH9-related disorders

MYH9-related disorders (OMIM #155100) are autosomal dominant IPDs, including May-Hegglin anomaly (MHA), Fechtner syndrome (FTNS), Sebastian syndrome (SBS), and Epstein syndrome (ES).[38)] All of these syndromes are associated with the *MYH9* gene, which

encodes non-muscle myosin heavy chain IIa (NMMHC-IIA), a component of the contractile cytoskeleton in many tissues, including megakaryocytes, platelets, leukocytes, and the kidneys.[38, 39] The altered distribution of NMMHC-IIA in platelet can be measured by immunohistochemistry or immunofluorescence.[39]Thrombocytopenia resulting from defective megakaryocytosis and typical cytoplasmic basophilic inclusion bodies of leukocytes in MYH9-related disorders are caused by aggregation of abnormal NMMHC-IIA.[6] According to several studies, MHA, FTNS, SBS, and ES are not separate entities but a single disorder with wide spectrum of clinical symptoms, e.g., from mild macrothrombocytopenia to the more severe form with sensory neural hearing loss, renal failure, and cataracts.[40-42] Platelet counts are typically in the range of 20–130 $\times 10^9$/L, with elevated mean platelet volume and mild bleeding symptoms.[6, 42] To date, several Korean MYH9-related disorders confirmed by genetic testing have been reported.[43-48]

Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia (XLT)

WAS (OMIM #301000) is a rare X-linked recessive IPD, with an incidence of approximately 1–4 per 1,000,000 live male births.[2, 6] Although the prevalence of most IPDs in Korean populations have not yet been determined, the prevalence of Korean WAS is known to be 0.33 per 1,000,000 individuals based on an epidemiological study performed from data of the national registry for primary immunodeficiencies.[49] The WAS protein (WASP) expressed in hematopoietic cell lineages has a fundamental role in signal transduction from receptors on the cell surface to the actin cytoskeleton.[2, 6, 50, 51] Thus, aberrant WASP expression results in defective proplatelet formation and diverse clinical manifestations of WAS, e.g., microthrombocytopenia, eczema, frequent infection due to immunodeficiency, and even malignancy.[2, 6, 50, 51] Microthrombocytopenia is the characteristics of WAS, and present at birth and varies between 5 and 50 $\times 10^9$/L.[2] Malignancies occur in 13% of patients with

WAS at an average age of 9.5 years old.[52)]

XLT (thrombocytopenia 1; OMIM #313900) is the milder variant form and is characterized by only thrombocytopenia with transient eczema and absent or minimal immunodeficiency.[51)] *WAS* gene-associated XLT can be misdiagnosed as chronic ITP, because it is a milder type of WAS without frequent infection or eczema.[6)] To date, several Korean patients with WAS or XLT confirmed by genetic testing have been reported.[53-60)] Additionally, the results of hematopoietic stem cell transplantation in Korean patients with WAS have been also reported.[54, 58, 61)] XLT is difficult to be differentially diagnosed clinically from aforementioned XLTDA (OMIM #300367). In case of XLT, there may be a family history of WAS, which will help to differentiate between two diseases. In addition, the platelet size (large platelet size in XLTDA, whereas the small platelet size in XLT) is helpful for differential diagnosis between the two diseases.

Defects in transmembrane glycoprotein signaling pathways

Glanzmann thrombasthenia (GT)

GT (OMIM #273800) is a rare autosomal recessive IPD with a prevalence of approximately 1 in 1,000,000 individuals, although a higher prevalence has been observed in some populations owing to increased rates of consanguineous marriages.[62)] GT typically develops with loss-of-function variants in *ITGB2A* or *ITGB3* genes, encoding GPIIb and GPIIIa, respectively.[63)] However, very rare gain-of-function (GOF) variants in the *ITGB3* gene have also been reported, resulting in enhanced fibrinogen binding and severe bleeding.[64)] To date, several Korean cases of GT have been diagnosed clinically or confirmed by flow cytometry, and some of these cases were further confirmed by genetic analysis.[65)] In patients with GT, there are quantitative and/or qualitative defects in the platelet GPIIb/IIIa complex at binding sites for fibrinogen, vWF, and fibronectin.[66, 67)] Thus, patients with GT exhibit normal platelet

count/morphology, but severely diminished platelet aggregation in response to ADP, epinephrine, serotonin, thrombin, and collagen. Platelet function analyser-100 (PFA-100) measurements is significantly abnormal in GT with prolonged closure times on both ADP/collagen or adrenaline/collagen cartridges.[2)] Additionally, impaired platelet agglutination in patients with GT is corrected by ristocetin, which induces the binding of vWF with GPIb/IX.[2)] Application of flow cytometry using antibodies to GPIIb (CD41)/GPIIIa (CD61) is also useful for diagnosis of GT.[2)]

Bernard-Soulier syndrome (BSS)

BSS (OMIM #231200) is a rare IPD that is typically transmitted in an autosomal-recessive manner; the prevalence is estimated to be less than 1 in 1,000,000 individuals.[6)] To date, less than 1,000 BSS cases have been reported and studied worldwide.[2, 6, 68)] No Korean BSS cases have been published to date. BSS is characterized by low platelet counts, typically ranging from less than 30 to 200 $\times 10^9$/L, and the presence of large platelets (macrothrombocytopenia) in peripheral blood smear.[6, 69)] These large platelets are associated with the abnormal development of platelet membranes due to GPIba abnormalities.[70)] In patients with BSS, platelets are defective in surface expression of GPIb-IX-V, which acts as a vWF receptor on platelets, owing to mutations in the *GP1BA, GP1BB,* or *GP9* genes.[2, 69, 71)] As a result, platelets in patients with BSS cannot adhere to the vascular subendothelium and are unable to be agglutinated by ristocetin.[68)] In a study by the International Consortium for BSS, 211 BSS families were found to have mutations in the *GP1BA* (28%), *GP1BB* (28%), or *GP9* (44%) genes.[68)] The closure time in PFA-100 is significantly prolonged in BSS on both cartridges.[2)] Detect of defects in GPIb-IX-V complex by antibodies to GPIb (CD42b) by flow cytometry is also useful for diagnosis of BSS.[72)]

Pseudo-vWD

Pseudo-vWD (OMIM #177820), also known as platelet-type vWD or bleeding disorder, platelet-type 3, results from GOF variants in the *GP1BA* gene.[73] Pseudo-vWD is an autosomal dominant genetic disorder of the platelets, and genetic testing of the *vWF* gene is normal.[73] GOF variants in *GP1BA* affect the qualitatively altered GPIb receptor, which then shows increases affinity to vWF.[74] Accordingly, large platelet aggregates and high-molecular-weight vWF multimers are removed from circulation, thus resulting in thrombocytopenia and altered vWF multimers. Ristocetin cofactor activity and altered vWF multimers are similar to vWD type 2B, a disorder of GOF variants in the *vWF* gene resulting in altered function of the A1 domain of vWF.[75] In both cases, increased affinity of the GP1b receptor and vWF A1 domain results in thrombocytopenia and abnormal vWF multimers. Thus, DNA analysis is required for differential diagnosis.[7]

22q11 deletion syndromes

In 22q11.21 deletion syndromes, including DiGeorge syndrome (OMIM #188400) and Velocardiofacial syndrome (OMIM #192430), the diseases may be related to the phenotype of BSS if the remaining single *GPIBB* gene contains an independently inherited mutation.[76] These 22q11 deletion syndromes are autosomal dominantly inherited disorders with an estimated incidence of 1 in 4,000 births and are characterized by congenital heart disease, specific facial features, thymic aplasia, frequent infections, cleft palate, hypocalcemia, hypoparathyroidism, learning disabilities, and developmental delay.[77] If patients have to undergo heart surgery because of congenital heart disease associated with 22q11.2 deletion syndrome, physicians should be aware of the serious bleeding risk in these patients.[78]

Conclusions

In the last few decades, researchers have elucidated many of the etiologies of IPDs. Genes involved in a variety of IPDs have been identified, and molecular characterization of these disorders is underway. This information enables a more accurate understanding of IPDs. In Korean studies on IPDs, case reports of various IPDs have been reported, albeit in small numbers. However, despite these advances, identification of patients with IPDs remains challenging. For more accurate and definitive diagnoses, advanced genetic approaches, including next-generation sequencing, are required for patients with suspected IPD.[79, 80] Although the NGS panel for IPDs has not yet been commercialized and popularized in Korea, interest in IPDs is increasing. As described in Table 2, K-PHOG has recently attempted genetic confirmation of IPDs using targeted exome sequencing as a multicenter study. Although this study has only just begun, it is expected that it will be useful for future large-scale research and establishment of Korean IPD registry. And it also may be useful for the future development of NGS panel for IPDs in Korea.

Conflicts of Interest

There are no potential conflicts of interest relevant to this article.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (grant number NRF-2017R1C1B5016851).

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Figure legends

Fig. 1. The identified genes associated with inherited platelet disorders: adapted from Lentaigne, *et al.*[7] Each of the genes can be classified according to the specific pathway that is disrupted in megakaryopoiesis or platelet formation. HSC, hematopoietic stem cell; MK, megakaryocyte; GP, glycoprotein; GPCR, G-protein-coupled receptors

Fig. 2. The diagnostic sequence and flow in inherited platelet disorders. WAS, Wiskott-Aldrich syndrome; XLT, X-linked thrombocytopenia; CAMT, congenital amegakaryocytic thrombocytopenia; RUSAT, radioulnar synostosis with amegakaryocytic thrombocytopenia; TAR, thrombocytopenia-absent radius syndrome; QPD, Quebec platelet disorder; XLTDA, X-linked thrombocytopenia with or without dyserythropoietic anemia; MYH9, MYH9-related disorders; BSS, Bernard-Soulier syndrome; vWD, von Willebrand disease; 22q11 del, 22q11 deletion syndrome; GPS, gray platelet syndrome; JS, Jacobsen syndrome; PTS, Paris-Trousseau syndrome; GT, Glanzmann thrombasthenia; HPS, Hermansky-Pudlak syndrome; CHS, Chediak-Higashi syndrome

Table 1. Genetic classification of inherited platelet disorders according to the process of megakaryopoiesis and platelet formation.

Process of platelet formation	Gene	Locus	Protein	Phenotype (OMIM number)	Inheritance	Clinical characteristics
THPO/MPL signaling pathway	*THPO*	3q27.1	Thrombopoietin	Thrombocythemia 1 (OMIM #187950)[81)]	AD	Familial thrombocytosis Increased megakaryocytes in bone marrow
	MPL	1p34.2	Thrombopoietin receptor	Congenital amegakaryocytic thrombocytopenia (OMIM #604498)[9)]	AR	Absence of megakaryocyte in bone marrow Thrombocytopenia Normal platelet size Elevated serum thrombopoietin Progressive bone marrow failure to aplastic anemia
				Thrombocythemia 2 (OMIM #601977)[82)]	AD	Familial thrombocytosis Increased megakaryocytes in bone marrow
Transcriptional regulation	*GATA1*	Xp11.23	GATA-binding factor 1	X-linked thrombocytopenia with or without dyserythropoietic anemia (OMIM #30036)[13-15)]	XR	Thrombocytopenia Large platelet size Variable severity of anemia and hemolysis Dyserythropoietic anemia
	FLI1	11q24.3	Friend leukemia integration 1 transcription factor	Jacobsen syndrome (OMIM #147791)[22, 23)] Paris-Trousseau type thrombocytopenia (OMIM #188025)[17, 22)] Chromosome 11q deletion syndrome[18)]	AD	Thrombocytopenia Large platelet size Giant α-granules due to fusion of small organelles Dysmegakaryocytopoiesis in bone marrow
	HOXA11	7p15.2	Homeobox protein Hox-A11	Radioulnar synostosis with amegakaryocytic thrombocytopenia 1 (OMIM #605432)[24)]	AD	Amegakaryocytic thrombocytopenia Radio-ulnar synostosis
	MECOM	3q26.2	MDS1 and EVI1	Radioulnar synostosis with amegakaryocytic thrombocytopenia	AD	Amegakaryocytic thrombocytopenia

			complex locus protein	2 (OMIM #616738)[25]		Radio-ulnar synostosis
	RBM8A	1q21.1	RNA binding motif protein 8A	Thrombocytopenia-absent radius syndrome (OMIM #274000)[31]	AR	Amegakaryocytic thrombocytopenia Absence of radius
Granule formation, trafficking, or secretion	*HPS1* *AP3B1* *HPS3* *HPS4* *HPS5* *HPS6* *DTNBP1* *BLOC1S3* *BLOC1S6*	10q24.2 5q14.1 3q24 22q12.1 11p15.1 10q24.32 6p22.3 19q13.32 15q21.1		Hermansky-Pudlak syndrome[33, 34] (OMIM #203300, #608233, #614072, #614073, #614074, #614075, #614076, #614077, #614171)	AR	Normal platelet count Platelet aggregation defect or abnormal response Platelet dense granule defect Oculocutaneous albinism Congenital neutropenia Pulmonary fibrosis Granulomatous colitis
	LYST	1q42.3	Lysosomal trafficking regulator	Chediak-Higashi syndrome (OMIM #214500)[35]	AR	Normal platelet count Platelet aggregation defect or abnormal response Platelet dense granule defect Oculocutaneous albinism Severe immunological deficiency Lack of NK cell function
	PLAU	10q22.2	Urinary plasminogen activator	Quebec platelet disorder (OMIM #601709)[83]	AD	Gain-of-function defect in fibrinolysis Thrombocytopenia or normal platelet count Degradation of platelet α-granule contents Platelet aggregation defect or abnormal response
	NBEAL2	3p21.31	Beige and Chediak-Higashi-domain protein	Gray platelet syndrome (OMIM #139090)[84]	AR	Thrombocytopenia Platelet α-granule defect Large sized platelets

						Platelet aggregation defect Gray platelets on light microscopy of Wright-stain Myelofibrosis
Cytoskeleton regulation	*MYH9*	22q12.3	non-muscle myosin heavy chain IIa	MYH9-related thrombocytopenia syndromes (OMIM #155100)[37, 40-42]	AD	Thrombocytopenia or normal platelet count Large sized platelets Nephritis Sensorineural hearing loss
	WAS	Xp11.23	WAS protein	Wiskott-Aldrich syndrome (OMIM #301000)[50]	XR	Thrombocytopenia Small sized platelets Immunodeficiency Eczema
				Thrombocytopenia 1 (OMIM #313900) = X-linked thrombocytopenia[51]	XR	Thrombocytopenia Small sized platelets Without profound immunodeficiency Defects of white blood cell cytoskeleton Transient eczema
Transmembrane GP signaling pathway	*ITGA2B* *ITGB3*	17q21.31 17q21.32	GP IIb GP IIIa	Glanzmann thrombasthenia (OMIM #273800)[63]	AR	Normal platelet count Platelet aggregation defect
	GP1BA *GP1BB* *GP9*	17p13.2 22q11.2 13q21.3	GP Ib GP Ib GP IX	Bernard-Soulier syndrome (OMIM #231200)[68, 69]	AR	Thrombocytopenia or normal platelet count Large sized platelet Platelet adhesion defect
	GP1BA	17p13.2	GP Ib	Pseudo-von Willebrand disease (OMIM #177820)[73, 74]	AD	Thrombocytopenia Large sized platelet Platelet adhesion defect
	GP1BB	22q11.21	GP Ib	22q11 deletion syndrome[76-78] - De George syndrome (OMIM #188400)	AD	Thrombocytopenia or normal platelet count Large sized platelet

				- Velocardiofacial syndrome (OMIM #192430)		Platelet adhesion defect
GPCR signaling pathway	*P2RY12*	3q25.1	ADP receptor	Bleeding disorder, platelet-type, 8 (OMIM #609821)[85]	AR	Platelet aggregation defect
	TBXA2R	19p13.3	Thromboxane A2 receptor	Bleeding disorder, platelet-type, 13 (OMIM # #614009)[86]	AD	Platelet aggregation defect
	TBXAS1	7q34	Thromboxane synthase	Thromboxane synthase deficiency (OMIM #614158)[87]	AD	Platelet aggregation defect
				Ghosal hematodiaphyseal syndrome (OMIM #231095)[88]	AR	Platelet aggregation defect
Other	*ANO6*	12q12	Transmembrane protein 16F	Scott syndrome (OMIM #262890)[89]	AR	Impaired surface exposure of phosphatidylserine of platelets

AD, autosomal dominant; ADP, adenosine 5'-diphosphate; AR, autosomal recessive; GP, glycoprotein; GPCR, G-protein-coupled receptors; XR, X-linked recessive.

Table 2. Current status of genetic confirmation of inherited platelet disorders in Korea.

Phenotype	Genetically confirmed Korean IPD patients	Diagnostic method
Congenital amegakaryocytic thrombocytopenia	1 male infant patient reported by Chung, *et al*[10]	Direct sequencing of *MPL*
Jacobsen syndrome	1 male premature neonate reported by Noh, *et al*[19]	Karyotype
	1 female prenatal case reported by Yoon, *et al*[21]	Karyotype through amniocentesis
	1 female infant reported by Shin, *et al*[20]	Chromosomal microarray and Karyotype
Thrombocytopenia-absent radius syndrome	1 male infant reported by Kim, *et al*[29]	Chromosomal microarray
	1 prenatal case reported by We, *et al*[30]	Fetal blood analysis
MYH9-related thrombocytopenia syndromes	1 male adult patient reported by Jang, *et al*[44]	Direct sequencing of *MYH9*
	5 families (20 patients) reported by Kook, *et al*[45]	Direct sequencing of *MYH9*
	1 family reported from Lee, *et al*[46]	Direct sequencing of *MYH9*
	1 female adult patient reported by Oh, *et al*[47]	Direct sequencing of *MYH9*
	7 patients (5 male and 2 female) reported by Han, *et al*[43]	Direct sequencing of *MYH9*
	1 female pediatric patient reported by Park, *et al*[48]	Direct sequencing of *MYH9*
	1 male patient by K-PHOG study (unpublished data)*	Targeted exome sequencing
Wiskott-Aldrich syndrome	1 male infant reported by Hwang, et al[90]	PCR-SSCP and direct sequencing of *WAS*
	1 male pediatric patient reported by Baek, et al [91]	Direct sequencing of *WAS*
	2 male infant reported by Jo, *et al*[53]	Direct sequencing of *WAS*
	1 male pediatric patient reported by Kang, *et al*[54]	PCR-SSCP of *WAS*
	1 male infant reported by Kim, *et al*[55]	Direct sequencing of *WAS*

	2 families reported by Kim, *et al*[56]	Direct sequencing of *WAS*
	1 male infant reported by Lee, *et al*[58]	Direct sequencing of *WAS*
	1 family reported by Park, *et al*[59]	PCR-SSCP and direct sequencing of *WAS*
	1 male adolescent patient reported by Yoon, *et al*[60]	Direct sequencing of *WAS*
X-linked thrombocytopenia	1 male pediatric patient reported by Lee, *et al* [57]	Direct sequencing of *WAS*
	1 male pediatric patient reported by Yoon, *et al*[60]	Direct sequencing of *WAS*
Glanzmann thrombasthenia	4 patients reported by Park, *et al*[65]	Direct sequencing of *ITGB3* and *ITGA2B*
	7 patients by K-PHOG study (unpublished data)*	Targeted exome sequencing

IPD, inherited platelet disorders; K-PHOG, Korean Pediatric Hematology Oncology Group; PCR-SSCP, polymerase chain reaction-single strand conformational polymorphism

*These data are under preparation for submission. After targeted exome sequencing, the found variants were validated by Sanger sequencing.

Fig. 1.

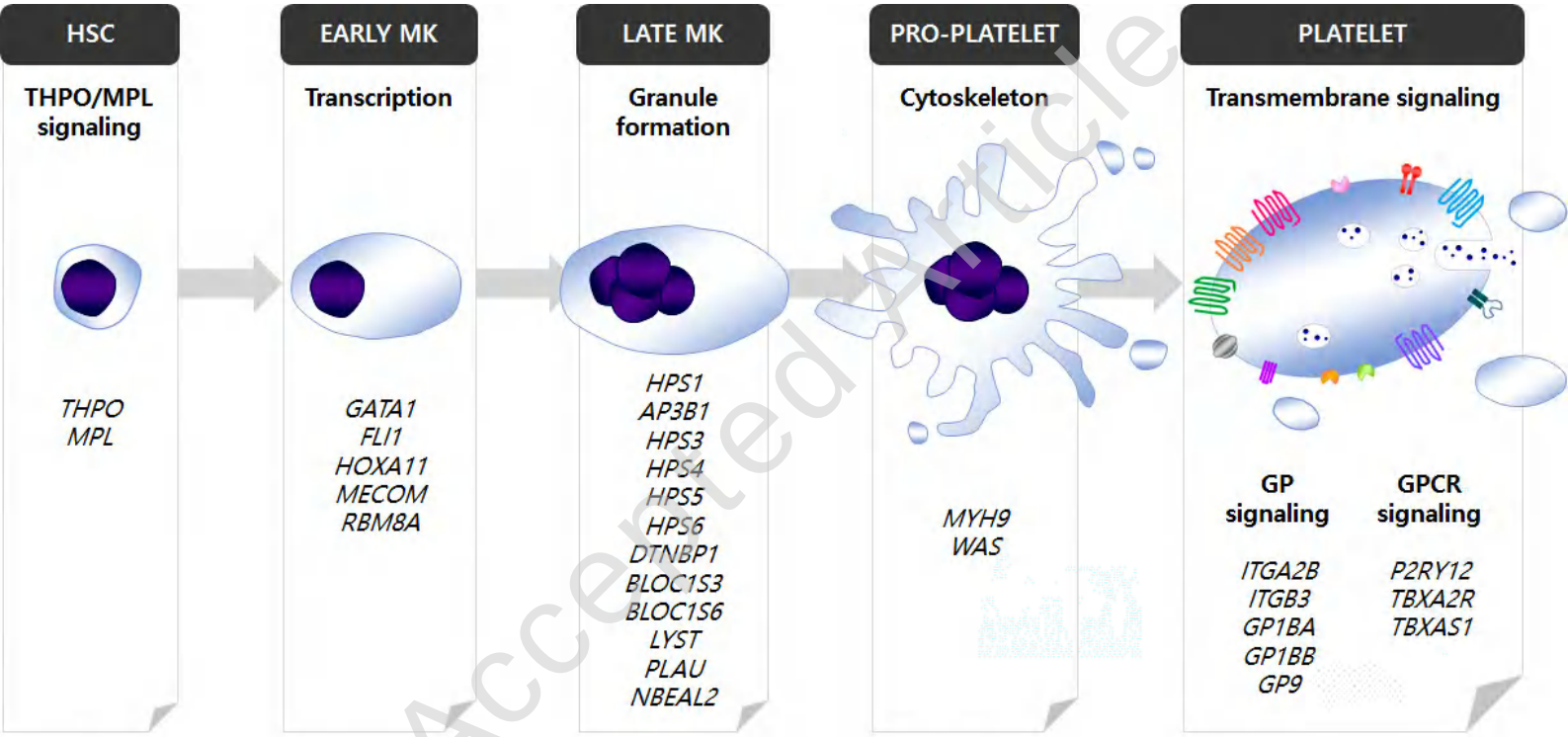

Fig. 2.