LA JOURNÉE ANNUELLE DU CRPP

28 NOVEMBRE 2022
AMPHITHÉATHRE CERIMED-FACULTÉ DE MÉDECINE
27 BD JEAN MOULIN 13005 MARSEILLE
9H30 À 16H30

Inherited Thrombocytopenias and Their Therapy

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Inherited thrombocytopenias: from genes to therapy

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Trends in Hematology/Oncology

research paper
haematologica 2002; 87:860-880
http://www.haematologica.ws/2002_08/860.htm

2002

INHERITED THROMBOCYTOPENIAS

8 genes

15 clinical entities

Table 1. Classification of inherited thrombocytopenias according to platelet size.

Inherited thrombocytopenias	*Abbreviation*	*OMIM[a]*	*S/NS[b]*	*Inherited Pattern[c]*	*Gene*	*Gene Localization*
Small platelets						
Wiskott-Aldrich syndrome	WAS	301000	S	X-L	WAS	Xp11
X-linked thrombocytopenia	XLT	313900	NS			
Normal-sized platelets						
Familial platelet disorder with predisposition to acute myelogenous leukemia	FPD/AML	601399	S	AD	CBFA2	21q22
Amegakaryocytic thrombocytopenia	CAMT	604498	NS	AR	c-mpl	1p34
Amegakaryocytic thrombocytopenia with radio-ulnar synostosis	CTRUS	605432	S	AD	HOXA11	7p15-14
Thrombocytopenia with absent radii	TAR	274000	S	AR	n.d.	n.d.
Other thrombocytopenias	n.d.	n.d.	S	AD	n.d.	10p12 Heterogeneity
Large platelets						
Bernard-Soulier syndrome	BSS	231200	NS	AD	GPIbα GPIbβ GPIX	 17p13 22q11 3q21
Velocardiofacial syndrome	VCFS	192430	S	AD	CGS[d] GPIbβ	 22q11
Platelet-type pseudo-von Willebrand's disease	PTvWD	177820	NS	AD	GPIbα	17p12
Benign Mediterranean macrothrombocytopenia	n.d.	n.d.	NS	AD	n.d.	n.d.
X-linked thrombocytopenia and dyserythropoiesis with or without anemia	XLTT	300367 314050	S	X-L	GATA-1	Xp11
Paris-Trousseau type thrombocytopenia	TCPT	188025/600588				
Jacobsen's syndrome	JBS	147791	S	AD	CGS[d] Fli-1 Ets-1	11q23
MYH9-related disease						
May-Hegglin anomaly	MHA	155100	NS	AD	MYH9	22q12-13
Sebastian syndrome	SBS	605249	NS			
Fechtner syndrome	FTNS	153640	S			
Epstein syndrome	EPTS	153650	S			
Gray platelet syndrome	GPS	139090	NS	AD	n.d.	n.d.
Montreal platelet syndrome	MPS	n.d.	NS	AD	n.d.	n.d.
Macrothrombocytopenia with platelet expression of glycophorin A	n.d.	n.d.	S	AD	n.d.	n.d.

[a]On line Mendelian inheritance in man; [b]S:syndromic form; NS:non-syndromic form; [c]A.D.:autosomal dominant; A.R.:autosomal recessive; X-L:X-linked; [d]contiguous gene syndrome.

Blood Reviews 48 (2021) 100784

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Inherited thrombocytopenias: an updated guide for clinicians

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2021

INHERITED THROMBOCYTOPENIAS

43 genes

45 clinical entities

Table 1
Main features of the inherited thrombocytopenias reported so far.

Disease (abbreviation, OMIM entry) [ref.]	Freq.[a]	Gene (locus)	Inh.[b]	Bleeding[c]	Degree of TCP[d]	Platelet size	Peculiar features
Forms with only thrombocytopenia							
Bernard-Soulier syndrome, biallelic form (bBSS, 231200) [118]	++++	*GP1BA* (17p13) *GP1BB* (22q11) *GP9* (3q21)	AR	S	++/+++	Giant	Severely defective platelet function due to marked defect of the GPIb/IX/V complex.
Bernard-Soulier syndrome, monoallelic form (mBSS, 153670) [119,120]	+++	*GP1BA* (17p13) *GP1BB* (22q11)	AD	A/Mi	+/++	Large	-
ACTN1-related thrombocytopenia (*ACTN1*-RT, 615193) [121]	+++	*ACTN1* (14q22)	AD	A	+/++	Large	-
Gray platelet syndrome (GPS, 139090) [1,122,123]	+	*NBEAL2* (Chr3)	AR	Mo/S	+/++	Large	Severe deficiency of platelet alpha granules, and in some cases of alpha/delta granules. Defective platelet function. Platelet count decreases over time. Splenomegaly, anemia, B12, Bone marrow fibrosis, splenomegaly, and dysregulation of the immune system with autoimmune diatheses are present in a significant proportion of patients.
Platelet-type von Willebrand disease (PTvWD, 177820) [15]	++	*GP1BA* (17p13)	AD	A/Mi	+/+++	Normal	Platelet count is normal in many patients but may greatly decrease under stress conditions.
GFI1b-related thrombocytopenia, monoallelic form (*GFI1b*-RT, 187900) [124]	++	*GFI1B* (9q34)	AD	A/Mo	+/++	Large	Deficiency of platelet alpha granules, and in some cases combined alpha/delta granule defect. Defective platelet function may be present. Red cells anisocytosis or anisopoikilocytosis in most cases. Aberrant platelet CD34 expression.
GFI1b-related thrombocytopenia, biallelic form (*GFI1b*-RT, 187900) [125,126]	+		AR	Mo/S	+++	Large	Deficiency of platelet alpha and delta granules. Defective platelet function. Aberrant platelet CD34 expression.
TUBB1-related thrombocytopenia (*TUBB1*-RT, 613112) [127]	+	*TUBB1* (20q13)	AD	A	+/++	Large	-
ITGA2B/ITGB3-related thrombocytopenia (*ITGA2B/ITGB3*-RT, 187800) [128]	+	*ITGA2B* (17q21), *ITGB3* (17q21)	AD	Mo	+/++	Large	Defective platelet function.
CYCS-related thrombocytopenia (*CYCS*-RT or THC6, 612004) [129]	+	*CYCS* (7p15)	AD	A	+	Normal	-
SLFN14-related thrombocytopenia (*SLFN14*-RT, 616913) [130]	+	*SLFN14* (17q12)	AD	Mo/S	+/++	Large	Defective platelet function. Deficiency of platelet delta granules.
FLI1-related thrombocytopenia, mono-allelic form (*FLI1*-RT, 617443) [131,132]	+	*FLI1*	AD	A/Mo	+	Large	Defective platelet function. Large fused alpha granules in some platelets.
FLI1-related thrombocytopenia, biallelic form (*FLI1*-RT, 617443) [133]	+	(11p24)	AR	Mo	++	Large	Defective platelet function. Large fused alpha granules in some platelets.
IKZF5-related thrombocytopenia (*IKZF5*-RT, na) [134]	+	*IKZF5* (10q26)	AD	A	+/++	Normal	Deficiency of platelet alpha granules.
Thrombocytopenia caused by monoallelic *THPO* mutation (*THPO*-RT, na) [135]	+	*THPO* (3q27)	AD	A	+	Normal	-
FYB-related thrombocytopenia (*FYB*-RT or THC3, 273900) [136]	+	*FYB* (5p13)	AR	Mi/Mo	++/+++	Small	-
TBPM7-related thrombocytopenia (*TBPM7*-RT, na) [137]	+	*TPBM7* (15q21)	AD	A	++	Large	-
TPM4-related thrombocytopenia (*TPM4*-RT, na) [138]	+	*TPM4* (19p13)	AD	A	+	Large	-
PTPRJ-related thrombocytopenia (*PTPRJ*-RT, na) [139]	+	*PTPRJ* (11p11)	AR	Mi/Mo	++/+++	Small	Defective platelet function.
PRKACG-related thrombocytopenia (*PRKACG*-RT, 616176) [140]	+	*PRKACG* (9q21)	AR	S	+++	Large	The two patients from the only reported family carried also a homozygous, likely pathogenic mutation in *GNE*.
Syndromic forms							
Wiskott-Aldrich syndrome (WAS, 301000) [141]	++++	*WAS* (Xp11)	XL	S	+++	Small	Severe immunodeficiency leading to early death. Eczema. Increased risk of malignancies and autoimmunity.
X-linked thrombocytopenia (XLT or THC1, 313900) [89]			A/Mo	++/+++	Small		Mild immunodeficiency. Mild and transient eczema. Increased risk of malignancies and autoimmunity.
Jacobsen syndrome [JBS, 147791], Paris-Trousseau thrombocytopenia (TCPT, 188025) [18,142]	++++	Deletions in 11q23	AD	Mi/S	++/+++	Normal/ Large	Physical growth delay, intellectual disability, craniofacial dysmorphisms, malformations of the heart, gastrointestinal tract, CNS, kidney, urinary tract, and/or skeleton; cryptorchidism; other malformations. Defective platelet function. Large fused alpha granules in some platelets; delta granule defect. Thrombocytopenia usually improves and may resolve over time.
	+++	*RBM8A* (1q21)	AR	S	+++	Normal	

(continued on next page)

Table 1 (continued)

Disease (abbreviation, OMIM entry) [ref.]	Freq.[a]	Gene (locus)	Inh.[b]	Bleeding[c]	Degree of TCP[d]	Platelet size	Peculiar features
Thrombocytopenia with absent radii (TAR, 274000) [14,143]							Reduced/absent MKs in the bone marrow. Bilateral radial aplasia +/- other upper and lower limb bone abnormalities. Possible kidney, cardiac, and/or CNS malformations. Platelet count raises over time and often normalizes.
GATA1-related disorders: X-linked thrombocytopenia with thalassemia (XLTT, 314050), X-linked thrombocytopenia with dyserythropoietic anemia (XLTDA, 300367) [144]	++	*GATA1* (Xp11)	XL	Mi/S	+/+++	Normal	Abnormalities of the erythroid series consisting in dyserythropoietic anemia or hemolytic anemia with laboratory abnormalities resembling beta-thalassemia and splenomegaly. Congenital erythropoietic porphyria may be present.
Platelet abnormalities with eosinophilia and immune-mediated inflammatory disease (PLTEII, 617718) [145,146]	++	*ARPC1B* (7q22.1)	AR	Mo	++/+++	Small	Immunodeficiency. Systemic inflammation, with variable presence of leukocytoclastic vasculitis, inflammatory colitis, eosinophilia, eczema, lymphadenomegaly, hepato-splenomegaly. Growth failure. Platelet count may be normal in some PLTEII patients.
(STRMK, 185070) [147]		*STIM1* (11p15)					Myopathy with tubular aggregates, susceptible asplenia or hyposplenia, congenital miosis, ichthyosis, short stature, mild cognitive impairment, migraines, and/or hyposthenia.
York platelet syndrome (YPS, na) [148]	+		AD	Mi	+/++	Normal	Myopathy with rimmed vacuoles. Platelet ultrastructural abnormalities, such as deficiency of alpha and delta granules, giant electron dense bodies and multilayered target-like bodies.
Takenouchi-Kosaki syndrome with macrothrombocytopenia (TKS, 616737) [149,150]	+	*CDC42* (1p36)	AD	A	++	Large	Defective growth and psychomotor development, intellectual disability, facial abnormalities, brain malformation. Other possible features include muscle tone abnormalities, immunodeficiency, eczema, hearing/visual disability, lymphedema, and cardiac, genitourinary, and/or skeletal malformations.
KDSR-related thrombocytopenia (*KDSR*-RT, na) [151,152]	+	*KDSR* (18q21)	AR	Mo	+++	Normal	Dermatologic involvement ranging from palmoplantar and anogenital hyperkeratosis/erythema to a more severe picture of lamellar ichthyosis. One family with no or very mild skin lesions but associated anemia has been reported.
ACTB-associated syndromic thrombocytopenia (*ACTB*-AST, na) [153]	+	*ACTB* (7p22)	AD	A	+/++	Large	Microcephaly, minor facial anomalies, mild intellectual disability, developmental delay. Other possible features include leukocytosis with eosinophilia, leukopenia and other malformations.
[illegible]	[illegible]	[illegible]	XL	[illegible]	[illegible]	[illegible]	Periventricular nodular heterotopia (CMDM [300049]). Non-syndromic cases presenting with isolated thrombocytopenia have been reported. Hemolytic anemia, myelofibrosis. Leukocytosis may be present.
(TBAS4, 616941) [154]		(2q21)					
GALE-related thrombocytopenia (*GALE*-RT, na) [156]	+	*GALE* (1p36)	AR	S	+++	Large	Anemia and recurrent neutropenia.
Forms predisposing to additional diseases							
MYH9-related disease (*MYH9*-RD, 155100) [40,41,42]	++++	*MYH9* (22q12)	AD	A/Mi	+/+++	Giant	Most patients develop extra-hematological manifestations, i.e. sensorineural deafness, nephropathy evolving into kidney failure, and/or cataracts. About half of patients present elevated liver enzymes without liver dysfunction. Most patients present basophilic "Döhle-like" inclusions in neutrophil granulocytes.
ANKRD26-related thrombocytopenia (*ANKRD26*-RT or THC2, 188000) [38,157]	+++	*ANKRD26* (10p12)	AD	A/Mi	++/+++	Normal	Propensity to acquire myeloid malignancies (about 10% of reported patients). Some patients have increased hemoglobin levels and/or leukocytosis. Mild deficiency of platelet alpha granules in some patients.
Familial platelet disorder with propensity to acute myelogenous leukemia (FPD-AML, 601399) [158,159]	+++	*RUNX1* (21q22)	AD	A/Mo	+/++	Normal	Propensity to acquire myeloid malignancies (over 40% of reported patients). Increased risk of T-cell acute lymphoblastic leukemia. Defective platelet function.
ETV6-related thrombocytopenia (*ETV6*-RT or THC5, 616216) [17,160]	++	*ETV6* (12p13)	AD	A/Mi	+/++	Normal	Propensity to acquire hematological malignancies (about 30% of reported patients), [illegible]

Table 1 (continued)

Disease (abbreviation, OMIM entry) [ref.]	Freq.[a]	Gene (locus)	Inh.[b]	Bleeding[c]	Degree of TCP[d]	Platelet size	Peculiar features
							especially childhood B-cell acute lymphoblastic leukemia.
Congenital amegakaryocytic thrombocytopenia (CAMT, 604498) [39,161]	+++	*MPL* (1p34.2)	AR	S	+++	Normal	Reduced/absent MKs in the bone marrow. Evolution to severe trilineage bone marrow aplasia during infancy or childhood in all patients.
[illegible]	+	*THPO* (3q27)	AR	S	+++	Normal	Reduced/absent MKs in the bone marrow. Evolution to severe trilineage bone marrow aplasia during infancy or childhood in all patients.
[illegible]	++	*MECOM* (3q26)	AD	S	+++	Normal	Reduced/absent MKs in the bone marrow. Bilateral radioulnar synostosis and/or hyperigenerative anemia are frequent features. Evolution to severe trilineage bone marrow aplasia during infancy or childhood in almost all patients. Some patients present other skeletal anomalies, cardiac and/or renal [illegible] B-cell deficiency.
Radioulnar synostosis with amegakaryocytic thrombocytopenia 1 (RUSAT1, 605432) [32]	+	*HOXA11* (7p15)	AD	S	+++	Normal	Reduced/absent MKs in the bone marrow. Bilateral radioulnar synostosis. Possible evolution to trilineage bone marrow aplasia during infancy or childhood. Some patients present other skeletal abnormalities and/or sensorineural deafness.
DIAPH1-related disorder (*DIAPH1*-RD, na) [45,46]	+	*DIAPH1* (5q31)	AD	A	+/++	Large	Patients develop progressive sensorineural deafness during infancy or childhood. Recurrent mild neutropenia in some cases.
GNE-related thrombocytopenia (*GNE*-RT, na) [47,48]	+	*GNE* 9p13.3	AR	Mi/S	+++	Large	Some patients presented myopathy with rimmed vacuoles with onset in early adulthood.
SRC-related thrombocytopenia (*SRC*-RT or THC6, 616937) [51–53]	+	*SRC* (20q11)	AD	Mo/S	+/+++	Large	Facial dysmorphism and/or severe osteoporosis in some cases. Some patients developed young-onset myelofibrosis and splenomegaly. Premature edentulism. Deficiency of platelet alpha granules.

Abbreviations: ref. = references. na = not available. nr= not reported. CNS = central nervous system. MKs = megakaryocytes.

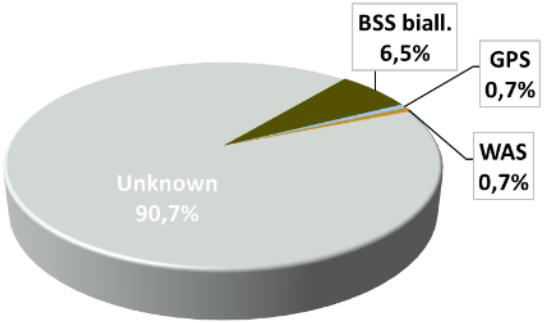
[a] Freq. = frequency. +, less than 10 reported families; ++, more than 10 reported families; +++, more than 50 reported families; ++++, more than 200 reported families.

[b] Inh. = inheritance. AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

[c] Bleeding = Severity of bleeding tendency in the majority of the patients reported for each disorder. A, absent; Mi, mild; Mo, moderate; S, severe.

[d] Degree of thrombocytopenia (TCP) = degree of thrombocytopenia in the majority of the patients reported for each disorder. +, platelet count > 100 x10^9/L; ++, platelet count 50 to 100 x10^9/L; +++, platelet count < 50 x10^9/L.

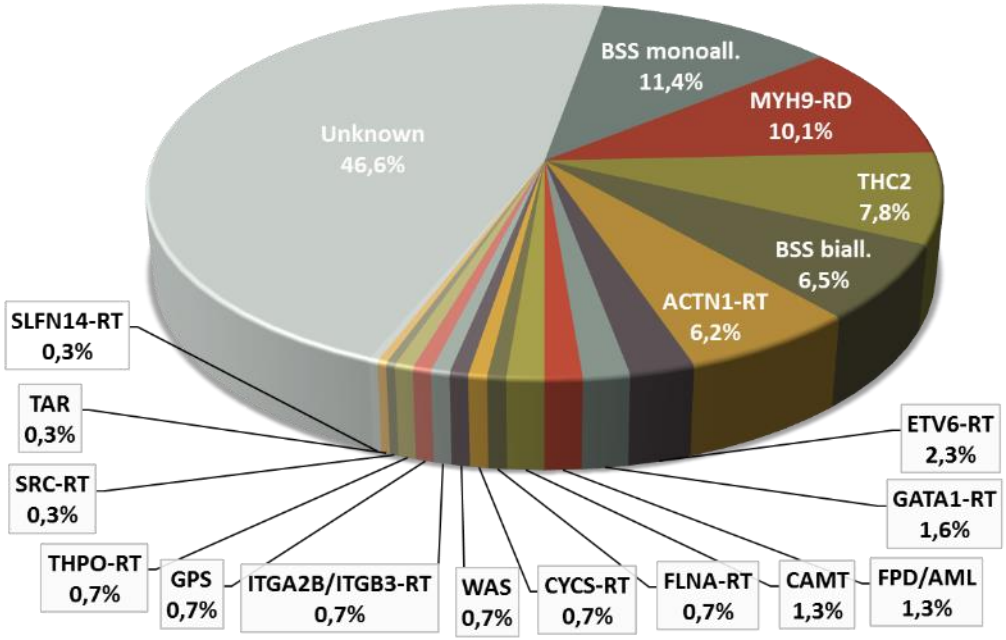
THE EVOLVING PHENOTYPE OF INHERITED THROMBOCYTOPENIAS



Few forms, all with severe bleeding tendency

2000

2022



Has the picture of inherited thrombocytopenias remained the same?

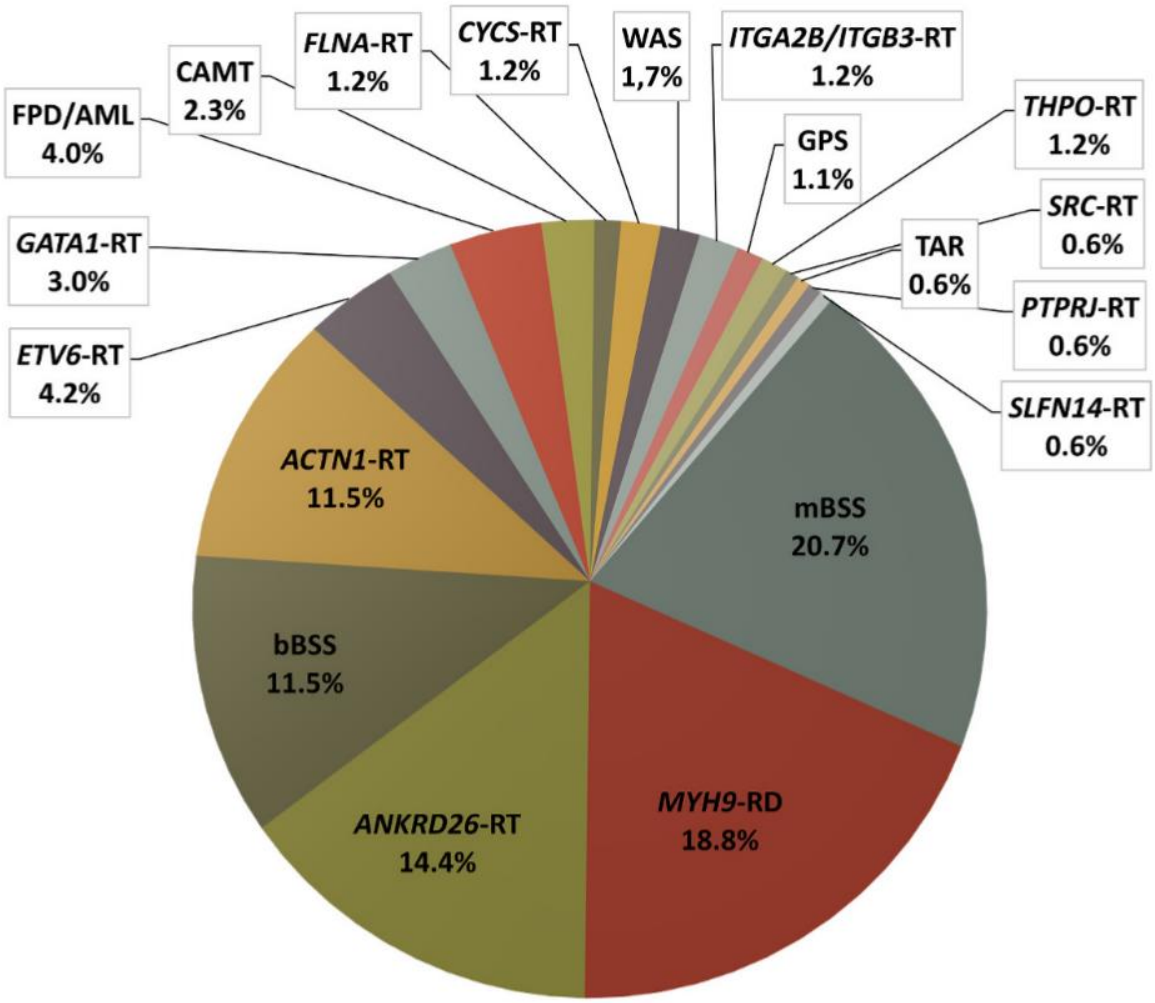
Inherited thrombocytopenias in 2022

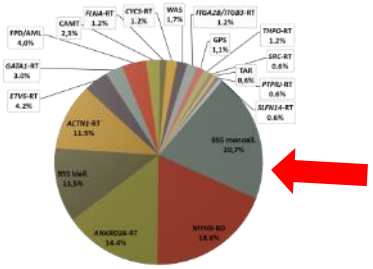
- How severe is the bleeding tendency?
- Predisposition to develop additional serious illnesses
- For which forms it is mandatory to make a definite diagnosis
- Which treatments for which diseases

Inherited thrombocytopenias in 2022

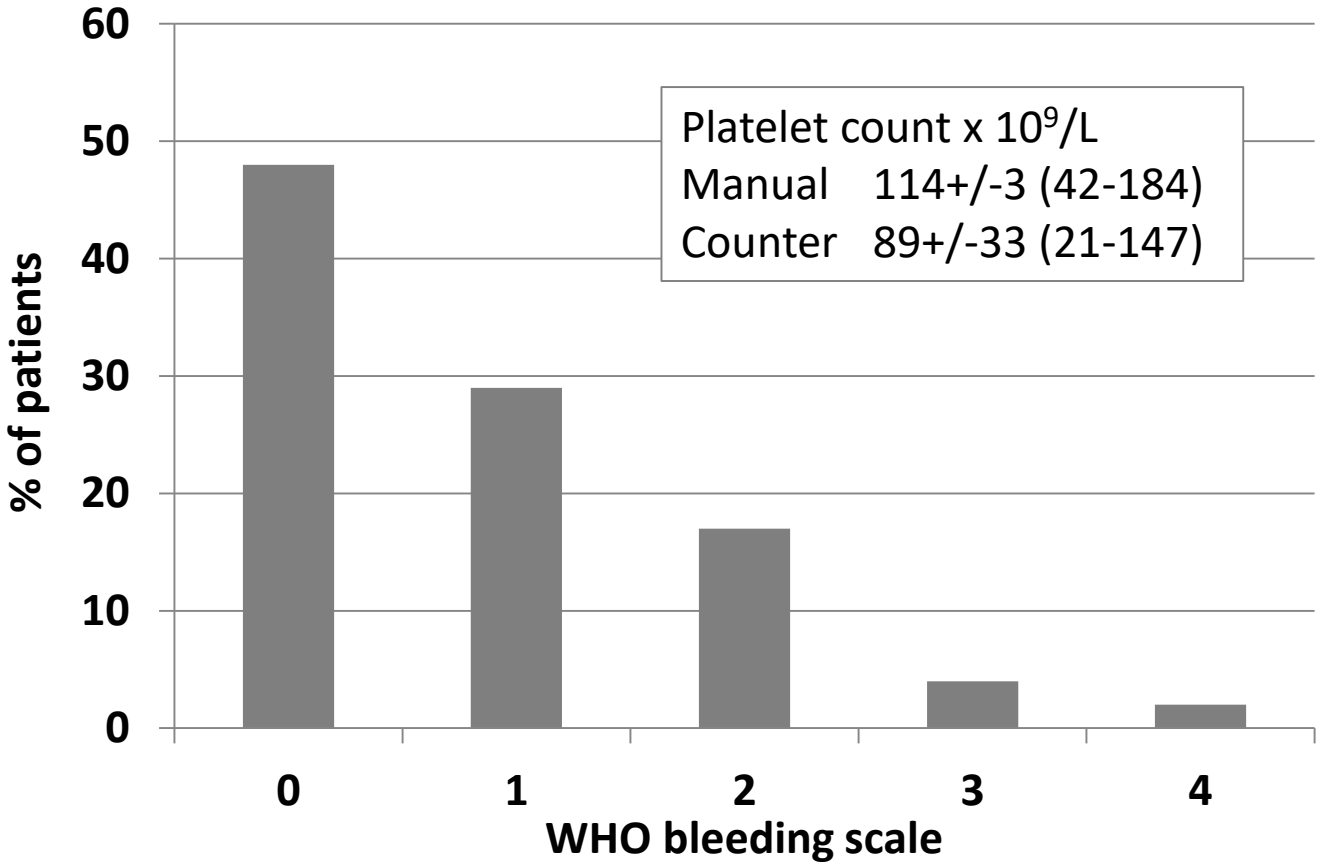
- **How severe is the bleeding tendency?**
- **Predisposition to develop additional serious illnesses**
- **For which forms it is mandatory to make a definite diagnosis**
- **Which treatments for which diseases**

Pavia case series of 335 consecutive families with inherited thrombocytopenias

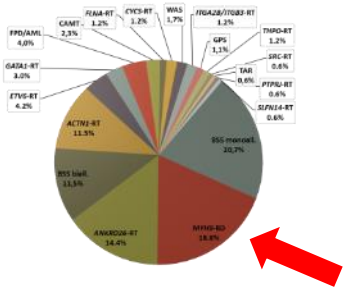




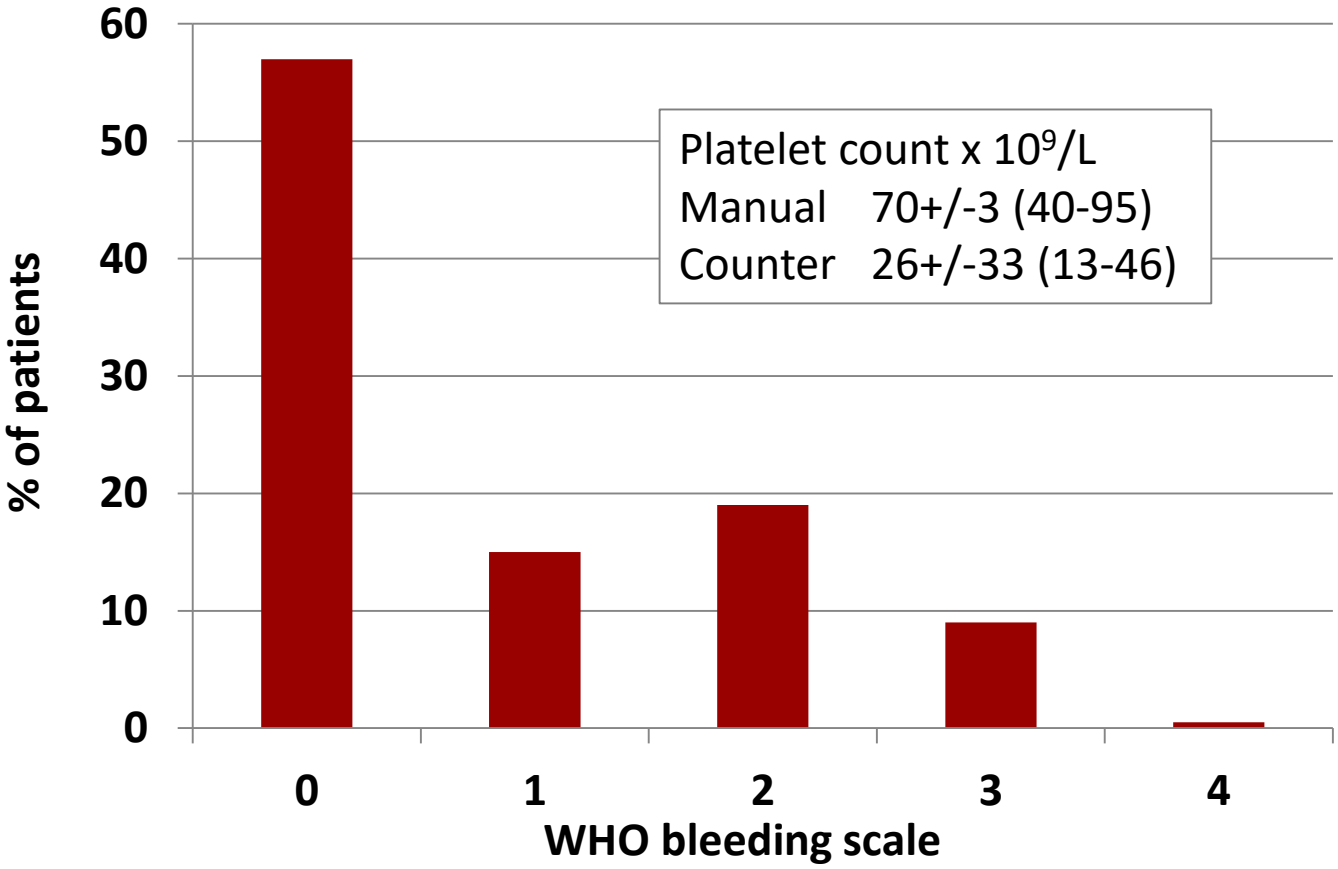
Bleeding tendency in 82 patients with monoallelic Bernard-Soulier syndrome due to 'Bolzano mutation'



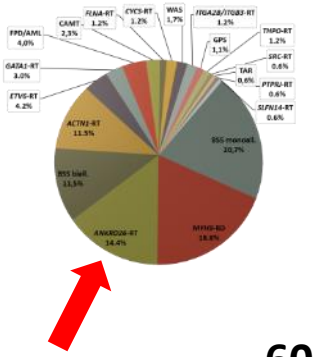
Haematologica 2012;97:82-8



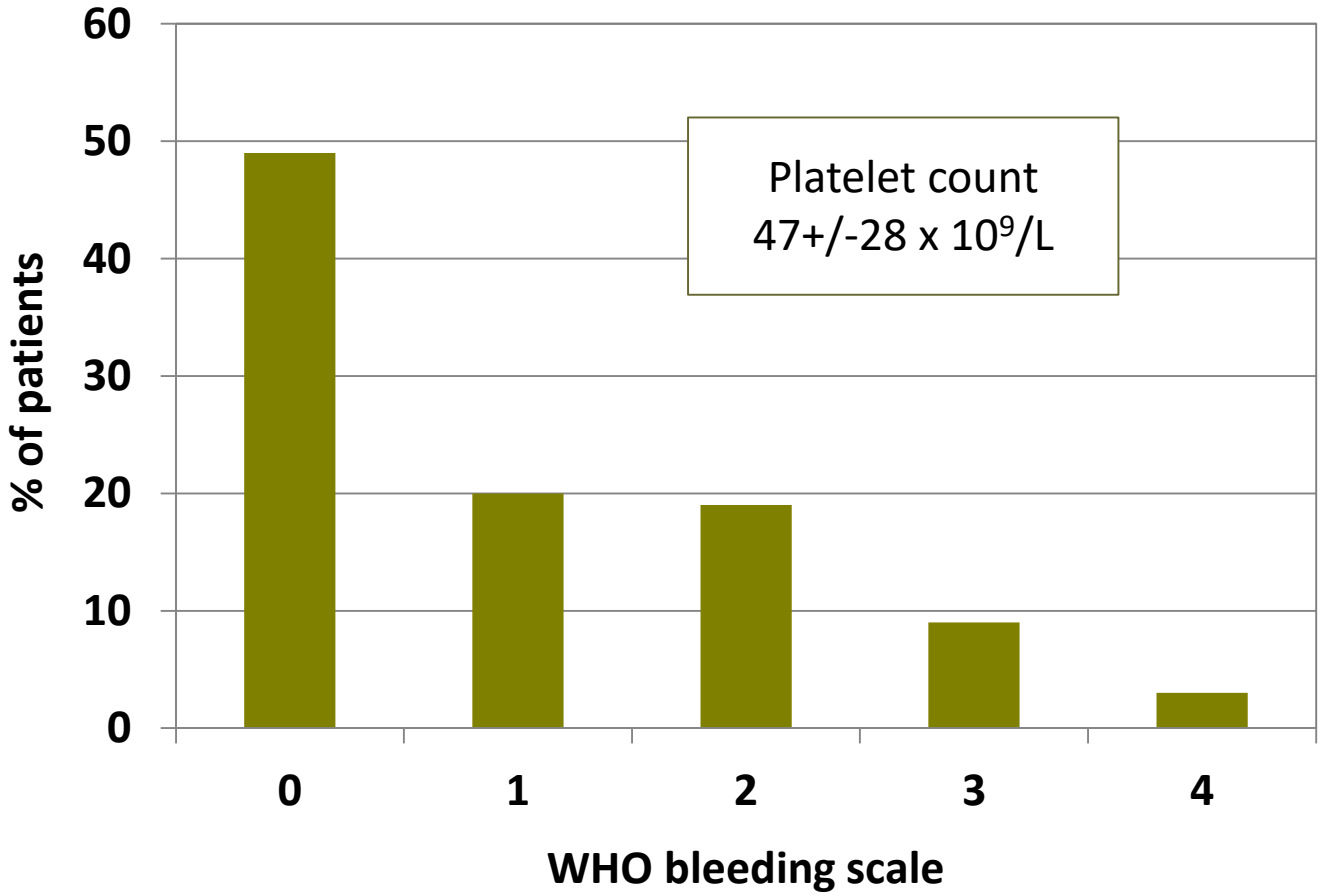
Bleeding tendency in 183 patients with *MYH9*-RD



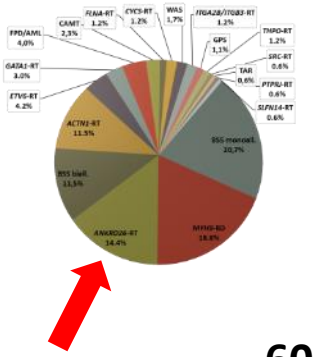
Hum Mutat 2014;35:236-47



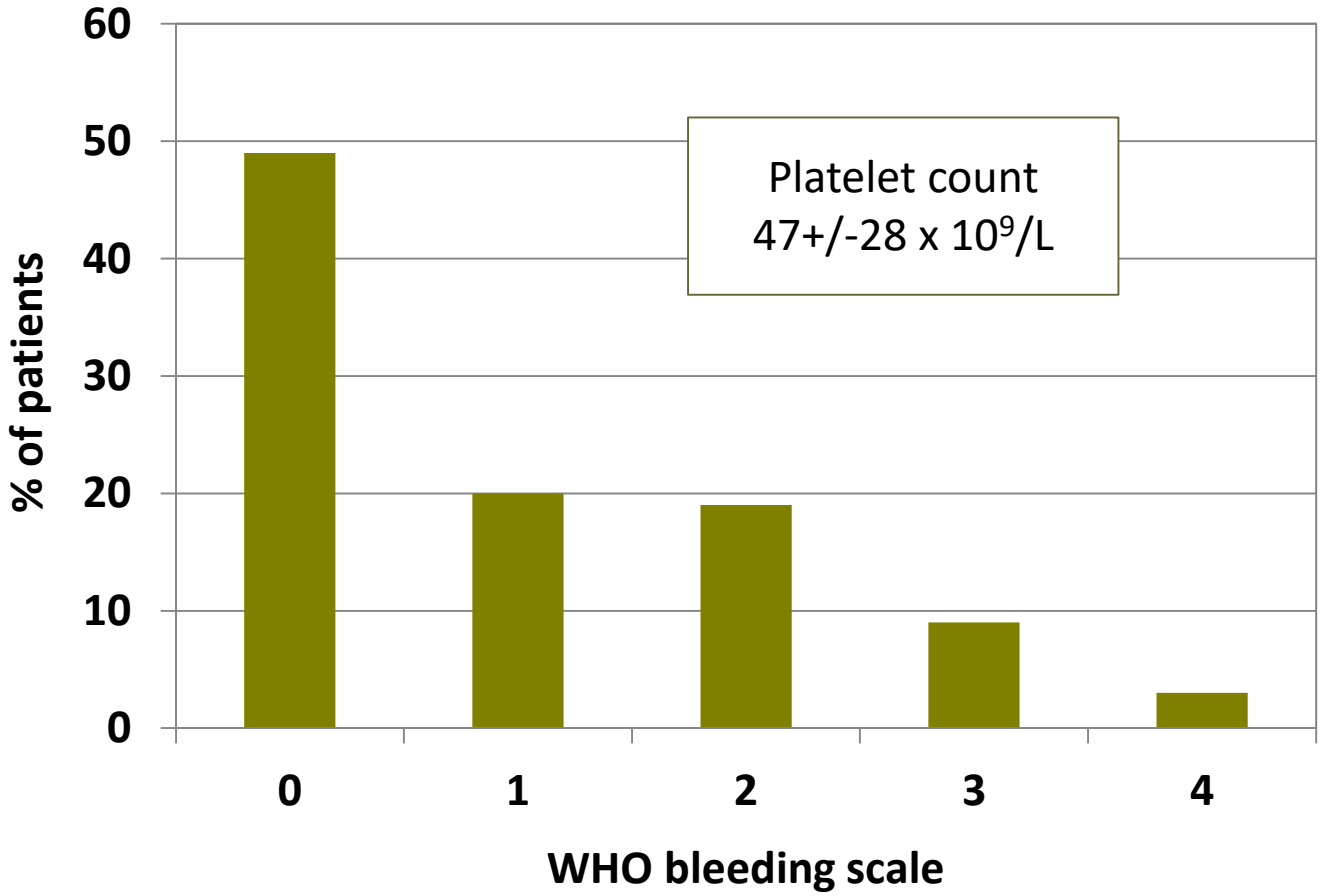
Bleeding tendency in 86 patients with *ANKRD26*-RT



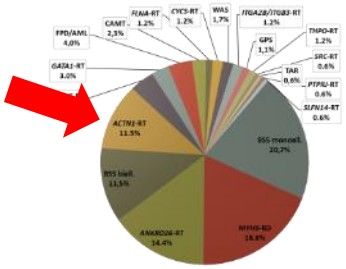
Blood 2011;117:6673-80



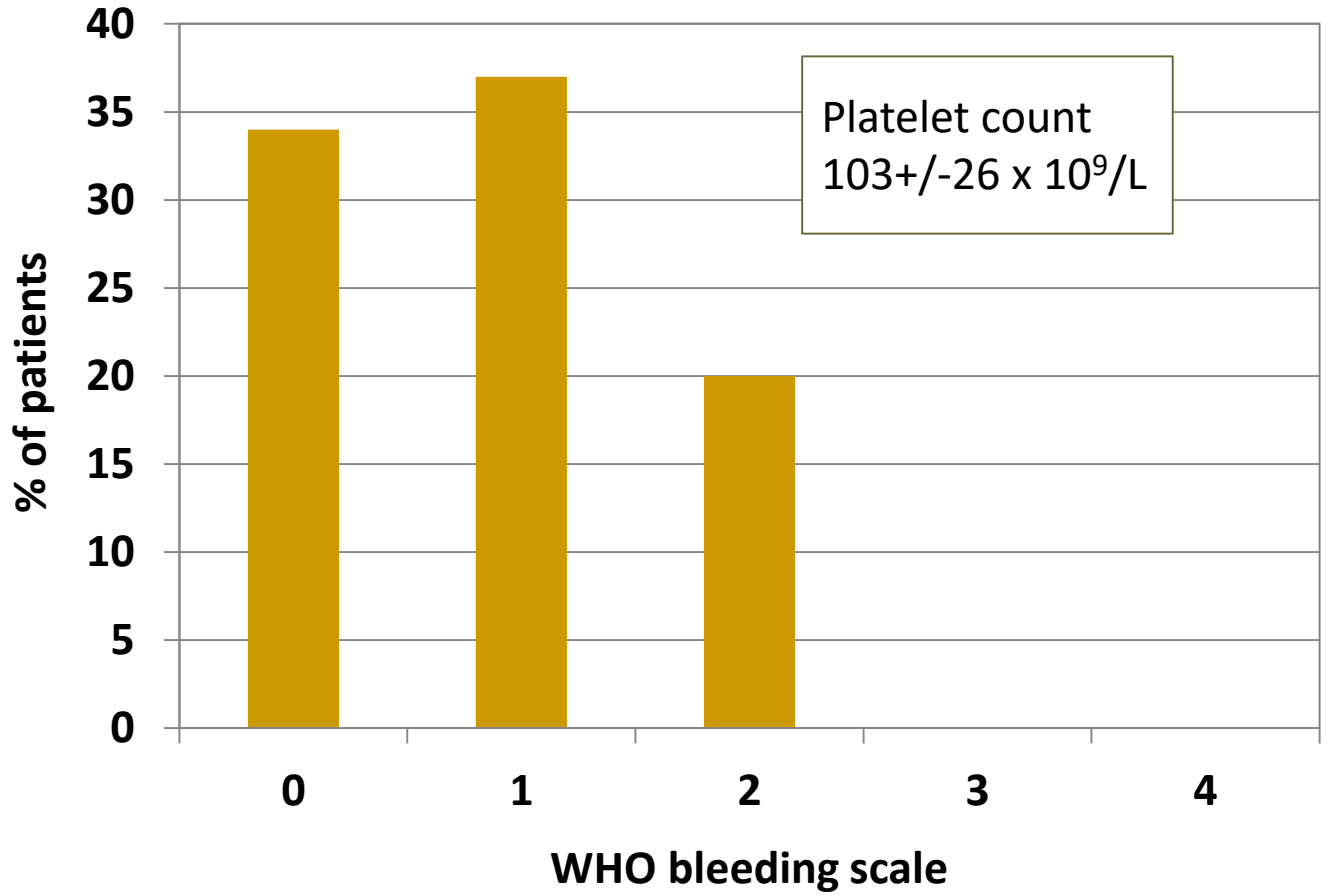
Bleeding tendency in 86 patients with *ANKRD26*-RT



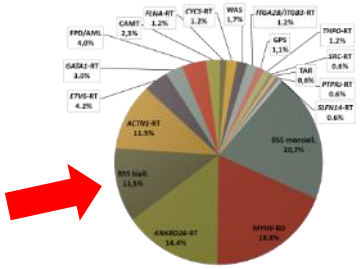
Blood 2011;117:6673-80



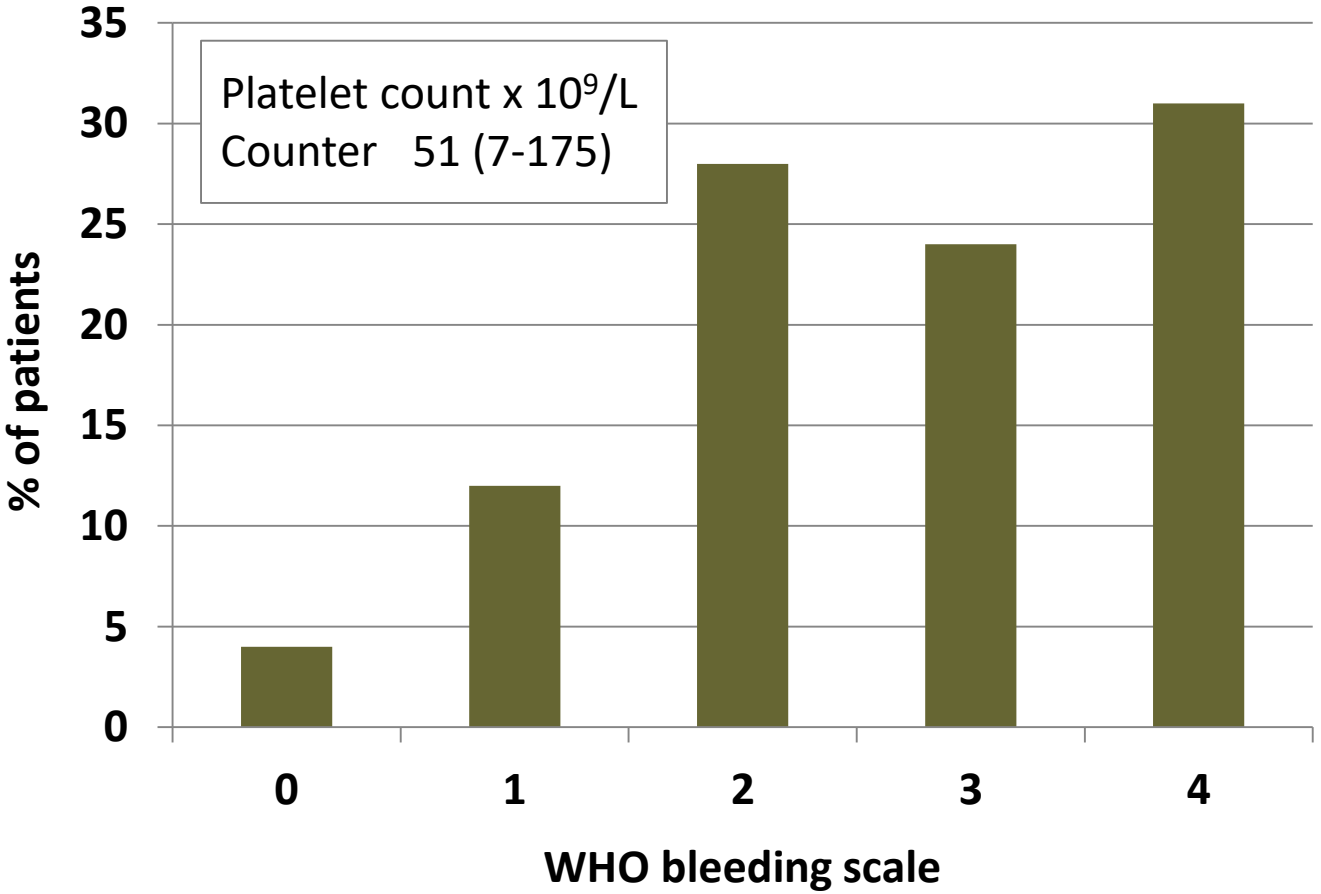
Bleeding tendency in 31 patients with *ACTN1*-RT



Blood 2015;125:869-72

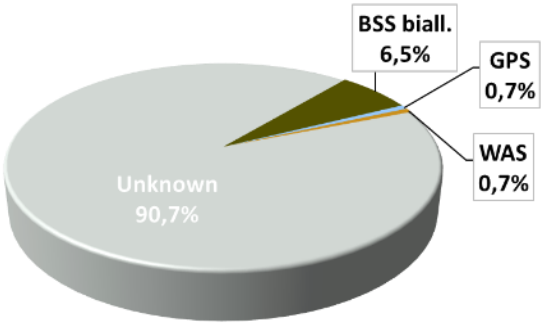


Bleeding tendency in 139 patients with biallelic Bernard-Soulier syndrome



Human Mutation 2014;35:1033-45

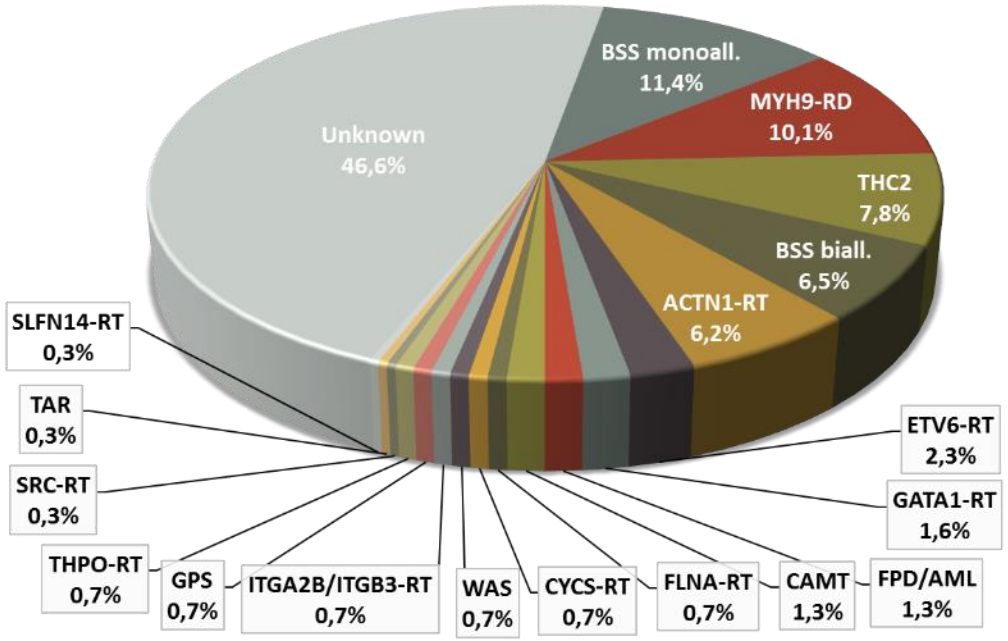
THE EVOLVING PHENOTYPE OF INHERITED THROMBOCYTOPENIAS



Few forms, all with severe bleeding tendency

2000

2022

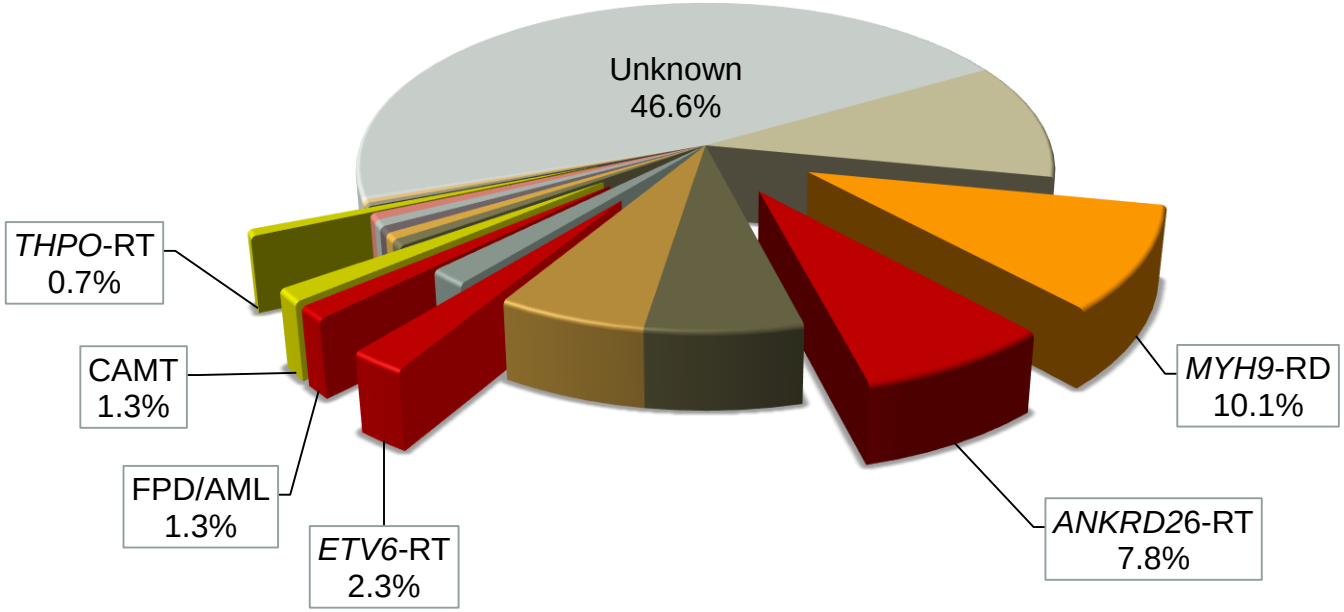


Many forms. Most patients with no or mild bleeding tendency

Inherited thrombocytopenias in 2022

- How severe is the bleeding tendency?
- Predisposition to develop additional serious illnesses
- For which forms it is mandatory to make a definite diagnosis
- Which treatments for which diseases

INHERITED THROMBOCYTOPENIAS AS PREDISPOSITION SYNDROMES: PAVIA SERIES OF 303 CONSECUTIVE FAMILIES



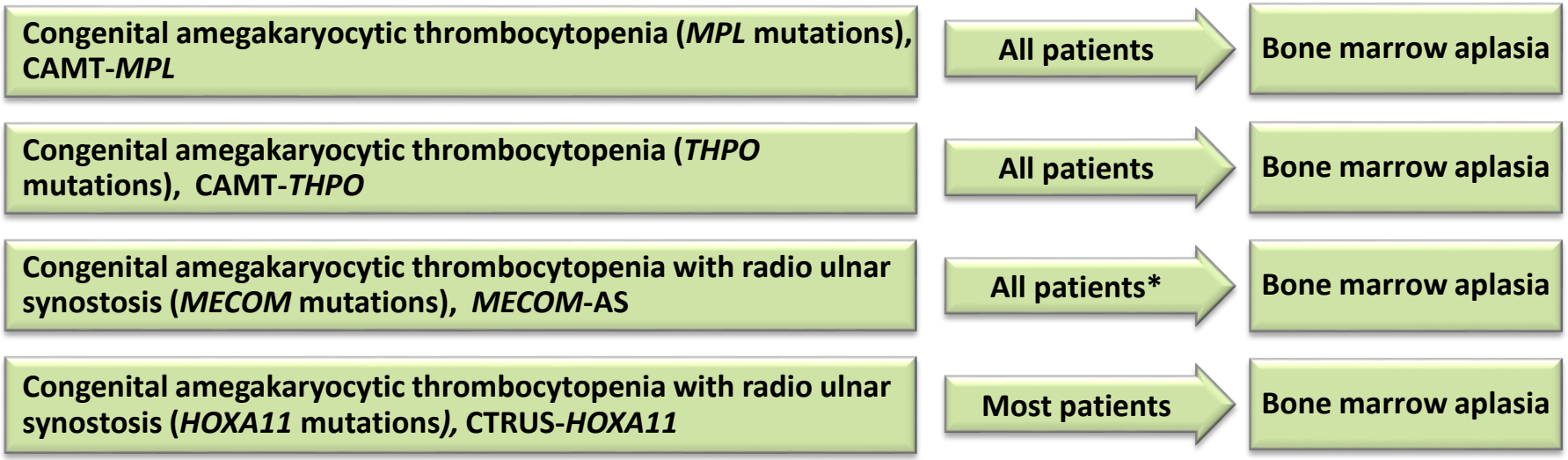
45% of patients with known ITs are at risk of life threatening disorders

Bone marrow aplasia

Hematological malignancies

Kidney failure
Deafness
Cataract

Inherited thrombocytopenias as predisposing syndromes



Inherited thrombocytopenias as predisposing syndromes

Congenital amegakaryocytic thrombocytopenia (*MPL* mutations), CAMT-*MPL*	All patients	Bone marrow aplasia
Congenital amegakaryocytic thrombocytopenia (*THPO* mutations), CAMT-*THPO*	All patients	Bone marrow aplasia
Congenital amegakaryocytic thrombocytopenia with radio ulnar synostosis (*MECOM* mutations), *MECOM*-AS	All patients*	Bone marrow aplasia
Congenital amegakaryocytic thrombocytopenia with radio ulnar synostosis (*HOXA11* mutations), CTRUS-*HOXA11*	Most patients	Bone marrow aplasia
Familial platelet disorder with propensity to acute myelogenous leukemia (*RUNX1* mutations), FPD/AML	40% of patients	Acute myeloid leukemia
ANKRD26-related thrombocytopenia (*ANKRD26* mutations), *ANKRD26*-RT	10% of patients	Acute myeloid leukemia
ETV6-related thrombocytopenia (*ETV6* mutations), *ETV6*-RT	30% of patients	Acute lymphoid/ myeloid leukemia

Inherited thrombocytopenias as predisposing syndromes

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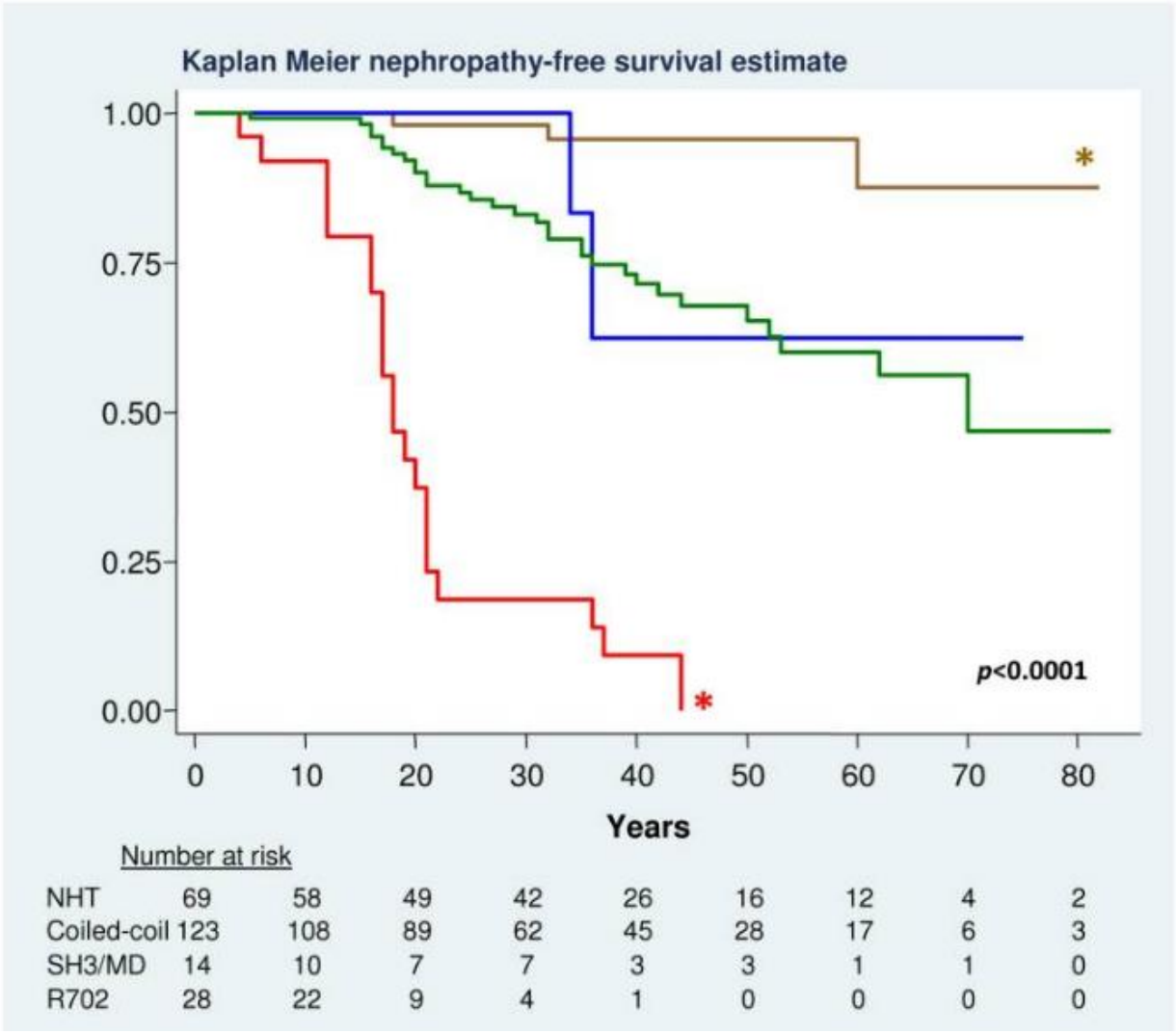
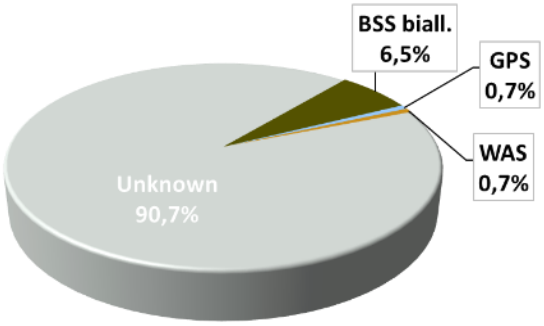
MYH9 related disease (*MYH9* mutations), *MYH9*-RD	25% of patients	Nephropathy

Occurrence of nephropathy in *MYH9*-RD (255 cases from 121 families) according to the region of NMMHC-IIA affected by mutation



Hum Mutat 2014;35:236–7

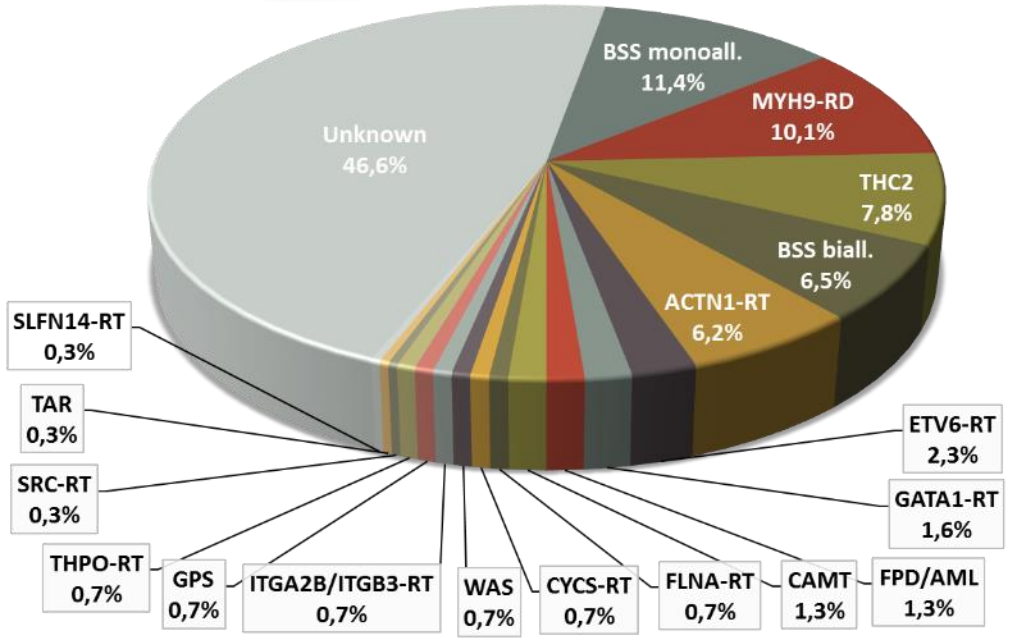
THE EVOLVING PHENOTYPE OF INHERITED THROMBOCYTOPENIAS



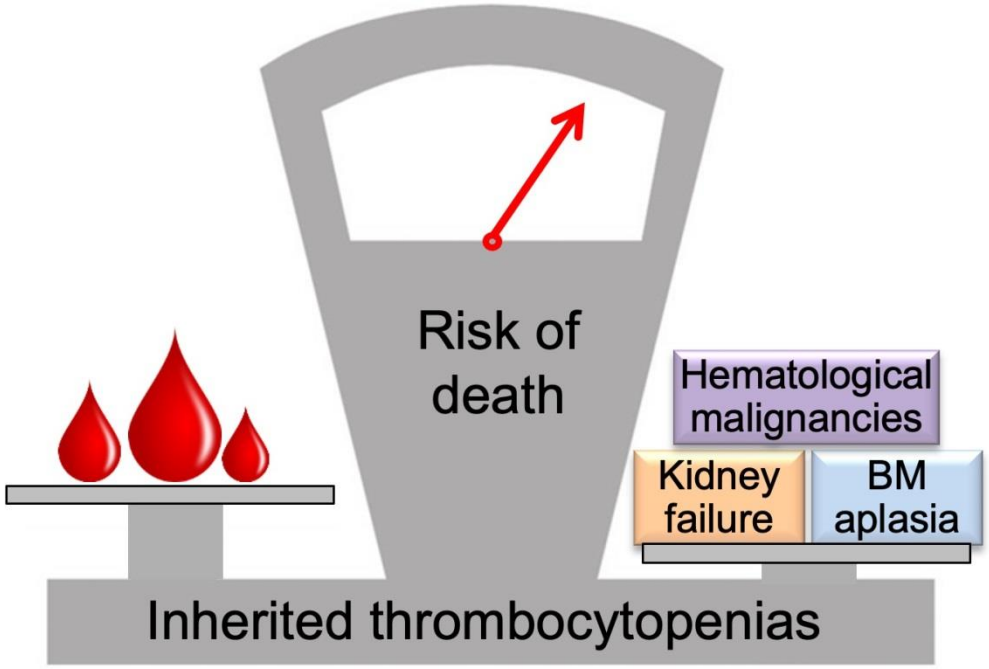
Few forms, all with severe bleeding tendency

2000

2022



Many forms. Most patients with no or very mild bleeding tendency. Many patients at risk of developing severe disorders


Risk of death
Hematological malignancies
Kidney failure
BM aplasia
Inherited thrombocytopenias

Inherited thrombocytopenias in 2022

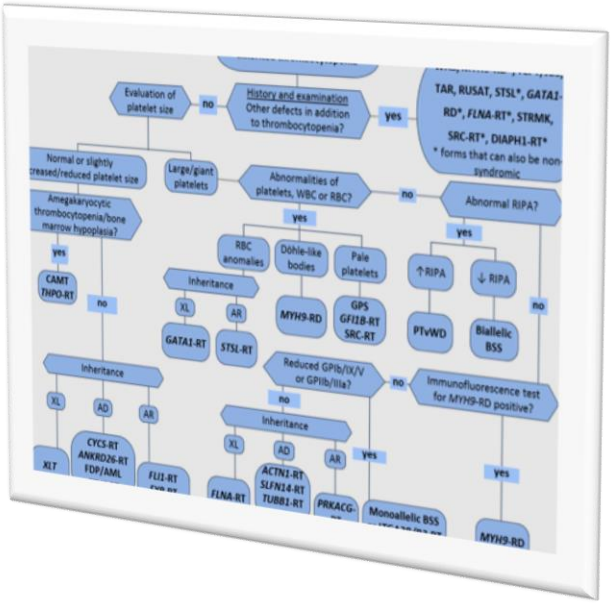
- How severe is the bleeding tendency?
- Predisposition to develop additional serious illnesses
- For which forms it is mandatory to make a definite diagnosis
- Which treatments for which diseases

INHERITED THROMBOCYTOPENIAS FOR WHOM A DEFINITE DIAGNOSIS CAN IMPROVE PATIENT PROGNOSIS (CRITICAL FORMS)

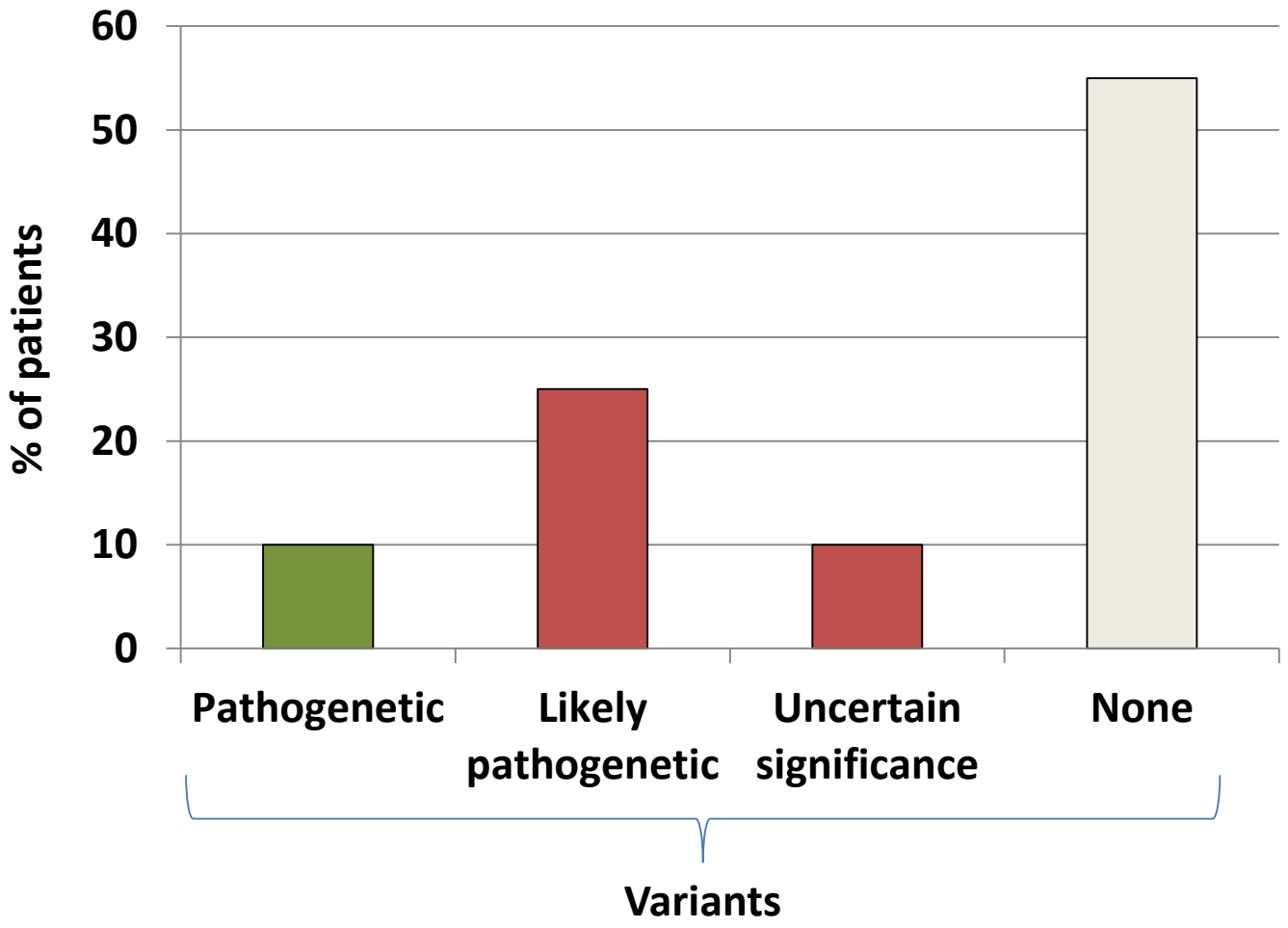
Reasons to make a precise diagnosis	ITs that benefit from a precise diagnosis
Identification of patients predisposed to develop additional severe disorders	*MYH9*-RD, FPD-AML, *ANKRD26*-RT, *ETV6*-RT, CAMT-*MPL*, CAMT-*THPO*, *MECOM*-AS, CTRUS-*HOXA11*
Identification of patients at high risk of bleeding on the occasion of hemostatic challenges in spite of a mild or moderate thrombocytopenia	bBSS, GPS, FPD-AML, *ITGA2B/ITGB3*-RT, JBS/TCPT, *SLNF14*-RT, *FLI1*-RT
Identification of patients who need early consideration for HSCT	CAMT-*MPL*, CAMT-*THPO*, WAS, *MECOM*-AS

Diagnosis of inherited thrombocytopenias:

clinical/laboratory approach or next generation sequencing?



High throughput sequencing of causative genes in 335 subjects with suspected inherited thrombocytopenia



Blood. 2019;134(23):2082-91

Exome sequencing in 116 patients with inherited thrombocytopenia that remained of unknown origin after systematic phenotype-driven diagnostic workup

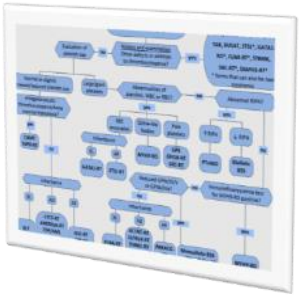
Caterina Marconi,[1*] Alessandro Pecci,[2,3*] Flavia Palombo,[1] Federica Melazzini,[2,3] Roberta Bottega,[4] Elena Nardi,[5] Valeria Bozzi,[3] Michela Faleschini,[4] Serena Barozzi,[3] Tania Giangregorio,[4] Pamela Magini,[6] Carlo L. Balduini,[2] Anna Savoia,[4,7] Marco Seri,[1,6] Patrizia Noris[2,3#] and Tommaso Pippucci[6#]

haematologica
Journal of the Ferrata Storti Foundation

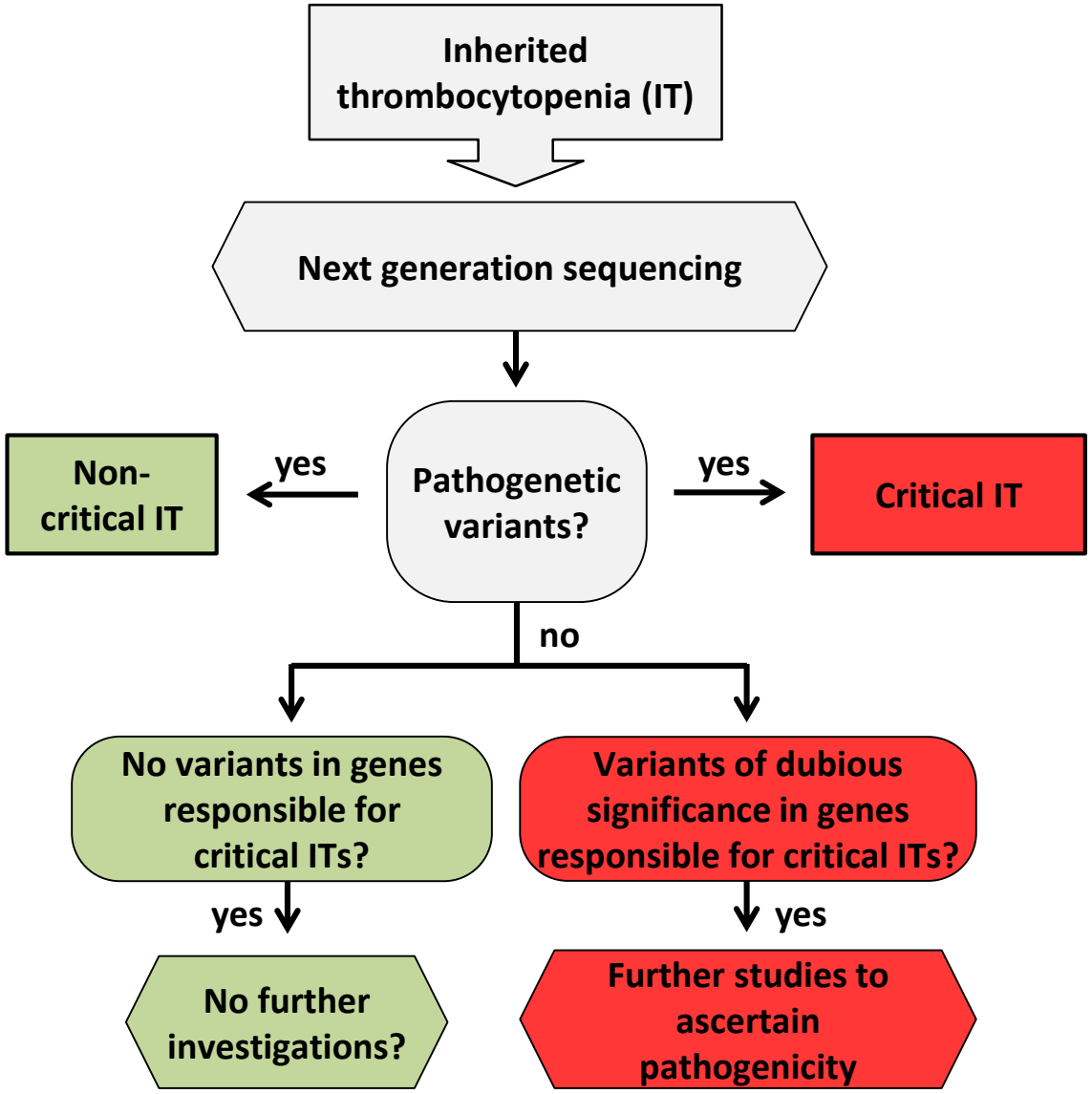
- **Discriminating between pathogenic and non-pathogenetic variants may be a major problem**

- **Next generation sequencing and clinical-laboratory approach are mutually supportive and their combination offers the best chance of reaching the right diagnosis**

+



DIAGNOSIS OF INHERITED THROMBOCYTOPENIAS IN CLINICAL PRACTICE



Inherited thrombocytopenias in 2022

- How severe is the bleeding tendency?
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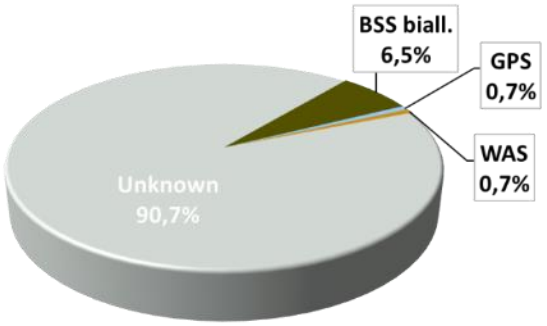
Treatment of ITs

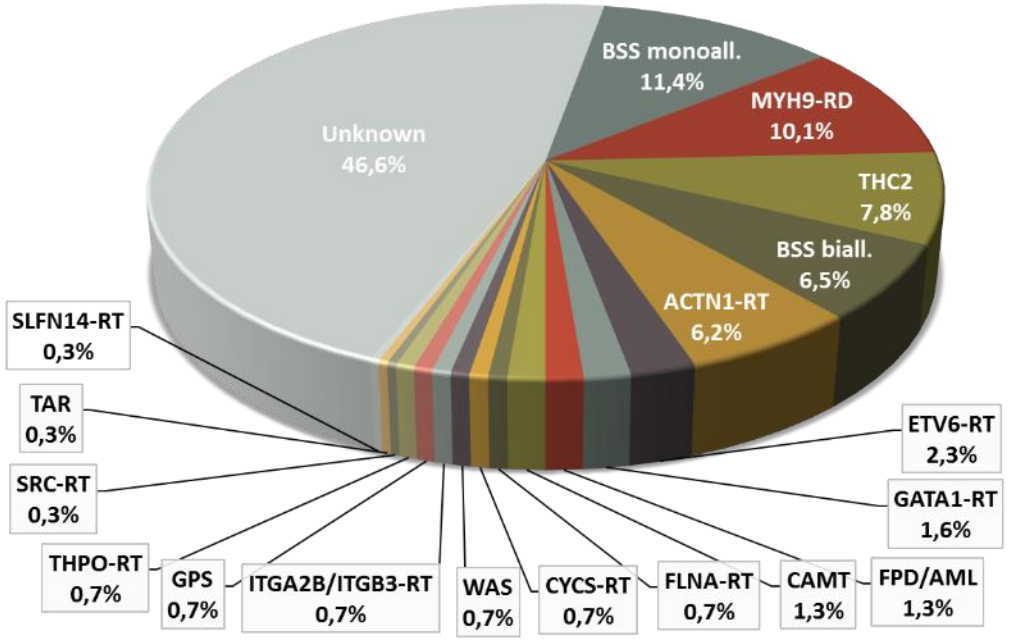


Platelet transfusion

2000

2022

?



Treatment of inherited thrombocytopenias

	Indications	Comments
Platelet transfusions	All inherited thrombocytopenias. To stop bleedings when local measures failed. To prepare patients to surgery	Leukoreduced platelet concentrates and HLA-matched donors lessen alloimmunization and refractoriness to platelet transfusion

Leukoreduction of platelet concentrates reduced alloimmunization from 45% to 17% and refractoriness from 13% to 3%
(N Engl J Med. 1997;337:1861-1869)

Consider gamma or x-irradiation of platelet concentrates in cases at risk of transfusion-associated GvHD

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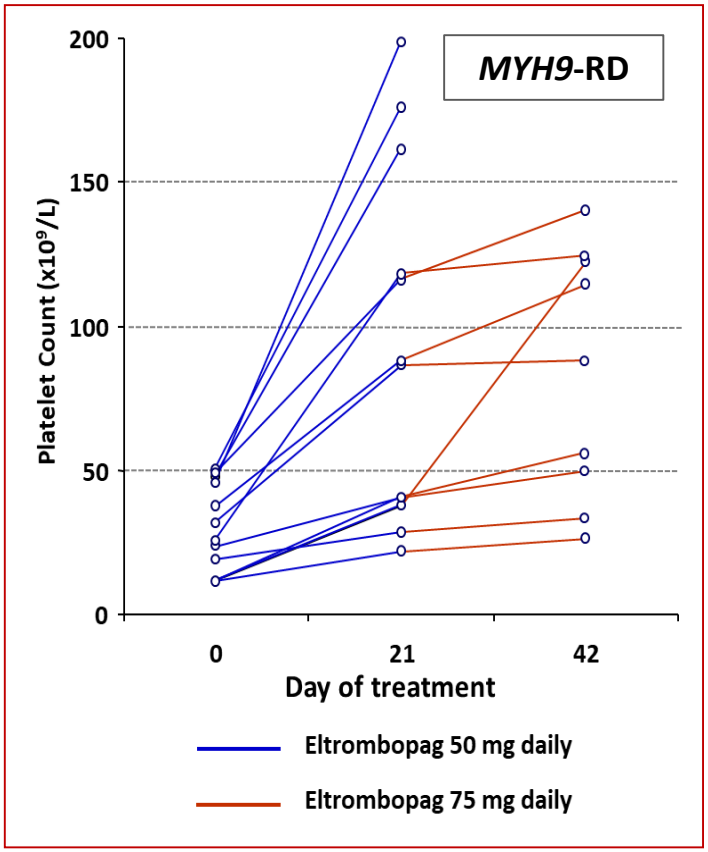
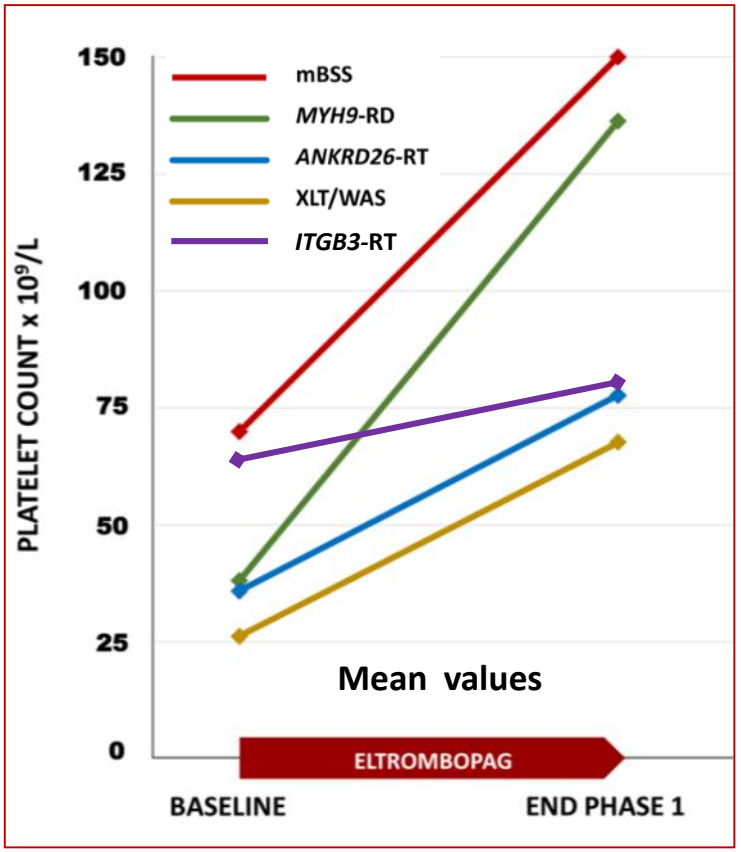
TPO-receptor agonists	❖ *MYH9*-related disease ❖ Wiskott–Aldrich syndrome/X-linked thrombocytopenia ❖ Monoallelic Bernard-Soulier syndrome ❖ *ANKRD26*-related thrombocytopenia ❖ Trombocytopenia with absent radii ❖ *DIAPH1*-related disorder	Efficacy in other conditions to be tested The efficacy and safety of long-term treatments (life-long?) remains to be demonstrated
	❖ Congenital amegakaryocytic thrombocytopenia due to *THPO* mutations	Restore entire hemopoiesis

Eltrombopag increases platelet count in inherited thrombocytopenias (at least in the forms in which it was tested)

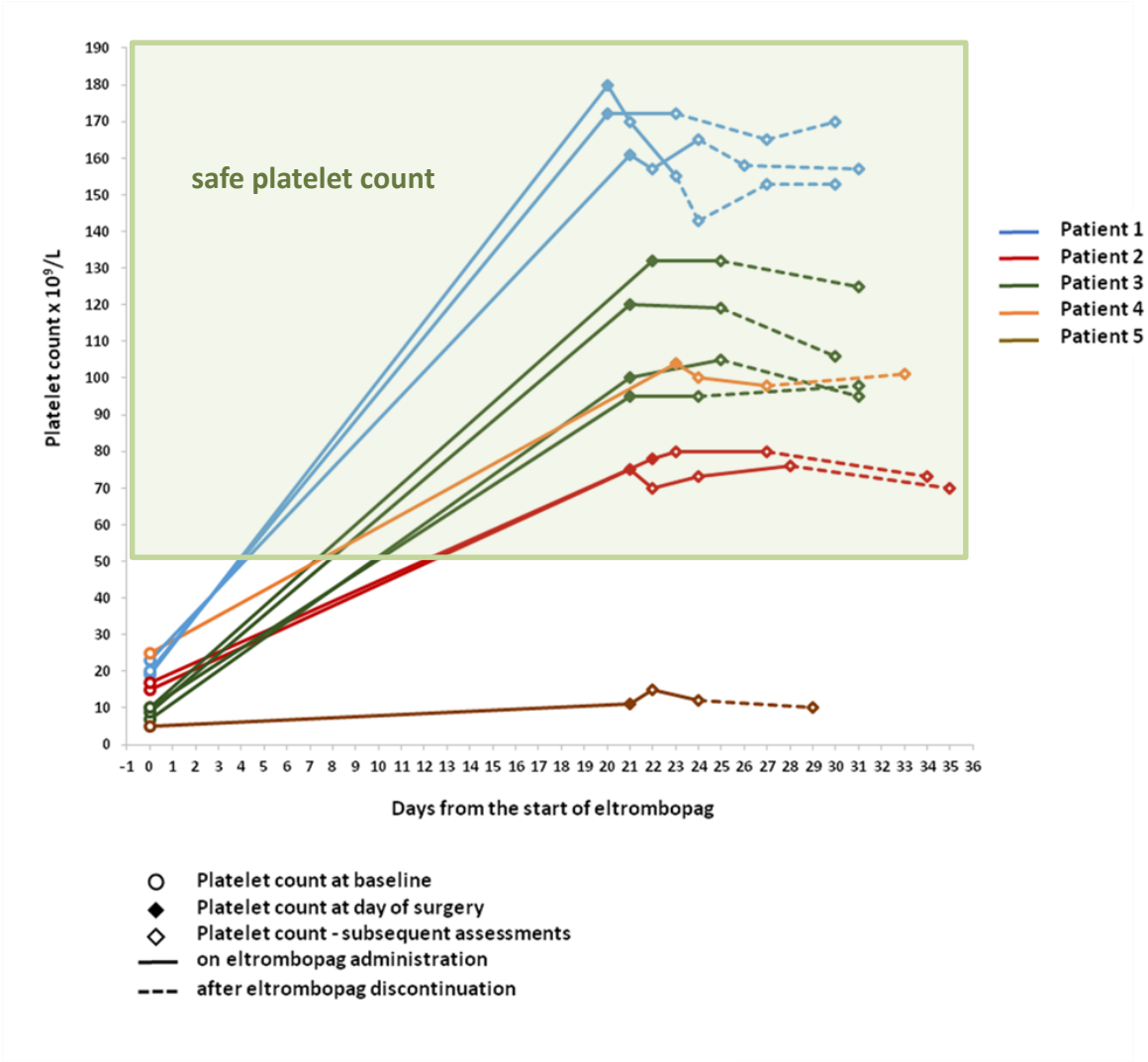




Blood 2010;116:5832-7

Haematologica 2020;105:820-8

Prospective study evaluating eltrombopag to substitute for platelet transfusion in preparation to 11 surgeries of 5 consecutive patients with severe *MYH9*-RD



Am J Hematol 2019;94:E199-E201

bjh research paper

Br J Haematol. 2021;192:366-74

Efficacy of romiplostim in treatment of thrombocytopenia in children with Wiskott–Aldrich syndrome

Retrospective analysis of romiplostim treatment in 67 children with WAS

Short term response (2-3 weeks)

33% complete response (from 30 to 247 x 10^9 plts/L)

27% partial response (from 17 to 73 x 10^9 plts/L)

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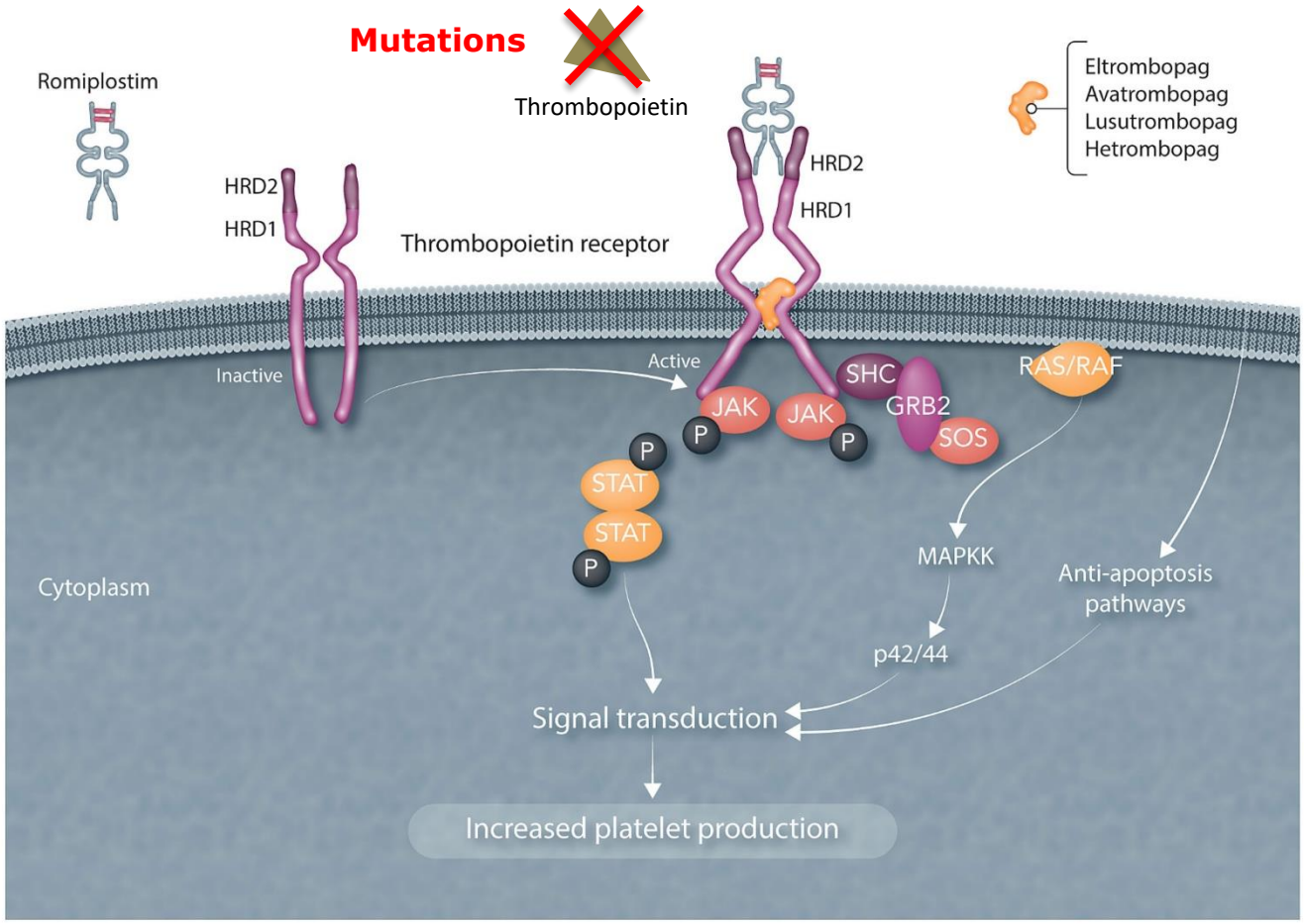
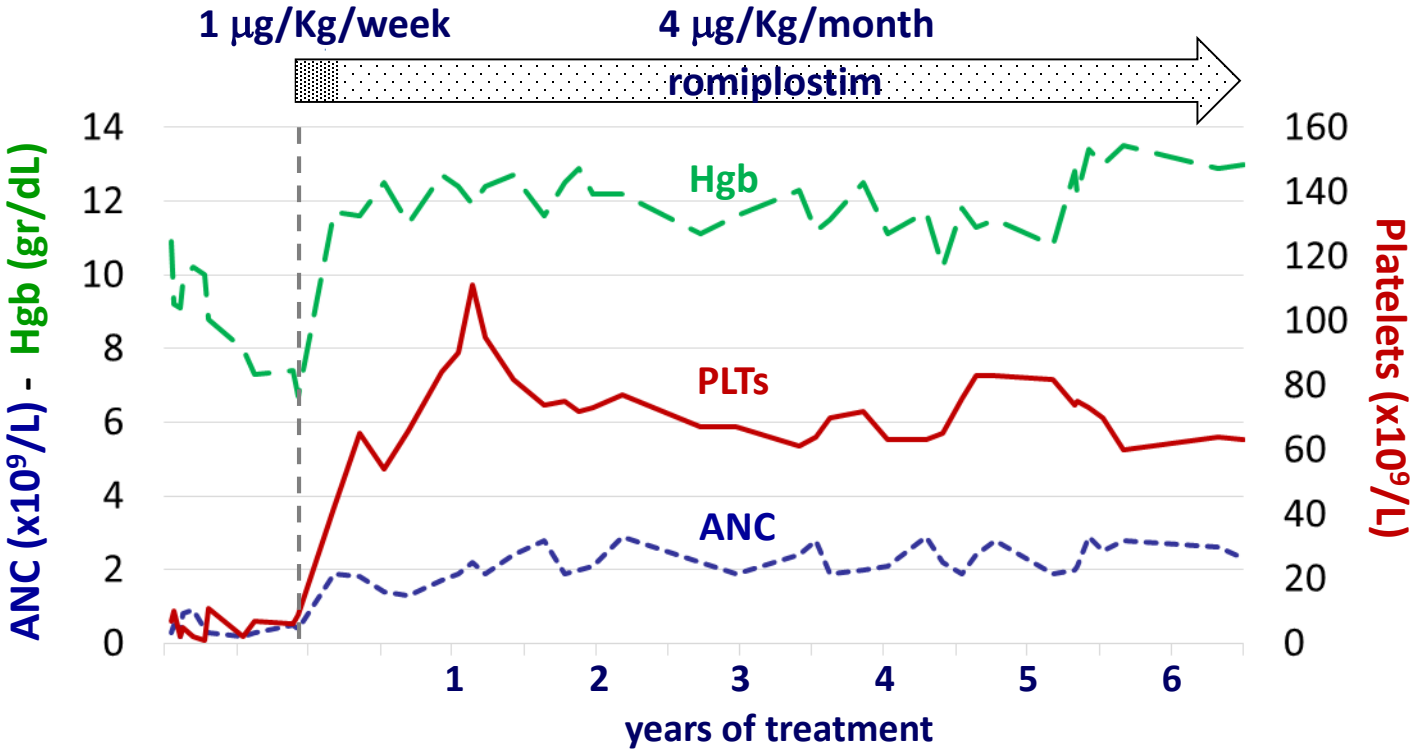
Congenital Amegakaryocytic Thrombocytopenia caused by *THPO* mutations



Romiplostim in CAMT due to *THPO* mutation



- Remission of bleeding
- Remission of infectious episodes
- Independence from RBC transfusions

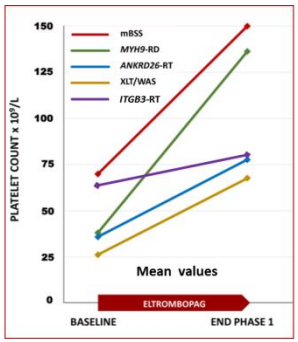
EMBO Mol Med. 2018;10:63-75

Short-term treatment with thrombopoietin receptor agonists works. Why not use these drugs for long-term treatment in patients with severe spontaneous bleeding?

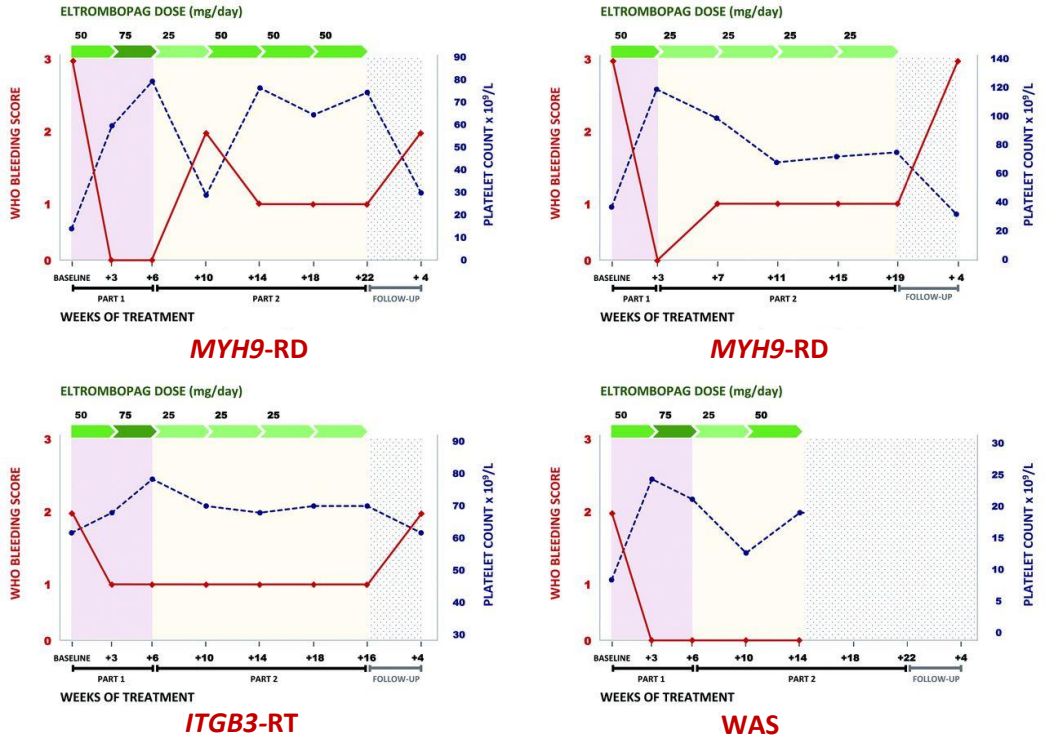
Ferrata Storti Foundation

Haematologica 2020
Volume 105(3):820-828

Eltrombopag for the treatment of inherited thrombocytopenias: a phase II clinical trial



Haematologica 2020;105:820-8



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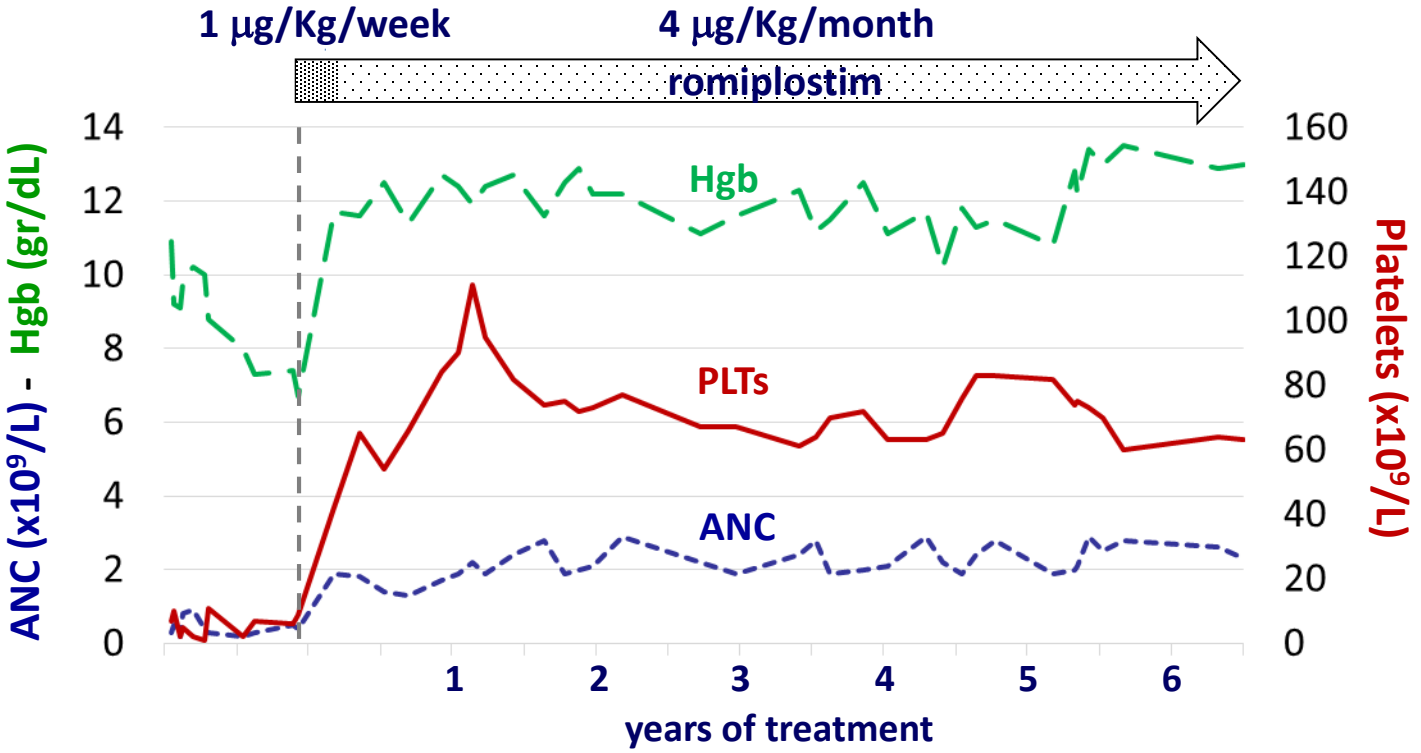
Short term response (2-3 weeks)
33% complete response (from 30 to 247 x 10^9 plts/L)
27% partial response (from 17 to 73 x 10^9 plts/L)

Long term response (1 year)
Most short-term responders (38/40) had a sustained response

Romiplostim in CAMT due to *THPO* mutation



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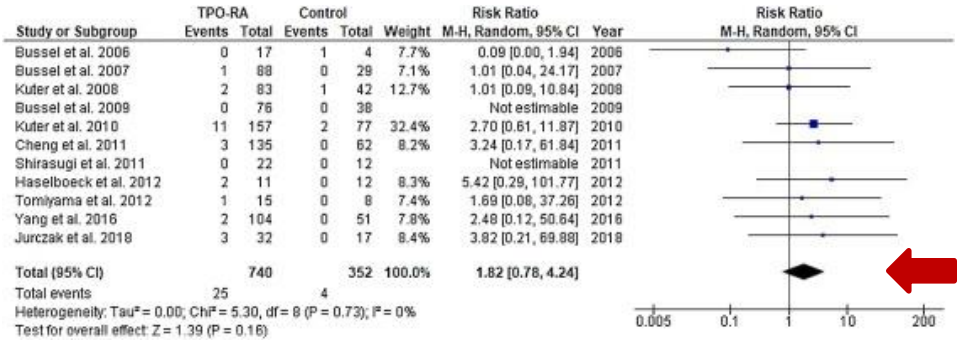
Potential risks of prolonged administration of thrombopoietin receptor agonists

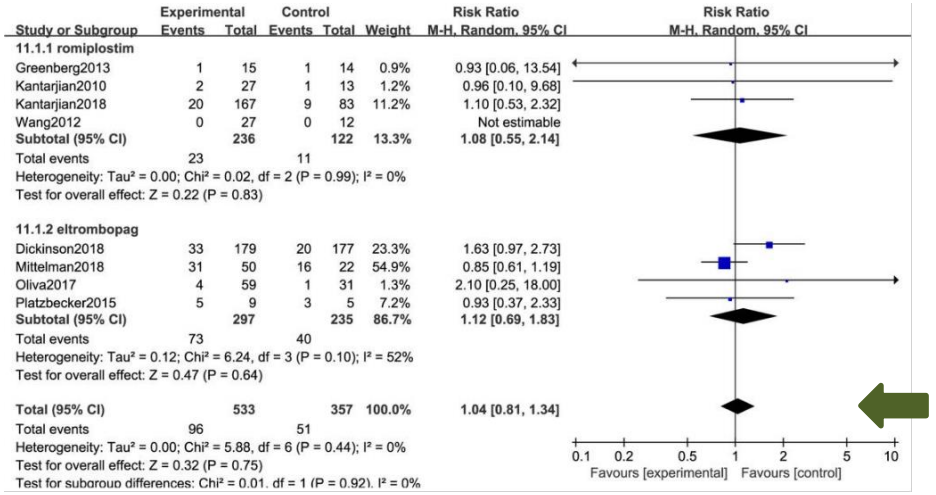
Risk of thrombosis with thrombopoietin receptor agonists for ITP patients: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2022;171:103581



Risk of thromboembolic events

RR 1.8

Safety and efficacy of eltrombopag and romiplostim in myelodysplastic syndromes: a systematic review and meta-analysis. Front Oncol. 2020;10:582686



Risk of leukemia

RR 1.04

Treatment of inherited thrombocytopenias

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Hematopoietic stem cell transplantation	❖ Wiskott–Aldrich syndrome ❖ Congenital amegakaryocytic thrombocytopenia due to *MPL* mutations ❖ *MECOM*-associated syndrome ❖ *GNE*-related disorder ❖ Severe Bernard-Soulier syndrome ❖ Gray platelet syndrome ❖ Thrombocytopenia with absent radii	Can cure patients and is the first line treatment for patients with poor prognosis

Outcome of HSCT in WAS and CAMT

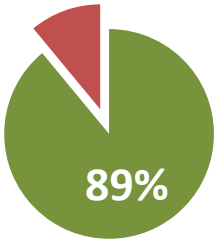
5 year survival

Better outcome

Wiskott-Aldrich syndrome

197 patients transplanted between 2006 and 2017

Blood 2022;139(13):2066-79.

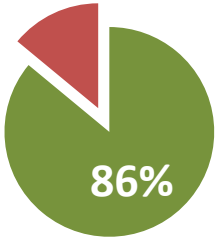


- Patients aged <5 years

Congenital amegakaryocytic thrombocytopenia-*MPL*

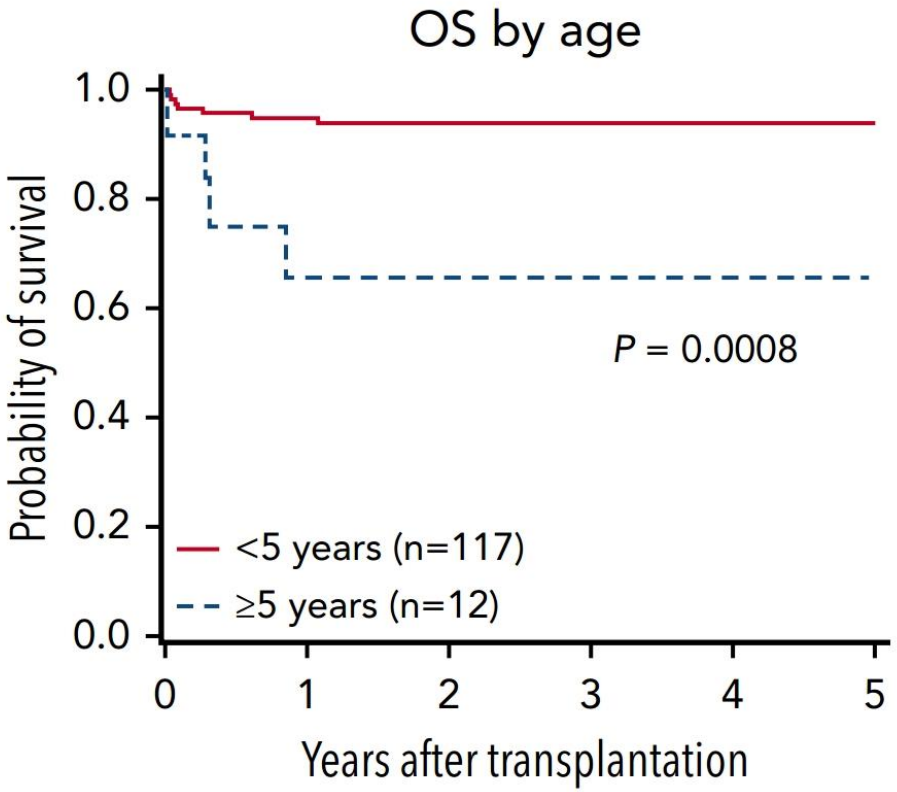
86 patients transplanted from 2000 to 2018

Transplant Cell Ther. 2022;28:101.e1-101.e6.



- diagnosis to HSCT <12 months
- HLA-matched donor

Hematopoietic stem cell transplantation in Wiskott-Aldrich syndrome



Blood 2020;135:2094-2105

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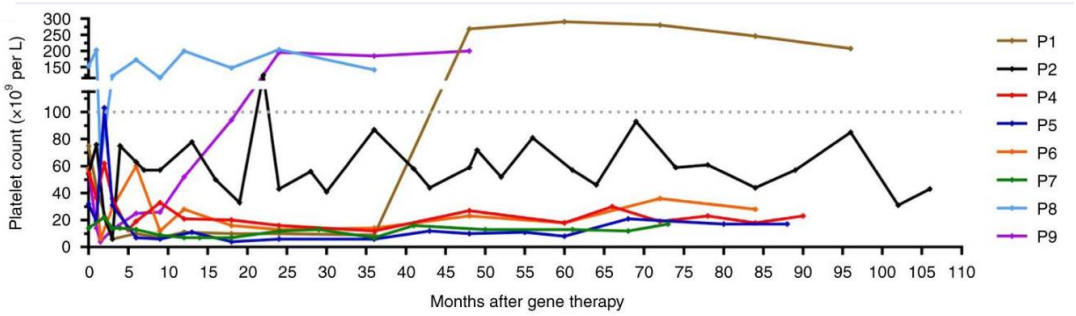
Hematopoietic stem cell transplantation	❖ Wiskott–Aldrich syndrome ❖ Congenital amegakaryocytic thrombocytopenia -*MPL* mutation ❖ *MECOM*-associated syndrome ❖ *GNE*-related disorder ❖ Severe Bernard-Soulier syndrome ❖ Gray platelet syndrome ❖ Thrombocytopenia with absent radii	Can cure patients and is the first line treatment for patients with poor prognosis
Gene therapy	❖ Wiskott–Aldrich syndrome	Can cure patients. Efficacy in other conditions not yet tested

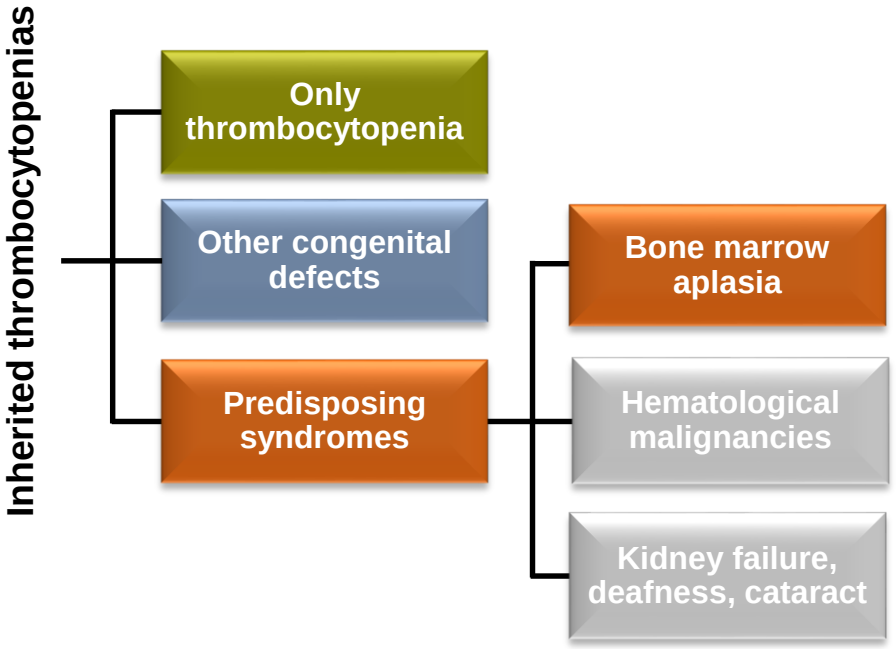
Gene therapy for Wiskott Aldrich syndrome

Gene therapy with γ-retroviral vector (Sci Transl Med. 2014;6:227ra33)
Correction of WAS protein expression in 9 of 10 patients, with partial or complete resolution of immunodeficiency, autoimmunity, and bleeding diathesis. Seven patients developed acute leukemia.

Gene therapy with lentiviral vector (*Nat Med*. 2022;28:71-80)
Correction of WAS protein expression in 8 patients, with partial or complete resolution of immunodeficiency, autoimmunity, and bleeding diathesis after a median follow-up of 7.6 years. Platelet count normalized in only 3 subjects, in 2 after splenectomy.



How to manage ITs predisposing to other disorders



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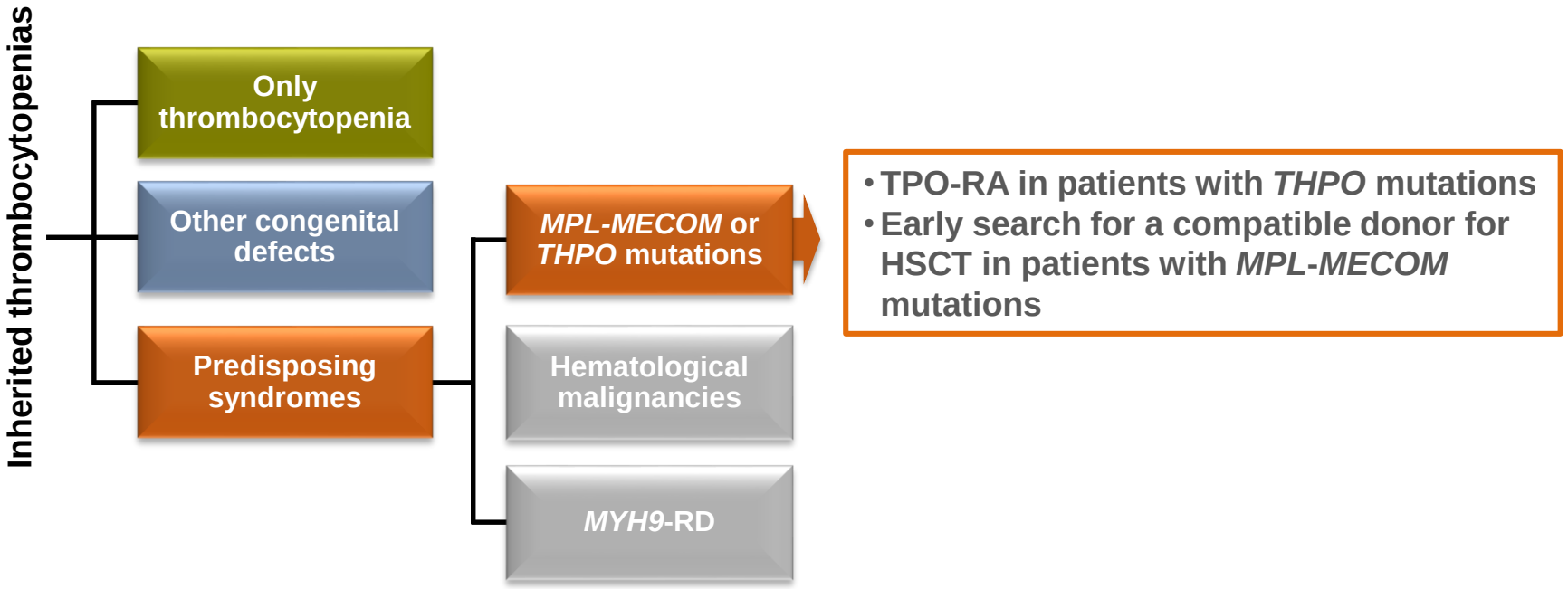
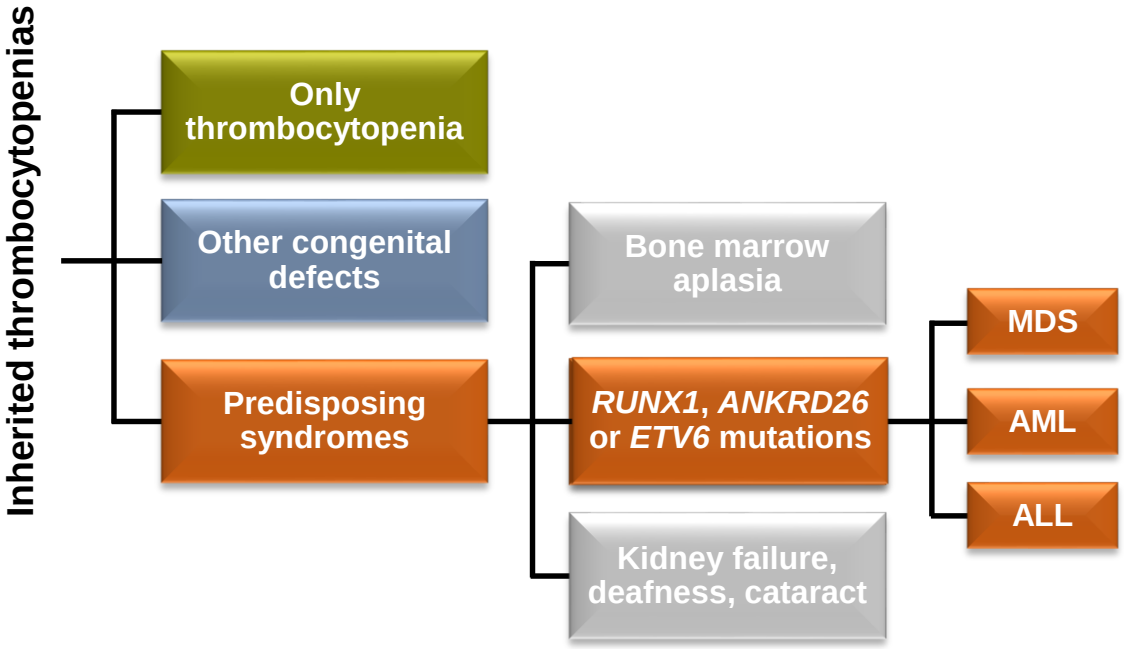


Classification of ITs



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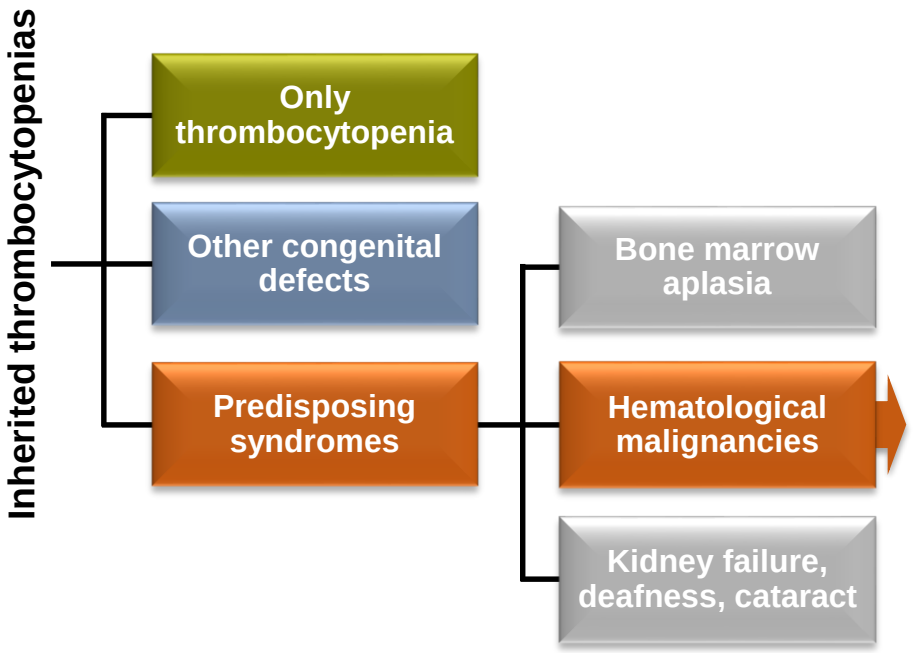


AT DIAGNOSIS

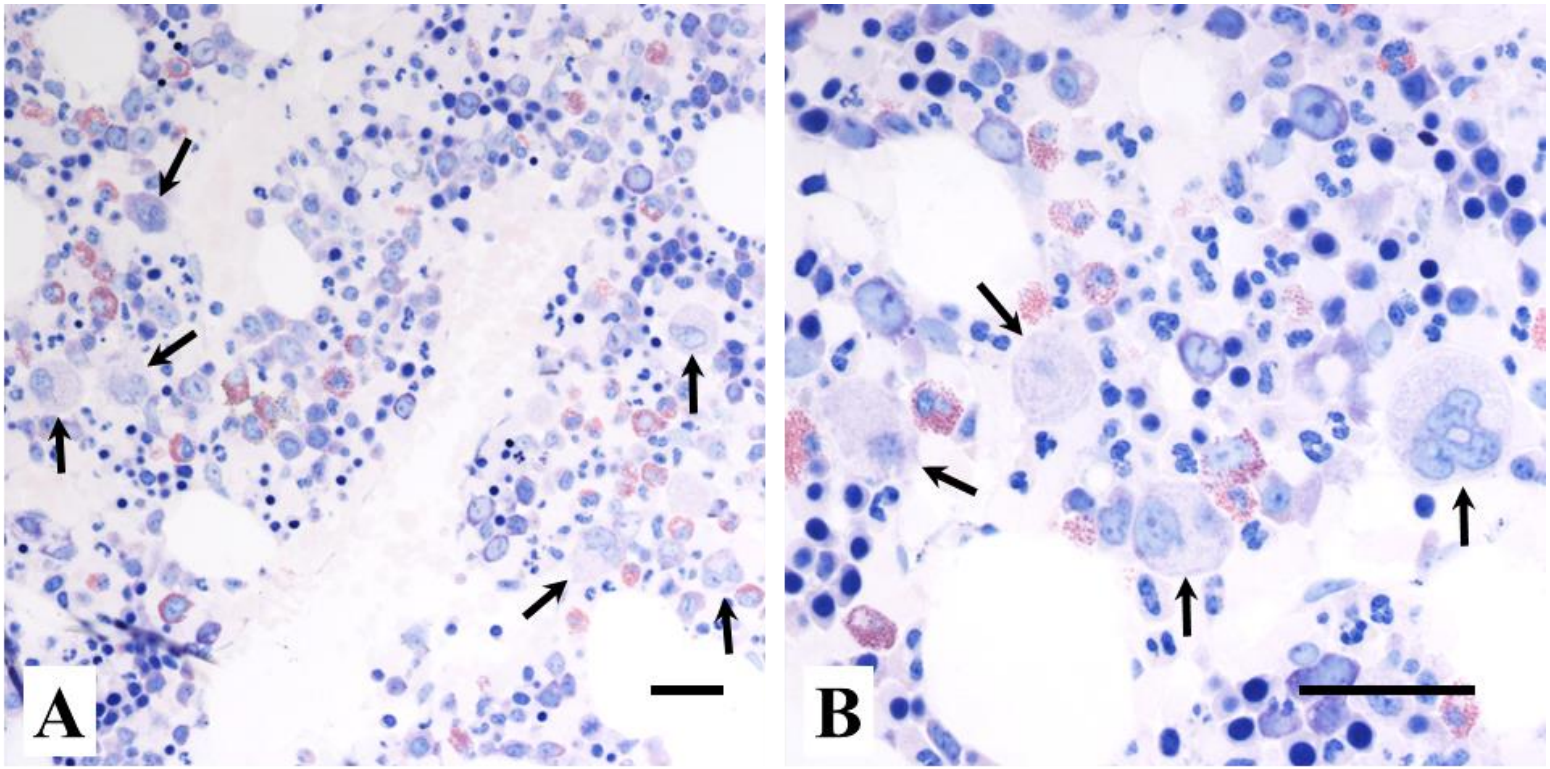
- Genetic counseling
- Physical examination
- CBC with differential
- Blood smear examination
- Bone marrow examination with cytogenetic analysis

EVERY 6-12 MONTHS

- Physical examination
- CBC with differential
- Blood smear examination
  - ↓ any change
- Bone marrow examination with cytogenetic analysis

ANKRD26-related thrombocytopenia (THC2)

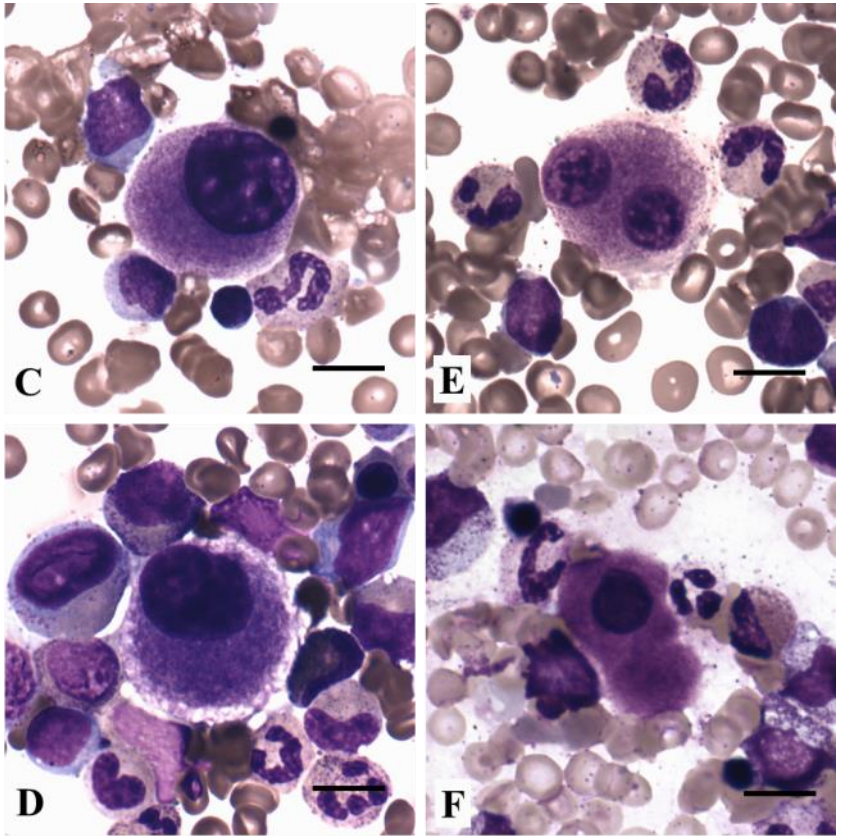
Bone marrow biopsy



Blood 2011;117:6673-80

ANKRD26-related thrombocytopenia (THC2)

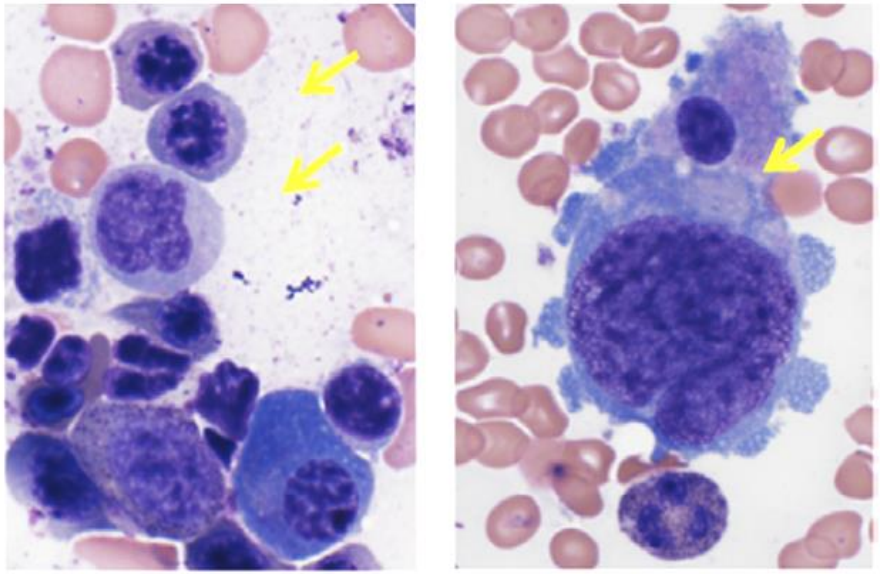
Bone marrow touch preparation



Blood 2011;117:6673-80

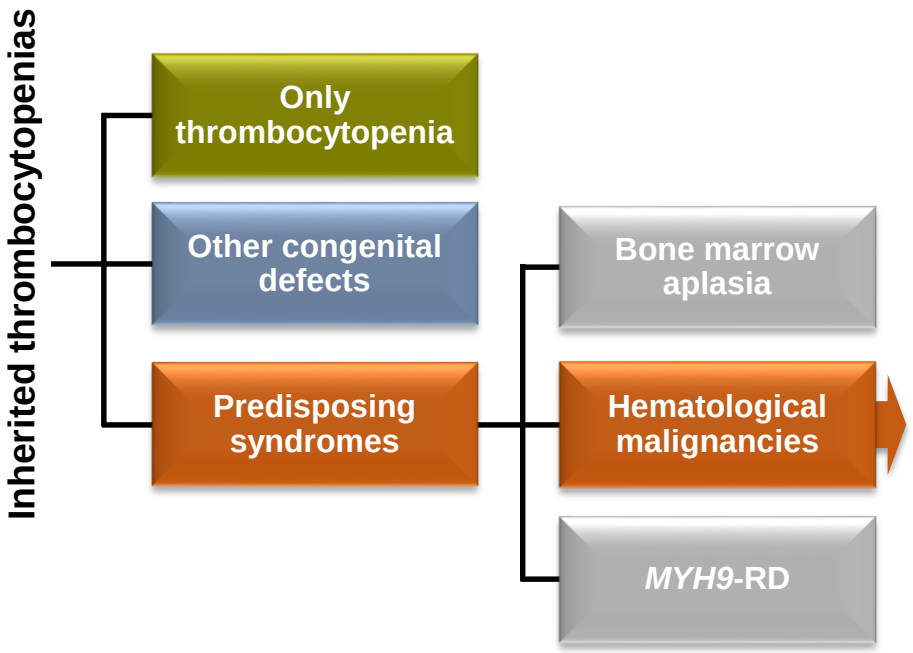
ETV6-related thrombocytopenia

Bone marrow touch preparation



Nat Genet 2015;47:535-8

How to manage ITs predisposing to other disorders



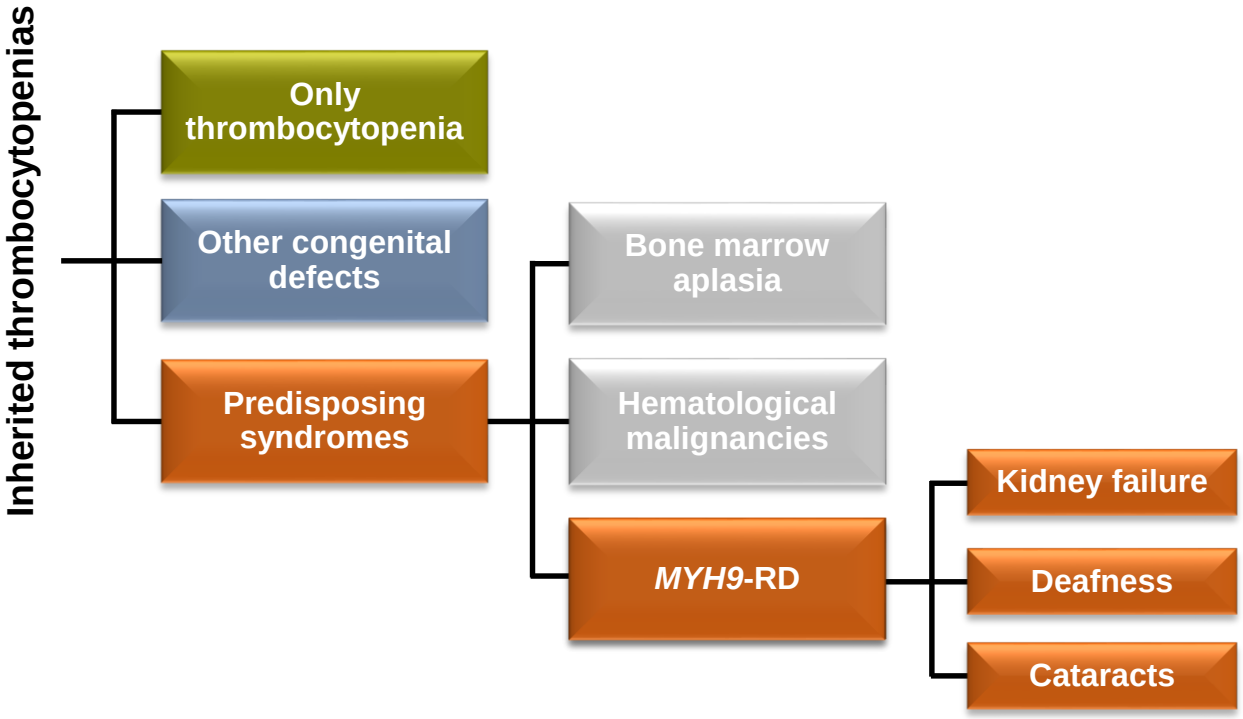
AT DIAGNOSIS

- Genetic counseling
- Physical examination
- CBC with differential
- Blood smear examination
- Bone marrow examination with cytogenetic analysis

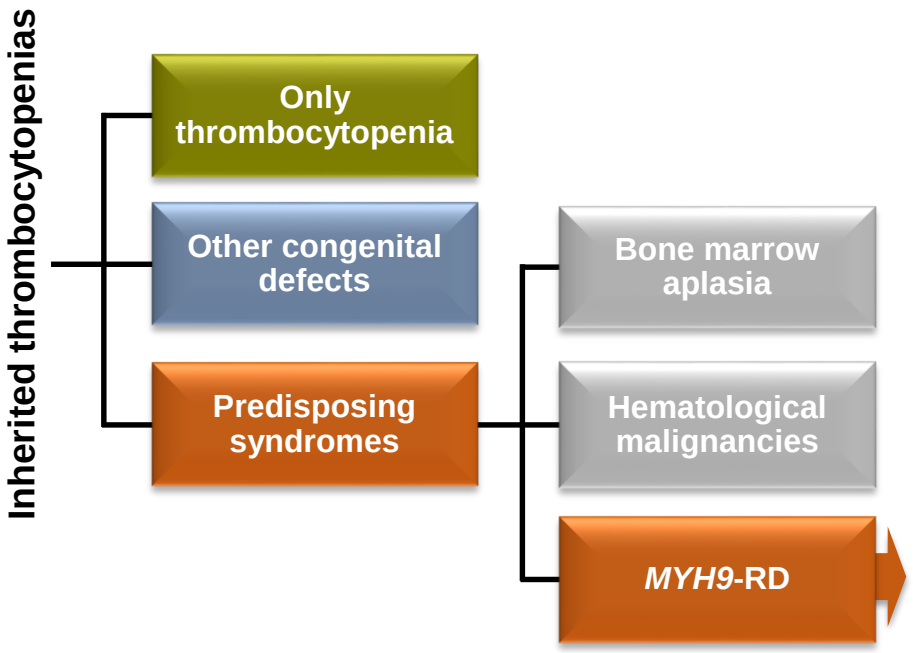
EVERY 6-12 MONTHS

- Physical examination
- CBC with differential
- Blood smear examination
  - ↓ any change
- Bone marrow examination with cytogenetic analysis
  - ↓ evolution towards leukemia
- In case of HSCT from a related donor: mutation screening

Classification of ITs



How to manage ITs predisposing to other disorders



GENERAL RECOMMENDATIONS

Avoid drugs and situations that could damage kidney and/or hearing function

KIDNEY

Search for proteinuria at regular intervals: in patients at high-risk of nephropathy every 6-12 months since the diagnosis

EAR

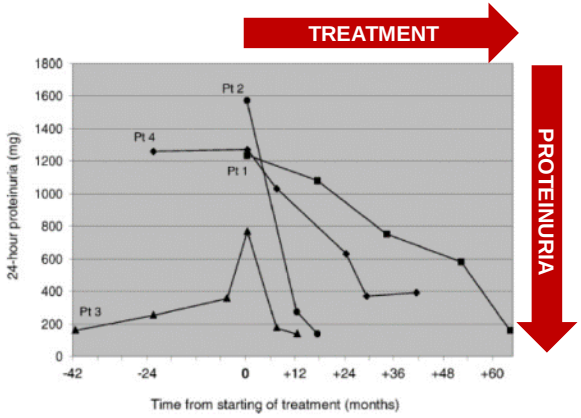
Monitor for sensorineural deafness by audiometric examination

EYES

Monitor for cataract by ophthalmological examination

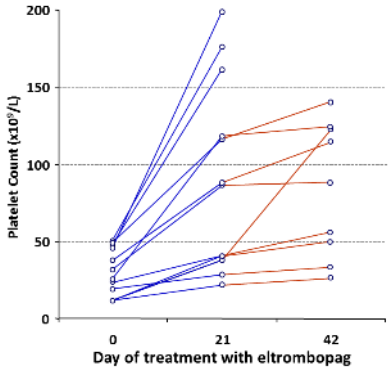
How to manage ITs predisposing to other disorders: *MYH9*-RD

Renin-angiotensin system blockade
reduces proteinuria of patients with progressive nephropathy
(*Nephrol Dial Transplant 2008;23:2690-2)*

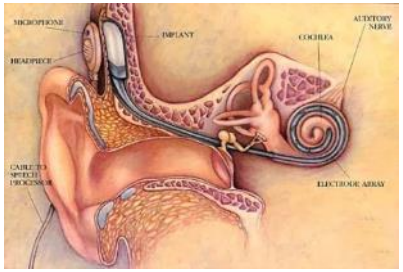


Cataract surgery

TPO-RAs
increase platelet count

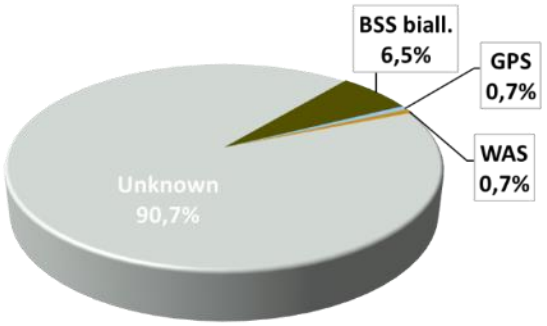


Cochlear implant
restores hearing in patients with severe deafness
(*Orphanet J Rare Dis 2014;9:100*)



We have effective treatments for all the defects of *MYH9*-RD!

Treatment of ITs

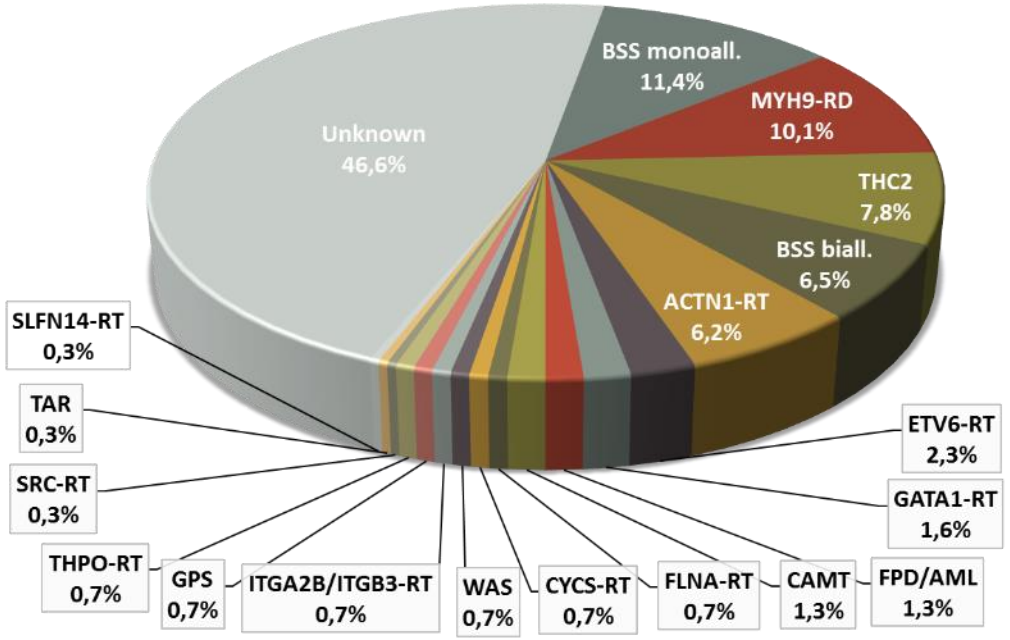


Platelet transfusion

2000

2022

Personalized treatments



LA JOURNÉE ANNUELLE DU CRPP

28 NOVEMBRE 2022
AMPHITHÉATHRE CERIMED-FACULTÉ DE MÉDECINE
27 BD JEAN MOULIN 13005 MARSEILLE
9H30 À 16H30

Inherited Thrombocytopenias and Their Therapy

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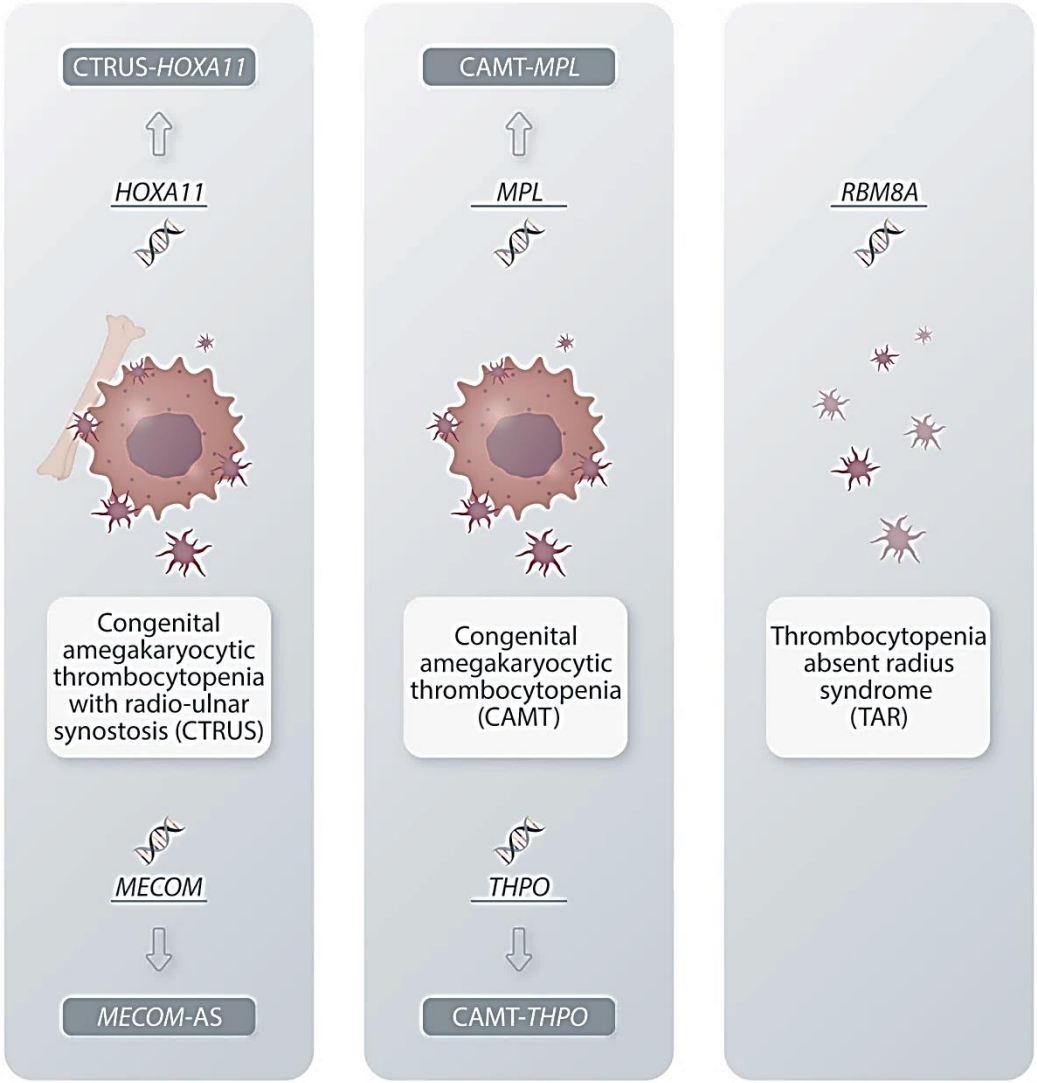
Ferrata-Storti Foundation - University of Pavia
Pavia, Italy

New names for congenital amegakaryocytic thrombocytopenias



Haematologica, Early view Oct 13, 2022

HemaSphere
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Perspective
OPEN ACCESS

The EHA Research Roadmap: Platelet Disorders

Carlo Balduini[1], Kathleen Freson[2], Andreas Greinacher[3], Paolo Gresele[4], Thomas Kühne[5], Marie Scully[6], Tamam Bakchoul[7], Paul Coppo[8], Tadeja Dovc Drnovsek[9], Bertrand Godeau[10], Yves Gruel[11], A. Koneti Rao[12], Johanna A. Kremer Hovinga[13], Michael Makris[14], Axel Matzdorff[15], Andrew Mumford[16], Alessandro Pecci[17], Hana Raslova[18], José Rivera[19], Irene Roberts[20], Rüdiger E. Scharf[21], John W. Semple[22], Christel Van Geet[23]

Congenital platelet disorders

- **To evaluate single-step NGS as the first-line diagnostic approach for congenital platelet disorders.**
- **To identify genotype/phenotype correlations.**
- **To evaluate the efficacy TPO-RA and identify drugs with TPO-independent action.**

Acquired nonimmune thrombocytopenia and acquired disorders of platelet function

- To clarify the clinical relevance of acquired platelet disorders in chronic liver and kidney disease.
- To define the clinical relevance of drug-induced platelet dysfunction in surgery/invasive procedures.
- To identify tests for distinguisching between immune- and non-immune thrombocytopenia.

Primary and secondary immune thrombocytopenia and fetal neonatal alloimmune thrombocytopenia

- To understand the immune pathophysiology of ITP for developing novel therapies.
- To define the role of screening for FNAIT.
- To better use the drugs we already have.

Heparin-induced thrombocytopenia and other drug-dependent immune thrombocytopenias

- To better understand the pathogenesis of DITPs for developing "safe drugs".
- To improve the diagnostic methods for DITPs.

Thrombotic thrombocytopenic purpura and other thrombotic microangiopathies

- To evaluate recombinant ADAMTS 13 in iTTP and cTTP.
- To understand the long-term impact of TTP-cognitive symptoms.
- To address the diagnostic and therapeutic unmet needs of thrombotic microangiopathies associated with specific conditions

Summary box: Main research & policy priorities

- **To perform clinical studies for improving diagnostic and therapeutic strategies for inherited platelet disorders.**
- **To define the clinical relevance and best management of acquired nonimmune thrombocytopenias and acquired disorders of platelet function.**
- **To develop new tools to define prognosis and personalize treatment of patients with immune-mediated forms of thrombocytopenia.**
- **To better understand the pathogenesis of drug-induced immune thrombocytopenias and develop simple diagnostic methods.**
- **To optimize the therapeutic approach to thrombotic thrombocytopenic purpura with particular attention to secondary forms with poor prognosis.**