Webinars

Constitutional thrombocytopenia

EuroBloodNet

Suspecting inherited thrombocytopenia

Maria L Lozano
Department of Hematology
Hospital General Universitario Morales Meseguer
University of Murcia
Murcia– Spain

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ERN-EuroBloodNet Topic on Focus: Constitutional thrombocytopenia

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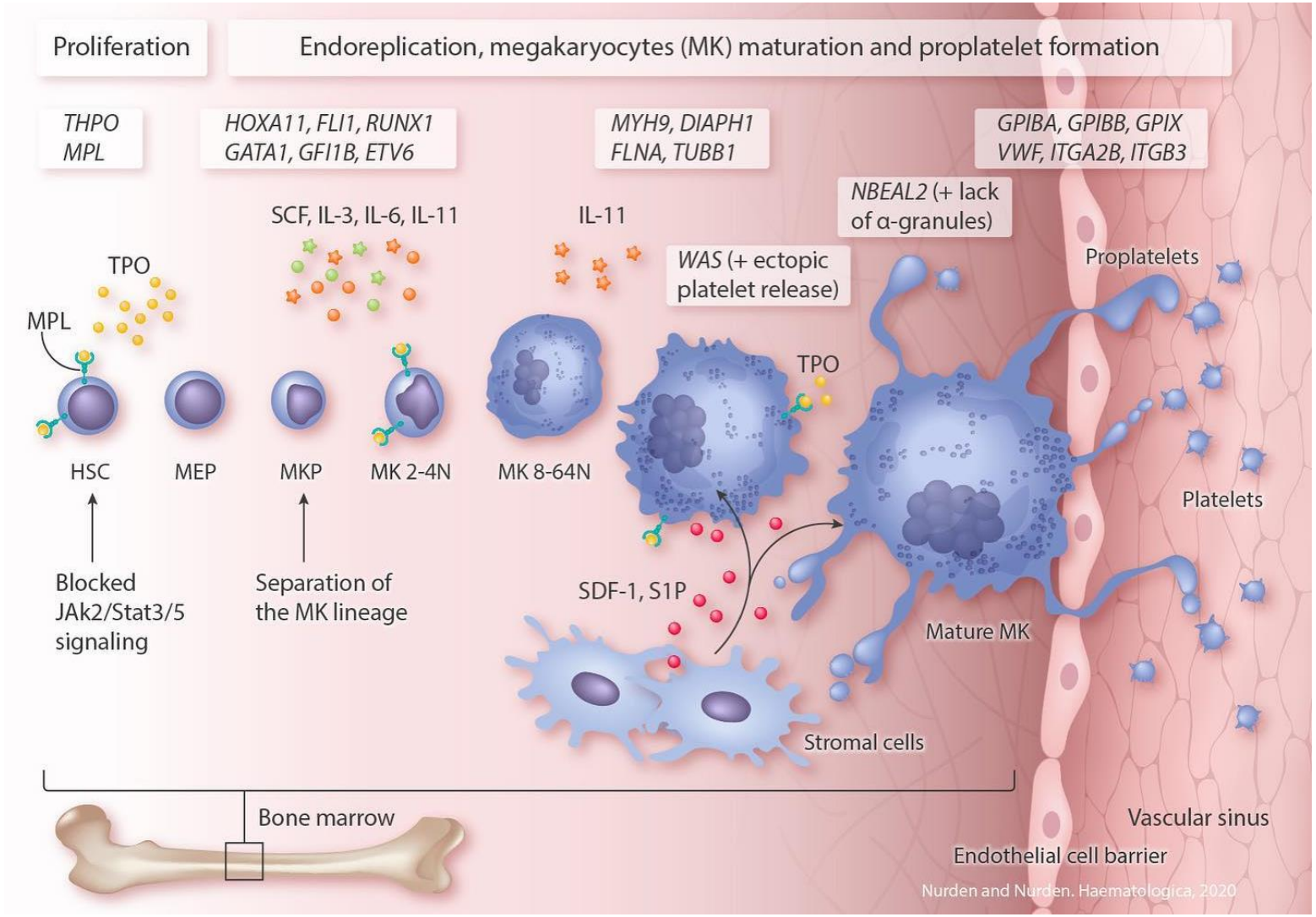
Conflicts of interest

Research support/PI	Amgen
Employee	-
Consultant / Honoraria	Amgen, Argenx, Grifols, Novartis, Sobi, UCB
Major stockholder	-
Speaker's fees	Amgen, Grifols, Novartis, Sobi
Scientific advisory board	Amgen, Argenx, Grifols, Novartis, Sobi, UCB

Learning objectives of the webinar

1. Become familiar with the major types of inherited thrombocytopenia and their variable presentation.
2. Avoid misdiagnosis of inherited thrombocytopenia with immune thrombocytopenia
3. Understand the need to recognize and investigate forms that predispose to other diseases

Inherited defects of selected genes cause thrombocytopenia



https://www.facebook.com/matildebongiovisualscience/photos/nurden-at-and-paquita-n-inherited-thrombocytopenias-history-advances-and-perspec/2618988981686364/

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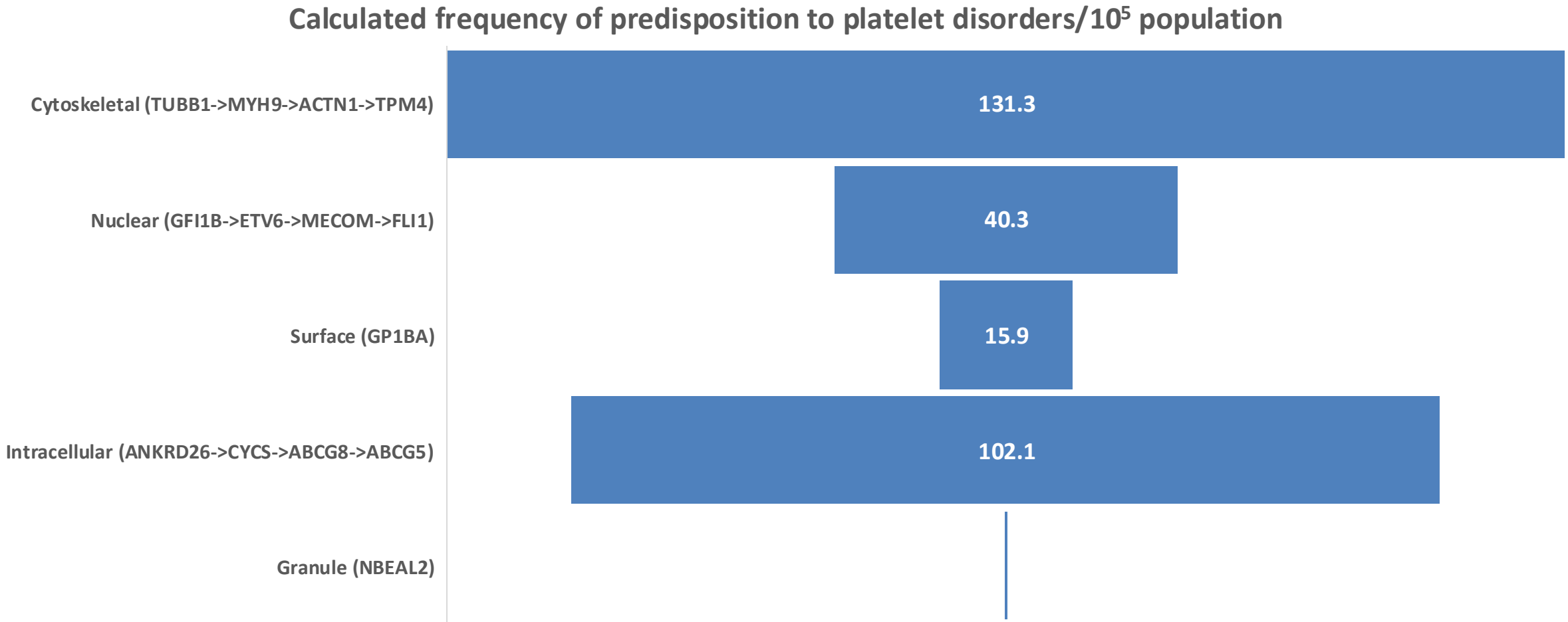
Chromosomal syndromes associated with thrombocytopenia

Chromosomal alteration	Incidence	Clinical manifestations	Incidence of thrombocytopenia
Trisomy 21	1 in 660	Cognitive retardation, hearing impairment, thyroid problems, heart defects, gastroenterological atresia, cataracts	7-28%
Trisomy 13	1 in 5000	Cleft lip and cleft palate; polydactyly, foot malformations; umbilical hernia; cardiac septal defects; ductus arteriosus; neural tube defects	54%
Trisomy 18	1 in 5000	Dolicocephaly, micrognathia, alterations in fingers, cardiac septal defects, renal, psychomotor retardation	86%
Turner síndrome (45, X)	1 in 2500	Coarctation of aorta, stenosis, short stature, ovarian failure, horseshoe kidney, ulnar valgus, low posterior capillary line, winged neck	31%
Di George síndrome (22q11.2 del) (AD)	1 in 4000	Typical facies, thymic abnormalities, hypocalcemia, velopharyngeal insufficiency, cardiac defects	30%
Jacobsen/Paris Trousseau syndrome [Del(11)(q23.3)] (AD)	1 in 100 000	Dysmorphogenesis of the hands and feet, cardiac defects and cognitive retardation	88%

AD, autosomal dominant

Frequency of deleterious variants in genes associated to inherited thrombocytopenia



In the general population, 0.329% of individuals have a clinically meaningful predicted loss-of-function variant in a gene associated to inherited platelet disorders

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Oved JH, et al. J Thromb Haemost. 2021;19:248-254

Classification of inherited thrombocytopenia

Only thrombocytopenia	Syndromic forms	Predisposition to additional disorders
Bernard Soulier síndrome (BSS)	Wiskott-Aldrich; XLT	MYH9-RD
Monoallelic BSS	SD Paris-Trousseau/Jacobsen (FLI1)	ANKRD26
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Gray platelet syndrome	GATA1-RT	ETV6-RT
Platelet type vWD	ARPC1B-RT	CAMT (MPL)
GFI1b-RT	Stormorken/York syndromes	CAMT (THPO)
TUBB1-RT	Takenouchi-Kosaki syndrome	MECOM-RT
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IKZF5-RT	GALE-RT	
TRPM7-RT	GNE-RT	
TPM4-RT		
PTPRJ-RT		
PRKACG-RT		
FYB-RT		
G6B		

When to suspect inherited thrombocytopenia

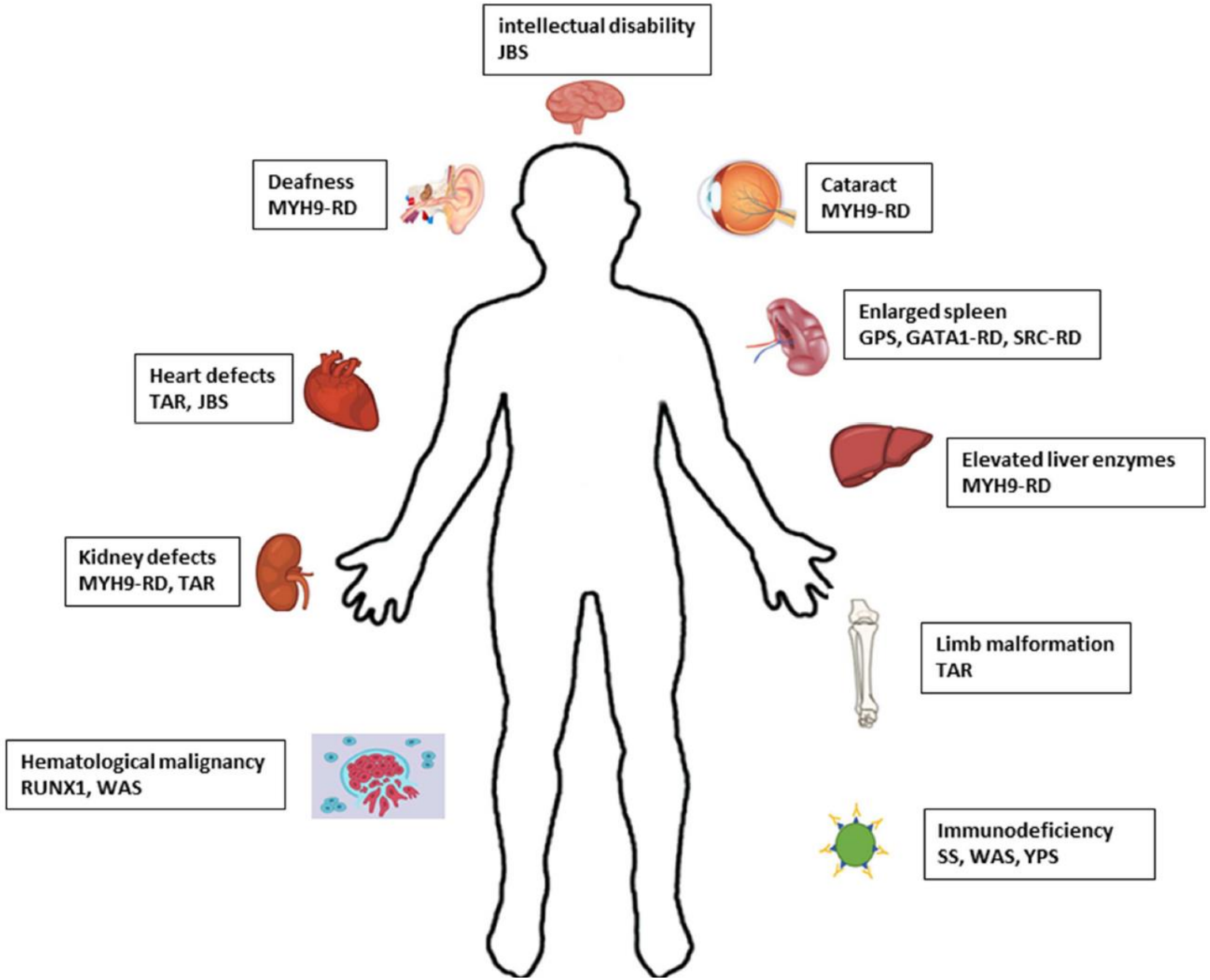
Step 1. Clinical presentation

- Family history of thrombocytopenia or hematological malignancies
- Excessive bleeding for platelet counts
- Refractory immune thrombocytopenia (ITP)
- Von Willebrand disease
- Additional findings

Step 2. Biological features

- Platelet counts and mean platelet volume
- Immature platelet fraction
- Blood smear
- Defects in other cell populations

Step 1 (Clinical presentation): syndromic phenotype of thrombocytopenias



Almazni I, et al. Front Cardiovasc Med. 2019;6:80

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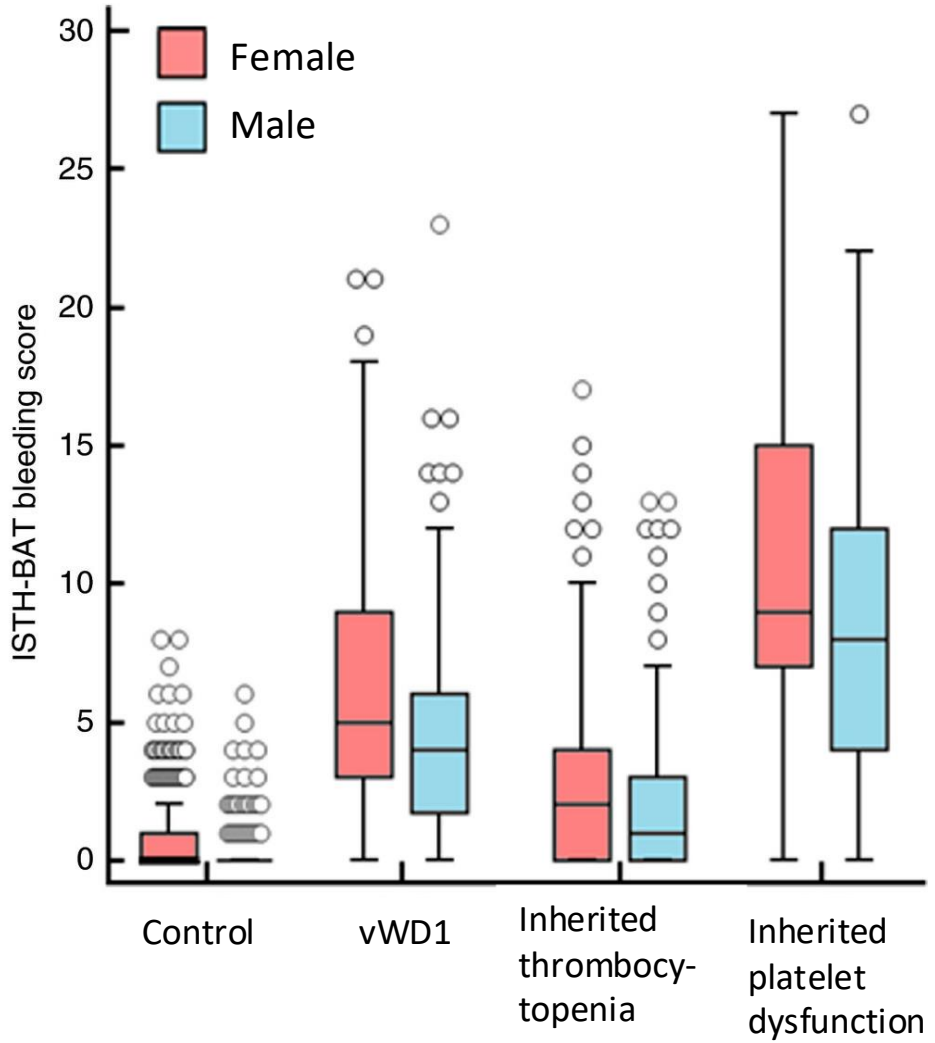
Step 1 (clinical presentation): tools to quantify bleeding

Bleeding Assessment Tools (BAT) have been developed to standardize bleeding history to improve diagnostic accuracy, quantify symptom severity, and predict future bleeding

The ISTH-BAT has been validated for vWD

The ISTH-BAT evaluation study shows its diagnostic utility for inherited platelet disorders with platelet dysfunction, but not for isolated thrombocytopenia



Gresele P, et al. J Thromb Haemost. 2020;18:732-739

vWD: von Wilebran disease

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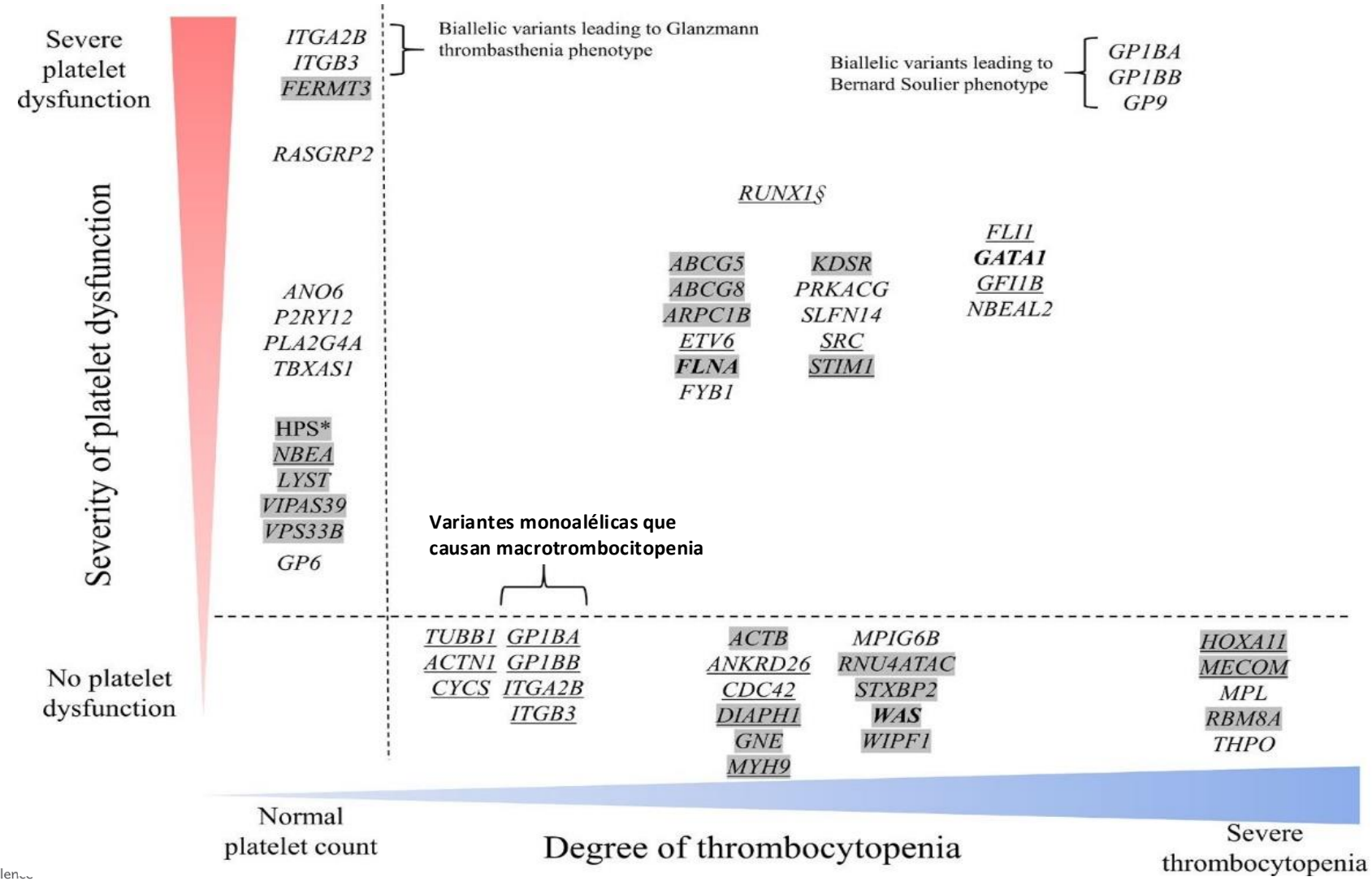
Step 1 (Clinical presentation): Degree of platelet dysfunction and thrombocytopenia



- Genes underlined: autosomal dominant inheritance
- Genes in bold: X-linked inheritance
- Genes neither underlined nor bold: autosomal recessive inheritance
- Genes with gray background: Syndromic presentations

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Perez Botero J, Di Paola J. J Thromb Haemost. 2021;19:2127-2136

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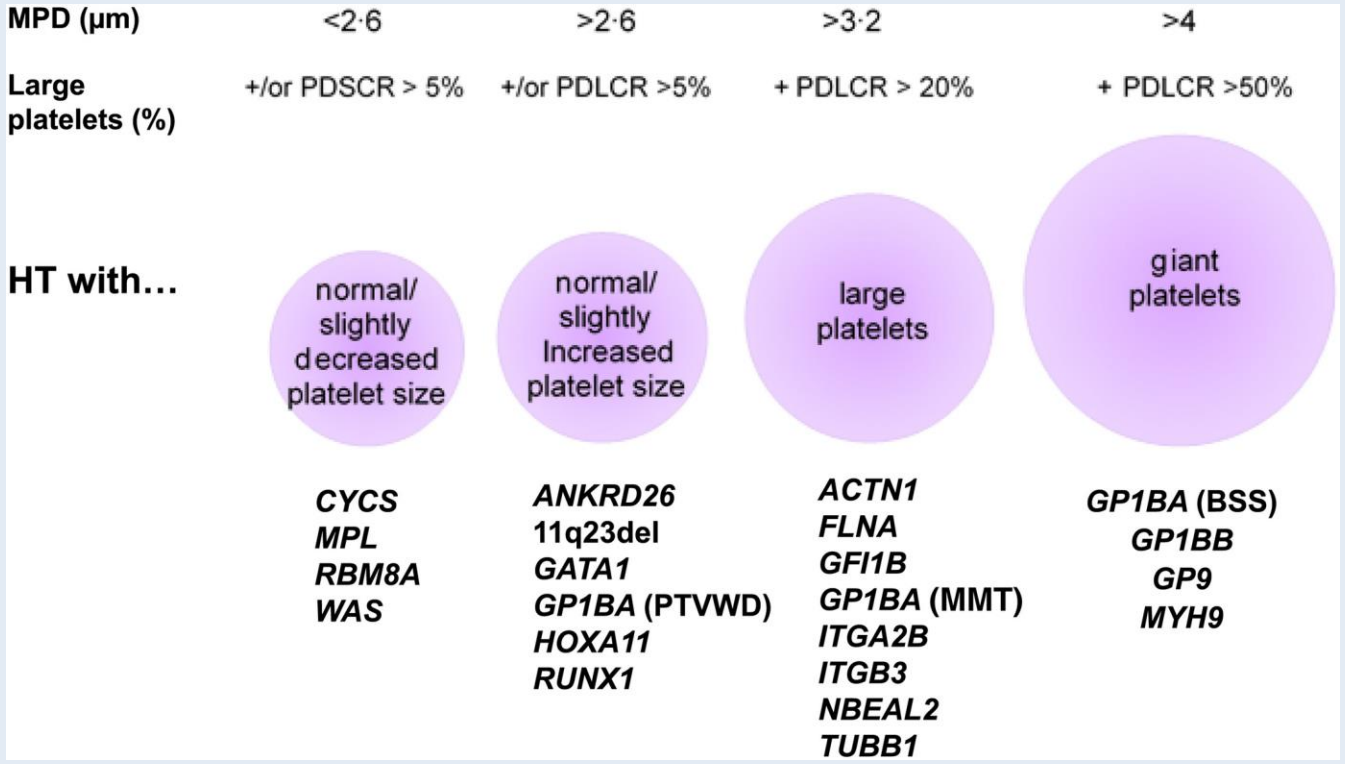
Step 2: Biological features

Platelet counts	<100,000/μl
	100,000-150,000/μl (possible)
Basic coagulation studies	Prothrombin time, activated partial thromboplastin time
	Quantification of von Willebrand factor, ristocetin cofactor and coagulant activity of factor VIII

Step 2 (biological features): platelet size and IPF



Immature Platelet Fraction (IPF)

- Increased in ITP and in inherited thrombopenias (particularly if macrothrombocytopenia)
- Inherited thrombocytopenias tend to have higher IPF than ITP

Collins J, et al. Br J Haematol. 2021;195:25-45

Step 2 (biological features): other findings from complete blood count and smear

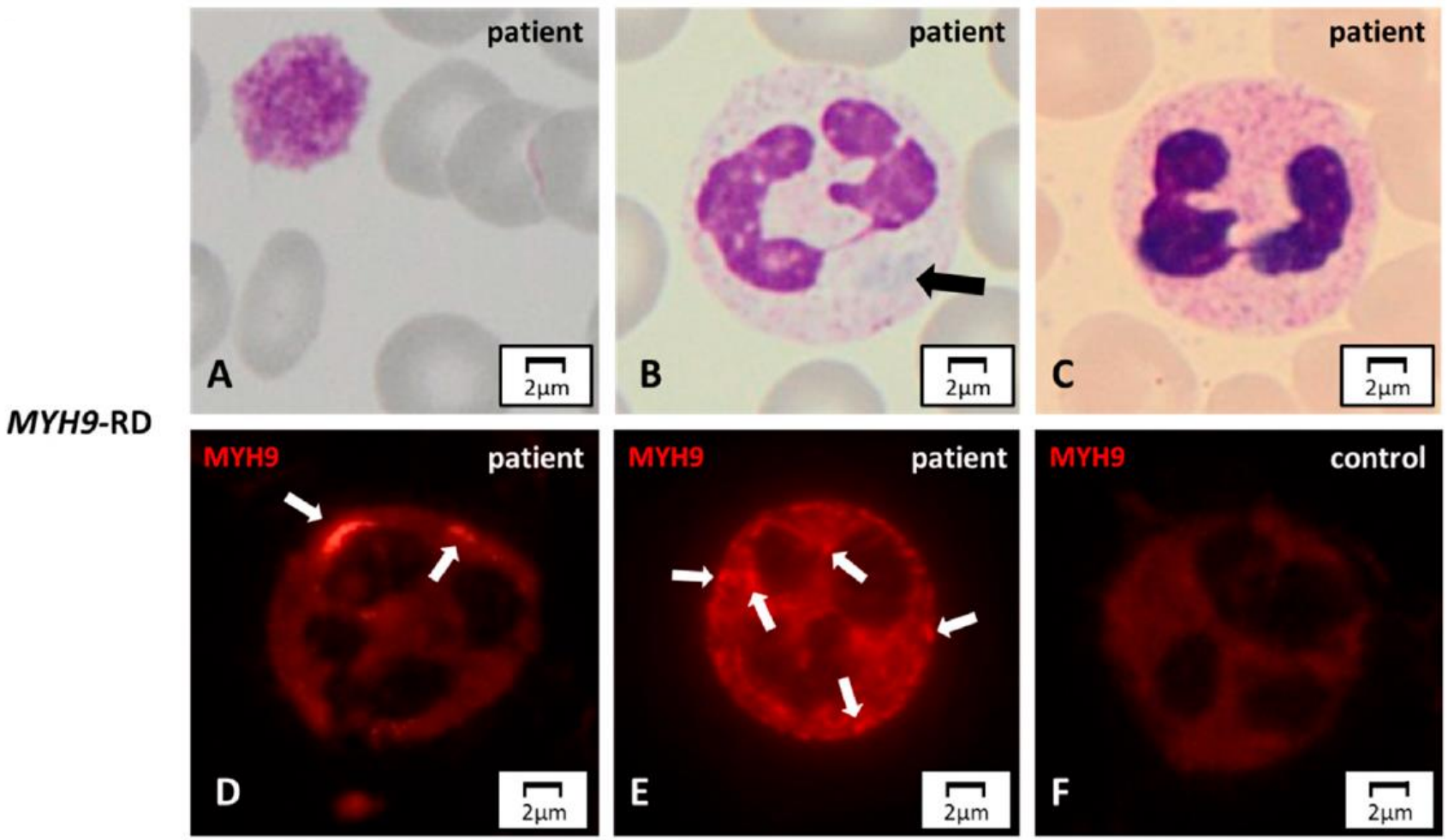
Abnormalities in other cell lines

- **Anemia**: GATA1-related disorders (X-linked), sitosterolemia (*ABCG5, ABCG8), GFI1B, GALE*
- **Neutropenia:** disorders related to *GATA1, DIAPH1, WAS, GALE*
- **Eosinophilia:** characteristic of thrombocytopenia related to *ARPC1B*
- **Pancytopenia:** congenital amegakaryocytic thrombocytopenia (*MPL, THPO, EVI1, HOXA11, MECOM*)
- **Hematologic malignancies**: *ETV6, ANKRD26, RUNX1*

Smear

- **Alpha granule deficiency:** pathogenic variants in *GATA1, GFI1B, NBEAL2, VIPAS39 and VPS33B*
- **Döhle bodies:** MYH9-related disorders

Peripheral blood smear and immunofluorescence



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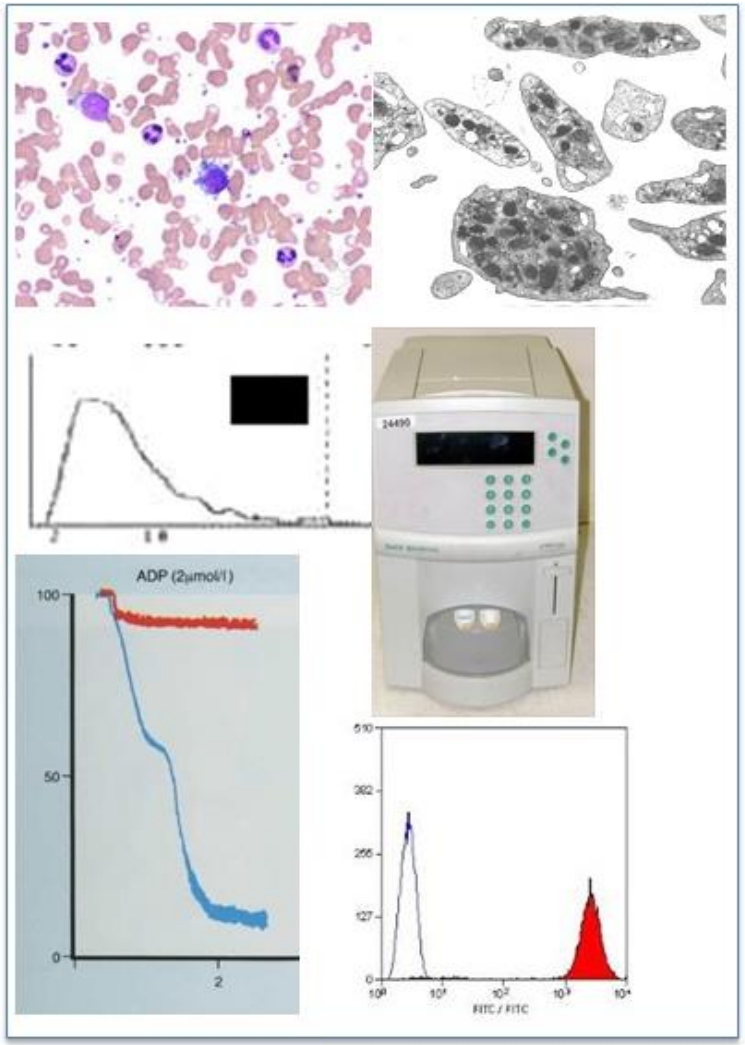
Zaninetti C, Greinacher A. J Clin Med. 2020;9:539

Biological phenotype and molecular diagnosis



Specific regions: Panel of genes

- Relatively inexpensive and limited number of data to be analyzed

Whole exome sequencing (WES)

- Identification of new genes

Whole genome sequencing (WGS)

- Identification of novel genes, non-coding variants and copy number

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TUBB1-RT	Take[illegible]-Rosaki [illegible]ome	MECOM-RT
ITGA2B/ITGB3-RT	K[illegible]R-RT	RUSAT (HOXA11)
CYCS-RT	ACTB-RT	DIAPH1-RT
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TRPM7-RT	GNE-RT	
TPM4-RT		
PTPRJ-RT		
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FYB-RT		
G6B		

Is it ITP?

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Unmet need: Diagnosis of ITP is one of exclusion

All patients	Potential utility	Unproven / uncertain
Patient history	Glycoprotein-specific antibody	TPO
Family history	Antiphospholipid antibodies	Reticulated platelets/ immature platelet fraction
Physical examination	Antithyroid antibodies and thyroid function	Platelet survival study
Complete blood count and reticulocyte count	Pregnancy test in women of childbearing potential	Bleeding time
Peripheral blood film	Antinuclear antibodies	Serum complement
Quantitative immunoglobulin level measurement	Viral PCR for EBV, CMV and parvovirus	
Blood group (Rh)	*H. Pylori*	
HIV	Bone Marrow (selected patients)	
HCV, HBV	Direct antiglobulin test	

12% of patients who are initially thought to have primary ITP turn out not to have it

CMV, cytomegalovirus; EBV, Epstein-Barr virus; TPO, thrombopoietin

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Provan D, et al. Blood Adv. 2019;3:3780-3817

Arnold DM, et al. Blood Adv. 2017;1:2414-2420

Clinical and laboratory differences between inherited thrombocytopenia and ITP

Clinical presentation

	Inherited thrombocytopenia	ITP
Family history	Yes/No	No
Onset	Life-long (young age)	Recent
Bleeding tendency	Mild	Variable
Response to platelet transfusion	Good	Poor
Response to ITP-directed pharmacologic therapy	No	Yes
Fatigue	Absent	Frequently present
Other autoimmune disorder	Not frequent	Frequent

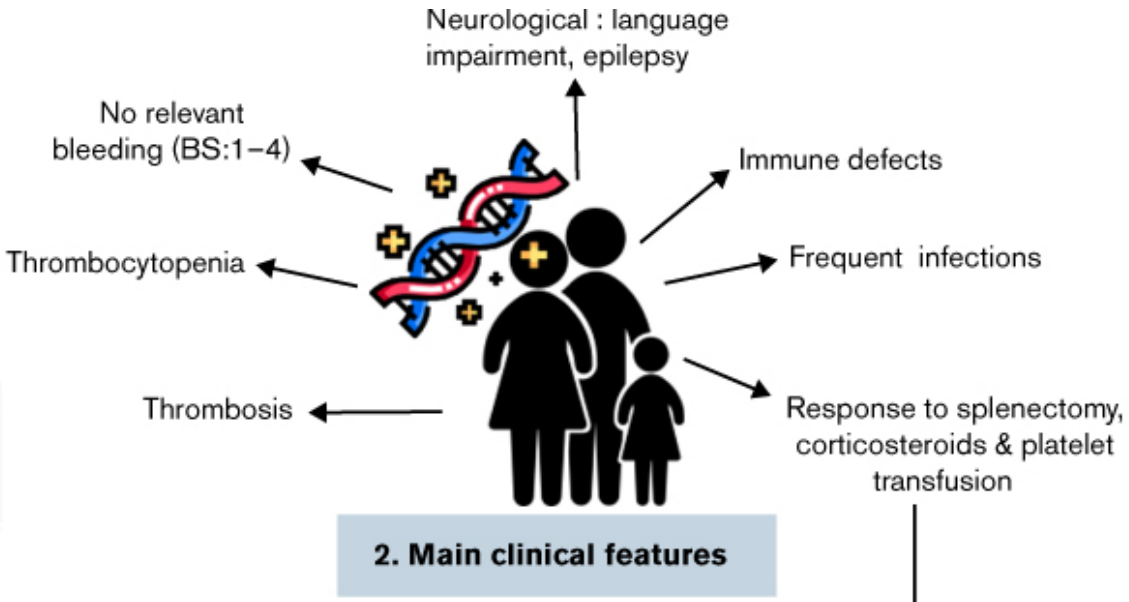
Biological features

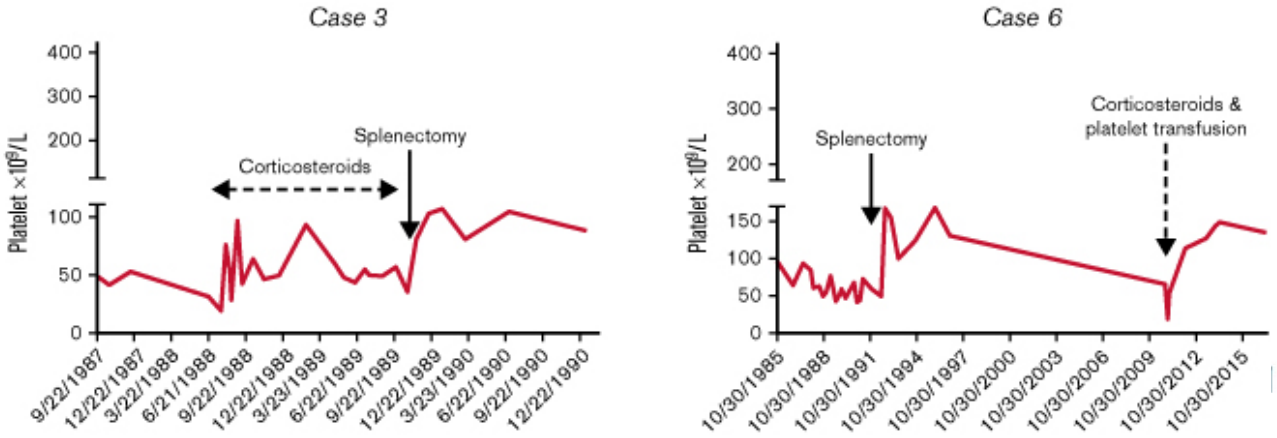
	Inherited thrombocytopenia	ITP
Previous normal platelet count	No	Yes
Blood smear	Variable	Normal or large platelet
Increased immature platelet fraction	Yes	Yes
Platelet count fluctuation	Rare	Frequent

However, this difference is not always so clear

Src-related thrombocytopenia: a fine line between a megakaryocyte dysfunction and an immune-mediated disease

Palma-Baqueros V, et al. Blood Adv 2022; 6: 5244–5255





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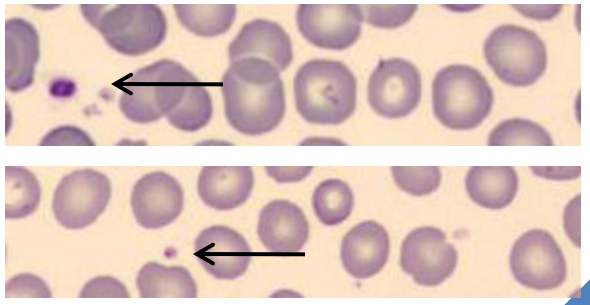
Case 1. Male diagnosed with childhood ITP with immune deficiency



Control

Patient

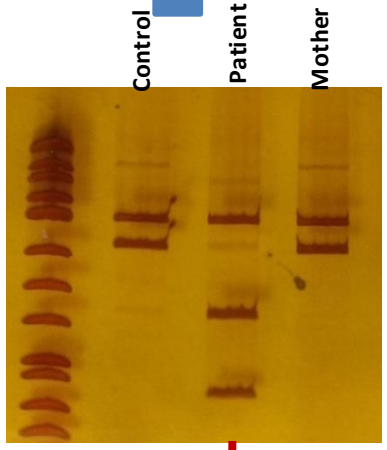
4-year-old patient with thrombocytopenia at birth (87x10^9/l; MPV 8 fl)

His 4 siblings and parents are healthy with normal blood counts

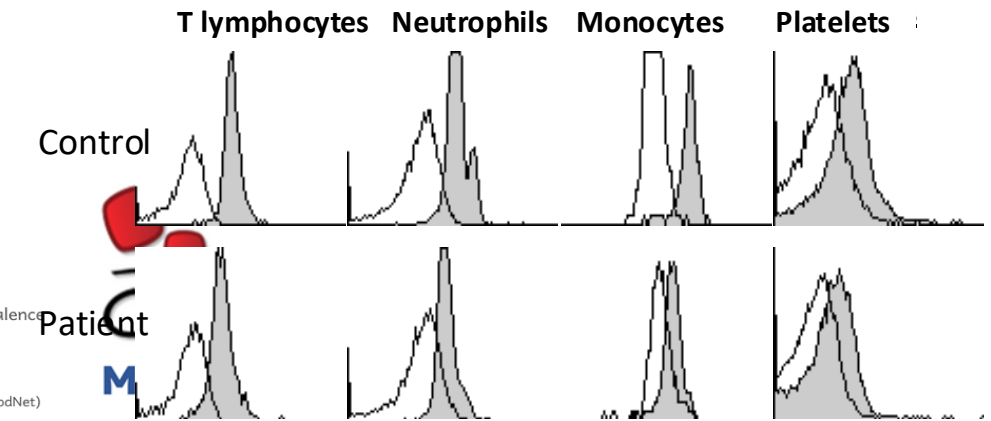
Diagnosis of ITP. Corticosteroids and IVIgG

No eczema but tendency to respiratory infections

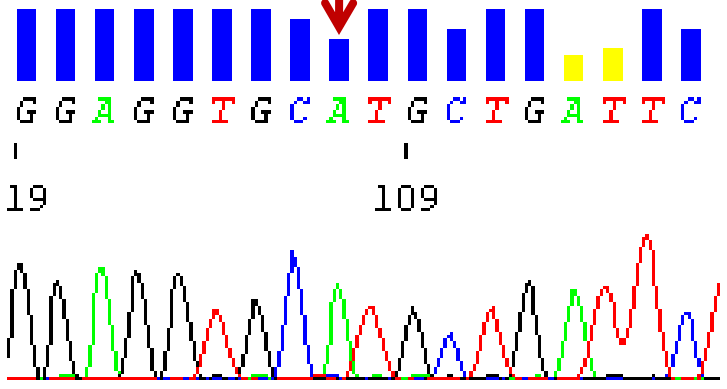
Decreased IgM, elevated IgA and IgD. Decreased CD3+8+, and memory LB. No immune response to HBsAg vaccination



WASP



WAS



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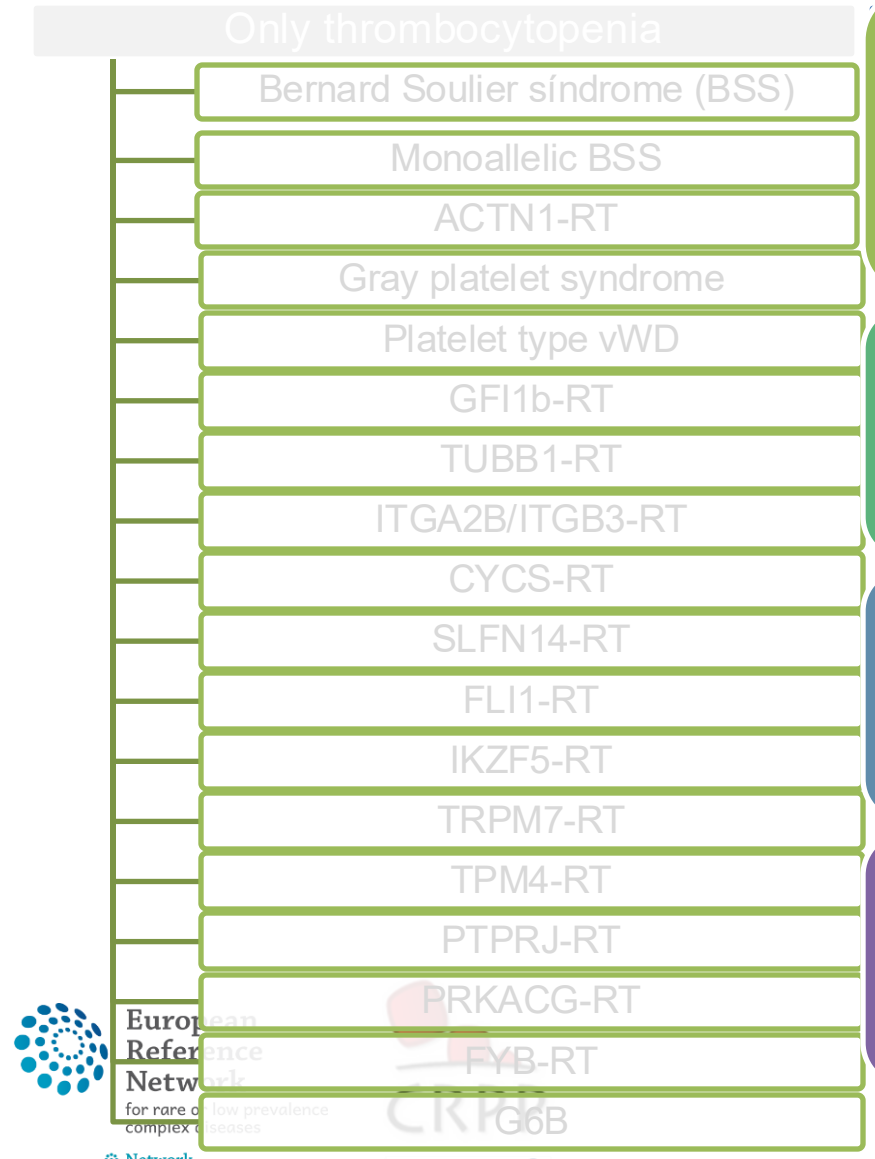
Childhood ITP with immune deficiency: Wiskott-Aldrich syndrome



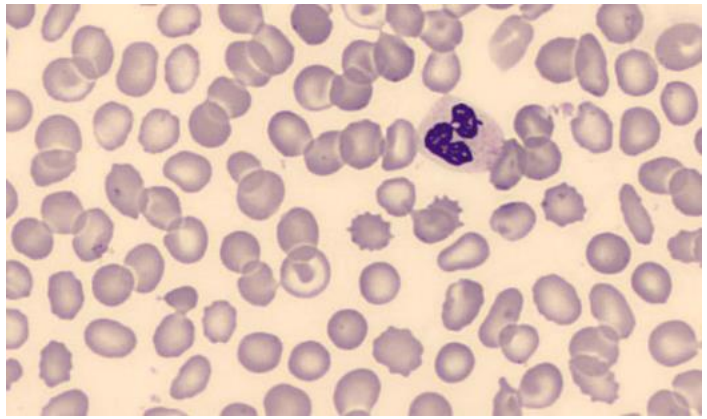
Wiskott Aldrich syndrome: a condition almost exclusively affecting males characterized by thrombocytopenia and bleeding, eczema, combined immunodeficiency, autoimmune manifestations and increased risk of developing tumors at any age.

Suspected diagnosis by family history, physical examination and thrombocytopenia with reduced platelet size, as well as altered antibody production.

Importance of determining the type of mutation and protein expression to predict the evolution of patients (in our case the IVS6+5 g>a mutation).

Transplantation can be considered if there is a suitable donor due to the risk of complications such as intracranial hemorrhage, autoimmune diseases, IgA nephropathy, neoplasms, etc.

Cases 2&3. ITP diagnosis with skin lesions



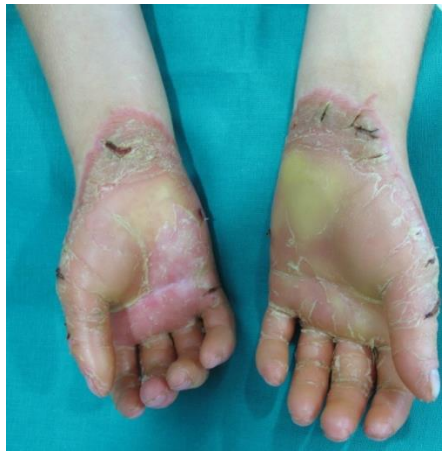
Patient 1: 15-year-old male who develops palmoplantar and anogenital hyperkeratosis at 12 months of age

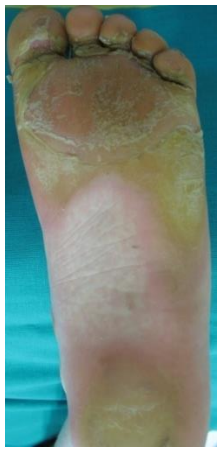
Patient 2: 21-year-old male who develops at 15 months of age diffuse hyperkeratosis on palms and soles (less marked than patient 1)

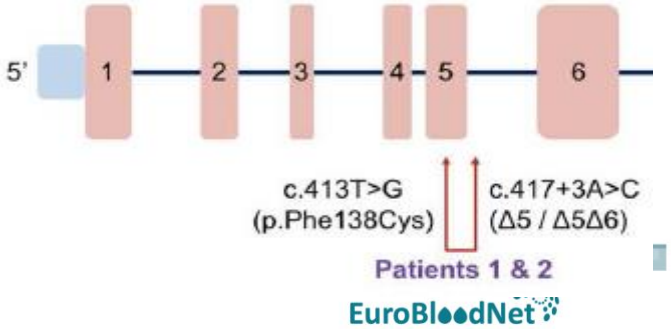
Patient 1: Diagnosed with ITP (platelets <15x10^9/l) at 2 years of age and started on corticosteroids; underwent splenectomy at 11 years of age

Patient 2: Diagnosed with ITP (platelets <10x10^9/l), and exposed for years to steroids

Takeichi T, et al. J Invest Dermatol. 2017;137:2344-53







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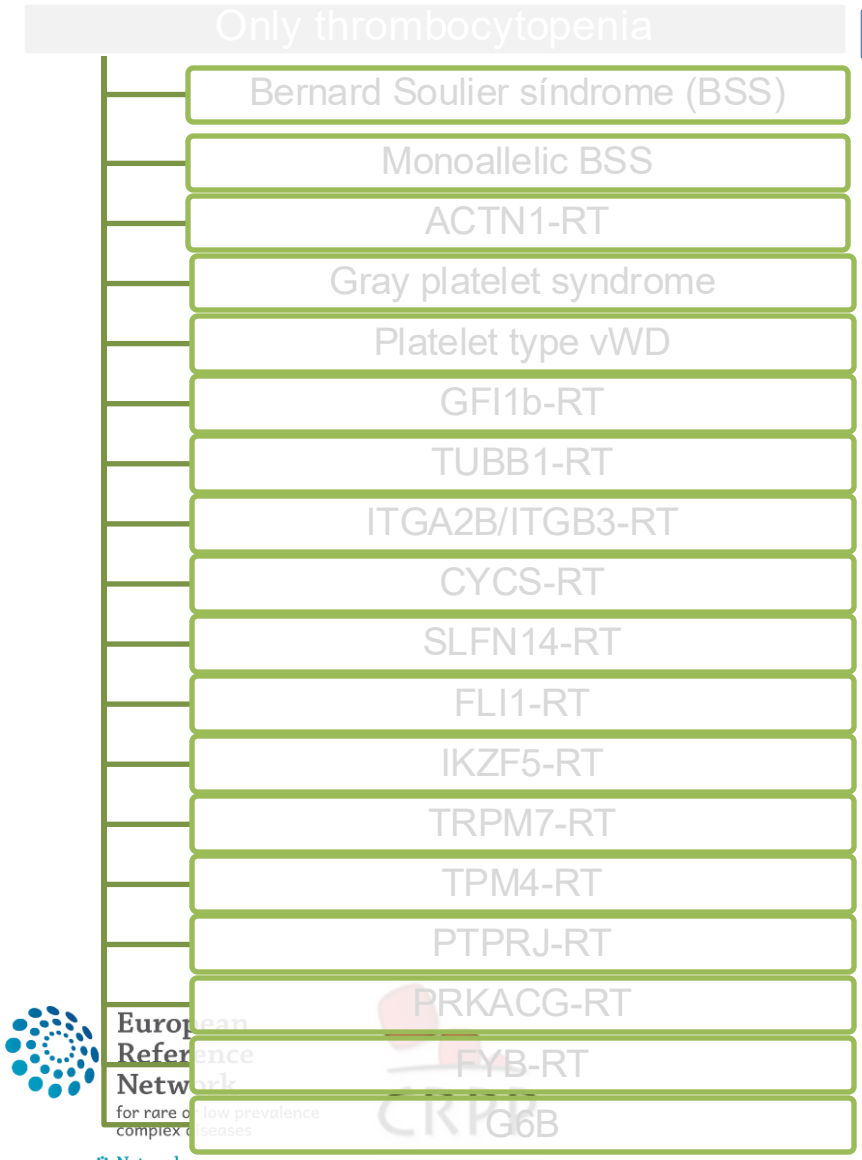
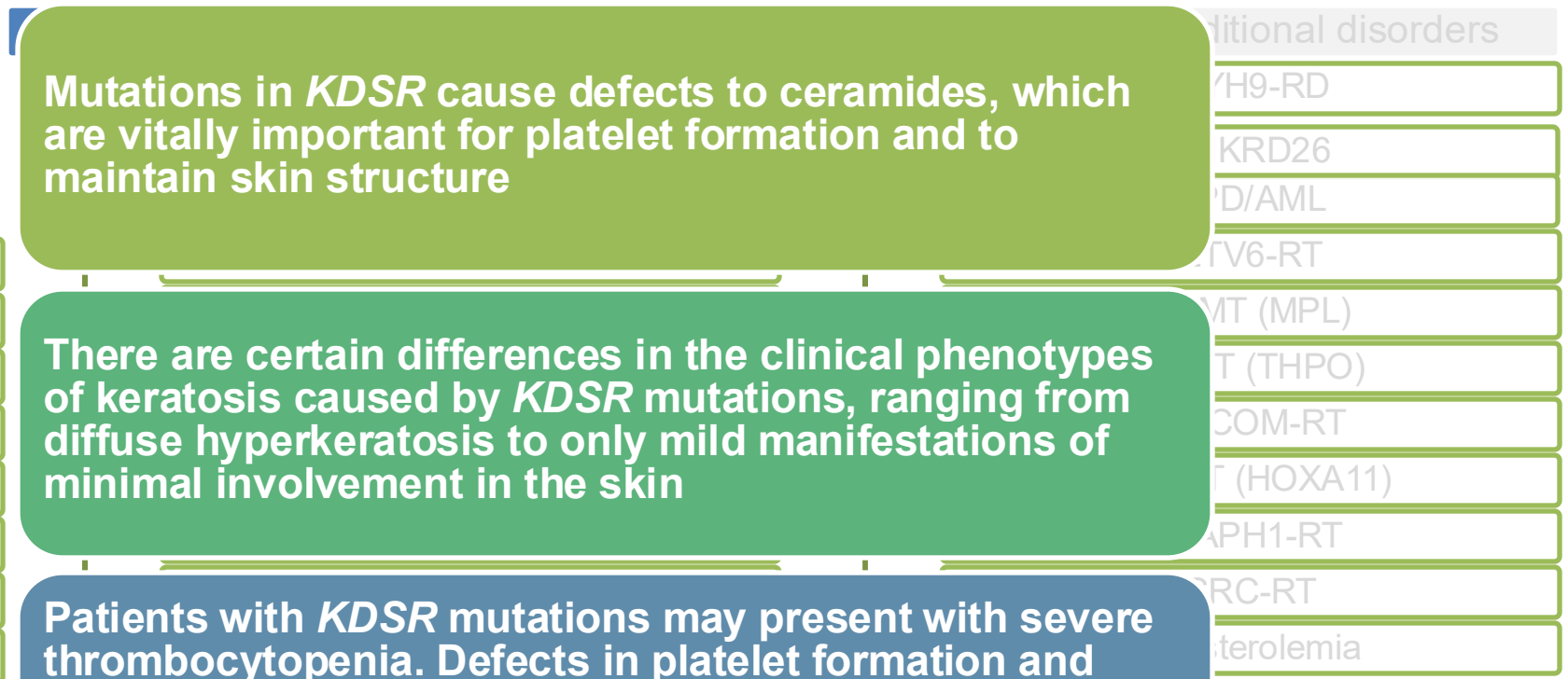
ITP and skin lesions: keratinization disorder with thrombocytopenia





Mutations in *KDSR* cause defects to ceramides, which are vitally important for platelet formation and to maintain skin structure

There are certain differences in the clinical phenotypes of keratosis caused by *KDSR* mutations, ranging from diffuse hyperkeratosis to only mild manifestations of minimal involvement in the skin

Patients with *KDSR* mutations may present with severe thrombocytopenia. Defects in platelet formation and release in the final stage of thrombopoiesis may be the primary cause of thrombocytopenia in patients with *KDSR* mutations

When patients with *KDSR* mutations have repeated bleeding due to thrombocytopenia, which is life-threatening, hematopoietic stem cell transplantation should be considered

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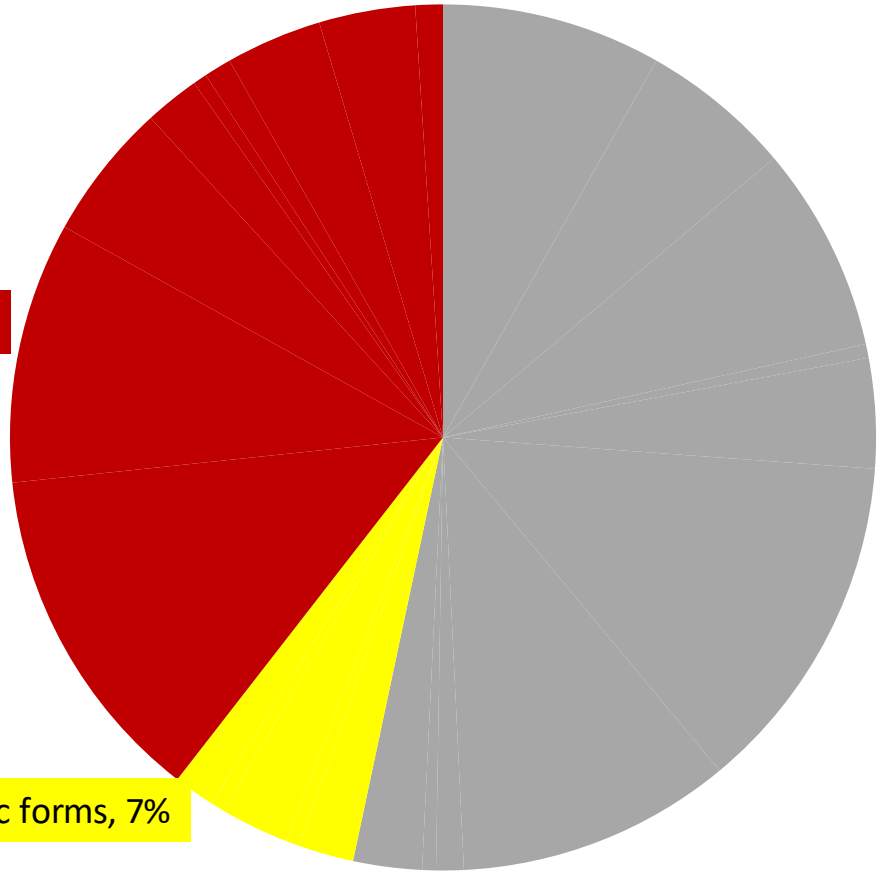
PRKACG-RT		
FYB-RT		
G6B		

Spanish group of inherited platelet disorders: inherited thrombocytopenia



Predisposition to additional disorders, 40%

Syndromic forms, 7%

195 patients with a definitive diagnosis of inherited thrombocytopenia (25 different forms)

Only thrombocytopenia, 53%

- Bernard Soulier síndrome (BSS), 16
- Gray platelet syndrome, 1
- ITGA2B/ITGB3-RT, 20
- TPM4-RT, 5
- GATA1-RT, 5
- MYH9-RD, 25
- ETV6-RT, 4
- DIAPH1-RT, 7
- Monoallelic BSS, 11
- GFI1b-RT, 8
- CYCS-RT, 2
- Wiskott-Aldrich; XLT, 4
- FLNA-RT, 1
- ANKRD26, 19
- CAMT (MPL), 1
- SRC-RT, 7
- ACTN1-RT, 15
- TUBB1-RT, 25
- TRPM7-RT, 1
- Thrombocytopenia absent radii, 1
- GALE-RT, 3
- FPD/AML, 10
- MECOM-RT, 2
- Sitosterolemia, 2

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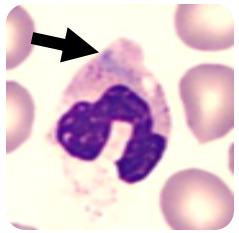
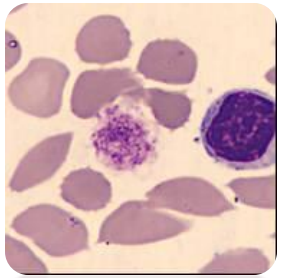
Case 4. ITP with deafness and end-stage renal disease





42-year-old patient with thrombocytopenia ($37x10^9$/l; MPV 14 fl)

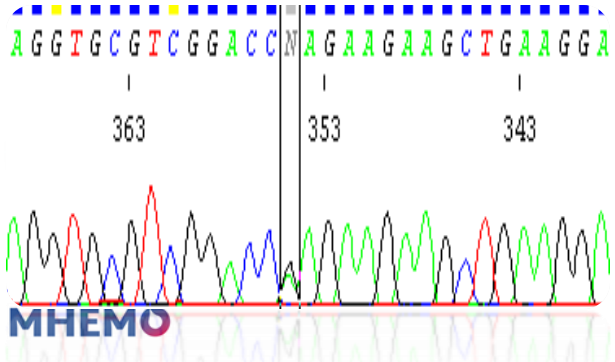
Diagnosis of ITP. Corticoids and splenectomy

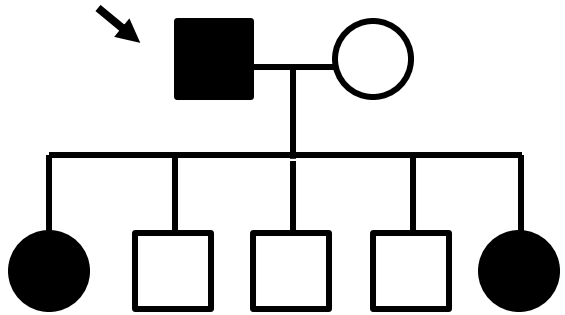
Bilateral hearing loss

End-stage renal disease. Underwent renal transplantation at 36 years of age

MYH9

c.5521G>A





22 years old.
Plt $66x10^9$/L. ↑MPV
Proteinuria

11 years old.
Plt $58x10^9$/L. ↑ MPV

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ITP with deafness and end-stage renal disease: MYH9-RD

Only thrombocytopenia

- Bernard Soulier síndrome (BSS)
- Monoallelic BSS
- ACTN1-RT
- Gray platelet syndrome
- Platelet type vWD
- GFI1b-RT
- TUBB1-RT
- ITGA2B/ITGB3-RT
- CYCS-RT
- SLFN14-RT
- FLI1-RT
- IKZF5-RT
- TRPM7-RT
- TPM4-RT
- PTPRJ-RT
- PRKACG-RT
- FYB-RT
- G6B

orders

MYH9-RD: most frequent cause of inherited macrothrombocytopenia

Mean age at diagnosis: 31 years

Autosomal dominant, but 35% of cases are sporadic

35% of patients are previously misdiagnosed with ITP

50% of patients have hepatic alterations

50% progressive sensorineural hearing loss (age at onset 31 years)

30% nephropathy (age of onset 30 years; most evolve to bilateral renal disease in 5-10 years)

18% presenile cataracts often bilateral (mean age 21 years)

rs

Case 5. Myelodysplastic syndrome in 40-year-old patient

40-year-old patient being followed up for bicytopenia (anemia and thrombocytopenia < $20x10^9$/l) in the last 3 years.

No platelet response to intravenous immunoglobulins or steroids.

After several bone marrow studies a diagnosis of refractory cytopenia with megakaryocyte dysplasia and intermediate risk IPSS-R (4 points) is established.

No findings in genetic studies (FISH, karyotype, MDS/LAM-related gene panel).

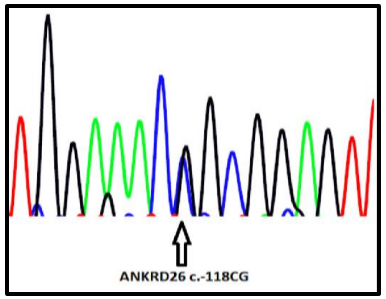
Patient has an HLA-matched sibling

WHO, 2022

Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
• Germline *RUNX1* P/LP variant[a] (familial platelet disorder with associated myeloid malignancy, FPD-MM)
• Germline *ANKRD26* P/LP variant[a] (Thrombocytopenia 2)
• Germline *ETV6* P/LP variant[a] (Thrombocytopenia 5)

Khoury, J.D., et al. Leukemia 2022; 36, 1703–1719

ANKRD26



Family screening: *de novo* mutation

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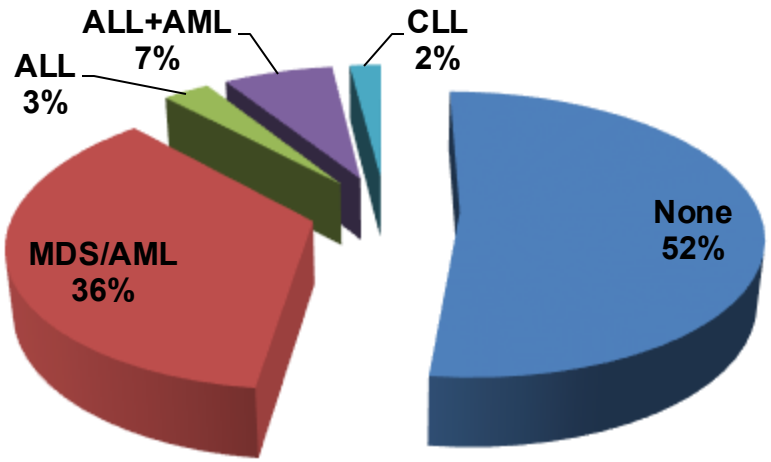
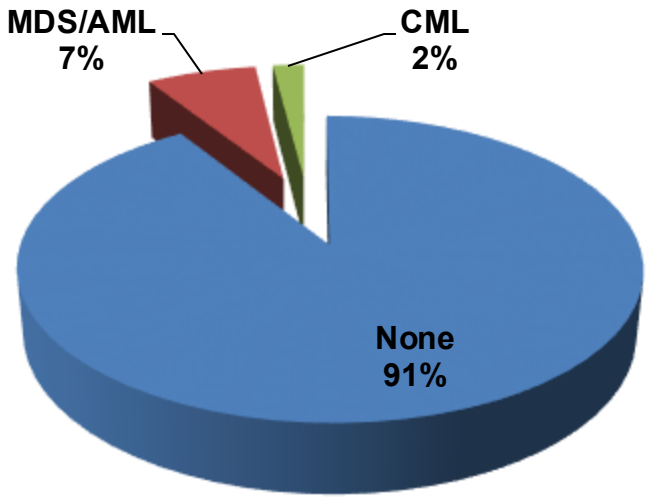
Inherited platelet disorders predisposing to myeloid neoplasms

FPD/AML (48%)



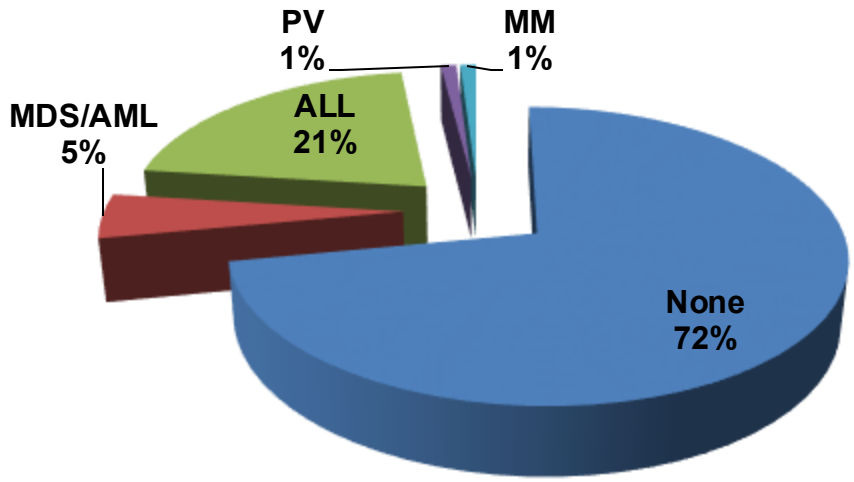
Latger-Cannard V, et al. Orphanet J Rare Dis. 2016;11:49

ANKRD26 (9%)



Noris P, et al. Blood. 2013;122:1987-9

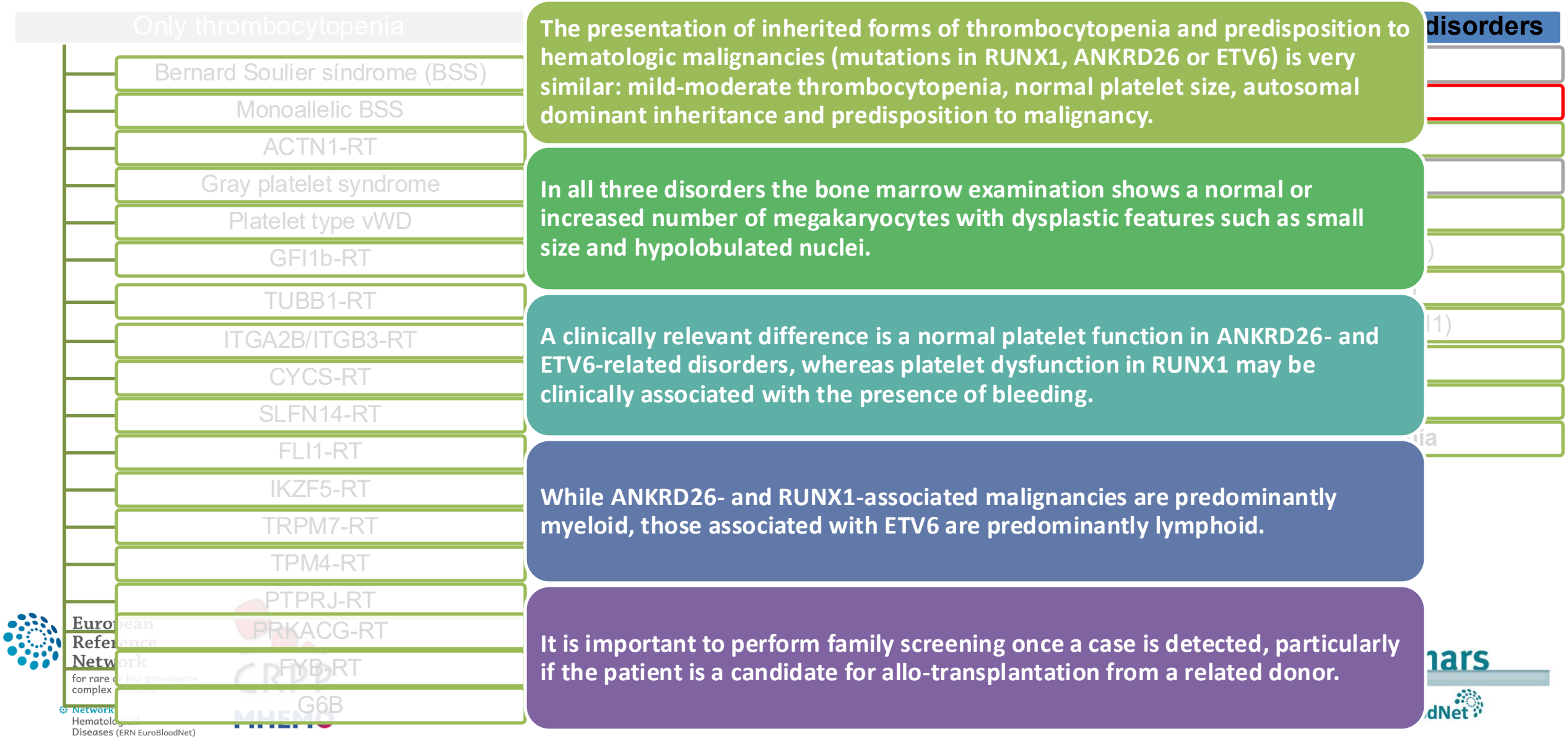
ETV6 (28%)



Feurstein S, et al. Int J Hematol. 2017;106:189-195

	FPD/AML (RUNX-1)	ANKRD26	ETV6
Mean platelet count ($x10^9$/l)	99	46	81
Mean age at the diagnosis of malignacy (years)	30	49	20

Myelodysplastic syndrome in 40-year-old patient: ANKRD26-RD



The presentation of inherited forms of thrombocytopenia and predisposition to hematologic malignancies (mutations in RUNX1, ANKRD26 or ETV6) is very similar: mild-moderate thrombocytopenia, normal platelet size, autosomal dominant inheritance and predisposition to malignancy.

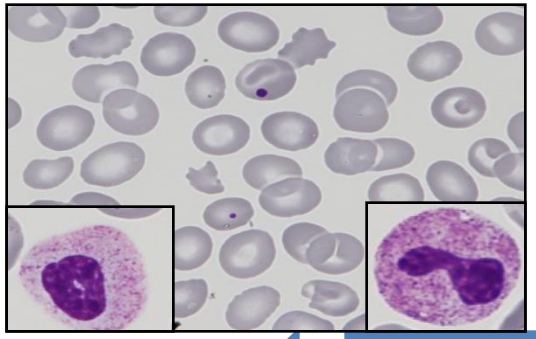
In all three disorders the bone marrow examination shows a normal or increased number of megakaryocytes with dysplastic features such as small size and hypolobulated nuclei.

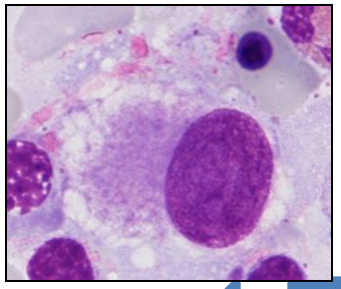
A clinically relevant difference is a normal platelet function in ANKRD26- and ETV6-related disorders, whereas platelet dysfunction in RUNX1 may be clinically associated with the presence of bleeding.

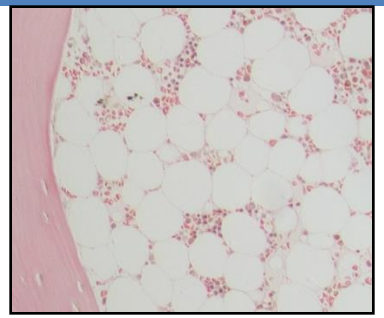
While ANKRD26- and RUNX1-associated malignancies are predominantly myeloid, those associated with ETV6 are predominantly lymphoid.

It is important to perform family screening once a case is detected, particularly if the patient is a candidate for allo-transplantation from a related donor.

Case 6. ITP progressing to dysplasia/aplasia



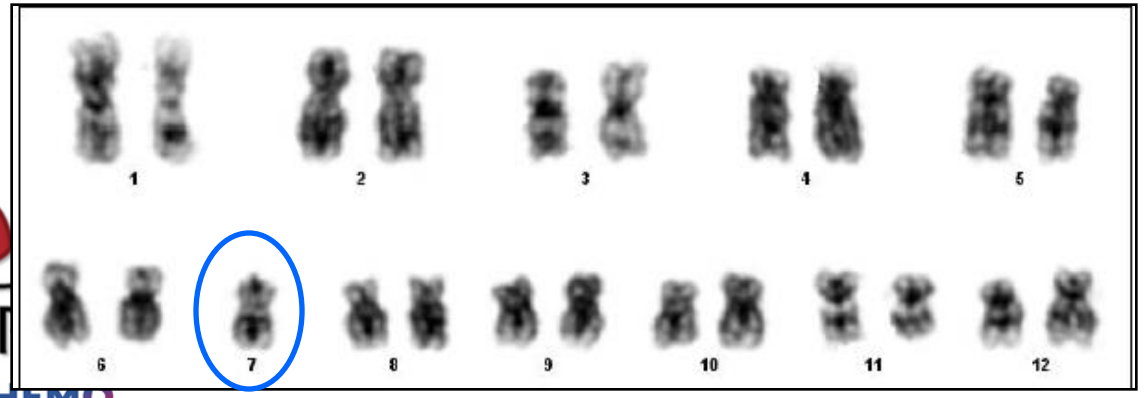




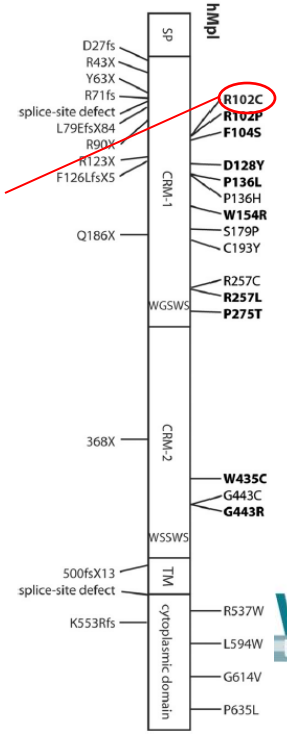
24-year-old patient referred for thrombocytopenia.

Diagnosed at 6 years of age with ITP. Treated with corticosteroids and splenectomy.

Progressive neutropenia. Dysplasia. Monosomy 7



Homozygosis p.Arg102Cys in *MPL*



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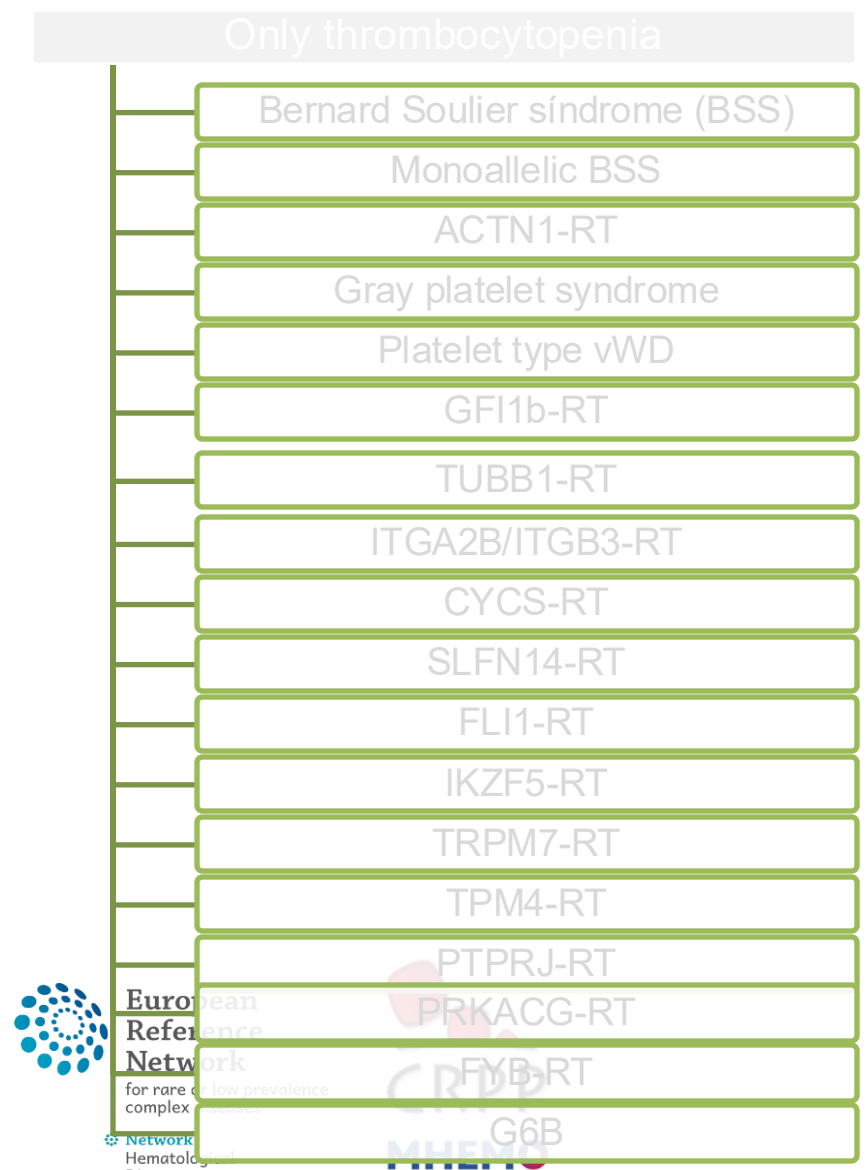
ITP progressing to dysplasia/aplasia: Congenital amegakaryocytic thrombocytopenia



CAMT (congenital amegakaryocytic thrombocytopenia): Inherited marrow failure not associated with other malformations.

Bi-allelic mutations in the receptor (c-mpl), and less frequently in the ligand (thrombopoietin, TPO), alter the signaling of this axis, essential for the maintenance and self-renewal of multipotent cells and for differentiation into megakaryocytes.

Thrombocytopenia at birth progresses to bone marrow aplasia.

While allogeneic transplantation is the only curative option in cases due to MPL mutations, Romiplostim has been shown to have optimal responses in the less frequent cases of patients with biallelic mutations in TPO.

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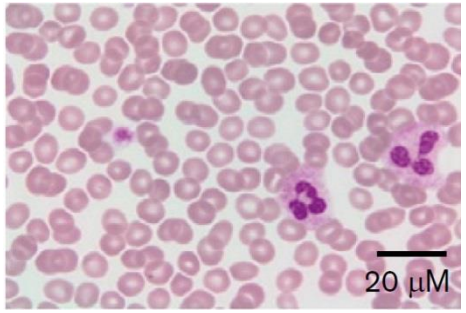
Case 7. Thrombocytopenia and sensorineural hearing loss since childhood



28-year-old patient referred for moderate thrombocytopenia and neutropenia.

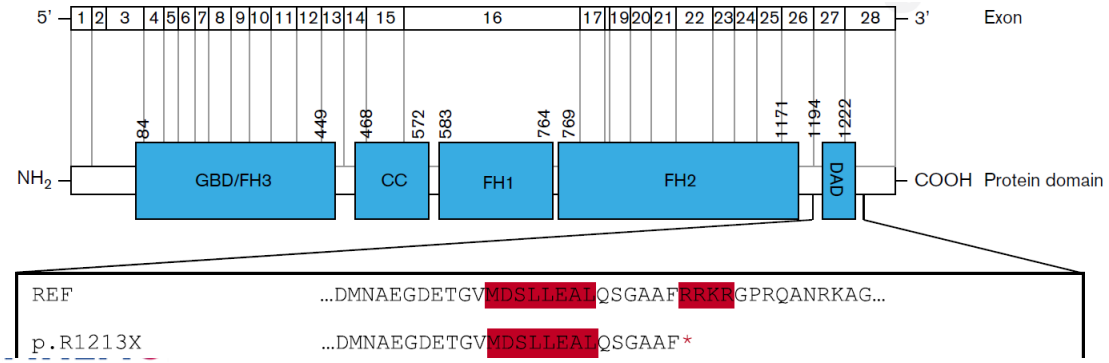
He presented sensorineural hearing loss since childhood.

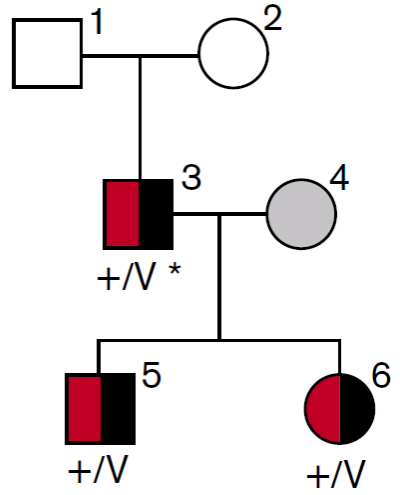
MYH9 mutations were ruled out.

Two bone marrow biopsies and one liver biopsy were performed without reaching a diagnosis.

He has two children, both with thrombocytopenia + neutropenia + deafness.

DIAPH1





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Thrombocytopenia and sensorineural hearing loss since childhood: DIAPH1-RT

Only thrombocytopenia

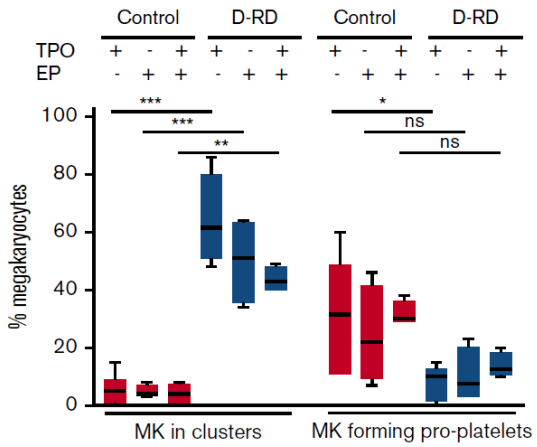
- Bernard Soulier síndrome (BSS)
- Monoallelic BSS
- ACTN1-RT
- Gray platelet syndrome
- Platelet type vWD
- GFI1b-RT
- TUBB1-RT
- ITGA2B/ITGB3-RT
- CYCS-RT
- SLFN14-RT
- FLI1-RT
- IKZF5-RT
- TRPM7-RT
- TPM4-RT
- PTPRJ-RT
- PRKACG-RT
- FYB-RT
- G6B

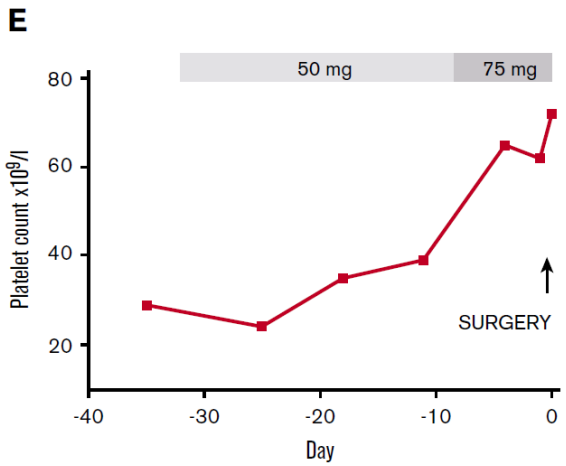
disorders

DIAPH1-RD: manifestations characterized by macrothrombocytopenia, neutropenia, and hearing loss.

Not associated with renal disease, cataracts, or neutrophil inclusions, which differentiates DIAPH1-RD from MYH9-RD, which also presents with macrothrombopenia and deafness.

Eltrombopag partially rescues deficient proplatelet formation of DIAPH1-RD MK cultures, and administration for short periods of TPO-RA may temporarily correct platelet counts.





Westbury SK, et al. Blood Adv. 2018;2:2341-2346

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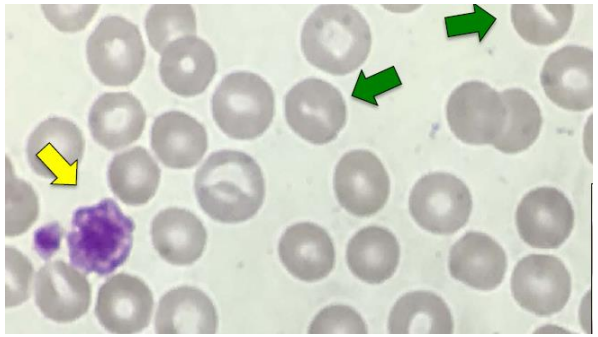
Case 8. Thrombocytopenia and xanthomas



46 year old patient referred for macrothrombocytopenia.

Complained from arthralgias, arthritis and mild cutaneous diathesis.

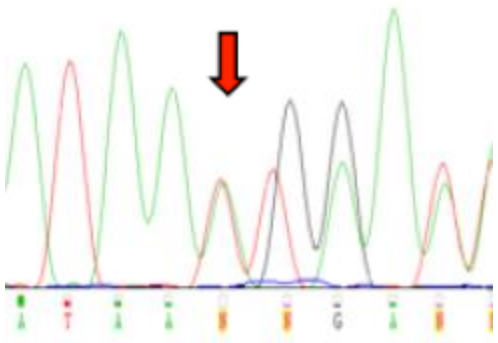
Familial hypercholesterolemia with xanthomas.

On examination she presented xanthelasmas (4 surgical interventions).

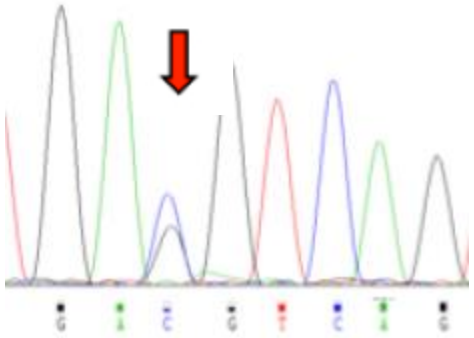
Plasma sterols	Patient	Normal range
Sitosterol (μM)	688	<10
Campesterol (μM)	170	<3
β-Colestanol (μM)	31	2-13
Cholesterol (mM)	3	2-7

ABCG5

p.F630L fs8X; c.1890delT



p.T305R; c.914C>G



Bastida JM, et al. J Thromb Haemost. 2017;15:1859-1866

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Thrombocytopenia and xanthomas: Sitosterolemia

Only thrombocytopenia

- Bernard Soulier síndrome (BSS)
- Monoallelic BSS
- ACTN1-RT
- Gray platelet syndrome
- Platelet type vWD
- GFI1b-RT
- TUBB1-RT
- ITGA2B/ITGB3-RT
- CYCS-RT
- SLFN14-RT
- FLI1-RT
- IKZF5-RT
- TRPM7-RT
- TPM4-RT
- PTPRJ-RT
- PRKACG-RT
- FYB-RT
- G6B

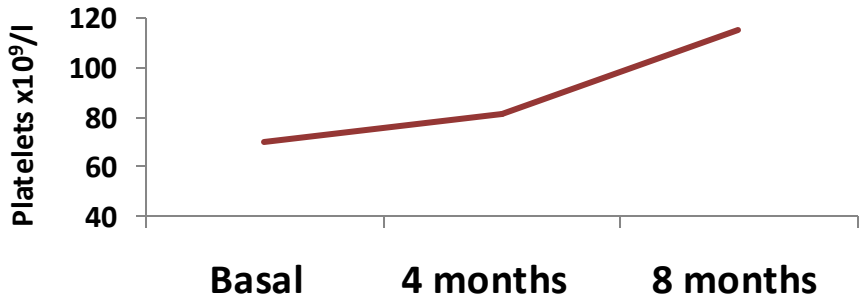
Rare recessive disorder characterized by increased plasma plant sterols.

Pathogenic variants in ABCG5 and ABCG8.

Tendon and skin xanthomas, premature atherosclerosis, arthritis and arthralgia.

Hematological abnormalities such as hemolytic anemia, macrothrombopenia and/or splenomegaly.

Ezetimibe improves the distribution of VLDL and HDL fractions, reducing the atherogenic profile, which may have a clinical benefit.



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Suspecting inherited thrombocytopenia

Consider a form of thrombocytopenia to be hereditary when there is no previous evidence of normal blood counts or other causes for it.

From theory

- Family history
- History of bleeding since infancy; more bleeding than expected by count
- Presence of other additional defects
- Large or dysmorphic platelets or megakaryocyte dysplasia

To practice

- Many forms are recessive. High percentage of de novo mutations
- In many cases patients do not bleed and there is no alteration of platelet functionality.
- There is a percentage of thrombocytopenia without other additional manifestations
- We still do not give the importance we should give to the peripheral blood smear

The percentage of patients with inherited thrombocytopenias diagnosed with ITP is very high

- 38% in ANKRDD26-RT (Noris P, et al. Blood. 2011;117:6673-80)
- 62% in Bernard Soulier (Sanchez-Guiu I, et al. Orphanet J Rare Dis. 2014;9:213)
- 35% in MYH9-RD (Rabbolini DJ, et al. Platelets. 2018;29:793-800)
- 31% of different forms (57/181); 77% inappropriately treated, and 26% splenectomized (Noris P, et al. Haematologica. 2014;99:1387-94)

We must offer the right treatment to patients

Bleeding

- Platelet transfusions, antifibrinolytic agents, desmopressin

Thrombopoietin receptor agonists

- Eltrombopag: MYH9-RD, Wiskott-Aldrich, DIAPH1-RD
- Romiplostim: THPO mutations

Allogeneic hematopoietic progenitor transplantation

- Congenital amegakaryocytic thrombopenia; Radioulnar synostosis with amegakaryocytic thrombocytopenia
- Wiskott-Aldrich
- Hematologic malignancies predisposing to hematologic malignancies (ANKRD26-RD, RUNX1-RD, ETV6-RD)

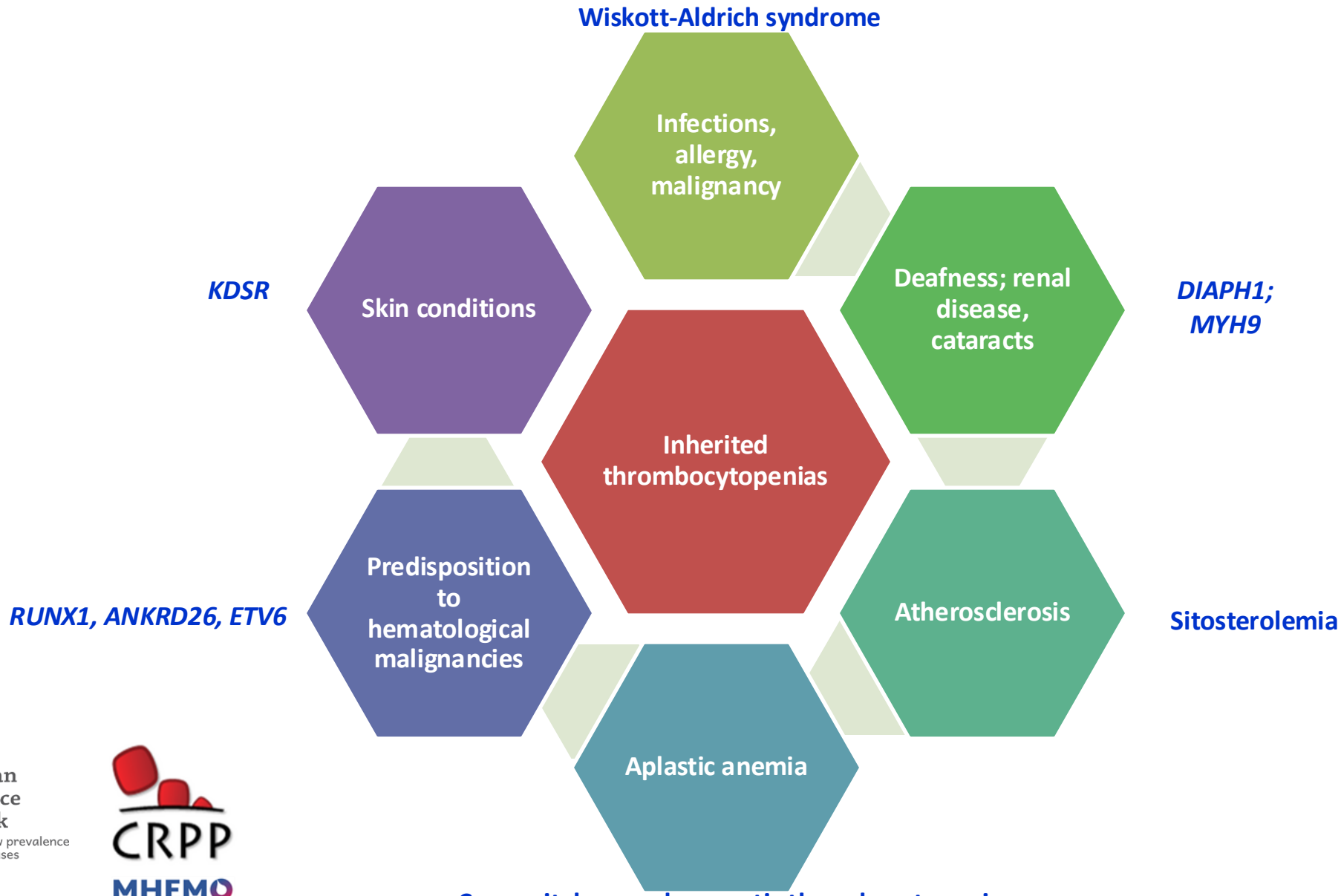
Extra-hematological manifestations (e.g. MYH9-RD)

- Renin-angiotensin or ARAII blockade
- Cochlear implants
- Cataract surgery

Predisposition to leukemias

- Family screening
- Genetic counseling
- Regular blood/marrow and cytogenetic testing

Suspecting and reaching a correct diagnosis is a vital approach in providing patients with appropriate management and prevent unnecessary treatments



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Thank you

Take home messages

1. Inherited thrombocytopenia is a heterogeneous spectrum of disorders ranging from isolated mild thrombocytopenia to forms that predispose to additional serious diseases.
2. Inherited thrombocytopenia is under-recognized; when it presents with isolated thrombocytopenia, it is often misdiagnosed as ITP, leading to inappropriate treatment.
3. In clinical practice, the recognition of lifelong thrombocytopenia not attributable to other causes is sufficient to investigate its genetic origin; a precise diagnosis has an impact on patient management and prognosis in many cases.