Sistema Socio Sanitario
Regione Lombardia
Fondazione IRCCS Policlinico San Matteo
ATS Pavia

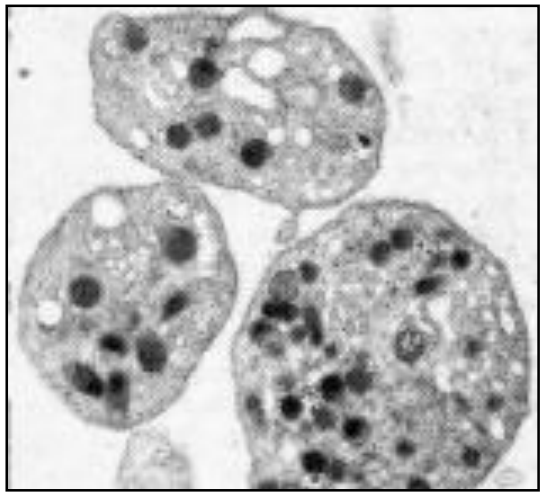
PIASTRINOPENIE COSTITUZIONALI «PERICOLOSE»: QUANDO L'APPARENZA INGANNA

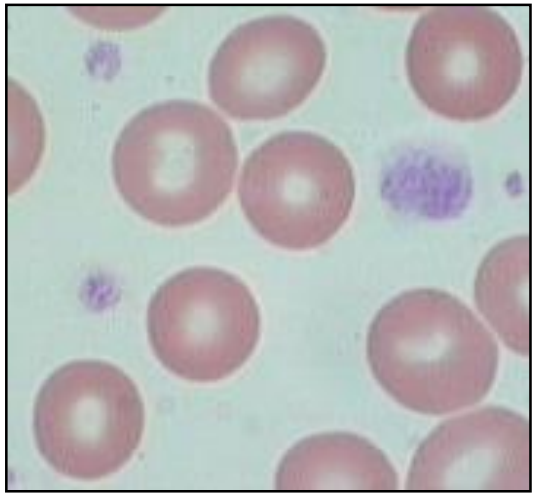
Federica Melazzini, MD PhD

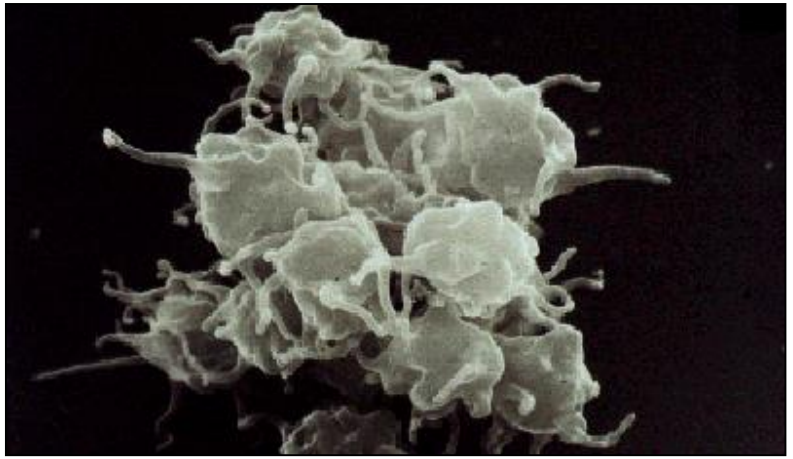
SC Medicina Generale I, Fondazione IRCCS Policlinico San Matteo

SUMMARY

- Inherited thrombocytopenias: past & present
- Cases
- Predisposing Syndromes
- Discussions & Conclusions

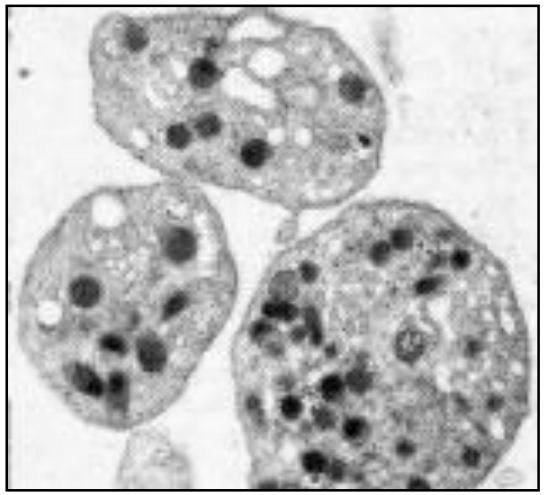


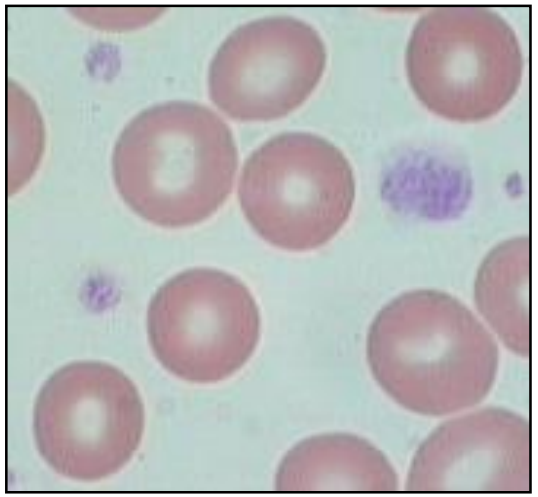


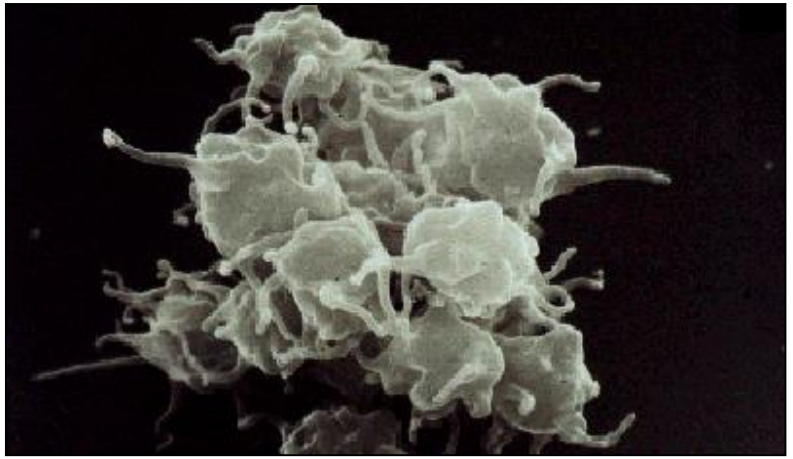


SUMMARY

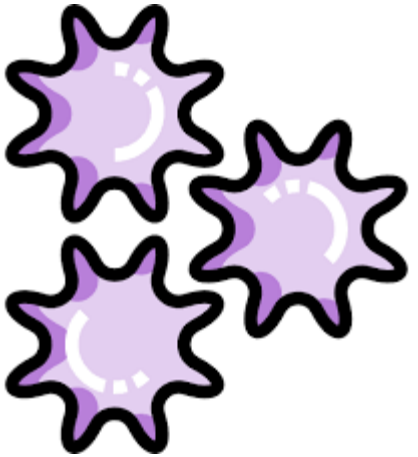
- Inherited thrombocytopenias: past & present
- Cases
- Predisposing Syndromes
- Discussions & Conclusions



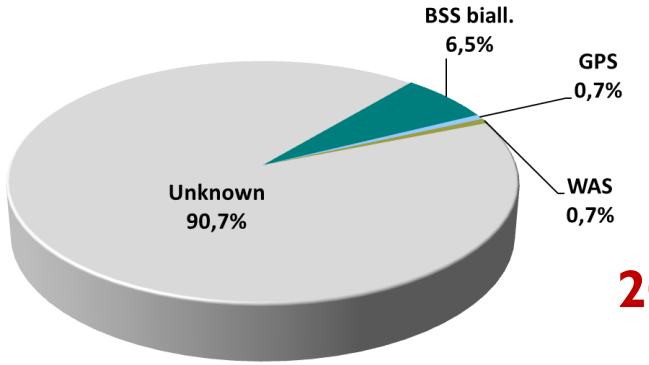




INHERITED THROMBOCYTOPENIAS



- Rare disorders
- Reduced platelet number (<150 x 10^9/L)
- Mainly primary haemostasis defects
- Bleeding tendency not always correlates with platelet count
- Often misdiagnosed (unnecessary therapies)
- Genetically heterogeneous though often with similar phenotypes



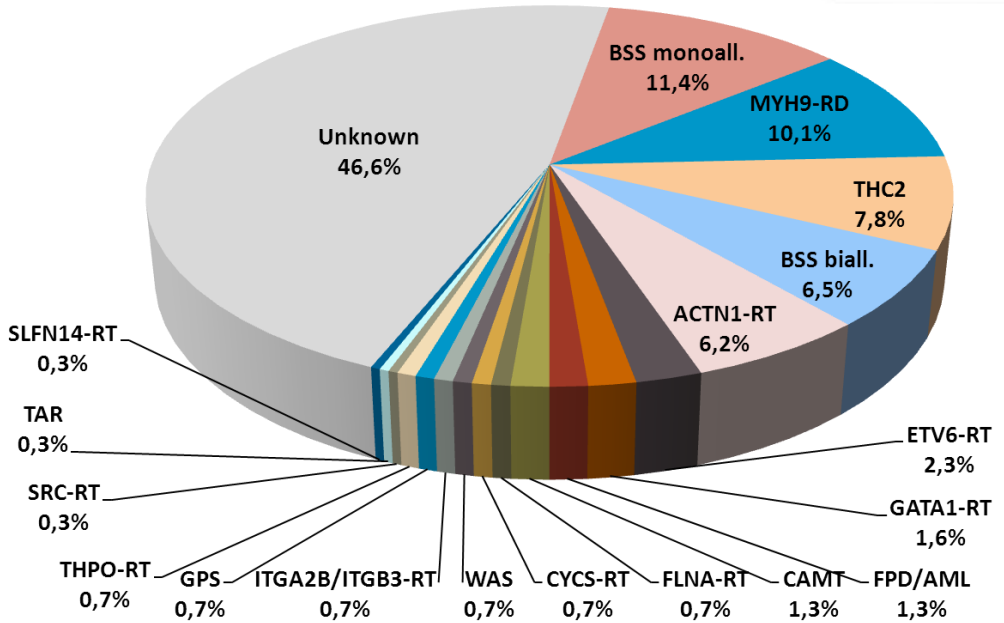
Few forms, all with severe bleeding

2000

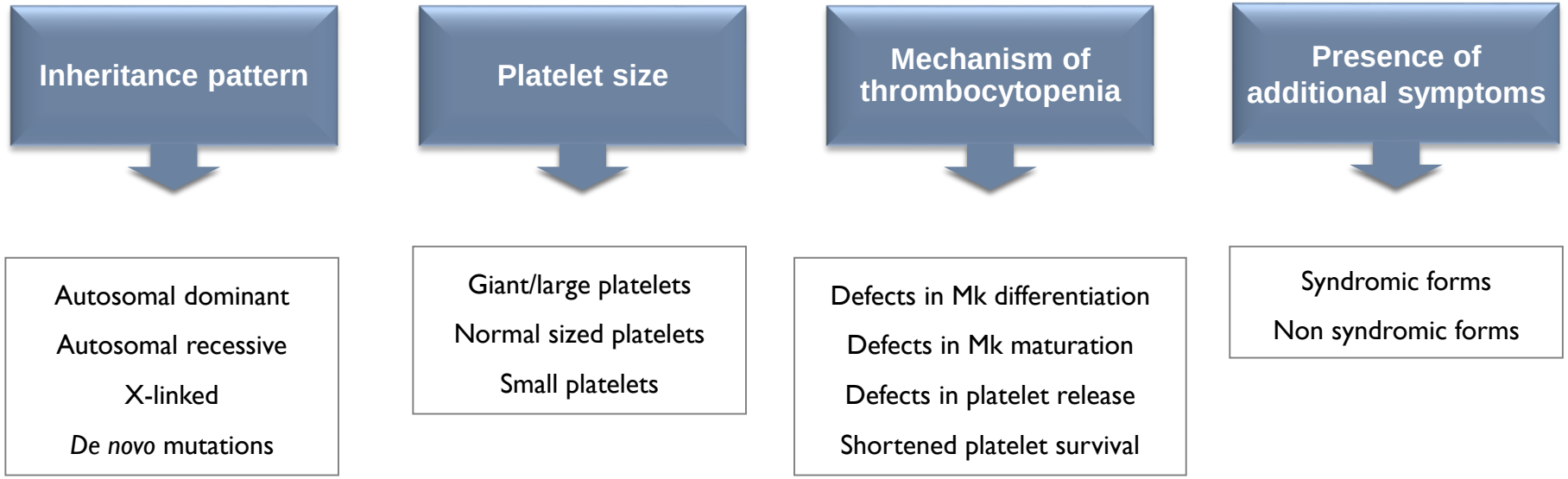
2023

Many forms. Mild or no bleeding in most cases

Risk of developing additional disorders



«OLD» CLASSIFICATION FOR ITs

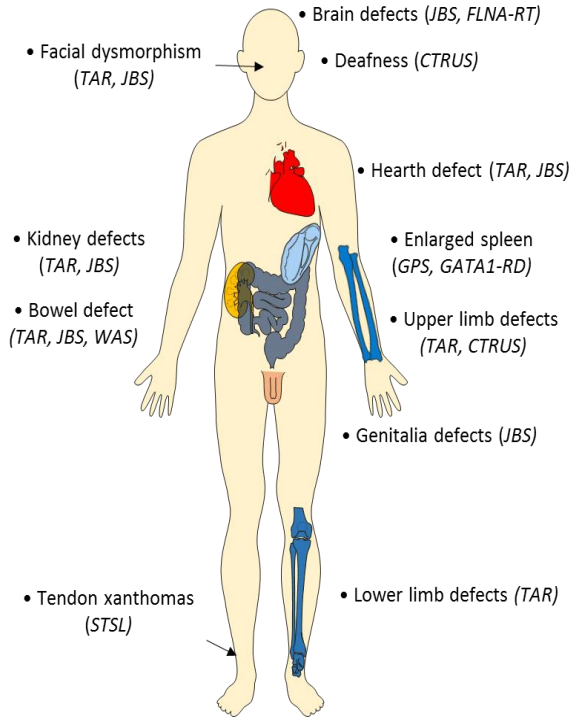


«NEW» CLASSIFICATION FOR ITs

ONLY thrombocytopenia

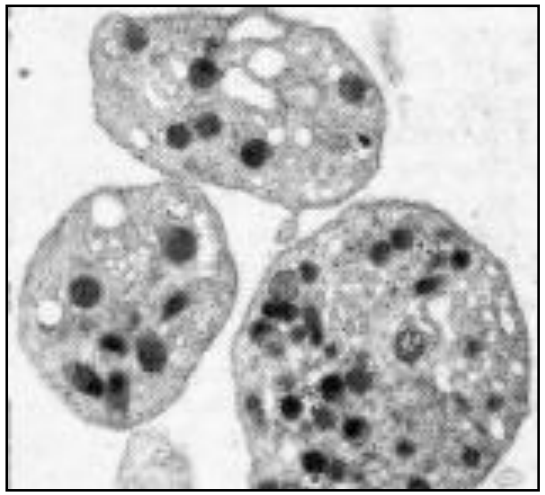
OTHER Congenital Defects

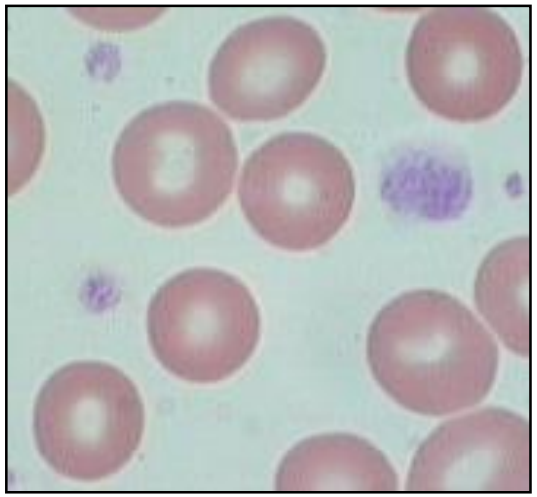
PREDISPOSING SYNDROMES

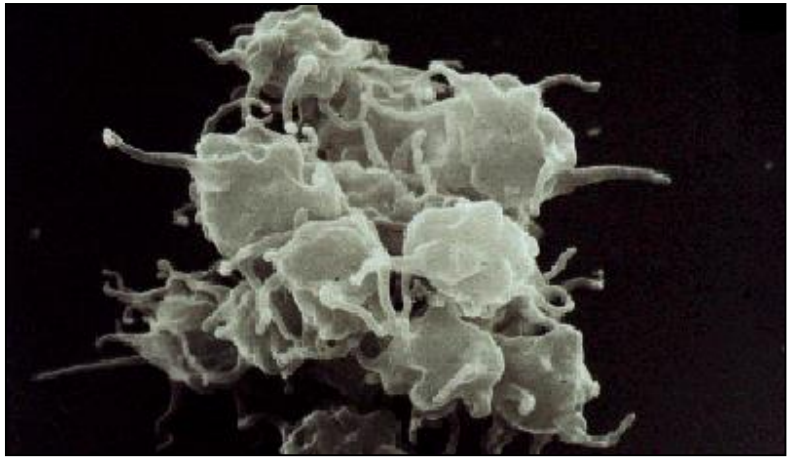


SUMMARY

- Inherited thrombocytopenias: past & present
- Cases
- Predisposing Syndromes
- Discussions & Conclusions





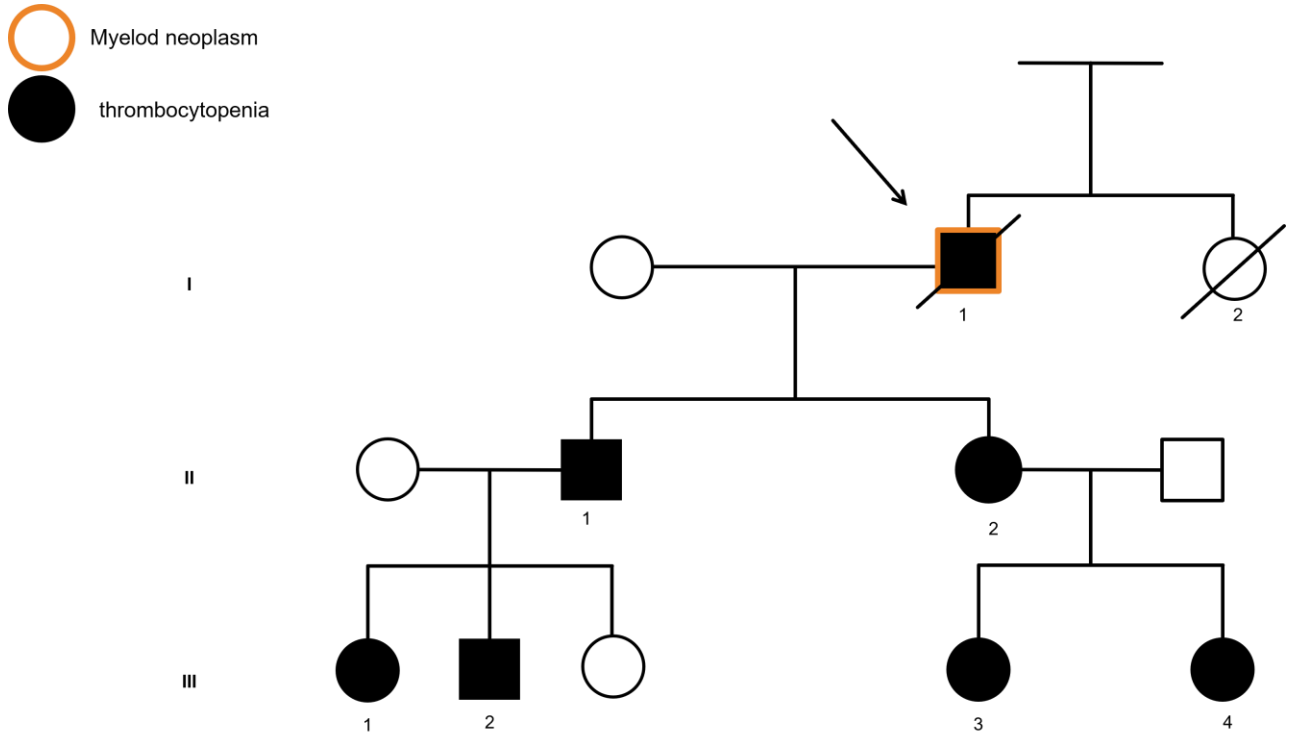


Male, 60 yrs. Chronic Thrombocytopenia .Mild bleedings.Previous “familial”(???) ITP dg

Lab: ↓ aggp to epinephrine; ↓ GpIaIIa expression

CMML type 2, CPSS
SCORE 2
HSCT
Exitus for severe GVHD

?



Male, 60 yrs. Chronic Thrombocytopenia .Mild bleedings.Previous "familial"(???) ITP dg

Lab: ↓ aggp to epinephrine; ↓ GpIaIIa expression

CMML type 2, CPSS SCORE 2
HSCT
Exitus for severe GVHD

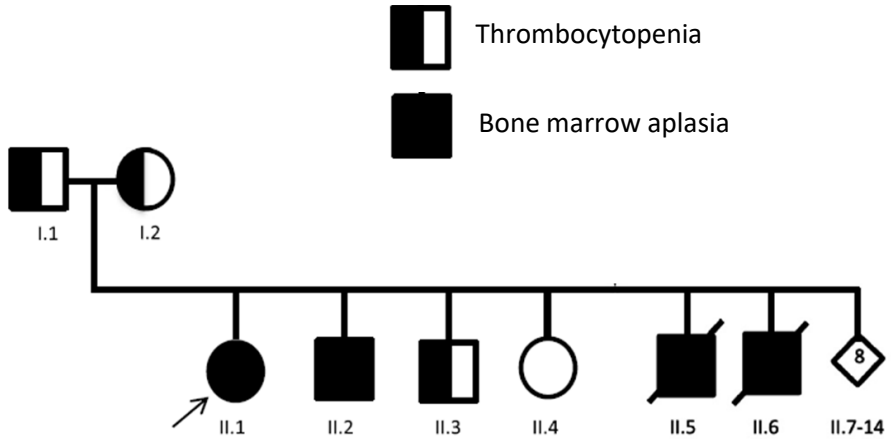
?

Female, 5 yrs. Inherited thrombcytopenia

Bone Marrow Aplasia 7 yrs

HSCT failure

?



Male, 60 yrs. Chronic Thrombocytopenia .Mild bleedings.Previous "familial"(???) ITP dg

Lab: ↓ aggp to epinephrine; ↓ GpIaIIa expression

CMML type 2, CPSS SCORE 2
HSCT
Exitus for severe GVHD

?

Female, 5 yrs. Inherited thrombcytopenia

Bone Marrow Aplasia 7 yrs

HSCT failure

?

Female. 32 yrs:AML. AD inherited thrombocytopenia (never mentioned before AML dg)

Successful HSCT from a sister

AML one year later

Also the donor develops AML

?

Male, 60 yrs. Chronic Thrombocytopenia .Mild bleedings.Previous "familial"(???) ITP dg

Lab: ↓ aggp to epinephrine; ↓ GpIaIIa expression

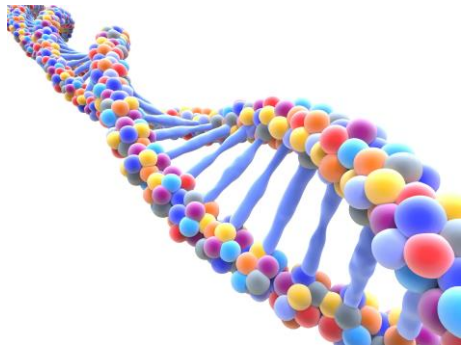
CMML type 2, CPSS SCORE 2
HSCT
Exitus for severe GVHD

?

Female, 5 yrs. Inherited thrombcytopenia

Bone Marrow Aplasia 7 yrs

HSCT failure



Female. 32 yrs:AML. AD inherited thrombocytopenia (never mentioned before AML dg)

Successful HSCT from a sister

AML one year later

Also the donor develops AML

?

Male, 60 yrs. Chronic Thrombocytopenia .Mild bleedings.Previous "familial"(???) ITP dg

Lab: ↓ aggp to epinephrine; ↓ GpIalla expression

CMML type 2, CPSS SCORE 2
HSCT
Exitus for severe GVHD

Germline monoallelic *RUNX1* mutation

Female, 5 yrs. Inherited thrombcytopenia

Bone Marrow Aplasia 7 yrs

HSCT failure

Germline biallelic *THPO* mutation

A TPO receptor agonist restores hemopoiesis

Female. 32 yrs: AML. AD inherited thrombocytopenia **(never mentioned before AML dg)**

Successful HSCT from a sister

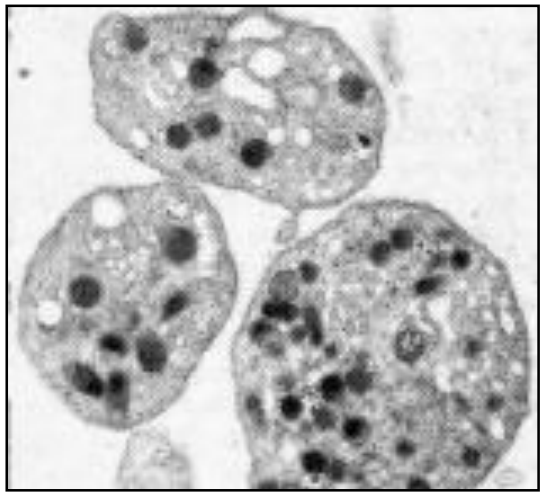
AML one year later

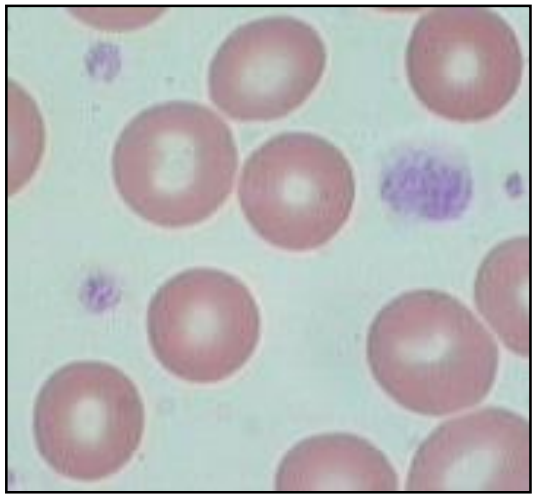
Also the donor develops AML

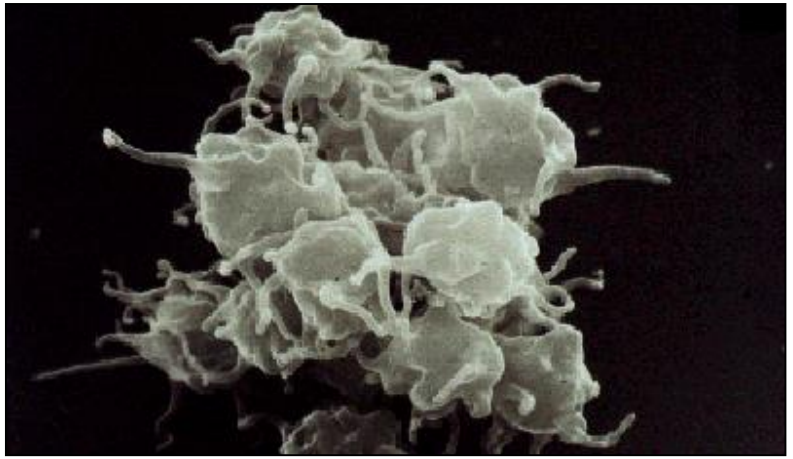
Germline monoallelic *ANKRD26* mutation In both women

SUMMARY

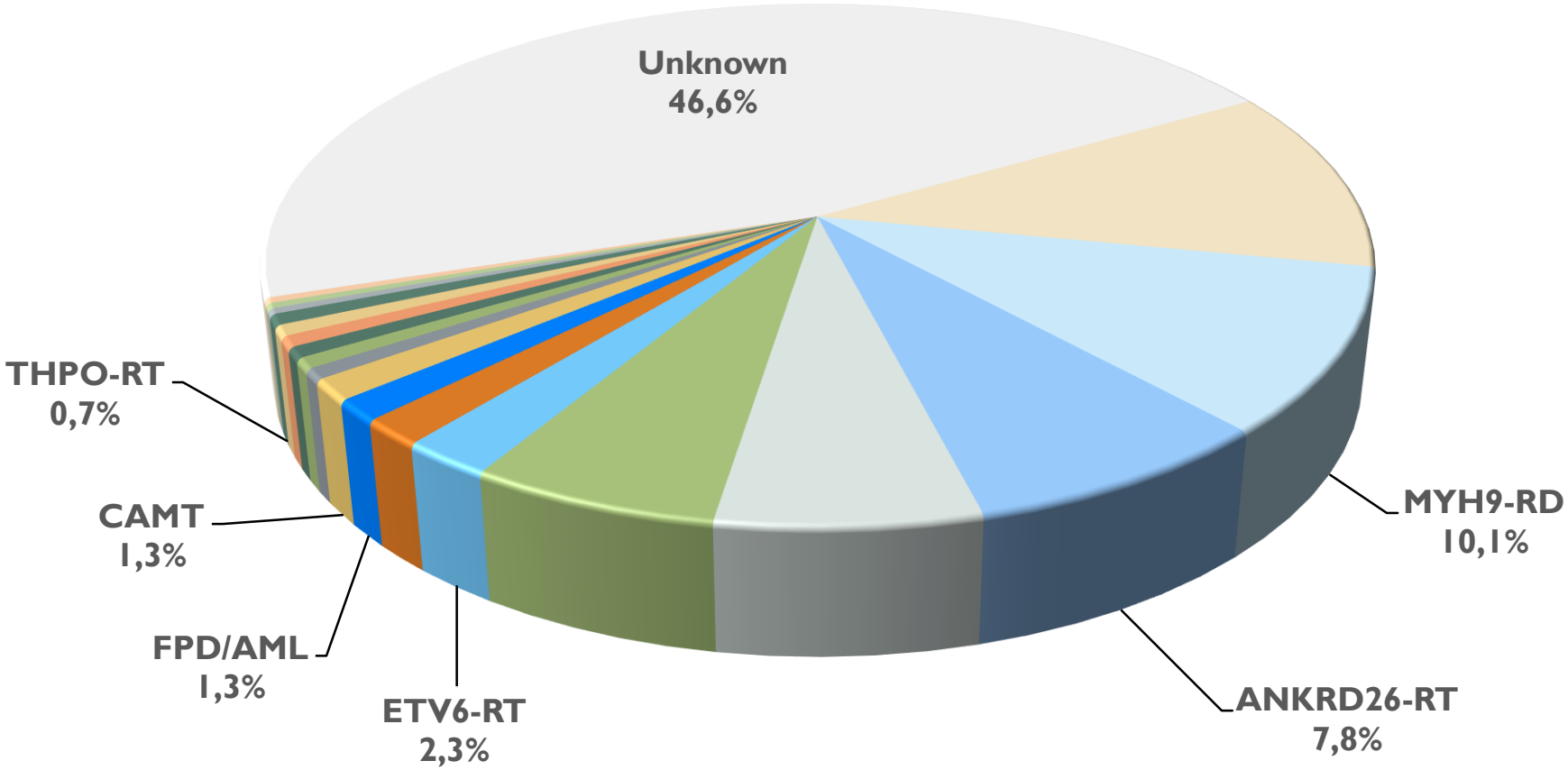
- Inherited thrombocytopenias: past & present
- Cases
- Predisposing Syndromes
- Discussions & Conclusions

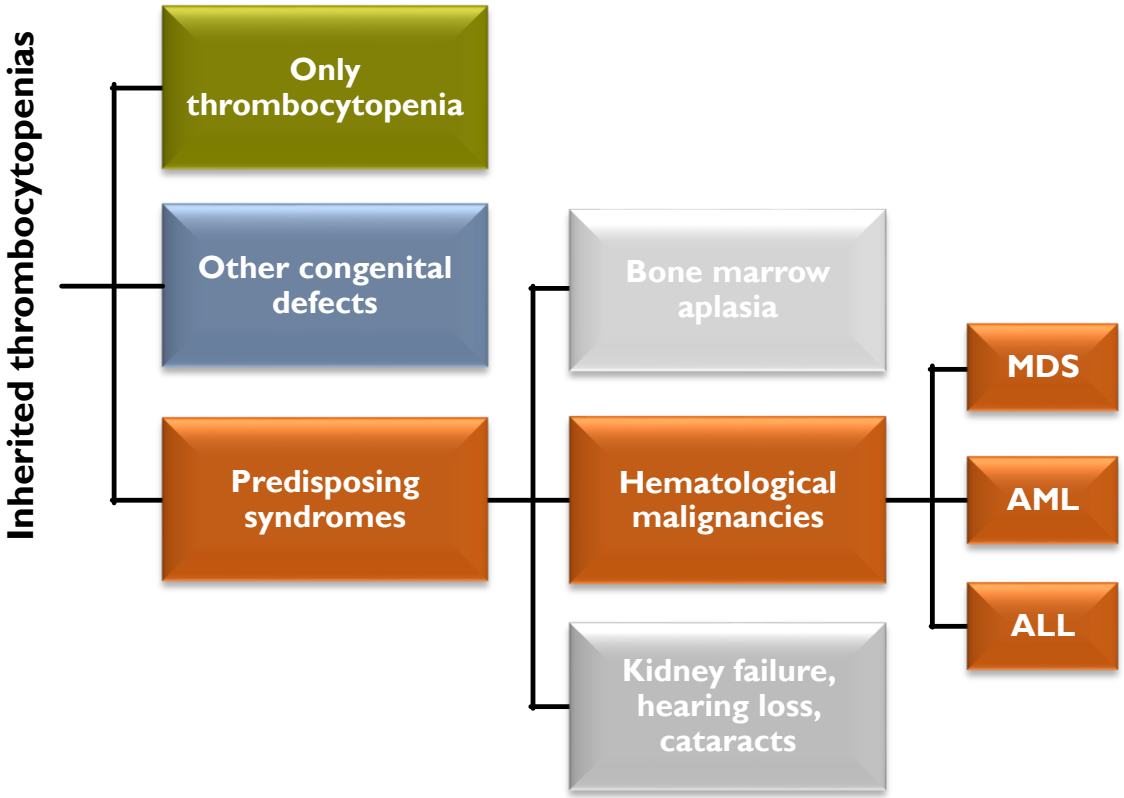


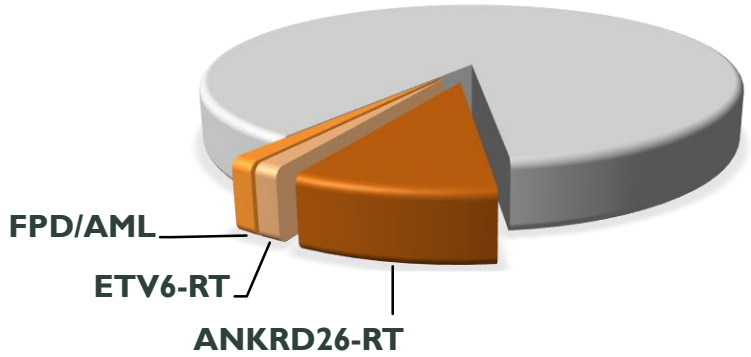




45% of patients with known inherited thrombocytopenias are at risk of developing additional disorders



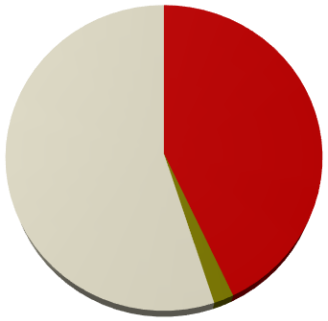

Inherited thrombocytopenias
Only thrombocytopenia
Other congenital defects
Predisposing syndromes
Bone marrow aplasia
Hematological malignancies
Kidney failure, hearing loss, cataracts
MDS
AML
ALL


FPD/AML
ETV6-RT
ANKRD26-RT

	ANKRD26-RT	FPD/AML	*ETV6*-RT
Gene	***ANKRD26***	***RUNX1***	***ETV6***
Transmission	AD	AD	AD
Relative frequency (% of known IT)	18%	3%	5%
Thrombocytopenia	Mild/moderate	Mild/absent	Mild
Platelet size	Normal	Normal	Normal
Platelet Function	Normal	Abnormal	Normal
Bleeding tendency	Absent/mild	Absent/moderate	Absent/mild

% of patients with hematological malignancies

FPD/AML
45%

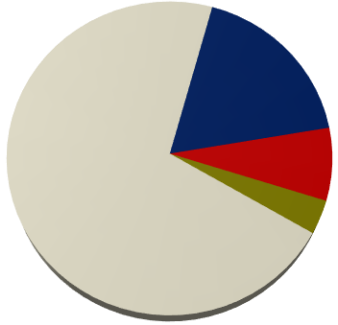


Any age,
median 34 yrs

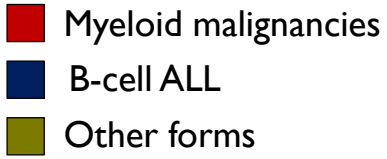
ANKRD26-RT
8%

Any age,
median 41 yrs

ETV6-RT
29%



B-ALL: childhood
Myeloid: any age



THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Myeloid neoplasms with germ line predisposition

Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with germ line *DDX41* mutation*
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation*
Myeloid neoplasms with germ line *ANKRD26* mutation*
Myeloid neoplasms with germ line *ETV6* mutation*
Myeloid neoplasms with germ line predisposition and other organ dysfunction
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with BM failure syndromes
Myeloid neoplasms associated with telomere biology disorders
JMML associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders
Myeloid neoplasms associated with Down syndrome*

*Lymphoid neoplasms also reported.

We do not know why patients with FDP/AML, *ANKRD26*-RT and *ETV6*-RT are prone to hematological malignancies.

However, these disorders have some common features:

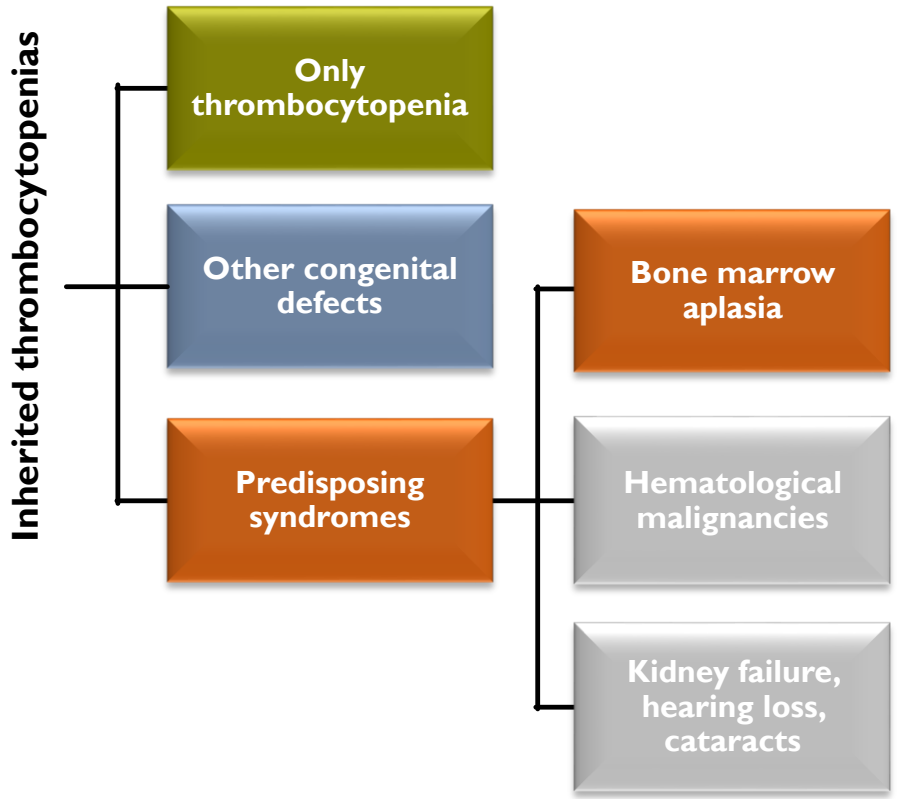
RUNX1 and **ETV6** are transcription factors and mutations result in loss of transcriptional repression. Mutation in **ANKRD26** affect the 5'UTR of the gene and result in loss of transcriptional repression by RUNX1.

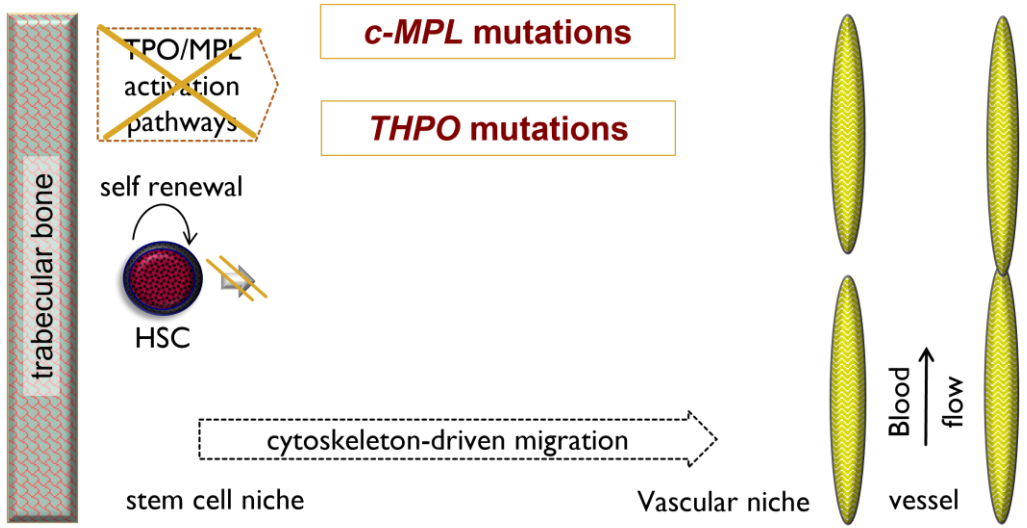
The balance between proliferation and differentiation of hemopoietic progenitors is deranged: increased proliferation.

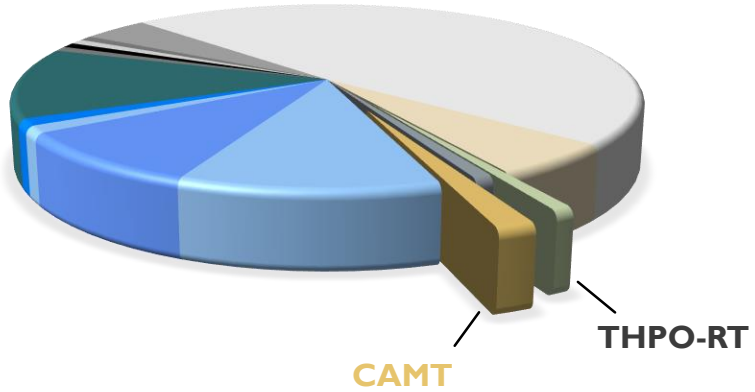
Penetrance of malignancies is incomplete: other factors are required for oncogenesis.

RECOMMENDATIONS

- Bone marrow examination with cytogenetic analysis at diagnosis
- Complete blood count and clinical examination at regular intervals (each year?)
- Any time significant changes in the blood counts are identified: repeat bone marrow examination (and cytogenetic analysis)
- In case patients develop hematological malignancies, HSCT is an important option. **If a related donor is available, exclude that he is affected too by the same disorder: transplanting from affected relatives exposes to the risk of developing again a new hematological malignancy**


Inherited thrombocytopenias
Only thrombocytopenia
Other congenital defects
Predisposing syndromes
Bone marrow aplasia
Hematological malignancies
Kidney failure, hearing loss, cataracts


trabecular bone
TPO/MPL activation pathways
c-MPL mutations
THPO mutations
self renewal
HSC
cytoskeleton-driven migration
stem cell niche
Vascular niche
Blood flow
vessel

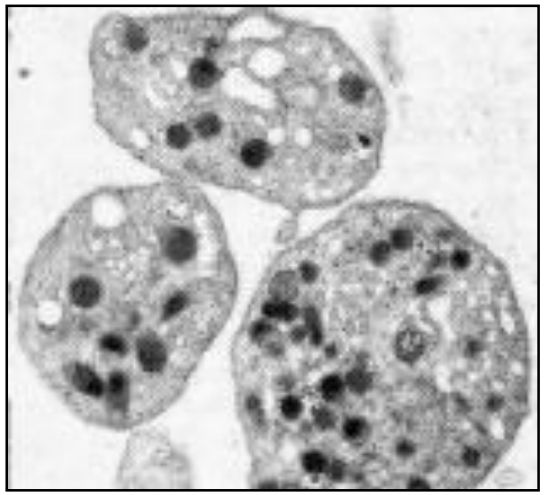

CAMT
THPO-RT

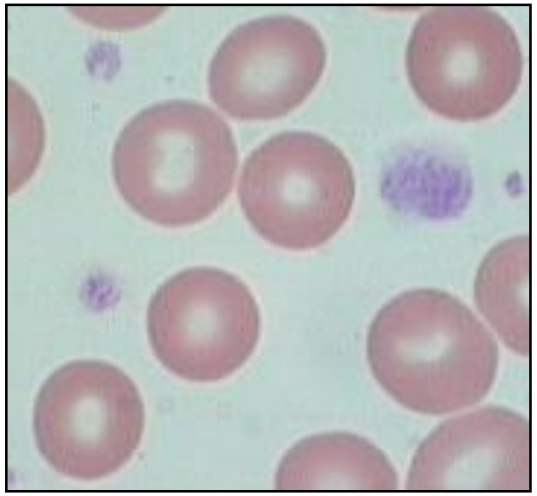
	CAMT	CAMT variant
Gene	***MPL***	***THPO***
Frequency	Low	Low
Transmission	AR	AR
Thrombocytopenia	Severe	Severe/moderate
Platelet size	Normal	Normal
Evolution into bone marrow aplasia	Infancy	Infancy/young adult
HSCT	Effective	Not effective

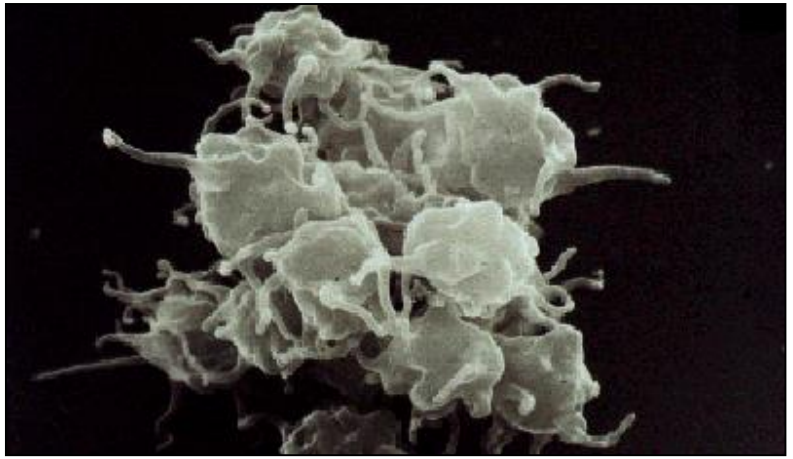
	CAMT	CAMT variant
Gene	***MPL***	***THPO***
Frequency	Low	Low
Transmission	AR	AR
Thrombocytopenia	Severe	Severe/moderate
Platelet size	Normal	Normal
Evolution into bone marrow aplasia	Infancy	Infancy/young adult
HSCT	**Effective**	**Not effective**

SUMMARY

- Inherited thrombocytopenias: past & present
- Cases
- Predisposing Syndromes
- Discussions & Conclusions





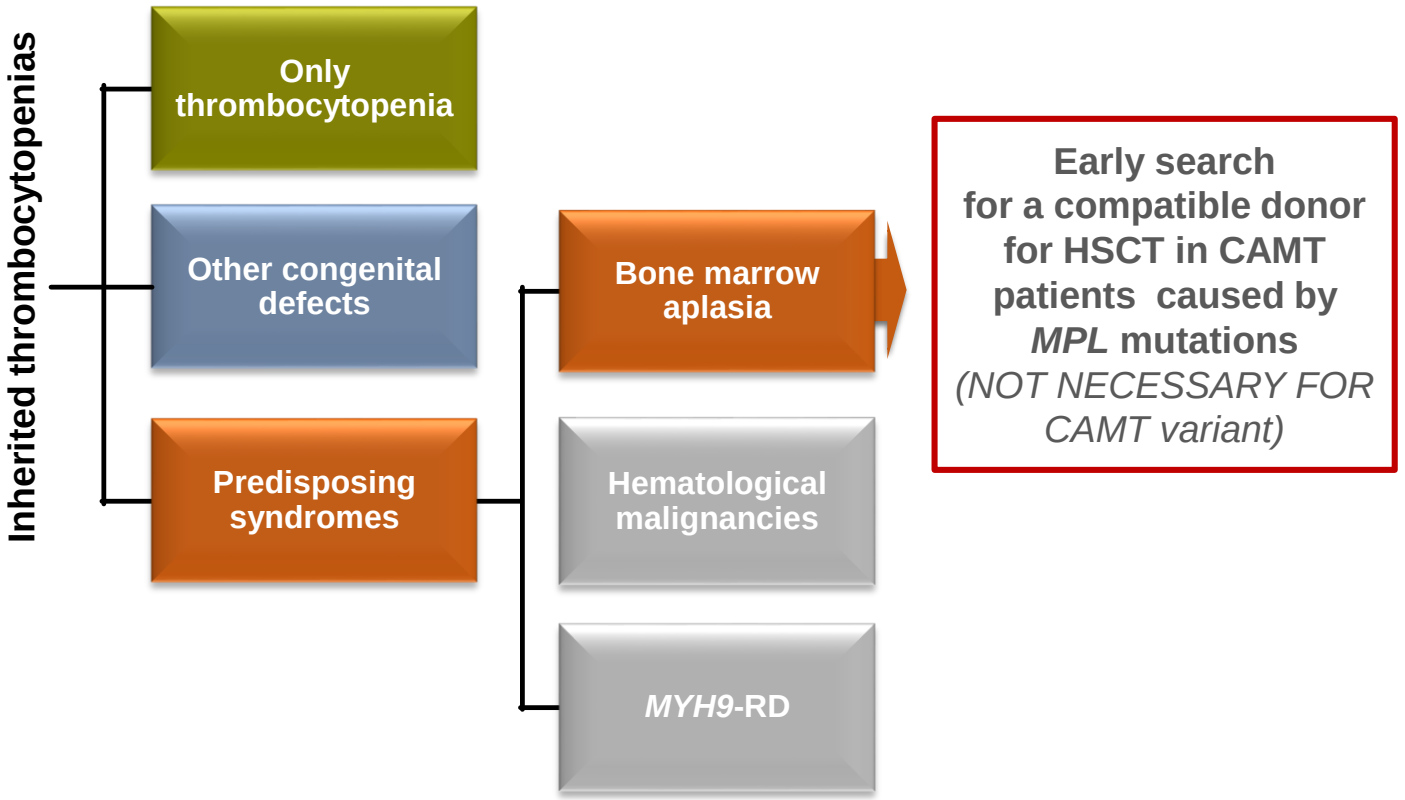


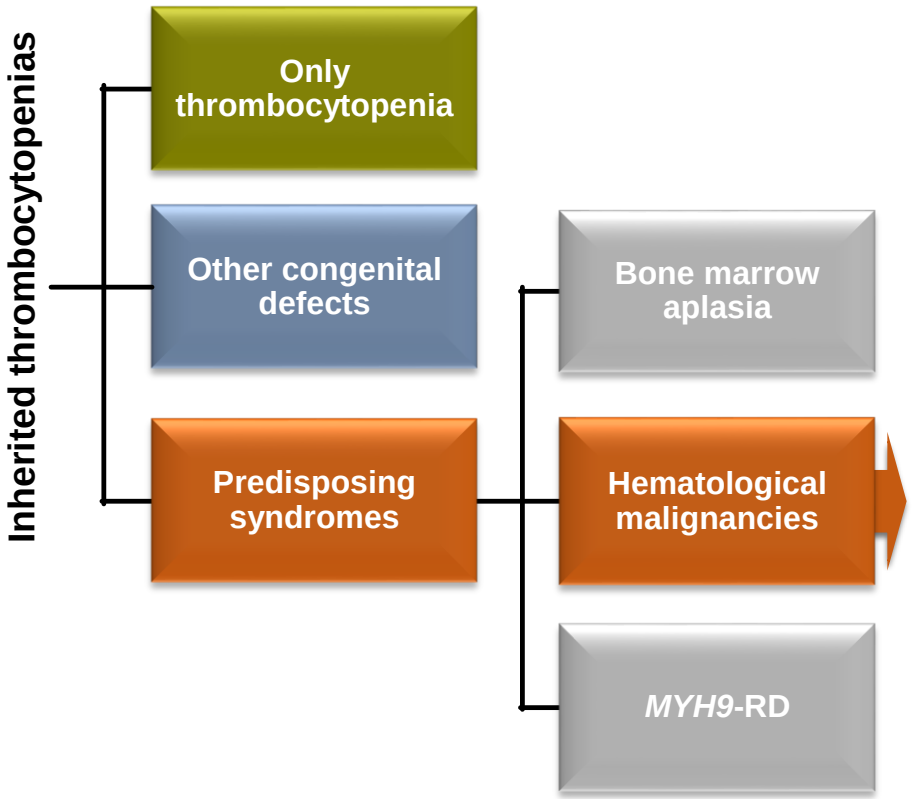
DISCUSSION

- ✓ Why look for a molecular diagnosis of an inherited thrombocytopenia?
- ✓ How to reach the molecular diagnosis of an inherited thrombocytopenia?

DISCUSSION

- ✓ Why look for a molecular diagnosis of an inherited thrombocytopenia?
- ✓ How to reach the molecular diagnosis of an inherited thrombocytopenia?


Inherited thrombocytopenias
Only thrombocytopenia
Other congenital defects
Predisposing syndromes
Bone marrow aplasia
Hematological malignancies
MYH9-RD
Early search for a compatible donor for HSCT in CAMT patients caused by MPL mutations (NOT NECESSARY FOR CAMT variant)



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, mutational screening

DISCUSSION

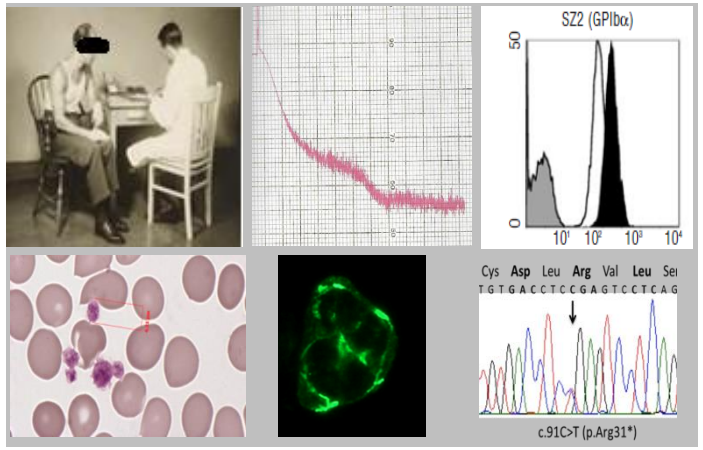
- ✓ Why look for a molecular diagnosis of an inherited thrombocytopenia?

- ✓ How to reach the molecular diagnosis of an inherited thrombocytopenia?

MULTI step diagnostic approach

SINGLE step diagnostic approach

MULTI step diagnostic approach

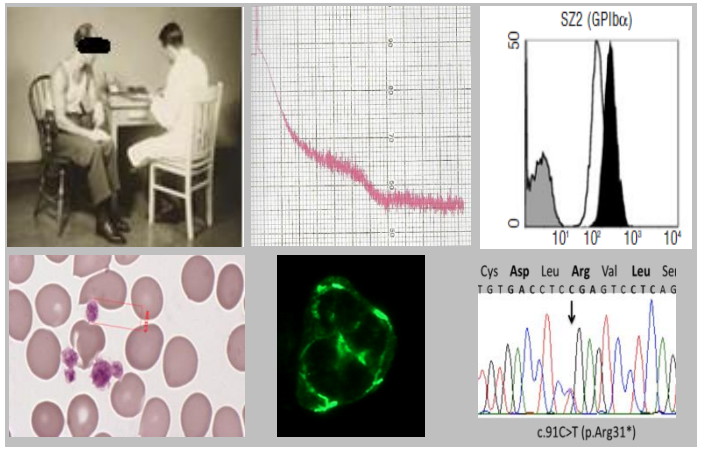


Time consuming

Performed in many non-specialized laboratories

SINGLE step diagnostic approach

MULTI step diagnostic approach



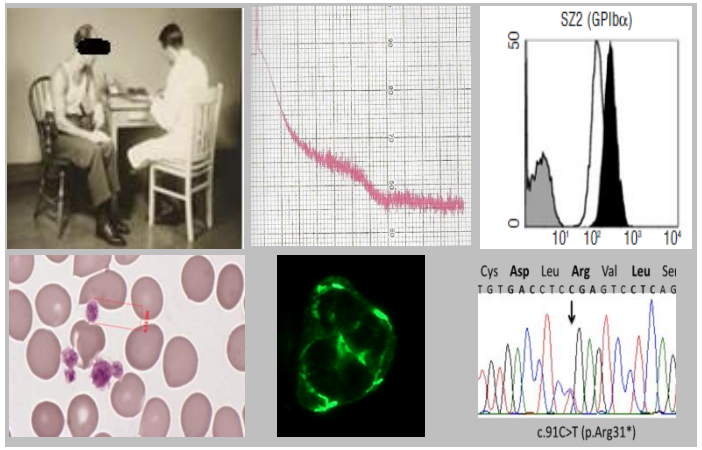
Time consuming

Performed in many non-specialized laboratories

SINGLE step diagnostic approach

- ✓ **Targeted NGS testing**
- ✓ **Whole exome sequencing (WES)**
- ✓ **Whole genome sequencing (WGS)**

MULTI step diagnostic approach



Time consuming

Performed in many non-specialized laboratories

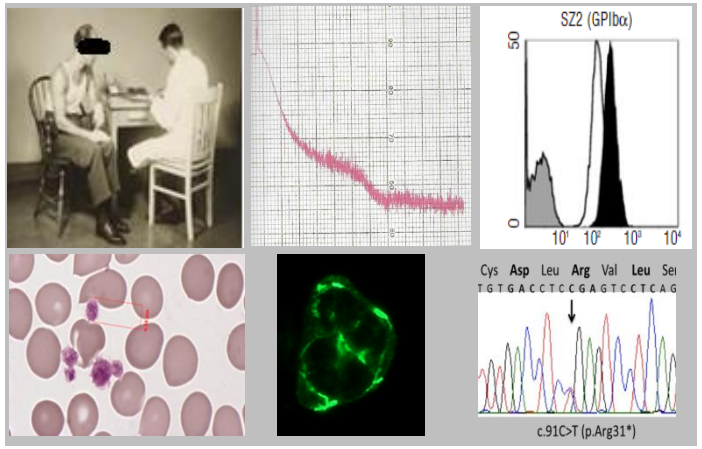
SINGLE step diagnostic approach

Available only in a few specialized laboratories

Quick if patient has known mutations

<u>Discriminating between pathogenic and non-pathogenetic variants may be a major problem</u>

MULTI step diagnostic approach

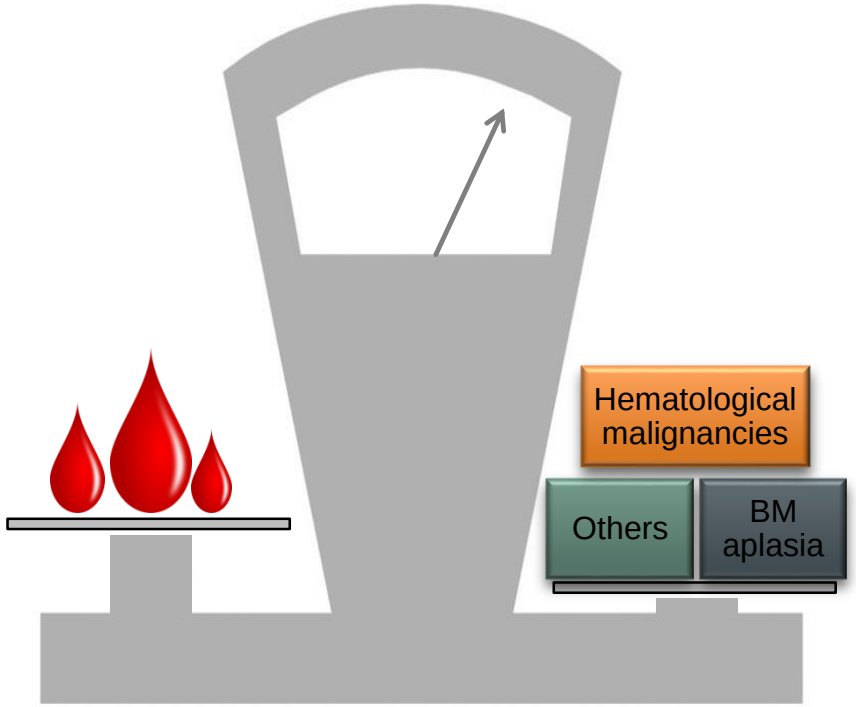


SINGLE step diagnostic approach

Targeted NGS testing

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

CONCLUSION



Bleeding is not the biggest risk for most patients with ITs
A multidisciplinary approach is required to reach the correct molecular diagnosis to arrange the most appropriate treatment and follow-up for all patients

GRAZIE!

Federica Melazzini

federica.melazzini@unipv.it

f.melazzini@smatteo.pv.it