Chapter 8
Immune and Inherited Thrombocytopenia in Children

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Abstract Immune thrombocytopenia (ITP), the most common isolated thrombocytopenia in children, is regarded collectively as various thrombocytopenic diseases commonly involved in immunological mechanisms. ITP children can be treated with multiple therapeutic modalities including novel biological agents. However, without available means of confirmative diagnosis yet, ITP more or less requires exclusion diagnosis. As recent investigation of inherited thrombocytopenic disorders has revealed that genetic thrombocytopenia is frequently overlooked, inherited thrombocytopenias (ITs) might become increasingly important as diseases of differential diagnosis. Misdiagnosis of ITP not only prevents IT patients from correct management but also exposes them to inappropriate and potentially harmful treatments. Therefore, correct diagnosis based on combined clinical examinations and gene analyses may become more necessary for appropriate management and treatment choice of children with thrombocytopenia.

8.1 Introduction

Immune thrombocytopenia (ITP), the most common isolated thrombocytopenia in children, is characterized by increased platelet destruction in the spleen and reticuloendothelial system and by impaired platelet production in the bone marrow [1, 2]. Formally, ITP stands for idiopathic thrombocytopenic purpura, which literally means that it has unknown cause. It therefore requires diagnosis based on exclusion of any definite disease. However, an accumulation of findings that include pre-existing infection or vaccination, effectiveness of splenectomy, and presence of antiplatelet antibodies and/or platelet antigen-responsive T cells has

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shed light on pathological mechanism(s) that are common both in ITP of unknown cause and thrombocytopenia associated with immunological diseases. Therefore, ITP is regarded not as a single disease but collectively as various thrombocytopenic diseases that are commonly involved in immunological mechanisms [1, 3].

As the categories of diseases covered by primary and secondary ITP have become more numerous, inherited thrombocytopenic disorders might become increasingly important as diseases of differential diagnosis [4]. Especially in cases of inherited thrombocytopenias (ITs) with inconspicuous characteristic features or findings other than thrombocytopenia, patients might be misdiagnosed as ITP patients who would show chronic course with inadequate therapeutic response to standard treatments for ITP. Moreover, recent advances in genetic analyses have increased knowledge of ITs, suggesting that genetic thrombocytopenia is frequently overlooked [5].

This article presents a review of recent findings related to clinical, diagnostic, and pathological aspects of childhood ITP as well as on those of inherited disorders with thrombocytopenia that should be examined as differential diagnoses of ITP.

8.2 Clinical Picture of ITP

ITP is representative of hemorrhagic disorders in children. With the help of the previous epidemiological studies [6, 7], the annual incidence of children with ITP is estimated at approximately 1000 children in Japan. However, the number of children with thrombocytopenia in the registry of the Japanese Society of Pediatric Hematology was 439 on an average annual basis from 2006 to 2009 [8], suggesting that ITP in children might be seen not only by pediatric hematologists but also by general pediatricians.

Figure 8.1 presents results of a population-based retrospective study conducted using the Japanese public health system disease registry [9]. Results show that the incidence of patients with ITP is associated closely with age and sex. Approximately 80% of children with ITP developed the disease before school age [10], although postadolescent patients tend to become more numerous gradually along with age. Three peaks of incidence are apparent across all age groups. The first is in children under 4 years of age, with boys predominant, the second in middle age with female predominance, and the third in elderly people.

Table 8.1 shows that major bleeding manifestations of children with ITP were purpura (92.6%) and nasal bleeding (29.7%), the frequency of which was significantly higher than that in adults with ITP. It is particularly interesting that intracranial hemorrhage, a severe complication, is extremely rare in children (0.1%), but less in adults (0.7%), suggesting an involvement of age-related physiological changes [10]. The clinical features at diagnosis, such as >10 years of age, $>2 \times 10^4$/μL of platelet counts, and the absence of precedent infection or vaccination, are correlated significantly with the risk of transition to chronic ITP [11].

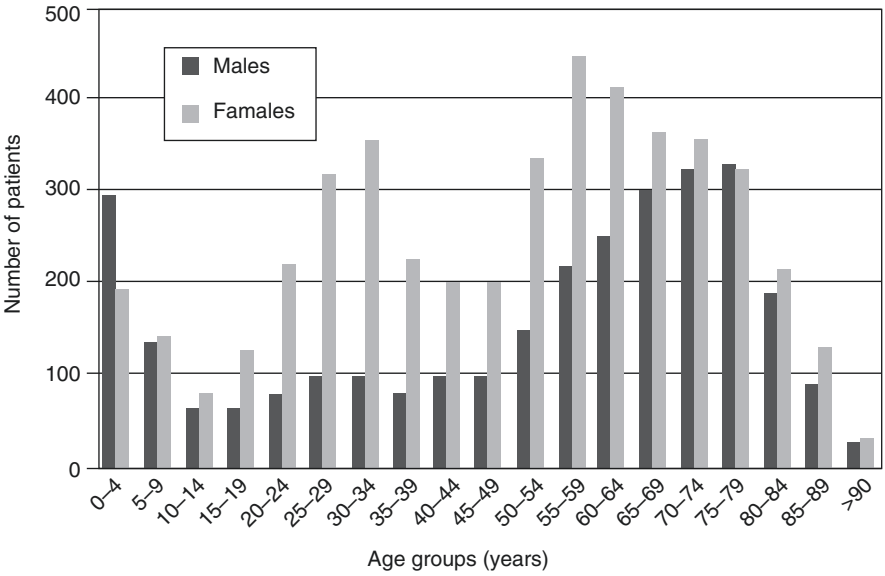

Fig. 8.1 Population-based epidemiological study of 7774 patients with ITP in a Japanese population [9]. A population of 7774 patients with ITP were analyzed retrospectively using the database registry of the Ministry of Health, Labour, and Welfare of Japan from 2004 to 2007

Table 8.1 Comparative study of hemorrhagic manifestations between pediatric and adult patients with ITP [9]

Hemorrhagic manifestations	Pediatric patients (%)	Adult patients (%)	*p* Value
Purpura	860 (92.6)	4300 (62.8)	$p < 0.001$
Gingival bleeding	175 (18.8)	1365 (19.9)	ns
Nasal bleeding	276 (29.7)	687 (10.0)	$p < 0.001$
Hematuria	54 (5.8)	453 (6.6)	ns
Melena	43 (4.6)	259 (3.8)	ns
Hypermenorrhea	11 (1.2)	264 (3.9)	$p < 0.001$
Intracranial hemorrhage	1 (0.1)	45 (0.7)	$p < 0.05$
Other bleedings	54 (5.8)	214 (3.1)	$p < 0.001$
Total	929	6845	

8.3 Immune-Mediated Mechanism(s) Causing Thrombocytopenia

Although clinical findings, such as frequent preceding infectious events and therapeutic effect of splenectomy, suggest the involvement of immunological mechanisms in the onset of ITP, it is also known that ITP children often lack direct evidence of immune-mediated mechanisms [1]. Recently, "a cryptic epitope model" in cellular and molecular pathogenesis has been presented for adult ITP, where

autoreactive CD4+ T cells that can recognize the cryptic peptides derived from platelets might promote peripheral B-cell production of antiplatelet GPIIb/IIa antibodies [12, 13].

Compared to ITP in adult, childhood ITP has clinical features that are often characterized by remission after a short duration and precedent events such as infection or vaccination, suggesting the background factors of physiologically and developmentally immature immunological regulation systems [14].

Not only peripheral platelets but also megakaryocytes in bone marrow can be targets of immunological responses attributable to the expression of GPIIb/IIIa molecules on the megakaryocytes, leading to impaired platelet production or aberrant megakaryopoiesis [15, 16].

8.4 International Standardization of Terminology, Definitions, and Outcome Criteria

The Japanese Society of Pediatric Hematology proposed conventional guidelines of diagnosis, treatment, and management for childhood ITP [17]. The guideline, in which ITP stands for idiopathic thrombocytopenic purpura of unknown causes, had been used for many years and prevailed in Japan. Recently, international standardization of terminology, definitions, and outcome criteria has been proposed and acknowledged around the country [3]. This standardization proposes ITP as "immune thrombocytopenia," which is not a single disease but comprising various diseases with thrombocytopenia commonly caused by immunological mechanisms.

Firstly, as shown in Table 8.2, the international standardization classifies ITP into two categories, primary and secondary ITP, in which the primary ITP corresponds to conventional ITP of unknown causes. The secondary ITP includes disorders showing thrombocytopenia, which are strongly associated with immunological pathogenesis, such as underlying immune-mediated diseases or drug-induced reactions. Consequently, several diseases that have been exclusive from conventional ITP can become inclusive of the secondary ITP, leading to increased importance of some inherited disorders with thrombocytopenia as diseases in differential diagnosis of ITP.

Secondly, the international standardization has introduced the concept of "phases of the disease (newly diagnosed, persistent, and chronic ITP)" in substitution of types of the disease (acute and chronic ITP) to avoid an uncertain type of disease at onset, for which confirmation by definition requires evaluation for a certain period. Moreover, it advises 12 months of observation until diagnosis of the chronic ITP to avoid excessive treatment for numerous patients who can have remission of thrombocytopenia within 12 months after onset. In addition, severe ITP is defined as the state with the presence of bleeding symptoms sufficient to

Table 8.2 Standardization of terminology, definitions, and outcome criteria in ITP [3]

A. Definitions of disease
Abbreviation of ITP: *i*mmune *t*hrombocyto*p*enia
Primary ITP
• Isolated thrombocytopenia (peripheral blood platelet count $<10 \times 10^4/\mu L$) in the absence of other causes or disorders that may be associated with thrombocytopenia
• The diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy
• The main clinical problem of primary ITP is an increased risk of bleeding, although bleeding symptoms may not always be present
Secondary ITP
• All forms of immune-mediated thrombocytopenia except primary ITP
• Secondary forms of thrombocytopenia that are due to an underlying disease or to drug exposure. The name of the associated disease should follow the designation, for example, secondary ITP (SLE associated) or (HIV associated)
B. Phase of the disease
Newly diagnosed ITP: within 3 months from diagnosis
Persistent ITP: between 3 and 12 months from diagnosis, includes patients not reaching spontaneous remission or not maintaining complete response off therapy
Chronic ITP: lasting for more than 12 months
Severe ITP: presence of bleeding symptoms at presentation sufficient to mandate treatment or occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose
C. Criteria for assessing response to ITP treatment
CR(complete response): platelet count $\geq 10 \times 10^4/\mu L$ and absence of bleeding
R(response): platelet count $\geq 3 \times 10^4/\mu L$ and at least twofold increase the baseline platelet count and absence of bleeding
NR(no response): platelet count $<3 \times 10^4/\mu L$ or less than twofold increase of baseline count or bleeding
Loss of CR or R: platelet count below $10 \times 10^4/\mu L$ or bleeding (from CR) or below $3 \times 10^4/\mu L$ or less than twofold increase of baseline platelet count or bleeding (from R)
D. Refractory ITP (all need to be met)
• Failure to achieve at least R or loss of R after splenectomy
• Need of treatment(s) to minimize the risk of clinically significant bleeding. Need of on demand or adjunctive therapy alone does not qualify the patient as refractory
• *Primary ITP confirmed by excluding other supervened causes of thrombocytopenia*

mandate treatment or occurrence of new bleeding symptoms requiring additional therapeutic intervention.

Thirdly, the international standardization has proposed outcome criteria that define the conditions to evaluate therapeutic effects: CR, complete response; R, response; NR, no response; and refractory state of ITP. Although these criteria are apparently rather broad and simple, the consensus criteria for therapeutic evaluation and disease states are indispensable for comparative and cooperative investigations among different study groups.

8.5 Treatments [17, 18]

8.5.1 Conventional Treatments

Steroid and intravenous immunoglobulin (IVIG) are two major conventional drugs in the first-line therapy for children with ITP. Children with newly diagnosed ITP presenting with bleeding symptom and $<2 \times 10^4/\mu L$ of platelet counts are treated with steroids (2 mg/kg) or IVIG (1–2 g/kg), although a wait-and-see approach might be used for patients with minimal bleeding. Approximately, 70–80% of children with newly diagnosed ITP are likely to have complete response within 6–12 months after diagnosis. For children with chronic, but not severe ITP, close observation without treatment is a possible consideration in cases of minimal bleeding, even at $<2 \times 10^4/\mu L$ of platelet count. However, patients with severe ITP in chronic phase or refractory ITP need treatment including second-line therapy.

Conventional second-line treatment for severe or refractory ITP includes splenectomy and immunosuppressive agents such as cyclophosphamide, cyclosporin A, and dapsone (diaphenylsulfone). Although splenectomy is a reliable second-line therapy, its application to children has become less frequent since the introduction of new agents such as rituximab and thrombopoietin receptor (TPO-R) agonists in clinical areas. A review of these two therapeutic agents is presented below.

8.5.2 Rituximab

Rituximab is a chimeric monoclonal antibody that targets CD20 antigen on the surface of B cells. It is applied initially to B-cell lymphoma and, then, expanded to autoimmune diseases. In contrast to the wide use of rituximab in adult patients, few data are available for the long-term efficacy of rituximab for childhood ITP [19, 20]. Recently, a retrospective study in Japan of the long-term effects of rituximab for 22 children with refractory ITP [21] reported that the initial CR rate as high as 41% (9/22) decreased gradually to a 14% (3/22) relapse-free CR rate at 5 years after the first rituximab therapy. Consequently, although sustained effects of rituximab on children with refractory ITP might occur only with low probability, repeated rituximab administration might be a promising therapy because patients who have received multiple courses of rituximab after relapse responded each time without adverse effects and obtained remission.

8.5.3 TPO-R Agonists

Eltrombopag and romiplostim, TPO-R agonists in the second generation, are low-molecular compounds that stimulate signaling through TPO-R without inducing a neutralizing antibody against TPO. TPO-R agonists were effective and safe in

approximately 80% of adult patients with refractory ITP [22, 23]. These agents have two specific properties: a loss of effect after withdrawal and an increased risk of myelofibrosis. Although TPO-R agonists are effective also for children with refractory ITP, a retrospective study of children receiving TPO-R agonists for up to 53 months revealed that one of 24 patients developed myelofibrosis in grade 2 [24]. The guideline of the American Society of Hematology continues to advise a cautious attitude related to TPO-R agonists for children with ITP [25].

8.6 Inherited Thrombocytopenia

Recent advances of genetic investigation of inherited thrombocytopenias (ITs) have greatly enhanced the understanding of ITs at the molecular and genetic levels, leading to identification of new responsible genes and a better characterization of ITs [4]. To date, ITs constitute at least 22 disorders caused by mutations of 25 genes with different degrees of complexity in phenotypes and variation in prognosis (Table 8.3) [5]. Conventionally, ITs are classified using characteristic small-, normal-, or large-sized platelets, respectively. The platelet size is denoted either by the mean platelet diameter (upper limit of normal range, 4 μm) or by the mean platelet volume (MPV) (normal range, 7.2–11.1 fL). Recently, with greater emphasis on symptoms, Pecci has categorized ITs into two groups according to symptoms and organs involved by ITs: syndromic and non-syndromic forms [5].

Despite increasing knowledge of ITs, its diagnosis remains difficult, and these disorders are probably still underdiagnosed. In fact, several patients with ITs might have had a prior wrong diagnosis of ITP [5, 63]. Therefore, physicians should consider ITs during differential diagnosis of ITP in children, especially those who exhibit chronic or refractory ITP with small- or normal-sized platelets, positive familial history, or skeletal malformation. Not only clinical examinations, including familial history, but also gene analyses are invariably important to make a correct diagnosis of ITs.

For this article, among ITs with identified entities and gene mutations, we specifically review mainly ITs with small- or normal-sized platelets. ITs with small platelets are represented by diseases with mutation in *WAS* gene, whereas ITs with normal-sized platelets consist of various syndromic forms of diseases that entail complications such as skeletal anomaly or predisposition to malignant diseases.

8.6.1 ITs with Small-Sized Platelets

Wiskott–Aldrich syndrome (WAS), an X-linked primary immunodeficiency caused by mutations of the *WAS* gene, is clinically characterized as having small-sized thrombocytopenia, increased susceptibility to infection, and refractory eczema

Table 8.3 Main clinical features of inherited thrombocytopenia

Disease (abbreviation, OMIM entry)	Inheritance	Gene (locus)	Platetlet size	Bleeding[a]	Main clinical feature	Reference
Syndromic forms						
MYH9-related disease (MYH9-RD, na)	AD	*MYH9* (22q12)	Large	A to Mi	Sensorineural deafness, nephropathy, cataract, and/or elevated liver enzymes. Giant platelets. Döhle-like inclusions in granulocytes. Also non-syndromic[b]	[26–28]
Wiskott–Aldrich syndrome (WAS, 301000)	XL	*WAS* (Xp11)	Small	S	Severe immunodeficiency leading to early death. Eczema	[29, 30]
					Increased risk of malignancies and autoimmunity	
					Reduced platelet sizw	
X-linked thrombocytopenia (XLT, 313900)	XL	*WAS* (Xp11)	Small	A to Mo	Mild immunodeficiency. Mild transient eczema	[29, 31]
					Increased risk of malignancies and autoimmunity	
					Also non-syndromic[b]	
Paris–Trousseau thrombocytopenia (TCPT, 188025)	AD	Deletions in 11q23	Normal	Mo to S	Physical growth delay, mental retardation, facial and skull dysmorphisms, malformations of the cardiovascular system, CNS, gastrointestinal apparatus, kidney, and/or urinary tract; other malformations	[32, 33]
Jacobsen syndrome (JBS, 147791)						
Thrombocytopenia-absent radius syndrome (TAR, 274000)	AR	*RBM8A* (1q21)	Normal	S	Bilateral radial aplasia +/– other upper and lower limb bone abnormalities. Kidney, cardiac, and/or CNS malformations. Reduced/absent megakaryocytes in BM	[33–35]
					Platelet count tends to raise over time	

Thrombocytopenia associated with sitosterolaemia (STSL, 210250)	AR	*ABCG5*, *ABCG8* (2p21)	Large	A to Mi	Tendon and tuberous xanthomas. Premature atherosclerosis. Hemolytic anemia with stomatocytosis	[34, 36, 37]
					Large platelets. Also non-syndromic[b]	
Radioulnar synostosis with amegakaryocytic thrombocytopenia (RUSAT, 605432)	AD	*HOXA11* (7p15)	Normal	S	Bilateral radio-ulnar synostosis +/− other malformations	[38–40]
		EVI1 (3q26)			Reduced/absent megakaryocytes in BM. Possible evolution to bone marrow aplasia	
GATA1-related disease: X-linked thrombocytopenia with thalassemia (XLTT, 314050), X-linked thrombocytopenia with dyserythropoietic anemia (XLTDA, 300367)	XL	*GATA1* (Xp11)		Mi to S	Hemolytic anemia with laboratory abnormalities resembling beta-thalassemia, splenomegaly, or dyserythropoietic anemia	[41]
					Congenital erythropoietic porphyria	
FLNA-related thrombocytopenia (FLNA-RT, na)	XL	*FLNA* (Xq28)	Large	Mi to Mo	Periventricular nodular heterotopia (OMIM 300049)	[42]
					Large platelets. Also non-syndromic[b]	
Non-syndromic forms						
Bernard–Soulier syndrome (BSS, 231200/153670)		*GP1BA* (17p13)	Large			[43–46]
Biallelic	AR	*GPIBB* (22q11)		S	Giant platelets	
Monoallelic	AD	*GP9* (3q21)		A to Mi	Large platelets	
Congenital amegakaryocytic thrombocytopenia (CAMT, 604498)	AR	*MPL* (1p34.2)	Normal	S	Reduced/absent megakaryocytes in BM. Evolution to fatal bonemarrow aplasia in infancy in all patients	[47]
Familial platelet disorder with propensity to acute myelogenous leukemia (FPD-AML, 601399)	AD	*RUNX1* (21q22)	Normal	A to Mo	Over 40% of patients acquire acute myelogenous leukemia or myelodysplastic syndromes. Increased risk of T acute lymphoblastic leukemia	[48]

(continued)

Table 8.3 (continued)

Disease (abbreviation, OMIM entry)	Inheritance	Gene (locus)	Platelet size	Bleeding[a]	Main clinical feature	Reference
ANKRD26-related thrombocytopenia (ANKRD26-RT or THC2, 188000)	AD	*ANKRD26* (10p12)	Normal	A to Mo	About 8% of patients acquire myeloid malignancies. Some patients have increased hemoglobin levels and/or leukocytosis	[49]
Gray platelet syndrome (GPS, 139090)	AR	*NBEAL2* (3p21)	Large	A to Mi	Platelet count decreases over time. Development of progressive myelofibrosis and splenomegaly. Elevated serum vitamin B12 levels. Pale platelets due to severe alpha-granule deficiency	[50, 51]
ACTN1-related thrombocytopenia (ACTN1-RT, 615193)	AD	*ACTN1* (14q24)	Large	A to Mi	Large platelets	[52, 53]
Platelet-type von Willebrand disease (PTvWD, 177820)	AD	*GP1BA* (17p13)		A to Mi	Platelet count can decrease under stress	[54]
ITGA2B/ITGB3-related thrombocytopenia (ITGA2B/ITGB3-RT, 187800)	AD	*ITGA2B* (17q21) *ITGB3* (17q21)	Large	Mi to Mo	Large platelets	[55]
ETV6-related thrombocytopenia (ETV6-RT, na)	AD	*ETV6* (12p13)	Normal	A to Mo	Increased risk of myeloid and lymphoid malignancies	[56, 57]
TUBB1-related thrombocytopenia (TUBB1-RT, 613112)	AD	*TUBB1* (20q13)	Large	A to Mi	Large platelets	[58]
CYCS-related thrombocytopenia (CYCS-RT or THC4, 612004)	AD	*CYCS* (7p15)	Normal/small	A	Normal/reduced platelet size	[59]
GFI1b-related thrombocytopenia (GFI1b-RT, 187900)	AD	*GFI1B* (9q34)	Large	Mo to S	Some pale platelets reflecting a variable alpha-granule deficiency	[60, 61]
PRKACG-related thrombocytopenia (PRKACG-RT, na)	AR	*PRKACG* (9q21)	Large	S	Large platelets	[62]

The content was quoted from the review of Pecci A [5] with additional modifications

AD autosomal-dominant, *AR* autosomal recessive, *XL* X-linked, *BM* bone marrow, *CNS* central nervous system, *na* not available

[a]Bleeding, severity of bleeding tendency in the majority of patients reported for each form: *A* absent, *Mi* mild, *Mo* moderate, *S* severe

[b]'Also non-syndromic' indicates syndromic forms for which some patients having only thrombocytopenia (without the associated defects) have been reported

[29, 30]. Also, X-linked thrombocytopenia (XLT), a mild variant of WAS, is derived from mutations that do not abolish WAS expression completely and which often present with mild thrombocytopenia [31]. These two are important diseases for differential diagnosis of boys with chronic ITP at an early age of onset. Hematological examinations show small thrombocytopenia decreases (MPV, 6.0–6.2 fL) and no increase of megakaryocytes in bone marrow. Compared to ITP, the risk of intracranial hemorrhage is increased in WAS and XLT because of impaired platelet aggregation.

8.6.2 ITs with Progression to Pancytopenia

Congenital amegakaryocytic thrombocytopenia (CAMT) is an autosomal recessive disease characterized by onset in the newborn period or early infancy, diminished megakaryocytes in bone marrow, increased TPO levels, and progression to pancytopenia [47]. This disease results from mutations of *MPL* gene encoding TPO-R, the signaling of which promotes megakaryocytic maturation and platelet production [64].

8.6.3 ITs with Skeletal Anomalies

Several disorders with skeletal malformation and distinct etiology are included in this category. Thrombocytopenia with absent radii (TAR) with autosomal recessive inheritance is characterized by defect of the radius, thrombocytopenia in early infancy showing alleviation with growth, and decreased megakaryocytes in BM [33, 35]. Actually, TAR results from mutations of *RBM8A* gene encoding a component of RNA-processing complexes [34].

Radioulnar synostosis with amegakaryocytic thrombocytopenia (RUSAT) is characterized by congenital fusion of the radius and ulna, with progression to pancytopenia [38]. Heterozygous mutations of homeotic gene, *HOXA11*, have been reported as a cause of RUSAT in two families with autosomal-dominant inheritance [39]. More recently, Niihori et al. identified de novo heterozygous missense mutations in *EVI1* gene as a novel entity of RUSAT [40]. Missense mutations were clustered within the eighth zinc finger motif of the C-terminal zinc finger domain of EVI1, suggesting that EVI1 has important functions in hematopoiesis and stem cell self-renewal, and in the development of forelimbs in humans. Patients with *EVI1* mutations were treated with stem cell transplantation at 4–18 months of age because of its more rapid progression of bone marrow failure as compared to that of RUSAT with *HOXA11* mutation.

8.6.4 ITs with Predisposition to Malignant Diseases

This category includes several diseases with distinct etiology. Familial platelet disorder with propensity to acute myeloid leukemia (FPD-AML) is an autosomal-dominant disease caused by mutations of *RUNX1* gene encoding the hematopoietic transcription factor [48, 65]. FPD-AML shows a mild to moderate thrombocytopenia, but those patients have an approximately 35% of lifetime risk to develop AML or MDS. The process to malignant development in FPD-AML might be involved by mutations in additional genes such as *CDC25C*, a cell cycle regulator [66].

Autosomal-dominant thrombocytopenia, thrombocytopenia 2 (THC2), is an autosomal-dominant disease caused by mutations of *ANKRD26* gene [49]. It shows moderate thrombocytopenia and platelet dysfunction. A small percentage (<5%) of patients with THC2 also present a lifetime risk of developing myeloid malignancies such as AML, MDS, and CMML.

More recently, germline mutations in *ETV6* were found to be responsible for a third form of autosomal-dominant thrombocytopenia that is predisposed to hematological malignancies and skin and colon cancers with an uncertain degree of risk [56, 57].

8.7 Conclusion

With unavailable means of confirmative diagnosis yet, childhood ITP more or less requires exclusion diagnosis. Inherited thrombocytopenia is a disease that should be considered because misdiagnosis of ITP not only prevents IT patients from correct management of their diseases, but it also exposes them to inappropriate and potentially harmful treatments. The combination of clinical examinations and gene analyses is expected to be important for the medical treatment of children with ITP.

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