













Management of inherited thrombocytopenia

Recommendations of the Group on Hemostasis of the Polish Society of Hematology and Transfusion Medicine, 2019

Krzysztof Chojnowski¹, Anna Klukowska², Magdalena Łętowska³,
 Wojciech Młynarski⁴, Andrzej Mital⁵, Jacek Musiał⁶, Maria Podolak-Dawdziak⁷,
 Jacek Trelński¹, Anetta Undas⁸, Tomasz Urański⁹, Jerzy Windyga¹⁰,
 Joanna Zdziarska¹¹, Krystyna Zawilska¹²

¹Department of Haemostasis and Haemostatic Disorders, Medical University of Lodz

²Department of Pediatrics, Hematology and Oncology, Medical University of Warsaw

³Department of Transfusion Medicine, Institute of Hematology and Transfusion Medicine, Warsaw

⁴Clinic of Pediatrics, Hematology and Oncology, Medical University of Lodz

⁵Department of Hematology and Transplantology, Medical University of Gdansk

⁶2nd Department of Internal Medicine, Jagiellonian University, Medical College, Krakow

⁷Department and Clinic of Hematology, Blood Neoplasms, and Bone Marrow Transplantation,
 Medical University, Wrocław

⁸Institute of Cardiology, Jagiellonian University, Collegium Medicum in Krakow

⁹Clinic of Pediatrics, Hematology and Pediatric Oncology, Pomeranian Medical University, Szczecin

¹⁰Clinic of Hemostatic Disorders and Internal Medicine, Institute of Hematology
 and Transfusion Medicine, Warsaw

¹¹Clinic of Hematology, University Hospital in Krakow

¹²INTERLAB Diagnostic and Treatment Center, Poznan

Summary

Inherited thrombocytopenias (IT) comprise a highly heterogeneous group of rare haemostatic disorders which vary in terms of degree of thrombocytopenia, platelet size, pattern of inheritance and clinical course. Due to difficult diagnosis and frequently mild clinical phenotype these disorders are often underdiagnosed. The purpose of this review is to provide clinical and laboratory characteristics of the most important types of IT. The currently available therapeutic options for these conditions are also recapitulated and discussed.

Key words: inherited thrombocytopenias, platelets, bleeding, diagnosis, treatment

J. Trans. Med. 2020; 13: 16–28

Introduction

Inherited thrombocytopenias (IT) are a group of rarely diagnosed bleeding disorders. The first description of inherited thrombocytopenia dates

back to 1948 and relates to a thrombocytopenic bleeding disorder named Bernard-Soulier syndrome (BSS) [1]. The implementation of automated cell counters has offered a new opportunity of broad-scale identification of patients with family

Correspondence address: prof. dr hab. n. med. Krzysztof Chojnowski, Department of Haemostasis and Haemostatic Disorders, Medical University of Lodz, Ciołkowskiego Street 2, 93–510 Lodz, e-mail: krzysztof.chojnowski@umed.lodz.pl

Translation: mgr Krystyna Dudziak

history of thrombocytopenia. It turned out that familial thrombocytopenias occur more frequently than previously thought. Baldulini et al. estimated IT incidence in Italy at 2.7/100,000 inhabitants [2]. A real breakthrough in genetic diagnostics of inherited disorders was however brought about with the recently introduced next generation sequencing (NGS) approach. NGS technology has identified almost 40 genes with thrombocytopenia-inducing mutations [1]. Inherited thrombocytopenia is a heterogeneous group of bleeding disorders of diverse phenotype. They may present as isolated thrombocytopenia or in combination with other hematological and non-hematological symptoms (Table 1). Some manifest with severe bleeding, others are mild or asymptomatic. The latter can only be detected in adulthood and are often erroneously diagnosed as primary immune thrombocytopenia [3]. Until quite recently, bleeding disorders were considered major symptoms of IT with impact on morbidity and mortality. Several previously unknown genetic defects leading to IT have recently been detected, most of which turned out to be associated with other life-threatening childhood or adulthood disorders. These co-morbidities are often more dangerous than the low platelet count [4]. Patients with *RUNX1*, *ANKRD26* and *ETV6*-related thrombocytopenias are predisposed to myeloid malignancies [5–7]. Mutations in the *MYH9* gene induce macrothrombocytopenia and increase the risk of nephropathy, sensorineural hearing loss and cataracts, while IT in the course of biallelic mutations in thrombopoietin gene (*THPO*) or thrombopoietin receptor (*MPL*) almost always transforms into severe bone marrow aplasia [8, 9]. It is therefore crucial to identify the cause of IT; this is important both for prognosis as well as counselling and choice of optimal management of coexisting disorders.

In the course of IT, the low platelet count is related to a defect of at least one stage of the complex process of platelet biogenesis. It is rarely the effect of shorter platelet survival time. Pathogenic mechanisms of IT involve: abnormal differentiation of hematopoietic stem cells into megakaryocytes, impaired megakaryocytes maturity resulting in immature, dysmorphic and dysfunctional forms, as well as abnormal release of progenitor cells from mature megakaryocytes and/or the conversion of progenitor cells into platelets in circulation [10] (Table 2).

There are types of IT in which low platelet count co-exists with impaired platelet function. This review does not include types of IT in which

qualitative platelet disorder determines the phenotype of bleeding disorder. Recommendations for management of thrombocytopenias with thrombocytopenia were described in a separate article [11], the updated version of which will soon appear in print.

Classification

According to platelet size (diameter) inherited thrombocytopenias can be classified into: normo-thrombocytopenias, macro-thrombocytopenias and micro-thrombocytopenias [12]. For prognostic purposes, it is useful to classify IT into: isolated IT, IT associated with other non-hematological disorders and IT associated with higher risk of other hematological disorders (Table 1, Figure 1).

Some inherited thrombocytopenias with other defects

Wiskott-Aldrich syndrome (WAS)

A rare X-linked recessive condition, typically diagnosed in infancy and characterized by micro-thrombocytopenia, skin lesions, immunodeficiency (recurrent infections) and higher incidence of autoimmune and some neoplastic disorders [13]. The condition primarily affects males. WAS also includes the benign form of the disease known as X-linked thrombocytopenia (XLT) [14].

The incidence rate for WAS is estimated at 4 cases per 1,000,000 males and is associated with mutation in the *WAS* gene located on chromosome Xp11-22. The *WAS* gene encodes the WAS protein (WASP) expressed in all hematopoietic cell lines. Disorders of WASP synthesis lead to defects of platelet signal transduction and consequently to presentation of clinical and laboratory symptoms. Over 300 different *WAS* gene mutations have been described, the most common of which are missense point mutations. Mutation type determines the severity of the WASP disorder/defect. Mutations that cause severe qualitative defect or absence of WASP lead to WAS while mutations associated with decrease in WASP concentration induce XLT or X-linked neutropenia (XLN). In WAS, the symptoms of bleeding disorders manifest in the first months of life as bruising, petechiae, bloody diarrhea, prolonged bleeding following circumcision. There is a risk of bleeding into the CNS. During the first six months of life infections are frequent, mostly bacterial and in particular of the respiratory tract and the middle ear. Opportunistic and viral infections are less common. Skin lesions and infections are not observed in people with XLT phenotype.

Table 1. Genetic mutations associated with inherited thrombocytopenias (according to *Thrombogenomics 2019* (<http://thrombo.cambridgenadiagnosis.org.uk>))

Defective gene	Disease	Pattern of inheritance	Bleeding disorder	Hemathological symptoms	Non-hemathological symptoms	Platelet size
<i>ABCA1</i>	Tangier Disease	AR or AD	Mild		Decrease in HDL cholesterol level, cardiovascular disorders	Normal
<i>ABCG5</i>	Sitosterolemia and macrothrombocytopenia	AR	Mild	Hemolytic anemia	Early atherosclerosis, jaundice	Large
<i>ABCG8</i>	Sitosterolemia and macrothrombocytopenia	AR	Mild	Hemolytic anaemia	Early atherosclerosis, jaundice	Large
<i>ACTN1</i>	Thrombocytopenia	AD	Asymptomatic/mild			Large
<i>ANKRD26</i>	Thrombocytopenia	AD	Mild	Acute myeloid leukemia, MDS		Normal
<i>ARPC1B</i>	Thrombocytopenia	AR	Mild/moderate	Eosinophilia	Immunodeficiency	Small
<i>CYCS</i>	Thrombocytopenia	AD	Asymptomatic			Normal
<i>DIAPH1</i>	Thrombocytopenia	AD	Mild		Hearing loss	Large
<i>ETV6</i>	Thrombocytopenia	AD	Asymptomatic/moderate	Red cell macrocytosis, acute lymphoblastic leukemia, DLBCL, polycythemia vulgaris		Normal
<i>FLI1</i>	Thrombocytopenia	AR	Mild/moderate			Large
<i>FLI1, deletion 11q23</i>	Paris-Trousseau Thrombocytopenia/Jacobsen Syndrome	AD or AR	Moderate/acute		Presentation depends on deletion size	Normal
<i>FLNA</i>	Macrothrombocytopenia	XL	Mild		Heart disorders, central nervous system disorders	Large
<i>FYB</i>	Thrombocytopenia	AR	Mild/moderate			Normal
<i>GATA1</i>	X-linked thrombocytopenia	XL	Mild/acute	Dyserythropic anemia, thalassemia		Normal
<i>GFI1B</i>	Macrothrombocytopenia	AD	Moderate/acute			Large
<i>GNE</i>	Thrombocytopenia associated myopathy	AR	Moderate/acute		Myopathy	Normal
<i>GP1BA</i>	Macrothrombocytopenia/monoallelic Bernard-Sullier syndrome	AD	Asymptomatic/mild			Large
<i>GP1BB</i>	Macrothrombocytopenia/monoallelic Bernard-Sullier syndrome	AD	Asymptomatic/mild			Large
<i>GP9</i>	Macrothrombocytopenia/monoallelic Bernard-Sullier syndrome	AD	Asymptomatic/mild			Large

→

Table 1 (cont). Genetic mutations associated with inherited thrombocytopenias (according to *Thrombogenomics 2019* (<http://thrombo.cambridgediagnosis.org.uk>))

Defective gene	Disease	Pattern of inheritance	Bleeding disorder	Hemathological symptoms	Non-hemathological symptoms	Platelet size
<i>HOXA11</i>	ATRU Syndrome	AD	Acute		Radius-elbow osteosis, syndactyly, hip dislocation, hearing loss	Normal
<i>ITGA2B</i>	Glanzmann's macrothrombocytopenia/thrombasthenia	AD	Mild/moderate			Large
<i>ITGB3</i>	Glanzmann's macrothrombocytopenia/thrombasthenia	AD	Mild/moderate			Large
<i>KDSR</i>	Erythrokeratosis with thrombocytopenia	AR	Mild		Symmetrical erythrokeratosis, "fish scale" skin	Normal
<i>MECOM</i>	ATRU Syndrome	AD	Acute		Radius-elbow osteosis, syndactyly, hip dislocation, hearing loss	Normal
<i>MPIG6B</i>	Thrombocytopenia with anemia	AR	Moderate/acute	Anemia, bone marrow aplasia	Splenomegaly	Normal
<i>MPL</i>	CAMT Syndrome	AR	Acute	Bone marrow aplasia, MDS, acute myeloid leukemia		Normal
<i>MYH9</i>	MYH9-dependent macrothrombocytopenia	AD	Mild		Hearing loss, nephropathy, cataracts	Huge
<i>PRKACG</i>	Macrothrombocytopenia	AR	Acute			Large
<i>PTPN11</i>	Noonan Syndrome	AD	Mild	Acute lymphoblastic leukemia, MDS, JMML	Facial dysmorphism, short stature, heart defects, hearing loss, skeletal disorders	Normal
<i>PTPRJ</i>	Thrombocytopenia	AR	Moderate			Small
<i>RBM8A</i>	TAR Syndrome	AR	Acute with a tendency to improve with age		No radial bones	Normal
<i>RUNX1</i>	FPD/AML Syndrome	AD	Asymptomatic/moderate	Acute myeloid leukemia, MDS, acute T-lymphoblastic leukemia		Normal
<i>SLFN14</i>	Thrombocytopenia	AD	Mild/acute			Large or normal
<i>SRC</i>	Thrombocytopenia	AD	Moderate/acute	Myelofibrosis	Splenomegaly, osteoporosis	Large
<i>STIM1</i>	Stormorken Syndrome/York Platelet Syndrome	AD	Asymptomatic/mild	Anemia	Immunodeficiency, myopathy, "fish scale" skin, asplenia	Normal
<i>THRO</i>	Thrombocytopenia	AR or AD	Mild/acute	Bone marrow aplasia		Normal
<i>TPM4</i>	Macrothrombocytopenia	AD	Mild			Large
<i>TRPM7</i>	Macrothrombocytopenia	AD	Mild			Large
<i>TUBB1</i>	Macrothrombocytopenia	AD	Asymptomatic/mild			Large
<i>WAS</i>	Wiskott-Aldrich Syndrome	XL	Acute	Neutropenia, higher risk of non-Hodgkin's lymphoma	Severe immunodeficiency, skin lesions	Small
<i>WAS</i>	X-linked thrombocytopenia (XLT)	XL	Asymptomatic/mild		Mild immunodeficiency or no immunodeficiency	Small

AD — autosomal dominant; AR — autosomal recessive; XL — linked to the X chromosome; DLBCL — diffuse B-cell lymphoma; MDS — myelodysplastic syndrome; JMML — Juvenile myelomonocytic leukemia

Table 2. Pathogenetic mechanisms of inherited thrombocytopenias (Its)

Disorders of platelet biogenesis		
Defective hematopoietic stem cells (HSCs) differentiation	Defective megakaryocyte maturation	Defective pro-platelet formation
<i>MPL</i>	<i>ANKRD</i>	<i>ACTN1</i>
<i>MECOM</i>	<i>11q23Deletions</i>	<i>FLNA</i>
<i>HOXA11</i>	<i>FLI1</i>	<i>GP1BA</i>
<i>RBM8A</i>	<i>ETV6</i>	<i>GP1BB</i>
<i>RUNX1</i>	<i>GATA1</i>	<i>GP9</i>
	<i>GFI1B</i>	<i>ITGA2B</i>
	<i>SLFN14</i>	<i>ITGB3</i>
	<i>FYB</i>	<i>TUBB1</i>
	<i>SRC</i>	<i>TRPM7</i>
		<i>TPM4</i>
		<i>CYCS</i>
		<i>DIAPH1</i>
		<i>PRKACG</i>
Shorter platelet survival time: <i>WAS</i> , <i>ARPC1B</i> , <i>GNE</i>		
Unknown defect: <i>STIM1</i>		

Immunodeficiencies may appear later in life, mostly autoimmune anemia, neutropenia and vasculitis. Malignancies, especially lymphomas, are common in WAS patients. A characteristic triad of symptoms for WAS is: thrombocytopenia, skin eczema and immunodeficiency. All these symptoms however, rarely present at diagnosis. Thrombocytopenia is observed since birth and is severe or mild with platelet count of 5–50 G/l. Characteristic are small platelets of approx. 1.8 μm in diameter and volume reduced by up to 50%. Platelet survival time is shorter. Immunodeficiencies are not observed at birth but develop later in life. Characteristic are low T cell counts, impaired B and T cell functions and a lower IgM concentration. Markedly reduced or absent is the formation of antibodies directed against polysaccharide antigens. The final WAS diagnosis requires molecular testing to confirm the *WAS* gene mutation. The management consists in treatment of bleeding events and infections, treatment of skin lesions and autoimmune complications. In the event of bleeding, HLA compatible and CMV negative, irradiated platelet concentrate (PC) is transfused. Splenectomy may contribute to significant increase in platelet count and moderation of bleeding symptoms. The only therapy leading to recovery is allogeneic hematopoietic stem cell transplantation (allo-HSCT). In the case of XLT, symptoms are less pronounced and allo-HSCT is often unnecessary.

Thrombocytopenia absent radius (TAR) syndrome

The syndrome is characterized by generally transient thrombocytopenia of < 50 G/l and bilateral absence of the radii [15]. Platelet size and morphology are within normal. The incidence rate for TAR is estimated at 0.5–1/100,000 inhabitants. The disease is inherited in an autosomal, recessive manner and results from mutation of the *RBM8A* gene (1q21.1) [16]. Thrombocytopenia may be congenital or develop within the first few weeks/months of life. Thrombocytopenia resolves with age and most school children with TAR syndrome have normal platelet count. Exacerbation of thrombocytopenia may however occur and is often associated with cow's milk allergy. Characteristic for TAR syndrome is usually the bilateral absence of radii in the presence of correctly shaped thumbs. The syndrome may manifest with other anomalies of the skeleton, heart, gastrointestinal tract or genitourinary system. The diagnosis of TAR is based on the coexistence of thrombocytopenia and absence of radii. It is confirmed by *RBM8A* mutation detected in genetic tests. Treatment of bleeding consists in administration of PC transfusions. Orthopedic intervention is required to improve limb function. Elimination of cow's milk from daily diet may prevent exacerbations of thrombocytopenia in older children.

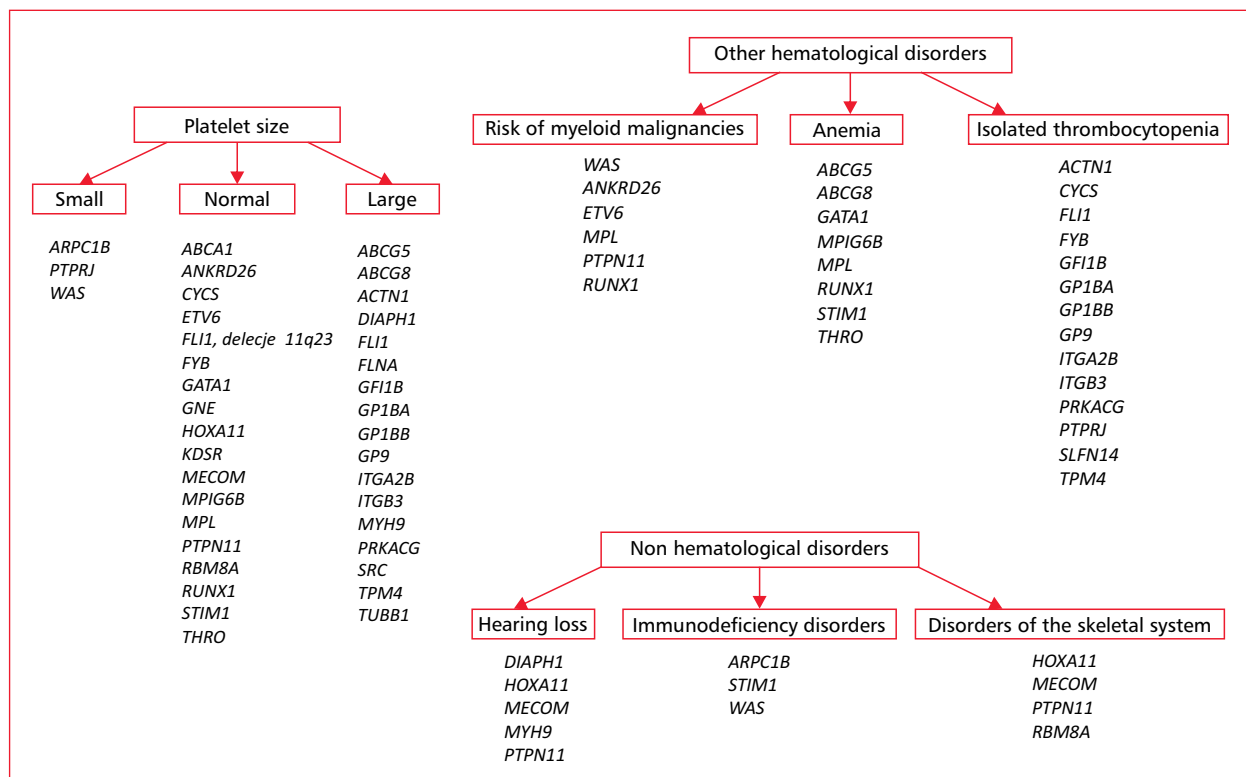


Figure 1. Genetic disorders in inherited thrombocytopenias — most common clinical and laboratory presentations

Amegakaryocytic thrombocytopenia with radioulnar synostosis (ATRUS)

It is an extremely rare type of thrombocytopenia associated with mutation in the *HOXA11* or *MECOM* gene [17]. It co-exists with abnormal attachment of the ulna and radius bones that limits the range of forearm movement. Up to date, less than 10 families with ATRUS have been described. Thrombocytopenia is detected already at birth. Platelet size and morphology are within normal. Later in life bone marrow aplasia may develop, although it is reported less frequently than in Congenital Amegakaryocytic Thrombocytopenia (CAMT).

Paris-Trousseau Thrombocytopenia and Jacobsen Syndrome

Deletion in the 11q23 chromosome region is the cause of Jacobsen syndrome and in 90% of cases it leads to Paris-Trousseau thrombocytopenia (MPT) associated with simultaneous *FLII* deletion [18]. In addition, MPT is observed in patients with biallelic mutations in the *FLII* gene. Characteristic are mild to moderate bleeding disorders, macrothrombocytopenia, impaired thrombin-induced platelet activation and the presence of abnormally

large alpha granules. The platelet count may gradually increase with age.

Stormorken Syndrome

In this rare autosomal dominant bleeding disorder platelets present constant hemostatic procoagulant activity which results in generation of phosphatidylserine-expressing platelet microparticles. Thrombocytopenia co-exists with mild bleeding tendency, thrombocytopathy, mild anemia, asplenia, tubular aggregate myopathy, myosis, headache, and ichthyosis. The syndrome is caused by *STIM1* gene mutation [19].

Congenital amegakaryocytic thrombocytopenia (CAMT)

A rare autosomal recessive bone marrow failure syndrome associated with absence of megakaryocytes in bone marrow. It is caused by mutation in the gene for the thrombopoietin (TPO) receptor (c-Mpl) [9]. Characteristic of CAMT Type-I is complete loss of functional c-Mpl receptors, associated with nonsense mutation of *MPL* gene, while for CAMT type-II characteristic are partially functional c-Mpl receptors. The disorder manifests as thrombocytopenia in the first month of life, often at

birth. CAMT type I is severe with median platelet count of < 20 G/L. Pancytopenia related to aplastic anemia occurs quite early in life. CAMT type II presents a milder form and the median platelet count is up to 35 G/L. Pancytopenia is observed at the age of 3–6 years or later. CAMT increases the risk of myelodysplastic syndrome and acute leukemia. Diagnosis is based on absence of megakaryocytic colony growth after adding thrombopoietin (TPO), the lack of Mpl mRNA in bone marrow nucleated cells, increased serum TPO concentration, and no c-Mpl expressed on cell surface. Confirmation of CAMT diagnosis is based on finding the causative mutation of the *MPL* gene (1p34). The only effective treatment for CAMT is allogeneic stem cell transplantation, preferably from a related donor. PC transfusions and antifibrinolytic drugs are recommended for treatment of bleeding episodes.

MYH9-related thrombocytopenia syndrome (MYH9-RD)

A group of autosomal dominant macro-thrombocytopenias often associated with sensorineural hearing loss, nephritis and pre-senile cataracts [8]. The gene mutated in all macro-thrombocytopenias of this group was mapped to chromosome 22q12-13 and identified as *MYH9*. It encodes the non-muscle myosin heavy-chain II A (NNMHC-IIa) which is a cytoskeletal contractile protein in megakaryocytes, platelets and neutrophils. Expression of the protein has also been detected in the kidneys and cochlea of the inner ear. NNMHC-II conditions cell mobility and cytoplasm structure. The bleeding disorder is usually mild and most often manifests with easy bruising, nosebleeds, and heavy menstrual bleeding. Bleeding severity depends on the degree of thrombocytopenia. No bleeding is reported for people with platelet counts > 50 G/L. Patients with no bleeding symptoms had no hemostatic support during surgery; no excessive bleeding was observed. Progressive hearing loss is the most common non-hematological symptom of *MYH9*-RD and occurs in approximately 60% of patients. First symptoms may appear in early childhood or at any time until 60. Chronic kidney disorders present with proteinuria, with or without hematuria, usually before 30 years of age and affect approximately 30% of patients with *MYH9*-RD. Within several years, 70% of such patients develop kidney failure with rapid progress to dialysis or kidney transplantation. Cataracts are reported in about 16% of patients with *MYH9*-RD, most often in the third decade of life. Platelet count is usually 20–130 G/L; the average platelet volume is increased.

Giant platelets, the size of erythrocytes, present in peripheral blood smear and in most patients Döhle-like bodies are detected in May-Grünwald-Giemsa staining. Döhle-like bodies are small, light-blue inclusions in the peripheral cytoplasm of neutrophils; they are large myosin aggregates. Monoclonal antibodies are used to detect abnormal NNMHC-IIa clusters. Fully reliable diagnosis of *MYH9*-RD can only be made after detection of the *MYH9* causative mutation.

MYH9-RD diagnosis should be taken into account when macro-thrombocytopenia co-exists with non-hematological symptoms and/or Döhle-like bodies in neutrophils. Detection of *MYH9* mutation has both diagnostic and prognostic value as there is a strong genotype-phenotype correlation with the risk of clinical evolution of non-hematological disorders [20]. Most *MYH9*-RD patients do not require treatment. Antifibrinolytic drugs are sufficiently effective for mucosal bleeding. Tooth extractions and minor surgical procedures should be performed under cover of desmopressin, and PC transfusions are recommended for major surgery. Following administration of thrombopoietin receptor (TPO-R) agonists most patients respond with increase in platelet count. Eltrombopag was administered prior to surgery. TPO-R agonists are not licensed for the treatment of inherited thrombocytopenias [21].

ANKRD26 related thrombocytopenia

An autosomal dominant disorder with moderate thrombocytopenia (approx. 50 G/L) and normal platelet size. The clinical course may be asymptomatic or present with mild bleeding disorder [22]. Cytological picture of bone marrow reveals micro-megakaryocytes and small-nucleus megakaryocytes with hypolobulation. The risk of myeloid malignancies increases 20 to 30 fold [6]. Diagnosis is confirmed by detection of *ANKRD26* mutation.

Familial platelet disorder with associated myeloid malignancy (FPD/MM) Syndrome

Familial platelet defect with predisposition for acute myeloid leukemia is associated with a mutation in the *RUNX1* gene. The disorder is inherited in an autosomal dominant pattern and up to date 45 such families have been described. Thrombocytopenia is mild to moderate, platelet size is normal. Over 40% of people with FPD/MM developed acute myeloid leukemia or myelodysplastic syndrome at the age of 30. Higher risk of developing T-cell acute lymphoblastic leukemia has also been reported [23].

ETV6-related thrombocytopenia (ETV6-RT)

The disorder is autosomal dominant characterized by asymptomatic course or mild skin or mucosal bleeding. Platelet count is moderate or slightly lower and ranges from 40 G/L to 115 G/L. The risk of developing acute lymphoblastic leukemia or non-Hodgkin's lymphoma is higher, even in childhood [7]. Polycythemia vera has also been described in an adult with *ETV6-RT*.

DIAPH1 — related thrombocytopenia

This variant of thrombocytopenia is caused by *DIAPH1* gene mutation which leads to macrothrombocytopenia with mild bleeding disorders and hearing loss [24]. Due to similar clinical manifestations, this type of macrothrombocytopenia should be differentiated from *MYH9-RD*-related variant.

Sitosterolaemia

A rare autosomal recessively inherited lipid metabolic disorder. It is characterized by hyperabsorption and reduced biliary excretion of dietary sterols, which leads to hypercholesterolemia, jaundice, premature development of atherosclerosis and abnormal haematological and liver tests. Sitosterolaemia is caused by the mutation in the *ABCG5* or *ABCG8* genes that encode the synthesis of sterol-transporting proteins, *ABCG5* (sterolin-1) and *ABCG8* (sterolin-2). The phenotype of the disorder is heterogenous — from asymptomatic to severe hypercholesterolemia with early onset of atherosclerosis. Some patients present hematological symptoms in form of macro-thrombocytopenia (thrombocytopenia with giant platelets), hemolytic anemia and splenomegaly [25].

X-linked macrothrombocytopenia with dyserythropoiesis

Associated with a mutation in the *GATA-1* (Xp11) gene encoding a transcription factor involved in proliferation of megakaryocytes and erythrocytes [26]. Affects only males; women are the carriers. Skin and mucous bleedings are observed already at birth. Bleeding severity may decrease with age. Platelet count is significantly reduced (approx. 20 G/L) and mean platelet volume (MPV) is higher. Megakaryocytes in bone marrow present morphological abnormalities and there are signs of megaloblastic renewal. Diagnosis is confirmed by finding the causative mutation. Transfusion of platelet concentrates (PC) is administered for treatment and prevention of bleeding.

Some isolated inherited thrombocytopenias***Monoallelic dominant******Bernard-Soulier syndrome***

Bernard-Soulier Syndrome (BSS) is a bleeding disorder inherited in an autosomal recessive manner which is characterised by thrombocytopenia with giant platelets, prolonged bleeding time and loss of ristocin-induced platelet aggregation. It is caused by a defect of GPIb/IX/V, a platelet complex that binds the von Willebrand factor. The defect is responsible for reduced vWf binding to platelet membrane and for impaired adhesion. The mutations responsible for BSS may be related to *GP1BA*, *GP1BB* and *GP9* genes. Heterozygotes are asymptomatic, with normal platelet counts and ristocin-induced platelet aggregation. Unlike other causative BSS mutations, the c.515C > T *GP1BA* mutation (p.Ala172Val) is inherited in an autosomal dominant manner (the so-called Bolzano mutation). It is likely to be the most common cause of inherited thrombocytopenia in Italy [27]. Thrombocytopenia is mild to moderate. The average platelet count for monoallelic BSS is approximately 80 G/l. Giant platelets (3.5 μ m in diameter) are present in blood smear. Due to the mild or asymptomatic course as well as the complexity of diagnostic procedure, the monoallelic BSS is recognized in adulthood. There are case reports of this inherited thrombocytopenia with heterozygous *GP1BA*, *GP1BB* and *GP9* mutations that were unsuccessfully treated as ITP.

ACTN1 — related thrombocytopenia

ACTN1 gene encodes for α -actinin 1 (one of two α -actinin 1 isoforms). Alterations of *ACTN1* have been identified as responsible for a mild form of IT [28]. The average platelet count is 100 G/L and only in one case was below 50 G/L. Thrombocytopenia is isolated, not associated with other disorders. Due to the mild course as well as the complexity of diagnostic procedure, *ACTN1*-related thrombocytopenia is recognized in adulthood. It is possibly the relatively most common cause of congenital macro-thrombocytopenia. In an Italian study, the *ACTN1* mutation was detected in 4.2% of people with familial thrombocytopenia.

TUBB1 — related thrombocytopenia

Inherited in an autosomal dominant manner, the disorder is rarely associated with macrothrombocytopenia. Thrombocytopenia is mild with

Table 3. Recommendations for diagnostic management of inherited thrombocytopenias

<p>Stage 1</p> <p>Candidates for IT diagnostic management are persons at any age:</p> <ul style="list-style-type: none">— with low platelet count, positive family history, and thrombocytopenia since birth/childhood— with other hematological or non-hematological symptoms characteristic for specific inherited disorder, apart from thrombocytopenia. <p>Adults with isolated thrombocytopenia if:</p> <ul style="list-style-type: none">— thrombocytopenia occurs since childhood or the fact cannot be excluded— thrombocytopenia, aplastic anemia, MDS or acute leukemia in first-degree relatives— low platelet count is relatively constant— platelet size (MPV and diameter) is normal or bigger than in immune thrombocytopenia (ITP)— other causes of thrombocytopenia, especially ITP, are unlikely
<hr/> <p>Stage 2</p> <p>Diagnostic management includes:</p> <ul style="list-style-type: none">— interview for thrombocytopenia (since when, platelet count, immediate family history, bleeding, administered treatment)— interview for co-existing morbidities and hematological malignancies in immediate family— physical examination with special focus on cutaneous and mucosal manifestations of bleeding disorders as well as symptoms characteristic for particular thrombocytopenia syndromes— laboratory tests:<ul style="list-style-type: none">• CBC, with platelet and reticulocyte parameters• for pseudothrombocytopenia in patients with isolated thrombocytopenia with no symptoms of bleeding disorder: platelet count in citrate buffer• flow cytometry platelet count with immature platelet fraction (IPF)• blood smear with platelet diameter, morphology and Döhle-like bodies in granulocytes• bone marrow aspiration in the presence of other hematological symptoms• platelet aggregation with basic agonists• genetic testing with NGS method

average platelet count of approximately 100 G/L. Mutations in *TUBB1* gene lead to disruption of microtubule assembly and impaired pro-platelet formation and platelet release [29].

ITGA2B — related familial thrombocytopenia

Homozygous and complex heterozygous *ITGA2B* gene mutations are responsible for Glanzmann thrombasthenia (GT) characterised by severe thrombocytopathy and normal platelet counts. In contrast, the specific p.Arg1026Trp *ITGA2B* mutation induces constitutive activation of α IIb β 3 receptor and impaired pro-platelet formation. The mutation has been described in members of 7 Japanese families with macro-thrombocytopenia [30]. The disorder is inherited in an autosomal dominant manner. Khoriaty et al. have recently described thrombocytopenia with normal platelet size in 6/9 members of a European family and associated it with the same mutation [31].

***PTPRJ* — related thrombocytopenia (*PTPRJ-RT*)**

The disorder is inherited in an autosomal recessive pattern. Thrombocytopenia is mild, associated with impairment of collagen or convulxin-induced platelet aggregation. Platelets are smaller in size, which differentiates *PTPRJ-RT* from other isolated ITs [32].

Diagnosis of inherited thrombocytopenias

The diagnostic process is two-stage (Table 3). Firstly, thrombocytopenia has to be determined as genetically conditioned (inherited). The second stage consists in differentiation procedures to identify the cause of inherited thrombocytopenia [33].

First-line tools for diagnosis of inherited thrombocytopenia are: personal and family medical history, physical examination and assessment of peripheral blood smear. Genetic background of thrombocytopenia should always be suspected

when there is no proof of acquired thrombocytopenia. Negative family history does not exclude the genetic background of the disorder. About 40% of patients with *MYH9*-RD mutation were diagnosed with sporadic disease caused by a de novo mutational event [8].

Low platelet count at birth or childhood as well as in close family members may be suggestive of congenital thrombocytopenia. Physical examination may facilitate recognition of a congenital disorder/syndrome with thrombocytopenia as one of symptoms. Crucial for IT diagnosis is correct evaluation of peripheral blood smear (Table 4). Platelet size and loss-of-function may direct IT diagnostics towards specific mutations. Presence of Döhle-like bodies in granulocytes points to *MYH9* — related thrombocytopenia. Red blood cell abnormalities facilitate diagnosis of IT associated with sitosterolemia or *GFI1b* and *GATA1* mutations. Every case of asymptomatic thrombocytopenia, requires determination of platelet count in blood collected in sodium citrate in order to exclude pseudothrombocytopenia.

The above procedures should be available for any person suspected of inherited thrombocytopenia. This is within the realm of possibility due to technological advancement and reduction in cost of genetic tests. Testing with next generation sequencing technology (NGS) is the method of choice. It should be performed in laboratories with extensive experience in testing hemostatic disorders. For reasons of economy, the test panel should every time include all known genes whose defects are related to quantitative and qualitative platelet disorders (eg. Thrombogenomics 2019 project standard (<http://thrombo.cambridgednadiagnosis.org.uk>)).

Moreover, genetic diagnostics is recommended for family donors of bone marrow dedicated for patients with myeloid malignancies induced by inherited thrombocytopenia.

Treatment of inherited thrombocytopenias

Management of inherited thrombocytopenias includes treatment and prevention of bleeding as well as management of IT — associated disorders.

General recommendations for management of inherited thrombocytopenias:

1. Symptomatic IT patients should be treated in special reference centers with appropriate diagnostic facilities and round-the-clock access to anti-hemorrhagic agents/drugs.

2. Non-steroidal anti-inflammatory drugs (NSAIDs), especially aspirin, are prohibited. Injury/trauma should be avoided. Oral hygiene with frequent dental control as well as hormonal control for heavy menstrual bleeding are recommended. All IT patients should be vaccinated for hepatitis A and B.
3. Depending on clinical symptoms, the type and degree of thrombocytopenia different therapies are used that should be adjusted to match pathogenesis and most likely complications.

Specific recommendations

Management of IT patients consists in:

1. **Treatment of bleeding episodes and prevention of perioperative, perinatal bleeding as well as bleeding during invasive procedures (Table 4).**

Most IT patients do not present spontaneous bleeding and require treatment only in trauma, invasive procedures and at delivery.

Platelet Concentrates (PC)

PC transfusions are the treatment of choice for major bleeding in IT patients, although there is always the risk of transfusion-transmitted infections and adverse reactions. Furthermore, the outcome of transfusion is conditioned by the ability of the recipient's immune system to produce antibodies against donor mismatched HLA antigens, as well as other polymorphic systems. To reduce the risk of alloimmunity, it is recommended to transfuse irradiated, leukocyte-reduced PC; according to some authors, also HLA compatible. PC transfusions are first choice treatment for life-threatening bleeds to critical sites (e.g. intramedullary, intracranial, intraocular hematoma, deep muscle bleeds, retroperitoneal space, pericardial cavity).

Local hemostatic agents

Tamponade or sponge with thrombin are used to arrest nosebleeds. Antifibrinolytic drugs in form of rinse are used to stop mucosal bleeding from the oral cavity. Gelatin sponge, fibrin glue or platelet gels are used as local haemostatic agents in surgical procedures.

Antifibrinolytic drugs

Used for management of mucousal bleeding from the oral cavity, nose and genital tract as well as for hemostatic coverage during tooth extractions. Tranexamic acid (TXA) is administered orally or intravenously, to adults usually at a dose of 3 g/d

Table 4. Inherited thrombocytopenia — therapeutic management in selected bleeding and clinical situations

1. No treatment required for symptoms like bruises, petechiae
2. Epistaxis — topical application of hemostatic and anti-fibrinolytic agents. If ineffective — platelet transfusions (PC) at a dose of 1 U/10 kg
3. Heavy menstrual bleeding — anti-fibrinolytics, hormonal drugs
4. Coverage of surgical procedures for patients with inherited thrombocytopenia

Management depends on type of surgery, platelet count, co-existing defect of platelet function, phenotype of bleeding disorder, history of bleeding with regard to surgical procedures and response to hemostatic treatment (PC). In cases of IT without significant abnormalities in platelet function perioperative recommendations used for immune thrombocytopenic (ITP) patients should be applied. For patients with dominant disorder in platelet function, recommendations for inherited thrombocytopathy should be followed [11]

Detailed recommendations

Tooth extraction — IT patients with no coexisting abnormalities in platelet function and platelet count > 30 G/L do not require PC transfusion. Extraction can be performed under coverage of tranexamic acid. For more complex extractions, follow recommendations for minor surgery.

Minor surgery — in IT patients with no significant platelet function disorder and without coagulation abnormalities — PC transfusion prior to surgery at doses required to increase platelet count > 50 G/L. After surgery, PC transfusions, depending on clinical indications.

Major surgery — in IT patients with no significant platelet function disorder and normal coagulation — PC transfusion before surgery at doses required to increase platelet count > 80 G/L. After surgery, PC transfusions, depending on clinical indications.

(1 g every 8 hrs); to children at a dose of 20 mg/kg/d (every 6–8 hrs). Contraindications for antifibrinolytic drugs are: bleeding from urinary tract/renal hematuria, renal impairment, acute venous or arterial thrombosis, disturbances of color vision.

Desmopressin (DDAVP)

According to expert reviews, desmopressin may effectively arrest/stop bleeding in patients with mild inherited thrombocytopenia. There is however no evidence from clinical trials. Desmopressin is administered at a dose of 0.3 µg/kg, in 30–50 ml 0.9% NaCl, by intravenous infusion for at least 30 minutes. The drug can also be inhaled at a dose of 300 µg for adults and 150 µg for children.

Thrombopoietin receptor agonists for short-term use

In most patients with *MYH9*-RD (second phase study), Eltrombopag effectively increased platelet count [34]. The drug was also administered to patients with *MYH9* and *ANKRD26* gene mutations prior to elective surgery [21], although it is not registered/licensed for use in this indication.

Recombinant activated factor VII (rFVIIa)

Experience in administration of rFVIIa to stop bleeding in IT patients is rather limited and mainly refers to patients with BSS (rFVIIa is not registered/licensed for use in this indication).

2. Treatment for long-term increase in platelet count for patients with severe symptomatic thrombocytopenia.

Splenectomy

No beneficial effect of splenectomy in the course of IT-related bleeding disorders has been reported. The exception here is WAS/XLT, where splenectomy resulted in significant increase in platelet count and bleeding arrest. On the other hand however, the frequency of infections was reported to increase. No effect of splenectomy was reported with regard to survival time for patients with WAS.

Long-term thrombopoietin receptor agonists

In patients with WAS/XLT, Eltrombopag was reported to induce platelet response in 5/8 patients. The drug was not registered/licensed for treatment of IT.

Allogenic hematopoietic stem cell transplantation (HSCT)

The treatment of choice for therapy of WAS and CAMT (mutations of *WAS* and *MPL* genes). To be considered as therapy for some patients with other clinically severe IT, including those with familial thrombocytopenia and predisposition to hematological malignancies (mutations in the

ANKRD26, *ETV6*, *RUNX1* genes). Also to be considered for therapy of *XLT*, *RUSAT*, *TAR* mutations; good post-transplantation effects were reported.

Gene therapy

An experimental method to be considered for patients with WAS for whom no compatible stem cell donor is available.

3. Multi-disciplinary treatment of defects and IT — associated disorders.

For the management of IT patients with non-hematological disorders, a cooperation between hematologist and specialists from other disciplines (ophthalmology, dermatology, ortopedy or nephrology) is strongly recommended.

References

- Noris P, Pecci A. Hereditary thrombocytopenias: a growing list of disorders. *Hematology Am Soc Hematol Educ Program*. 2017; 2017(1): 385–399, doi: [10.1182/asheducation-2017.1.385](https://doi.org/10.1182/asheducation-2017.1.385), indexed in Pubmed: [29222283](https://pubmed.ncbi.nlm.nih.gov/29222283/).
- Balduini CL, Pecci A, Noris P. Inherited thrombocytopenias: the evolving spectrum. *Hamostaseologie*. 2012; 32(4): 259–270, doi: [10.5482/ha12050001](https://doi.org/10.5482/ha12050001), indexed in Pubmed: [22972471](https://pubmed.ncbi.nlm.nih.gov/22972471/).
- Balduini CL, Savoia A, Seri M. Inherited thrombocytopenias frequently diagnosed in adults. *J Thromb Haemost*. 2013; 11(6): 1006–1019, doi: [10.1111/jth.12196](https://doi.org/10.1111/jth.12196), indexed in Pubmed: [23510089](https://pubmed.ncbi.nlm.nih.gov/23510089/).
- Melazzini F, Zaninetti C, Balduini CL. Bleeding is not the main clinical issue in many patients with inherited thrombocytopenias. *Haemophilia*. 2017; 23(5): 673–681, doi: [10.1111/hae.13255](https://doi.org/10.1111/hae.13255), indexed in Pubmed: [28594466](https://pubmed.ncbi.nlm.nih.gov/28594466/).
- Latger-Cannard V, Philippe C, Bouquet A, et al. Haematological spectrum and genotype-phenotype correlations in nine unrelated families with *RUNX1* mutations from the French network on inherited platelet disorders. *Orphanet J Rare Dis*. 2016; 11: 49, doi: [10.1186/s13023-016-0432-0](https://doi.org/10.1186/s13023-016-0432-0), indexed in Pubmed: [27112265](https://pubmed.ncbi.nlm.nih.gov/27112265/).
- Noris P, Favier R, Alessi MC, et al. *ANKRD26*-related thrombocytopenia and myeloid malignancies. *Blood*. 2013; 122(11): 1987–1989, doi: [10.1182/blood-2013-04-499319](https://doi.org/10.1182/blood-2013-04-499319), indexed in Pubmed: [24030261](https://pubmed.ncbi.nlm.nih.gov/24030261/).
- Melazzini F, Palombo F, Balduini A, et al. Clinical and pathogenic features of *ETV6*-related thrombocytopenia with predisposition to acute lymphoblastic leukemia. *Haematologica*. 2016; 101(11): 1333–1342, doi: [10.3324/haematol.2016.147496](https://doi.org/10.3324/haematol.2016.147496), indexed in Pubmed: [27365488](https://pubmed.ncbi.nlm.nih.gov/27365488/).
- Balduini CL, Pecci A, Savoia A. Recent advances in the understanding and management of *MYH9*-related inherited thrombocytopenias. *Br J Haematol*. 2011; 154(2): 161–174, doi: [10.1111/j.1365-2141.2011.08716.x](https://doi.org/10.1111/j.1365-2141.2011.08716.x), indexed in Pubmed: [21542825](https://pubmed.ncbi.nlm.nih.gov/21542825/).
- Ballmaier M, Germeshausen M. Congenital amegakaryocytic thrombocytopenia: clinical presentation, diagnosis, and treatment. *Semin Thromb Hemost*. 2011; 37(6): 673–681, doi: [10.1055/s-0031-1291377](https://doi.org/10.1055/s-0031-1291377), indexed in Pubmed: [22102270](https://pubmed.ncbi.nlm.nih.gov/22102270/).
- Savoia A. Molecular basis of inherited thrombocytopenias. *Clin Genet*. 2016; 89: 154–62, doi: [10.1111/cge.12607](https://doi.org/10.1111/cge.12607), indexed in Pubmed: [25951879](https://pubmed.ncbi.nlm.nih.gov/25951879/).
- Chojnowski K, Klukowska A, Łętowska M, et al. Zasady postępowania we wrodzonych zaburzeniach czynności płytek krwi. *Acta Haematol Pol*. 2009; 40: 731–52.
- Noris P, Biino G, Pecci A, et al. Platelet diameters in inherited thrombocytopenias: analysis of 376 patients with all known disorders. *Blood*. 2014; 124(6): e4–e10, doi: [10.1182/blood-2014-03-564328](https://doi.org/10.1182/blood-2014-03-564328), indexed in Pubmed: [24990887](https://pubmed.ncbi.nlm.nih.gov/24990887/).
- Massaad MJ, Ramesh N, Geha RS. Wiskott-Aldrich syndrome: a comprehensive review. *Ann N Y Acad Sci*. 2013; 1285: 26–43, doi: [10.1111/nyas.12049](https://doi.org/10.1111/nyas.12049), indexed in Pubmed: [23527602](https://pubmed.ncbi.nlm.nih.gov/23527602/).
- Albert MH, Bittner TC, Nonoyama S, et al. X-linked thrombocytopenia (*XLT*) due to *WAS* mutations: clinical characteristics, long-term outcome, and treatment options. *Blood*. 2010; 115(16): 3231–3238, doi: [10.1182/blood-2009-09-239087](https://doi.org/10.1182/blood-2009-09-239087), indexed in Pubmed: [20173115](https://pubmed.ncbi.nlm.nih.gov/20173115/).
- Toriello HV. Thrombocytopenia-absent radius syndrome. *Semin Thromb Hemost*. 2011; 37(6): 707–712, doi: [10.1055/s-0031-1291381](https://doi.org/10.1055/s-0031-1291381), indexed in Pubmed: [22102274](https://pubmed.ncbi.nlm.nih.gov/22102274/).
- Al-Qattan MM. The Pathogenesis of Radial Ray Deficiency in Thrombocytopenia-Absent Radius (*TAR*) Syndrome. *J Coll Physicians Surg Pak*. 2016; 26(11): 912–916, doi: [2476](https://doi.org/10.2476/27981927), indexed in Pubmed: [27981927](https://pubmed.ncbi.nlm.nih.gov/27981927/).
- Niihori T, Ouchi-Uchiyama M, Sasahara Y, et al. Mutations in *MECOM*, Encoding Oncoprotein *EVI1*, Cause Radioulnar Synostosis with Amegakaryocytic Thrombocytopenia. *Am J Hum Genet*. 2015; 97(6): 848–854, doi: [10.1016/j.ajhg.2015.10.010](https://doi.org/10.1016/j.ajhg.2015.10.010), indexed in Pubmed: [26581901](https://pubmed.ncbi.nlm.nih.gov/26581901/).
- Favier R, Akshoomoff N, Mattson S, et al. Jacobsen syndrome: Advances in our knowledge of phenotype and genotype. *Am J Med Genet C Semin Med Genet*. 2015; 169(3): 239–250, doi: [10.1002/ajmg.c.31448](https://doi.org/10.1002/ajmg.c.31448), indexed in Pubmed: [26285164](https://pubmed.ncbi.nlm.nih.gov/26285164/).
- Lacruz RS, Feske S. Diseases caused by mutations in *ORAI1* and *STIM1*. *Ann N Y Acad Sci*. 2015; 1356: 45–79, doi: [10.1111/nyas.12938](https://doi.org/10.1111/nyas.12938), indexed in Pubmed: [26469693](https://pubmed.ncbi.nlm.nih.gov/26469693/).
- Pecci A, Klersy C, Gresele P, et al. *MYH9*-related disease: a novel prognostic model to predict the clinical evolution of the disease based on genotype-phenotype correlations. *Hum Mutat*. 2014; 35(2): 236–247, doi: [10.1002/humu.22476](https://doi.org/10.1002/humu.22476), indexed in Pubmed: [24186861](https://pubmed.ncbi.nlm.nih.gov/24186861/).
- Rodeghiero F, Pecci A, Balduini CL. Thrombopoietin receptor agonists in hereditary thrombocytopenias. *J Thromb Haemost*. 2018; 16(9): 1700–1710, doi: [10.1111/jth.14217](https://doi.org/10.1111/jth.14217), indexed in Pubmed: [29956472](https://pubmed.ncbi.nlm.nih.gov/29956472/).
- Noris P, Perrotta S, Seri M, et al. Mutations in *ANKRD26* are responsible for a frequent form of inherited thrombocytopenia: analysis of 78 patients from 21 families. *Blood*. 2011; 117(24): 6673–6680, doi: [10.1182/blood-2011-02-336537](https://doi.org/10.1182/blood-2011-02-336537), indexed in Pubmed: [21467542](https://pubmed.ncbi.nlm.nih.gov/21467542/).
- Liew E, Owen C. Familial myelodysplastic syndromes: a review of the literature. *Haematologica*. 2011; 96(10): 1536–1542, doi: [10.3324/haematol.2011.043422](https://doi.org/10.3324/haematol.2011.043422), indexed in Pubmed: [21606161](https://pubmed.ncbi.nlm.nih.gov/21606161/).
- Stritt S, Nurden P, Turro E, et al. BRIDGE-BPD Consortium. A gain-of-function variant in *DIAPH1* causes dominant macrothrombocytopenia and hearing loss. *Blood*. 2016; 127(23): 2903–2914, doi: [10.1182/blood-2015-10-675629](https://doi.org/10.1182/blood-2015-10-675629), indexed in Pubmed: [26912466](https://pubmed.ncbi.nlm.nih.gov/26912466/).
- Yoo EG. Sitosterolemia: a review and update of pathophysiology, clinical spectrum, diagnosis, and management. *Ann Pediatr Endocrinol Metab*. 2016; 21(1): 7–14, doi: [10.6065/apem.2016.21.1.7](https://doi.org/10.6065/apem.2016.21.1.7), indexed in Pubmed: [27104173](https://pubmed.ncbi.nlm.nih.gov/27104173/).

29. Millikan PD, Balamohan SM, Raskind WH, et al. Inherited thrombocytopenia due to GATA-1 mutations. *Semin Thromb Hemost.* 2011; 37(6): 682–689, doi: [10.1055/s-0031-1291378](https://doi.org/10.1055/s-0031-1291378), indexed in Pubmed: [22102271](https://pubmed.ncbi.nlm.nih.gov/22102271/).
30. Noris P, Perrotta S, Bottega R, et al. Clinical and laboratory features of 103 patients from 42 Italian families with inherited thrombocytopenia derived from the monoallelic Ala156Val mutation of GPIb (Bolzano mutation). *Haematologica.* 2012; 97(1): 82–88, doi: [10.3324/haematol.2011.050682](https://doi.org/10.3324/haematol.2011.050682), indexed in Pubmed: [21933849](https://pubmed.ncbi.nlm.nih.gov/21933849/).
31. Kunishima S, Okuno Y, Yoshida K, et al. ACTN1 mutations cause congenital macrothrombocytopenia. *Am J Hum Genet.* 2013; 92(3): 431–438, doi: [10.1016/j.ajhg.2013.01.015](https://doi.org/10.1016/j.ajhg.2013.01.015), indexed in Pubmed: [23434115](https://pubmed.ncbi.nlm.nih.gov/23434115/).
32. Kunishima S, Kobayashi R, Itoh TJ, et al. Mutation of the beta1-tubulin gene associated with congenital macrothrombocytopenia affecting microtubule assembly. *Blood.* 2009; 113(2): 458–461, doi: [10.1182/blood-2008-06-162610](https://doi.org/10.1182/blood-2008-06-162610), indexed in Pubmed: [18849486](https://pubmed.ncbi.nlm.nih.gov/18849486/).
33. Kunishima S, Kashiwagi H, Otsu M, et al. Heterozygous ITGA2B R995W mutation inducing constitutive activation of the α IIb β 3 receptor affects proplatelet formation and causes congenital macrothrombocytopenia. *Blood.* 2011; 117(20): 5479–5484, doi: [10.1182/blood-2010-12-323691](https://doi.org/10.1182/blood-2010-12-323691), indexed in Pubmed: [21454453](https://pubmed.ncbi.nlm.nih.gov/21454453/).
34. Khoriaty R, Ozel AB, Ramdas S, et al. Genome-wide linkage analysis and whole-exome sequencing identifies an ITGA2B mutation in a family with thrombocytopenia. *Br J Haematol.* 2019; 186(4): 574–579, doi: [10.1111/bjh.15961](https://doi.org/10.1111/bjh.15961), indexed in Pubmed: [31119735](https://pubmed.ncbi.nlm.nih.gov/31119735/).
35. Marconi C, Di Buduo CA, LeVine K, et al. Loss-of-function mutations in cause a new form of inherited thrombocytopenia. *Blood.* 2019; 133(12): 1346–1357, doi: [10.1182/blood-2018-07-859496](https://doi.org/10.1182/blood-2018-07-859496), indexed in Pubmed: [30591527](https://pubmed.ncbi.nlm.nih.gov/30591527/).
36. Pecci A. Diagnosis and treatment of inherited thrombocytopenias. *Clin Genet.* 2016; 89: 141–53, doi: [10.1111/cge.12603](https://doi.org/10.1111/cge.12603), indexed in Pubmed: [25920516](https://pubmed.ncbi.nlm.nih.gov/25920516/).
37. Zaninetti C, Gresele P, Bertomoro A, et al. Eltrombopag for the treatment of inherited thrombocytopenias: a phase 2 clinical trial. *Haematologica.* 2019 [Epub ahead of print], doi: [10.3324/haematol.2019.223966](https://doi.org/10.3324/haematol.2019.223966), indexed in Pubmed: [31273088](https://pubmed.ncbi.nlm.nih.gov/31273088/).