Inquadramento Generale delle Piastrinopenie Congenite

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Siset Training Center
Corso Malattie Emorragiche
4-8 giugno 2018

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Piastrinopenie Congenite
Take Home Message

- Distinguere le piastrinopenie congenite da quelle acquisite per evitare trattamenti inutili o dannosi

- Considerare che il rischio emorragico spontaneo è normale o basso nella maggior parte delle condizioni

- Considerare che le piastrinopenie congenite possono associarsi 1) a patologie di altri organi o apparati 2) ad aumentato rischio di patologie ematologiche maligne

Piastrinopenie Congenite

Approccio Diagnostico

Piastrinopenie congenite = Piastrinopenie Croniche

Obiettivo principale per il clinico:

distinguere le trombocitopenie acquisite (>> le forme immuni, ma anche da mielodisplasia, mielofibrosi, da farmaci etc.) da quelle congenite

Caso Clinico n.1

- Lorena M. donna di 55 aa, in buona salute, non disturbi particolari

- Piastrinopenia (= 35-45 x 10^6/µL) in tutti gli emocromi eseguiti negli ultimi 20 aa. Primo riscontro durante la I gravidanza all'eta' di 30 aa. Somministrati corticosteroidi, con lieve incremento della conta piastrinica (fino a 65 x 10^6/µL). MPV 15 fL

- 2 parti vaginali senza complicanze emorragiche, 1 aborto spontaneo a 5 mesi

- Assenza di diatesi emorragica spontanea, mestruazioni nella norma

- Una figlia su due affetta da piastrinopenia (= 40.000/µL) senza diatesi emorragica, madre di due figli, di cui uno con piastrinopenia (=45.000/µL).

Caso Clinico n.1

- *Assenza di sintomi*
- *Evidenza di piastrinopenia costante durante un arco di tempo di decenni (dalla nascita?). Riscontro occasionale di piastrinopenia. Assenza di risposta alla terapia corticosteroidea*
- *Assenza di emorragie dopo "challenge emostatico"*
- *Assenza di emorragie spontanee*
- *Ereditarietà con modalità autosomico dominante*

Caso Clinico n.2

- Stefano C., giovane uomo di 30 aa, con conta piastrinica stabilmente oscillante tra 14 e 20 x 10^6 /µL, MPV 15 fL
- Diatesi emorragica lieve (ematomi dopo traumi lievi)
- Sordità neurosensoriale, cataratta bilaterale, insufficienza renale cronica
- Madre, piastrinopenica affetta da IRC in dialisi, deceduta all'età di 28 aa. dopo splenectomia (eseguita per correggere la piastrinopenia?)

Caso Clinico n.2

- *Piastrinopenia congenita*
- *Dissociazione tra conta piastrinica ed entità dei sintomi*
- *Coinvolgimento di altri organi ed apparati: forma "sindromica"*
- *Ereditarietà della piastrinopenia e dell'insufficienza renale. Splenectomia necessaria?*

Caso Clinico n.3

- Riccardo P., ragazzo di 11 aa con diatesi emorragica m
  epistassi recidivanti (1-2 episodi/mese) richiedenti talvolta tamponamento, facile formazione di ematomi spontanei

- Sanguinamento eccessivo dopo intervento di tonsillectomia all'età di 8 aa, necessario re-intervento per emostasi chirurgica.

- Conta piastrinica tra 80 e 90 x 10^6/µL

- Splenomegalia (diametro longitudinale 14 cm)

Caso Clinico n.3

- *Piastrinopenia congenita, diatesi emorragica spontanea severa*

- *Diatesi emorragica post-chirurgica severa*

- Conta piastrinica tra 80 e 90 x 10^6/µL
  Dissociazione tra conta piastrinica e sintomi emorragici

- Splenomegalia (diametro longitudinale 14 cm)
  Splenomegalia inusuale a 11 aa

Caso Clinico n.4

- Nadia B., giovane donna di 33 aa con piastrinopenia (10-50 x 10^6/µL) dall'età di 7 aa, resistente a corticosteroidi e immunoglobline ev. Assenza di sintomi emorragici, eccetto menorragie all'inizio dell'età fertile

- Splenectomia all'età di 17 aa

- Successivamente conta piastrinica tra 50 e 70 x 10^6/µL

Caso Clinico n.4 (continua)

- *Piastrinopenia congenita. Assenza di risposta a corticosteroidi e Ig ev. Diatesi emorragica spontanea assente*

- Splenectomia all'età di 17 aa

- *Assenza di risposta alla splenectomia*

- *Familiarità*

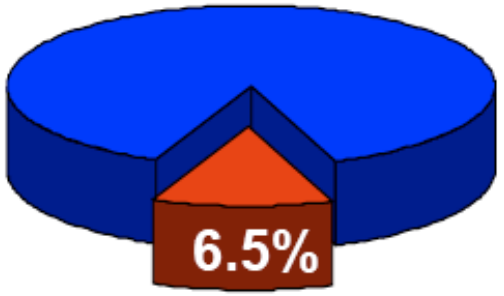
Trombocitopenie Congenite (TC)

- Disordini rari (1/100.000)
- Conta piastrinica ridotta (< 150 x 10^9/L)
- Difetti dell'emostasi primaria
- Diatesi emorragica non sempre correlata con la conta piastrinica
- Eterogenei da un punto di vista genetico sebbene spesso con un fenotipo simile
- **Spesso non riconosciute (somministrate terapie non necessarie)**

Genetic thrombocytopenias are often misdiagnosed with ITP

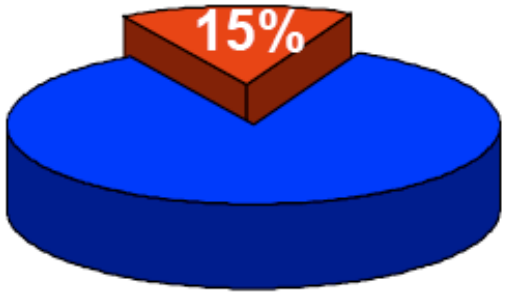
170 children diagnosed as ITP: a genetic form has been subsequently identified in 11. All of them had received steroids, ivIgG and/or alpha-interferon

(J Ped Hematol Oncol 2003;25:548
Thromb Res 2007;119:741)



undue therapies

7 of 46 adults-children with genetic thrombocytopenias have been splenectomized because misdiagnosed with ITP *(Haematologica 2004;89:1218)*



Courtesy of C.L. Balduini

To differentiate inherited from acquired thrombocytopenias, consider:

- **Medical history**
- **Systems review**
- **Blood count**
- **Peripheral blood film**

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- Medical history
- Systems review
- Blood count
- Peripheral blood film

Quando Sospettare una Trombocitopenia Congenita Importanza della Storia Clinica

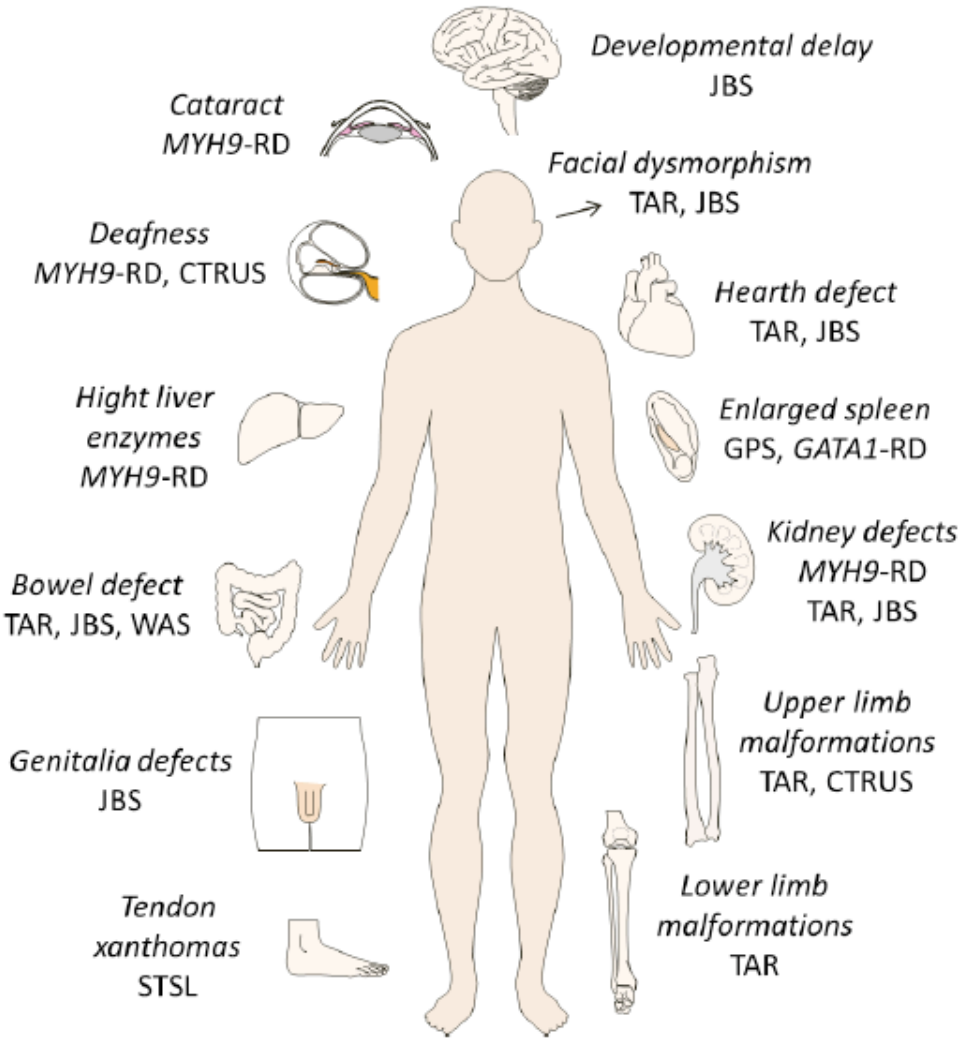
- Riscontro accidentale di ridotta conta piastrinica in emocromi successivi (*domanda chiave: ha mai avuto una conta piastrinica normale?*)
- Riscontro di familiarita' per trombocitopenia
- Da escludere in presenza di nuovi sintomi emorragici in un adulto con piastrinopenia. Conta piastrinica e sintomi emorragici rimangono costanti nelle TC

To differentiate inherited from acquired thrombocytopenias, consider:

- Medical history
- Systems review
- Blood count
- Peripheral blood film

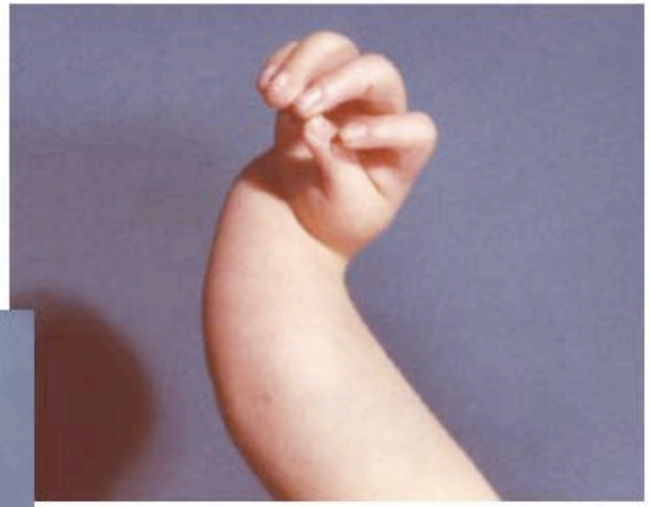
Approximately 50 % of Inherited Thrombocytopenia Are Syndromic Disorders

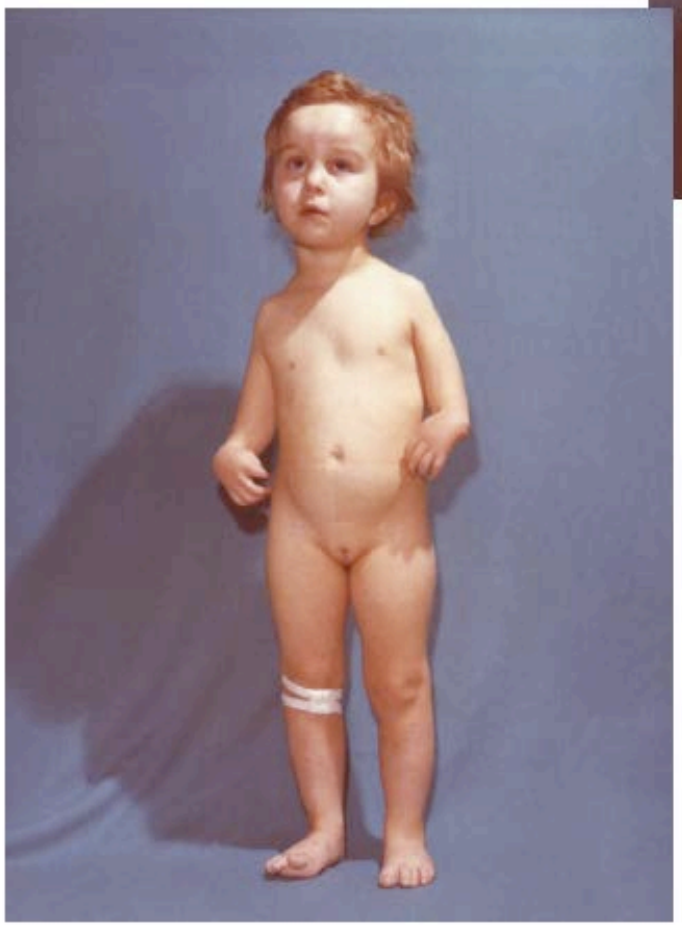
Elements of physical examination suggesting that thrombocytopenia is genetic



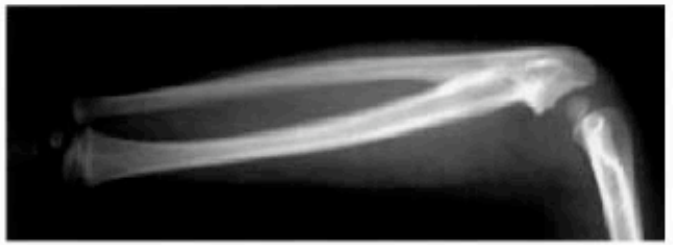
Balduini et al, Sem Thromb Hemost 2013;39:161-171

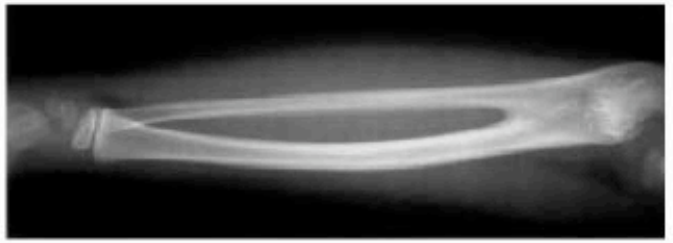
Trombocitopenia con assenza del radio





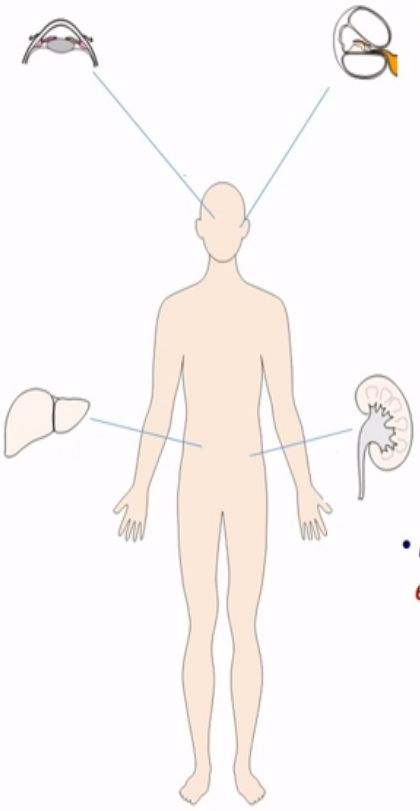
Trombocitopenia con sinostosi radio-ulnare





Courtesy of C.L. Balduini

Acquired manifestations in 351 consecutive patients enrolled in the Italian registry for *MYH9*-related disease



18%: Juvenile cataracts
(mean age: 21 years)

- *Bilateral in 65% of cases*

55%: Sensorineural deafness
(mean age: 31 years)

- *Mild hearing loss to profound deafness*
- *Progressive in most cases*

50%: Abnormalities of liver enzymes

- *No liver dysfunction*

30%: Nephropathy
(mean age: 29 years)

- *Progressive: in most cases, it evolves to end-stage renal disease within 5-10 years*

A. Pecci *ISTH 2017, Berlin*

To differentiate inherited from acquired thrombocytopenias, consider:

- Medical history
- Systems review
- Blood count
- Peripheral blood film

Per Differenziare Trombocitopenie Congenite da Quelle Acquisite….

- Numero e **volume** delle piastrine..

Essential Features of Inherited Thrombocytopenia According to Platelet Size

Disease (abbreviation, MIM) references	No. of families	Inheritance	Gene (localization)	Other features
Large platelets				
MYH9-related disease (*MYH9*-RD, nd)[13]	220	AD	*MYH9* (22q12–13)	Giant platelets, leukocyte inclusions, cataracts, nephropathy, deafness, elevated liver enzymes
Paris-Trousseau thrombocytopenia (TCPT, 188025/600588), Jacobsen syndrome (JBS, 147791)[51]	200	AD	Large deletions (11q23)	Cardiac and facial defects, developmental delay +/− other defects
Biallelic and monoallelic Bernard–Soulier syndrome (BSS, 231200)[30]	140 and 53	AR-AD	*GP1BA* (17p13), *GPIBB* (22q11), *GP9* (3q21)	Giant platelets (biallelic forms)
Gray platelet syndrome (GPS, 139090)[52]	26	AD-AR	*NBEAL2* (3p21.1)	Giant and "pale" platelets, evolutive myelofibrosis, splenomegaly, high serum vitamin B12
Platelet-type von Willebrand disease (PTVWD, 177820)[53]	20	AD	*GPIBA* (17pter-p12)	Possible giant platelets, platelet count goes down under stress
FLNA-related thrombocytopenia (FLNA-RT, nd)[54]	4	XL	*FLNA* (Xq28)	Platelets from small to giant; usually associated with periventricular nodular heterotopia (MIM 300049)
TUBB1-related thrombocytopenia (TUBB1-RT, nd)[32]	1	AD	*TUBB1* (6p21.3)	Giant platelets
GATA1-related diseases (*GATA1*-RD) (Dyserythropoietic anemia with thrombocytopenia - nd, 300367 - X-linked thrombocytopenia with thalassemia - XLTT, 314050)[15,16]	10	XL	*GATA1* (Xp11)	Hemolytic anemia, possible unbalanced globin chain synthesis, possible congenital erythropoietic porphyria
ITGA2B/*ITGB3*-related thrombocytopenia (*ITGA2B*/*ITGB3*-RT, nd)[31,55]	8	AD	*ITGB3 (17q21.32)* *ITGA2B (17q21.31)*	None
Thrombocytopenia associated with sitosterolemia (STSL, 210250)[5]	6	AR	*ABCG5*, *ABCG8* (2p21)	Stomatocytosis, possible anemia, tendon xanthomas, atherosclerosis

Balduini et al, Sem Thromb Hemost 2013;39:161-171

Essential Features of Inherited Thrombocytopenia According to Platelet Size

Normal-sized platelets				
Thrombocytopenia with absent radii (TAR, 274000)[19]	133	AR	*RBM8A* (1q21.1)	Platelet count tends to rise during aging; reduced megakaryocytes bilateral radial aplasia, with or without other malformations
Congenital amegakaryocytic thrombocytopenia (CAMT, 604498)[56]	56	AR	*MPL* (1p34)	Reduced megakaryocytes, evolution into bone marrow aplasia
Familial platelet disorder and predisposition to acute myelogenous leukemia (FPD/AML, 601399)[17]	30	AD	*CBFA2* (21q22)	Development of leukemia or myelodysplastic syndrome in 40% of patients
ANKRD26-related thrombocytopenia (*ANKRD26*-RT or THC2, 313900)[18,57]	22	AD	*ANKRD26* (10p2)	Risk of leukemia
Congenital thrombocytopenia with radio-ulnar synostosis (CTRUS, 605432)[58]	8	AD	*HOXA11* (7p15–14)	Reduced megakaryocytes. Possible evolution into aplasia; radio-ulnar synostosis +/− other defects
CYCS-related thrombocytopenia (*CYCS*-RT or THC4, 612004)[59]	1	AD	*CYCS* (7p15.3)	None
Small platelets				
Wiskott–Aldrich syndrome (WAS, 301000)[14]	4 per million[a]	XL	*WASP* (Xp11)	Severe immunodeficiency
X-linked thrombocytopenia (XLT, 313900)[14]				No or mild immunodeficiency

Balduini et al, Sem Thromb Hemost 2013;39:161-171

Per Differenziare Trombocitopenie Congenite da Quelle Acquisite….

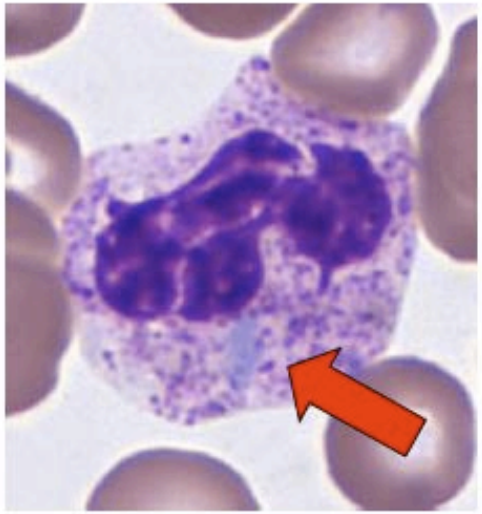
- Striscio periferico…

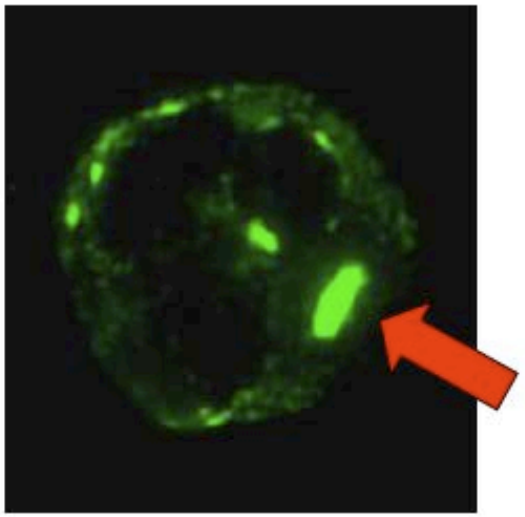
Peripheral blood film features suggesting that thrombocytopenia is genetic

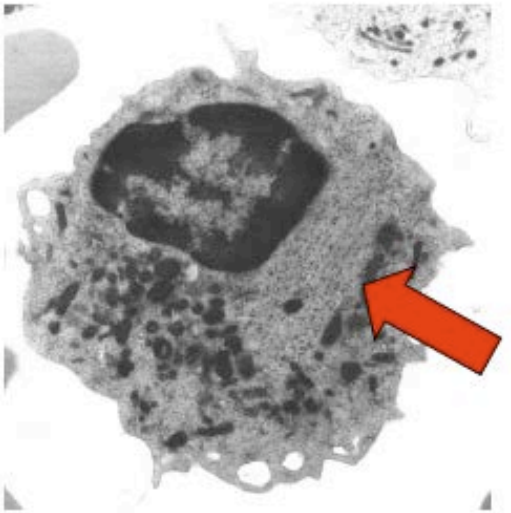
- **Small platelets** *(Wiskott-Aldrich syndrome, X-linked thrombocytopenia)*
- **Large platelets** *(Most inherited thrombocytopenias)*
- **"Pale“ platelets** *(Gray platelet syndrome)*
- **Giant platelet granules** *(Paris-Trousseau, Jacobsen's syndrome)*
- **Döhle-like bodies in neutrophil cytoplasm** *(MYH9-related disease)*
- **Red cell anisocytosis** *(GATA-1 mutations)*
- **Neutropenia** *(Congenital amegakaryocytic thrombocytopenia evolving toward bone marrow aplasia)*

Peripheral blood films in inherited thrombocytopenias

Neutrophil inclusions (Döhle-like bodies)



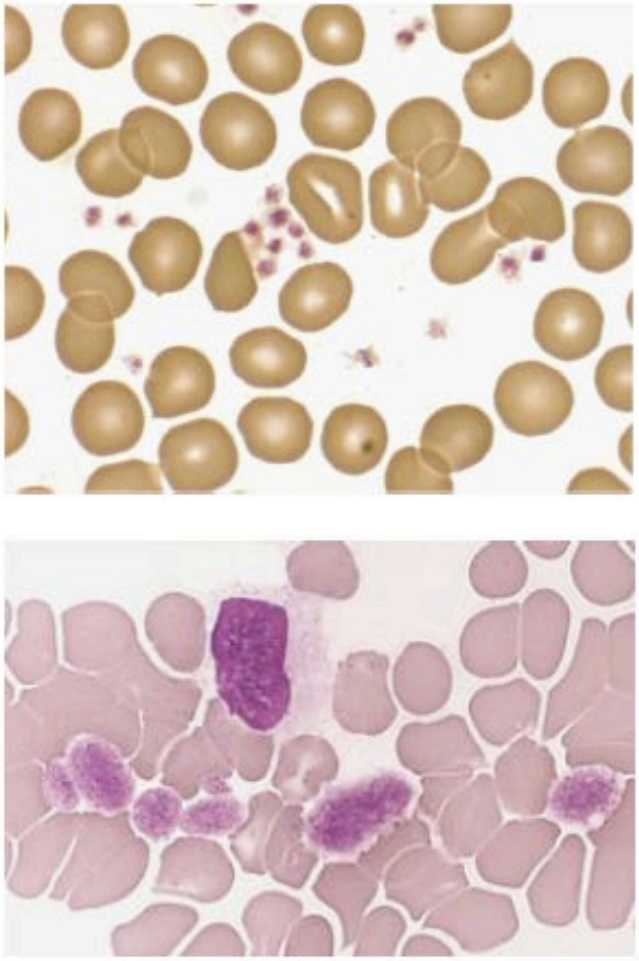


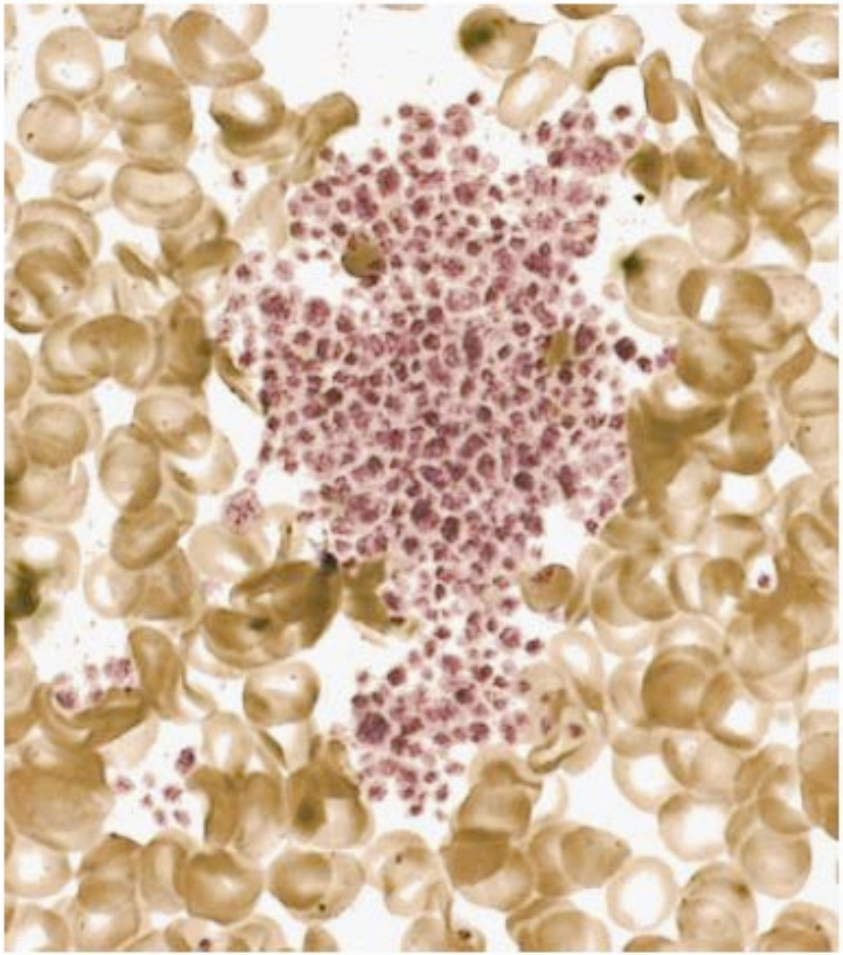


MYH9-related disease
(May-Hegglin anomaly, Sebastian and Fechtner syndromes)

Courtesy of C.L. Balduini

Peripheral blood films in von Willebrand disease type 2B and Platelet Type-vW disease



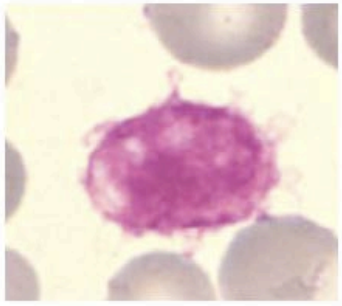


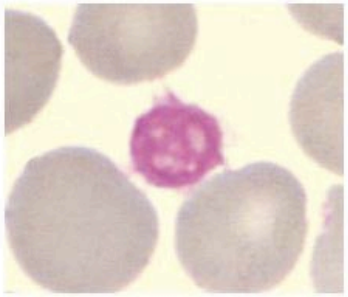
Small and large platelet clumps, large and giant platelets

Courtesy of C.L. Balduini

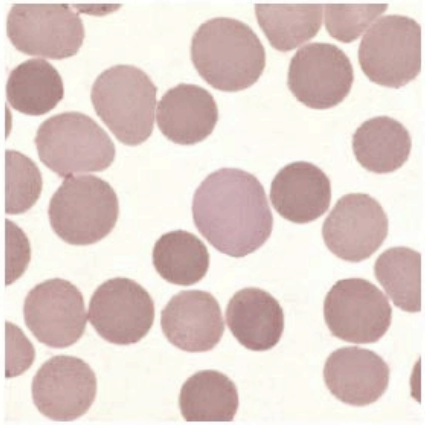
Peripheral blood films in inherited thrombocytopenias

Vacuolated platelets

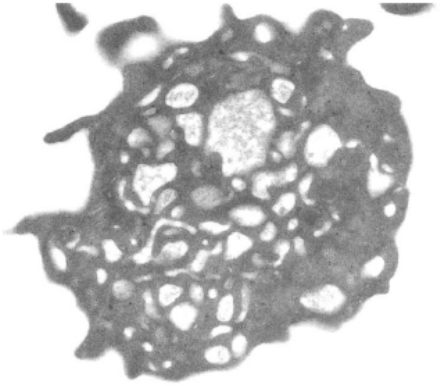




Red cell anisocytosis with microcytosis



Vacuolated platelets



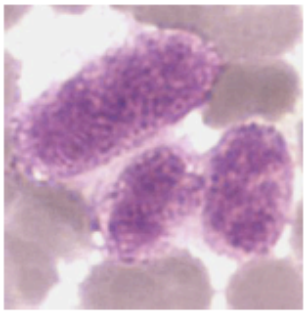
X-linked thrombocytopenias due to *GATA-1* mutations

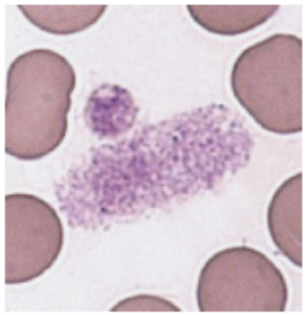
Courtesy of C.L. Balduini

Peripheral blood films in inherited thrombocytopenias

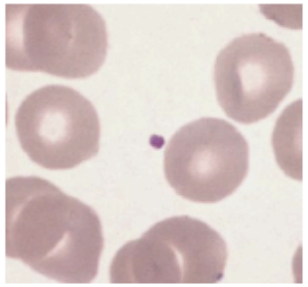
Very large platelets

MYH9-related disease





Bernard-Soulier syndrome



Wiskott-Aldrich syndrome

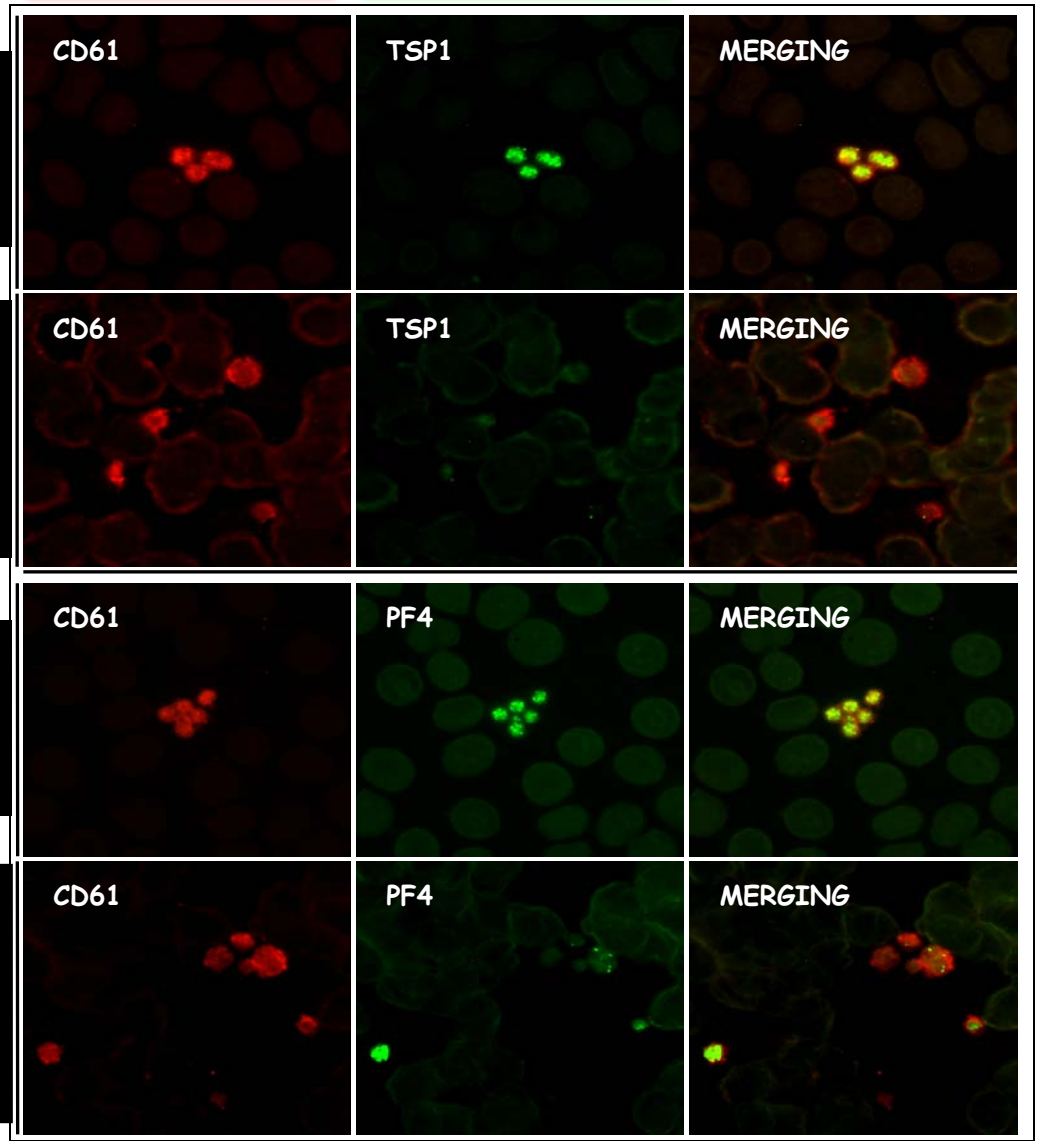
Very small platelets

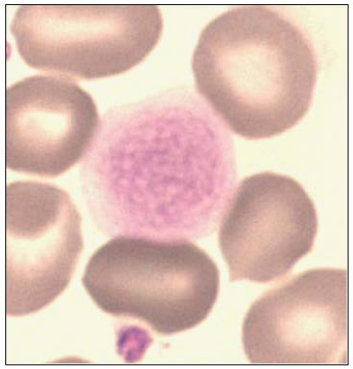
Courtesy of C.L. Balduini

α-Granule Protein Deficiency in Gray Platelet Syndrome

CD61 = platelet surface antigen

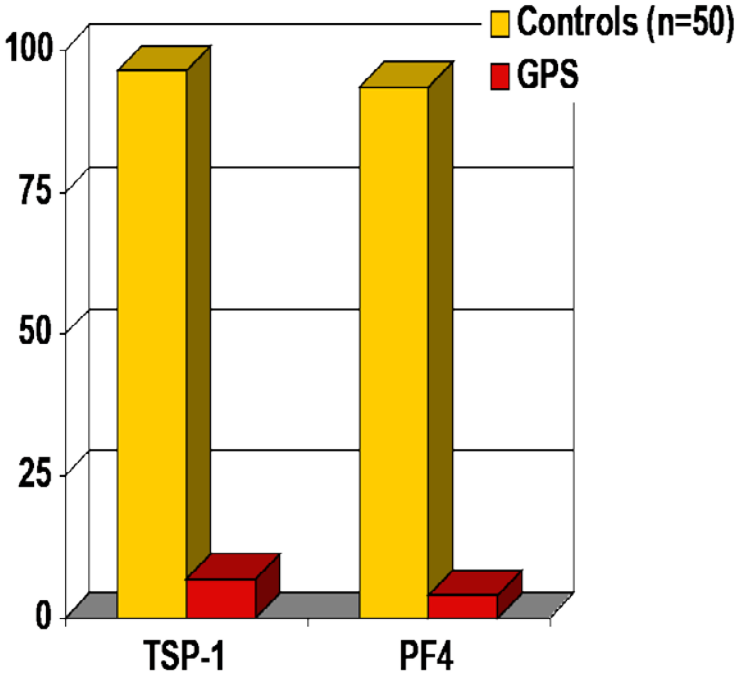
TSP1, PF4 = α-granule proteins





Pale and giants platelets

% of platelets with >5 pos granules



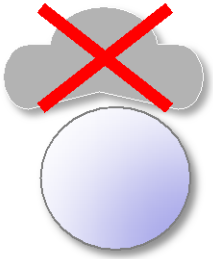
De Candia et al JTH 2007

Gray Platelet Syndrome

- Macrotrombocitopenia e piastrine «grigie»
- Livelli elevati Vit B12
- Splenomegalia

RUNX1

CBFβ



Familial platelet disorder/predisposition to acute myelogenous leukemia

Thrombocytopenia

Normal size platelet

Predisposition to leukemia

ANKRD26

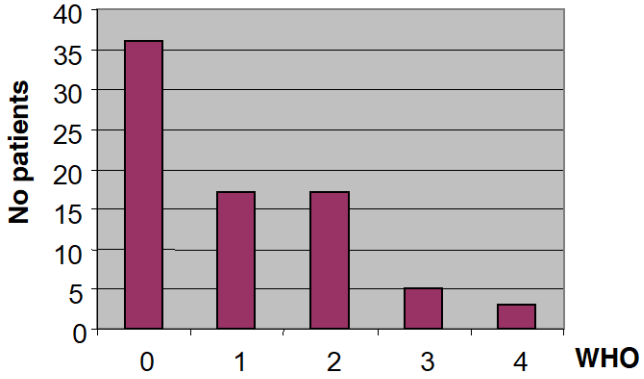
ANKRD26 related disease

Unknown function

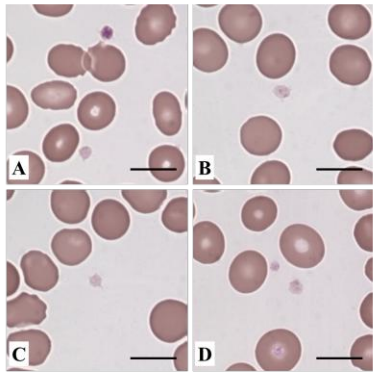
Savoia A. 2013

Features of ANKRD26RD

- **Mild bleeding tendency**
  (petechiae, ecchymosis, gum bleeding, epistaxis, menorrhagia)

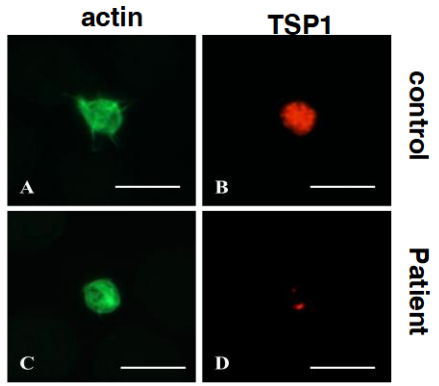


- **Moderate thrombocytopenia**
  ($47.5 \pm 28.3 \times 10^9$/L)



- **Platelet normal size**
  (MPV: 9.3 ± 1.6 fL)

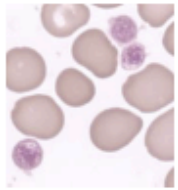
- **α-granule deficiency**

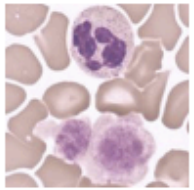


Noris et al, Blood 117:6673-6680, 2011

INHERITED THROMBOCYTOPENIAS WITH LARGE OR GIANT PLATELETS

- Platelet-type vWD/Pseudo-vWD
- Mediterranean macrothrombocytopenia
- Dyserythropoietic anemia with thrombocytopenia
- X-linked thrombocytopenia with thalassemia
- Paris-Trousseau thrombocytopenia and Jacobsen syndrome
- *GFI1B*-related thrombocytopenia
- *ACTN1*-related thrombocytopenia
- *FLNA*-related thrombocytopenia
- *ITGA2B/ITGB3*-related thrombocytopenia
- • *TUBB*1-related thrombocytopenia
- • Gray platelet syndrome
- • Bernard-Soulier syndrome
- • *MYH9*-related disease





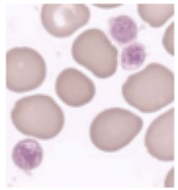
Balduini et al, Sem Thromb Hemost 2013;39:161-171

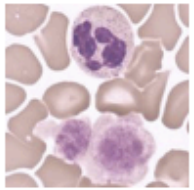
INHERITED THROMBOCYTOPENIAS WITH SMALL PLATELETS

- Wiskott-Aldrich syndrome
- X-linked thrombocytopenia
- Congenital amegakaryocytic thrombocytopenia

INHERITED THROMBOCYTOPENIAS WITH LARGE OR GIANT PLATELETS

- Platelet-type vWD/Pseudo-vWD
- Mediterranean macrothrombocytopenia
- Dyserythropoietic anemia with thrombocytopenia
- X-linked thrombocytopenia with thalassemia
- Paris-Trousseau thrombocytopenia and Jacobsen syndrome
- *GFI1B*-related thrombocytopenia
- *ACTN1*-related thrombocytopenia
- *FLNA*-related thrombocytopenia
- *ITGA2B/ITGB3*-related thrombocytopenia
  - *TUBB*1-related thrombocytopenia
  - Gray platelet syndrome
  - Bernard-Soulier syndrome
  - *MYH9*-related disease





Balduini et al, Sem Thromb Hemost 2013;39:161-171

INHERITED THROMBOCYTOPENIAS WITH SMALL PLATELETS

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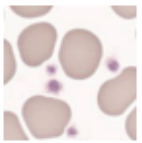
INHERITED THROMBOCYTOPENIAS WITH NORMAL-SIZE PLATELETS

- Congenital amegakaryocytic thrombocytopenia with radio-ulnar synostosis
- Thrombocytopenia with absent radii
- Familial platelet disorder with predisposition to AML
- *CYCS*-related thrombocytopenia
- *ANKRD26*-related thrombocytopenia



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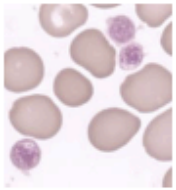
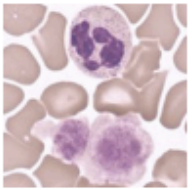
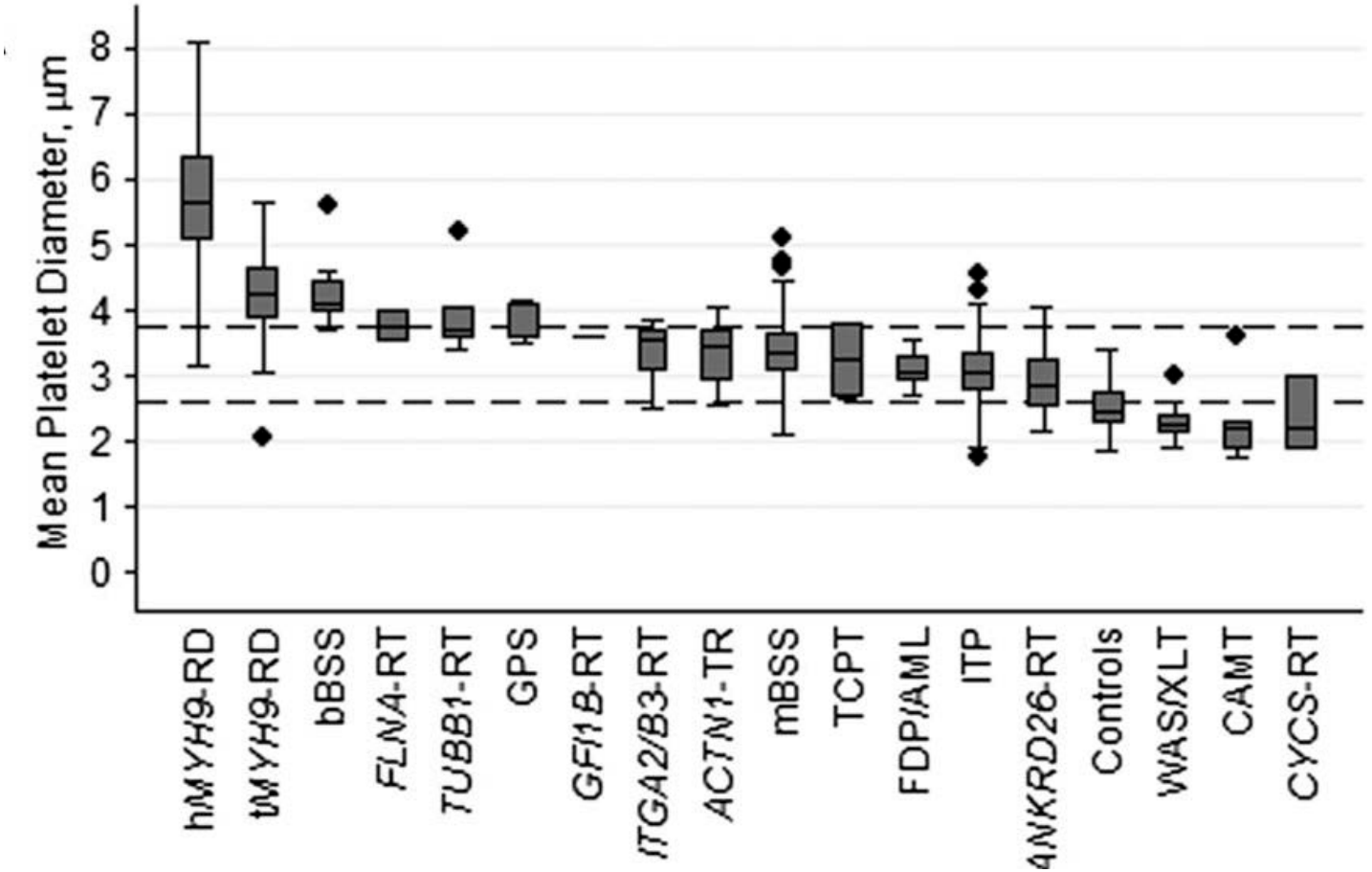




Balduini et al, Sem Thromb Hemost 2013;39:161-171

Platelet size matters….



The dashed horizontal lines indicate the best cutoff values for distinguishing ITs with giant platelets (upper lines) and those with normal or slightly decreased platelet size (lower lines) from the other forms of ITs and immune thrombocytopenia

Patrizia Noris et al. Blood 2014;124:e4-e10

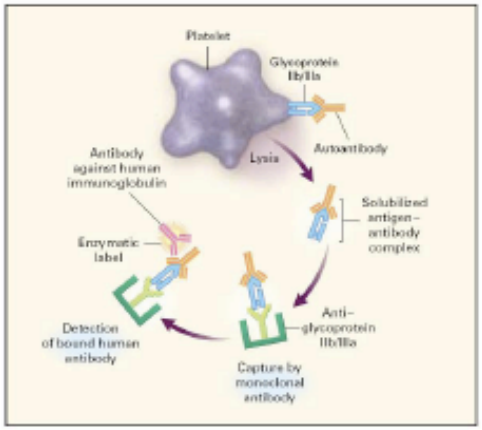
To differentiate inherited from acquired thrombocytopenias, consider:

- **Medical history**

Other laboratory testing ?

- **Blood count**
- **Peripheral blood film**

Direct test for the measurement of platelet-specific antibodies



N Engl J Med 2002;346:995

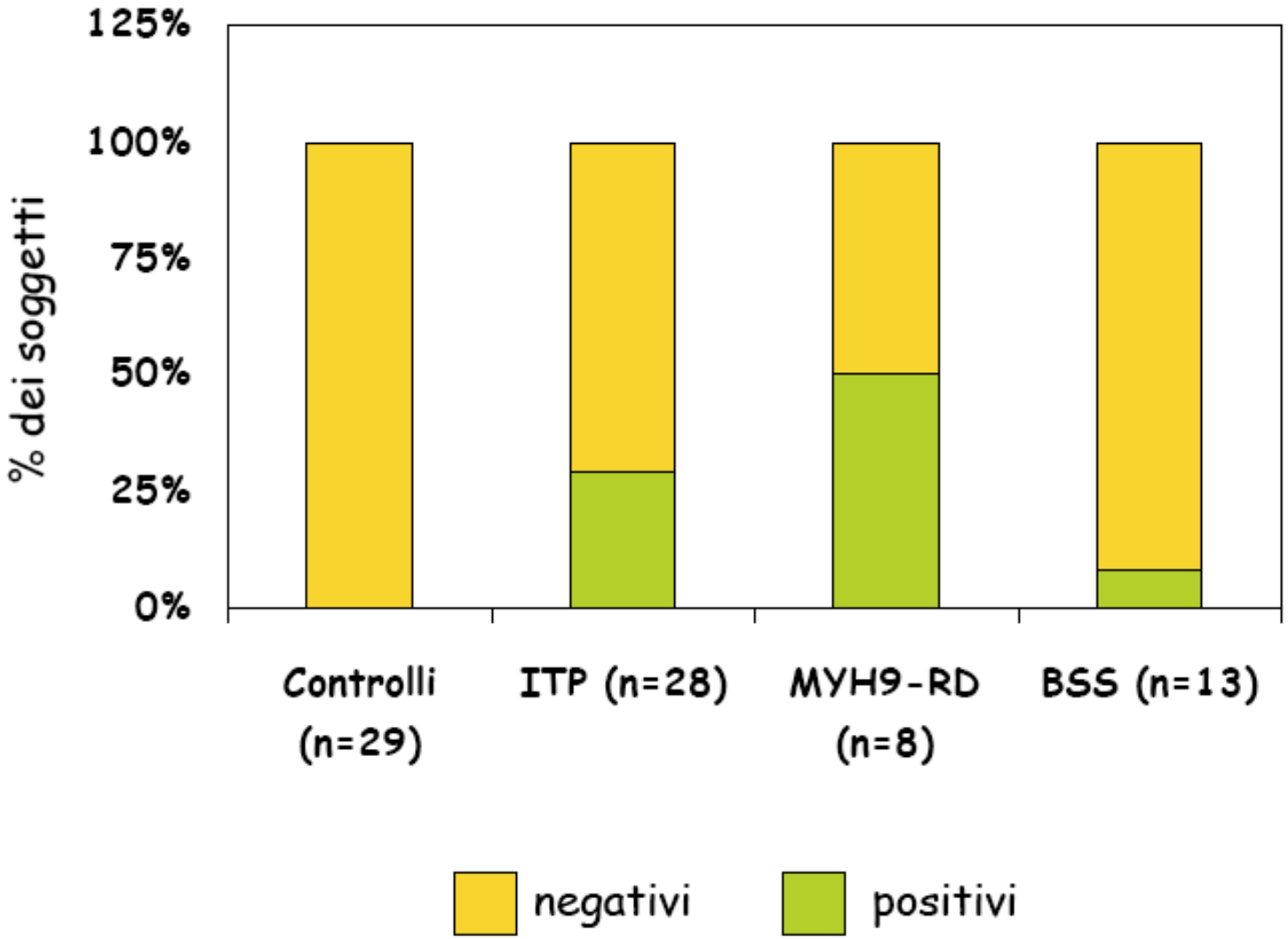
Sensitivity: 49 – 66%

Specificity: 78 – 92%

therefore

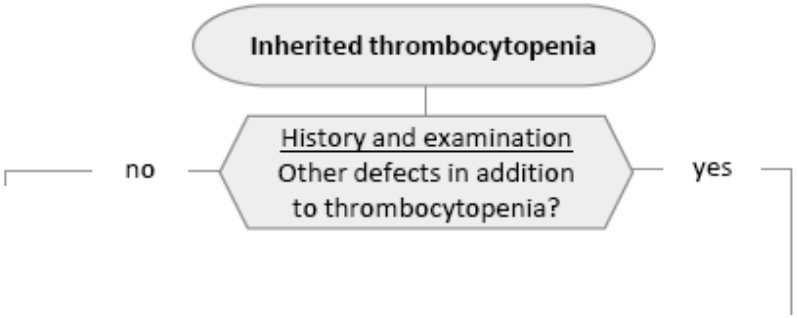
- **A negative test cannot be used to rule out the diagnosis of ITP**
- **A positive test cannot be used to make the diagnosis of ITP**

AUTO-ANTICORPI ANTI-PIASTRINE



Courtesy of C.L. Balduini

DIAGNOSTIC ALGORITHM FOR INHERITED THROMBOCYTOPENIAS



Haematologica 2003;88:582-92 → *Haematologica 2004;89:1219-25* → *Semin Thromb Hemost 2013;39:161-71*

Inquadramento del Paziente con Piastrinopenia Cronica

Storia clinica personale e familiare

Esame obiettivo

Emocromo

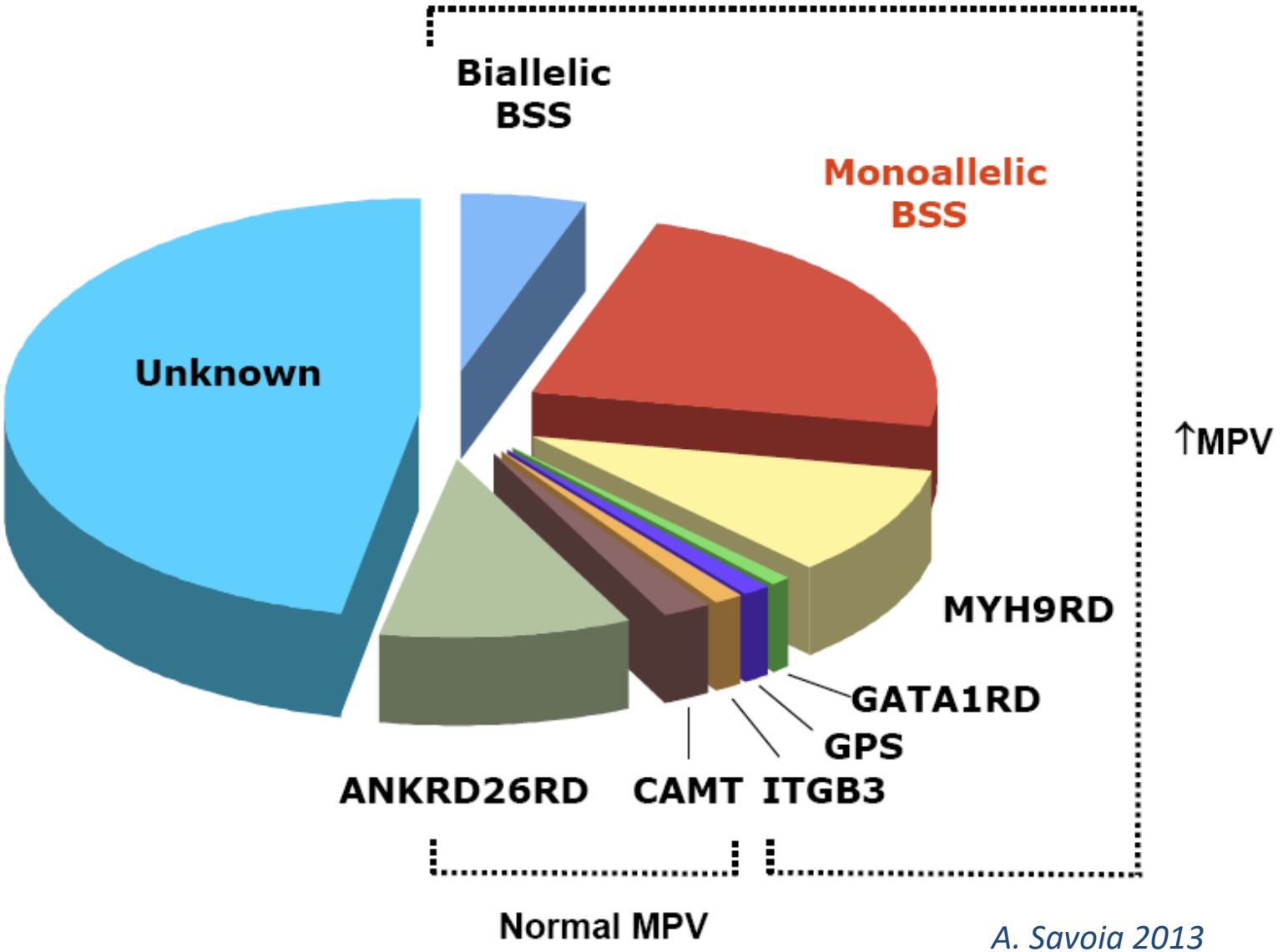
Striscio periferico

Aspirato midollare, test HCV e HIV, Helicobacter Pylori

Esami autoimmunità: anticorpi anti-piastrine, anti-fosfolipidi, anti-nucleo, anti-tiroidei

Application of diagnostic algorithm

Case series of 210 consecutive families



A. Savoia 2013

Pazienti valutati presso l'ambulatorio SMET per piastrinopenia cronica nel biennio 2016-17

Patient (gender/yrs)	Plt (x 10 ^{3}/uL)	MPV (fl)	BAT score	Diagnosis (method)	
M/ 52	39	15.8	0	MYH9-RD	Familial TP
F/12	18	19.3	0	MYH9-RD	Familial TP
F/33	64	21.4	0	Biallelic Bernard-Soulier (*GP9* mutation)	Splenectomy; Familial TP
F/30	44	15.1	4	Biallelic Bernard-Soulier (*GP9* mutation)	Familial TP
F/15	91	15.1	2	Monoallelic Bernard-Soulier (heterozigous *GP1BA* mutation)	Familial TP
F/30	62	18.1	0	ACTN1 mutation	Familial TP
M/23	40	22.4	0	MYH9-RD	Familial TP
F/25	81	15.8	0	MYH9-RD	Steroids, plt transfusions, Familial TP
F/55	100	15	0	MYH9-RD	Familial TP
F/33	111	12.4	0	none	Ab anti-plt positive; no familial TP
F/25	101	17.4	0	none	Familial TP
F/36	81	12.3	0	Monoallelic Bernard-Soulier (heterozigous *GP1BA* mutation)	Familial TP
M/47	19	8.9	2	ANKRD26 + GATA1	Familial TP
M/45	?	?	0	ANKRD26 + GATA1	Steroids, Ivlg, TPO mimetics, Familial TP
F/16	50	9.8	0	ANKRD26 + GATA1	Familial TP

Caso Clinico n.1

- Lorena M. donna di 55 aa, in buona salute, non disturbi particolari

- Piastrinopenia (= 35-45 x 10^6/µL) in tutti gli emocromi eseguiti negli ultimi 20 aa. Primo riscontro durante la I gravidanza all'eta' di 30 aa. Somministrati corticosteroidi, con lieve incremento della conta piastrinica (fino a 65 x 10^6/µL). MPV 15 fL

- 2 parti vaginali senza complicanze emorragiche, 1 aborto spontaneo a 5 mesi

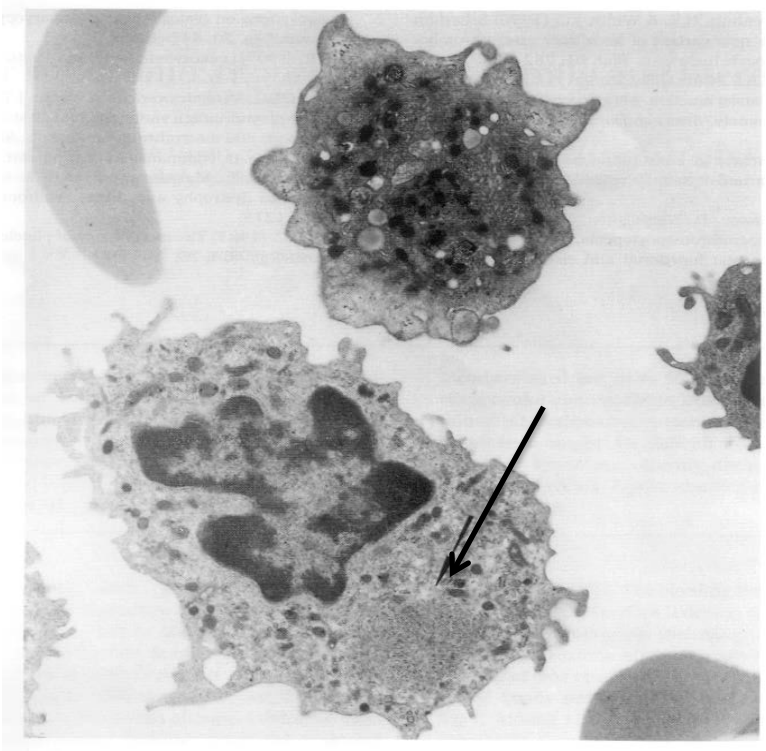
- Assenza di diatesi emorragica spontanea, mestruazioni nella norma

- Una figlia su due affetta da piastrinopenia (= 40.000/µL) senza diatesi emorragica, madre di due figli, di cui uno con piastrinopenia (=45.000/µL).

Caso Clinico n.1

- Allo striscio periferico piastrine giganti, MPV = 15 fL
- ME: inclusi leucocitari
- Trasmissione autosomica dominante
- Immunofluorescenza: positiva per la presenza di aggregati di MYH9
-

DIAGNOSI: Malattia correlata alla catena pesante della miosina 9 (MYH9-RD)



Caso Clinico n.2

- Stefano C., giovane uomo di 30 aa, con conta piastrinica stabilmente oscillante tra 14 e 20 x 10^6 /µL, MPV 15 fL
- Diatesi emorragica lieve (ematomi dopo traumi lievi)
- Sordità neurosensoriale, cataratta bilaterale, insufficienza renale cronica
- Madre, piastrinopenica affetta da IRC in dialisi, deceduta all'età di 28 aa. dopo splenectomia (eseguita per correggere la piastrinopenia?)

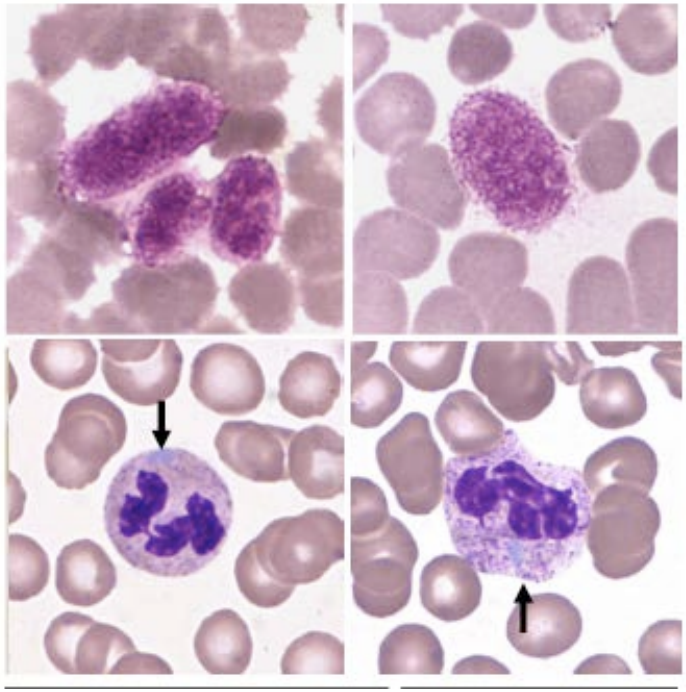
Caso Clinico n.2 (cont)

- Allo striscio periferico piastrine giganti, MPV = 15 fL (v.n. < 10)
- Trasmissione autosomica dominante
- T.E. 14’ (vn < 9’)
- Mutazione *MYH9* R702C

DIAGNOSI: Sindrome di Fechtner (MYH9-RD)

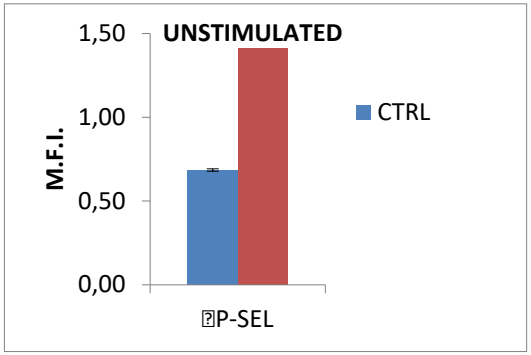
Paziente operato di cataratta bilateralmente dopo eltrombopag, portatore di protesi acustica, ha iniziato da pochi mesi emodialisi per insufficienza renale terminale. Nel 2012 linfoma di Hodgkin’s (prevalenza linfocitaria) trattato con CHT ed attualmente in remissione. È in attesa di essere messo in lista per trapianto di rene

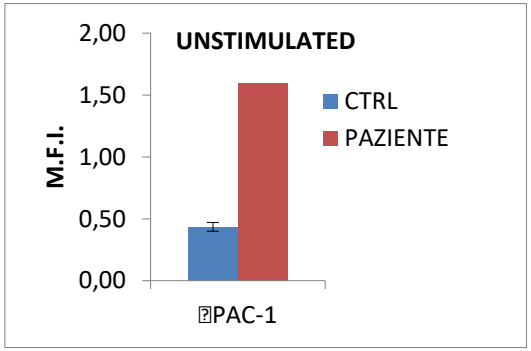
Caso Clinico n.2

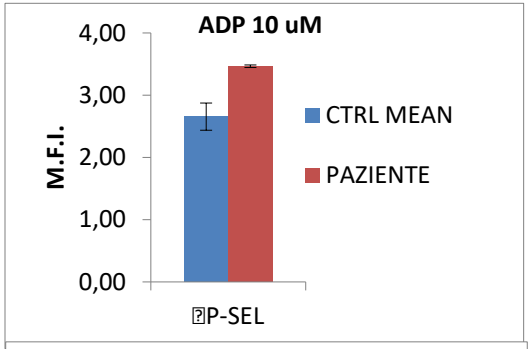


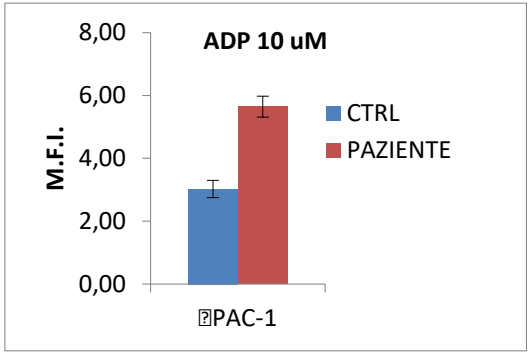
Piastrine giganti (MPV = 15 fL)

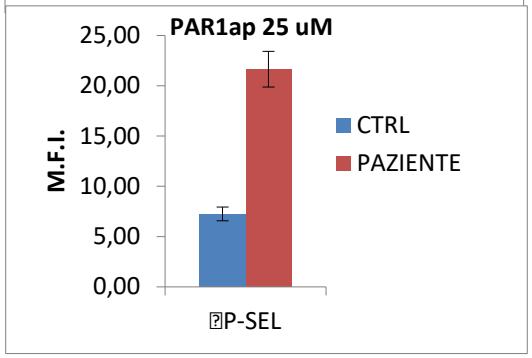
Aggregati di miosina nei neutrofili (inclusi leucocitari)

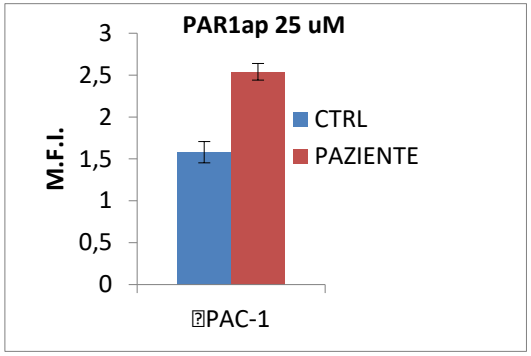












Le piastrine sono iperreattive ai normali agonisti
Correlazione con la scarsita' dei sintomi emorragici (?)

Caso Clinico n.3

- Riccardo P., ragazzo di 11 aa con diatesi emorragica r
  epistassi recidivanti (1-2 episodi/mese) richiedenti talvolta tamponamento, facile formazione di ematomi spontanei

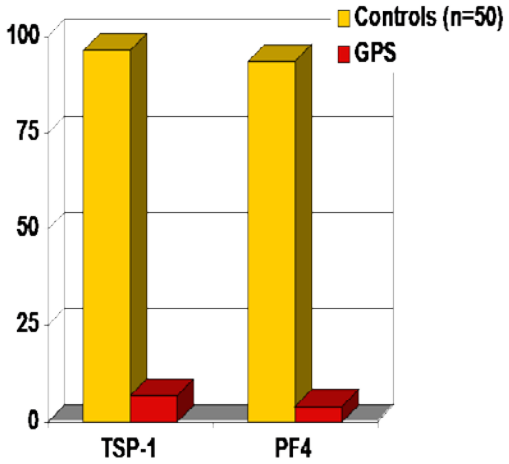
- Sanguinamento eccessivo dopo intervento di tonsillectomia all'età di 8 aa, necessario re-intervento per emostasi chirurgica.

- Conta piastrinica tra 80 e 90 x 10^6/µL

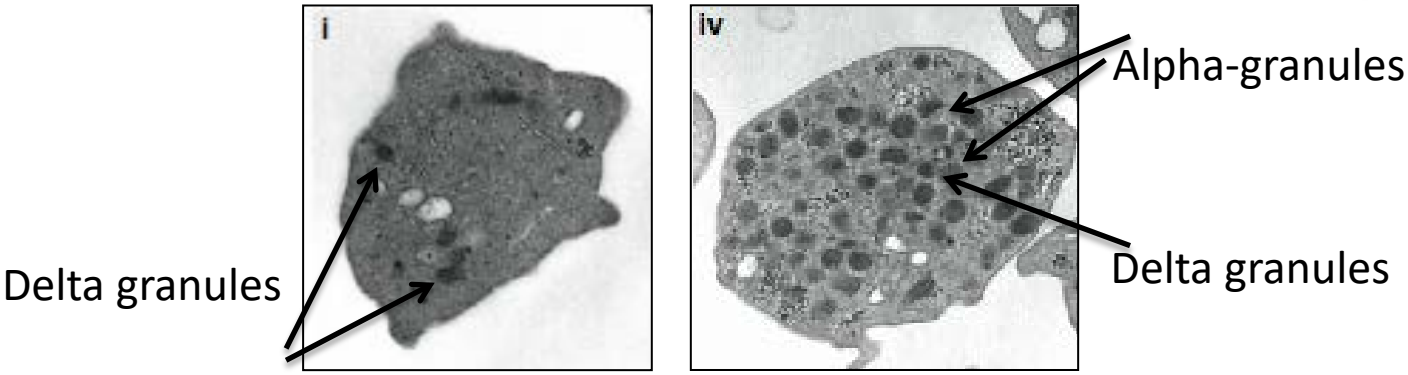
- Splenomegalia (diametro longitudinale 14 cm)
- Genitori normali per conta piastrinica e diatesi emorragica

Caso Clinico n.3

- Tempo di emorragia sec Ivy >20 ‘ (v.n. < 8’)
- Mielofibrosi grado 2
- Carenza di granuli α piastrinici (microscopia elettronica ed immunofluorescenza per trombospondina)
- Mutazione biallelica *NBEAL2*

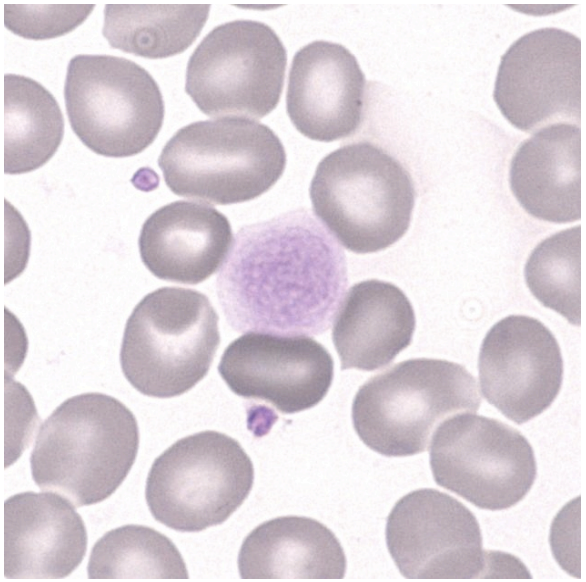


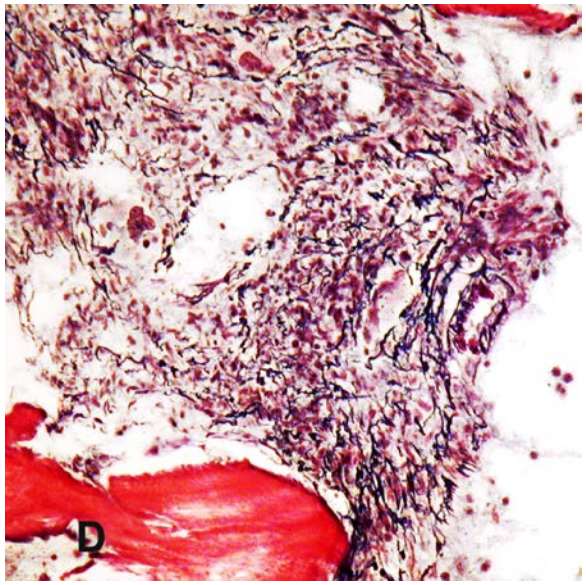
- **Diagnosi: Gray Platelet Syndrome**
- Modalità di trasmissione autosomica recessiva,
- Entrambi I genitori avevano mutazione di un allele di *NBEAL2*



Gray Platelet Syndrome

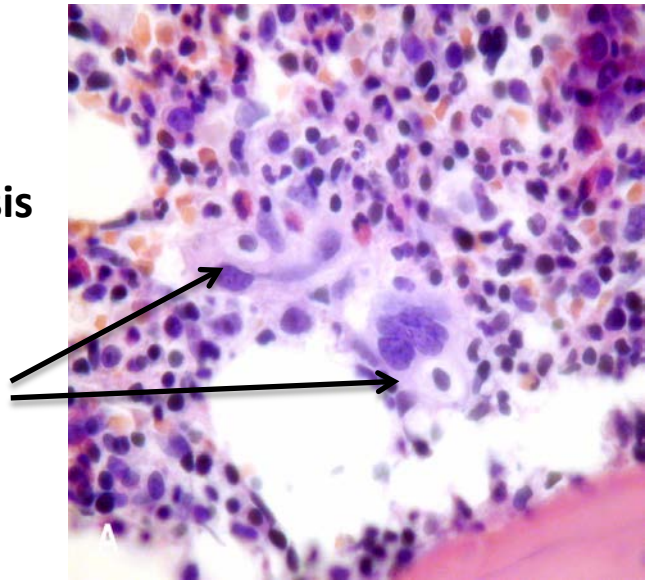
Lack of alpha-granules

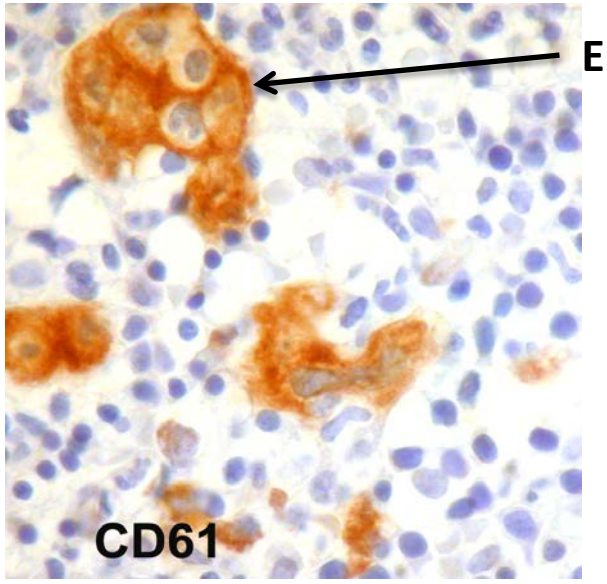




Bone marrow fibrosis (grade 2)

Emperipolesis





Emperipolesis

Larocca et al, Platelets 2015

Gray Platelet Syndrome

- Macrotrombocitopenia e piastrine «grigie»
- Livelli elevati Vit B12
- Splenomegalia

Caso Clinico n.4 (continua)

- Nadia B., giovane donna di 33 aa con piastrinopenia (10-50 x 10^6/µL) dall'età di 7 aa, resistente a corticosteroidi e immunoglobline ev. Assenza di sintomi emorragici, eccetto menorragie all'inizio dell'età fertile (ISTH-BAT=1)

- Splenectomia all'età di 17 aa

- Successivamente conta piastrinica tra 50 e 70 x 10^6/µL

- Teresa B di 28 aa, cugina di primo grado di Nadia, piastrinopenica dall'età di 7-8 aa (pia=50 x 10^6/µL). Diatesi emorragica cutanea lieve, epistassi (2-3/anno) per cui si è recata in PS in due occasioni.

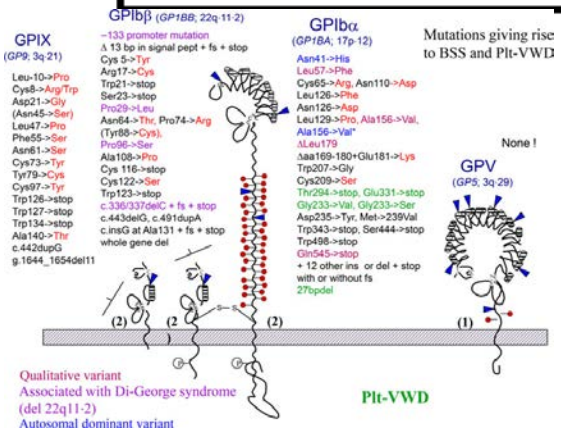
Caso Clinico n.4 (continua)

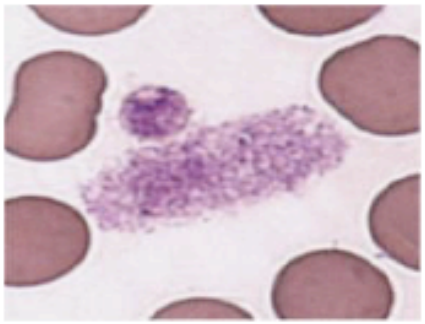
- Macrotrombocitopenia
- Agglutinazione da ristocetina ad alte dosi assente
- Riduzione del 50% dell'espressione della GPIb piastrinica
- Mutazione omozigote del gene della GP9
- **Diagnosi: S. di Bernard-Soulier omozigote**

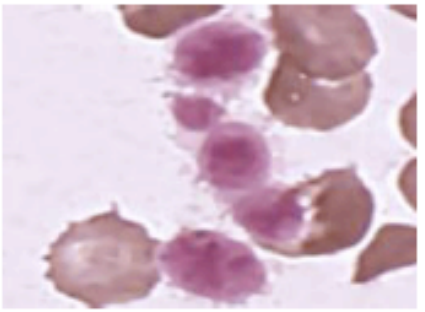
Bernard-Soulier syndrome

common Bolzano variant

	Biallelic form	Monoallelic form
Genetics	Autosomal recessive	Autosomal dominant
Bleeding	Severe/mild	Mild
Thrombocytopenia	Variable degree	Mild
GPIb-IX-V expression	Usually absent	50% (carrier of p.Ala156Val)
Ristocetin induced platelet agglutination	Absent	Normal or marginally impaired







Savoia A. 2013

Piastrinopenia Cronica: non Solo ITP

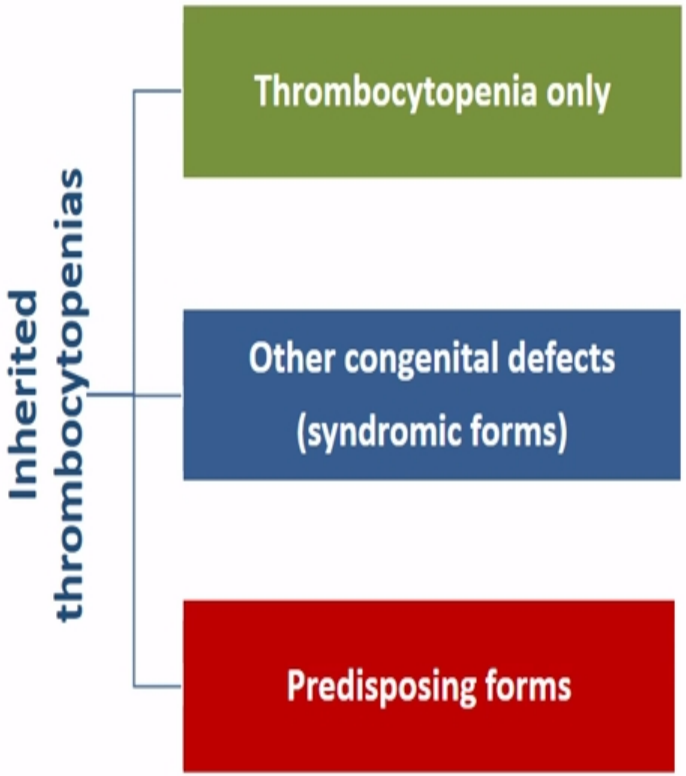
Stefano C,
Sindrome di Fetchner

Nadia e Teresa B,
S. di Bernard-Soulier

Lorena M,
MHY9-RD

Riccardo P,
Gray Platelet Syndrome

- Inherited thrombocytopenias: 32 disorders caused by mutations of 30 different genes



A. Pecci ISTH 2017 Berlin

Inherited thrombocytopenias predisposing to hematological malignancies

Overview

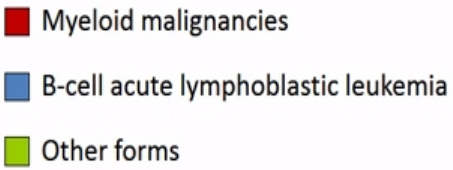
	ANKRD26-RT	FPD/AML	*ETV6*-RT
Gene	*ANKRD26*	*RUNX1*	*ETV6*
Relative frequency (% of known forms)	18%	3%	5%
Transmission	AD	AD	AD
Thrombocytopenia	Mild/moderate	Mild/absent	Mild
Platelet size	Normal	Normal	Normal
Platelet function	Normal	Abnormal*	Normal
Bleeding tendency	Absent/mild	Absent/moderate	Absent/mild

* Heterogeneous abnormalities, most frequently delta-granule deficiency/release defect

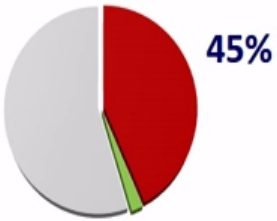
A. Pecci *ISTH 2017, Berlin*

Inherited thrombocytopenias predisposing to hematological malignancies

% of patients with hematological malignancies (review of the literature)



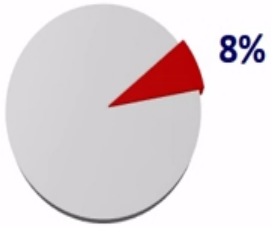
FPD-AML (*RUNX1*)



Any age, median 34 yrs.

(55 families)

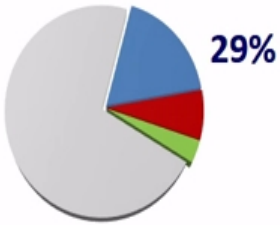
***ANKRD26*-RT**



Any age, median 41 yrs.

(73 families)

***ETV6*-RT**



B-ALL: childhood Myeloid: any age

(20 families)

A. Pecci *ISTH 2017, Berlin*

Piastrinopenie Congentie
Take Home Message

- Distinguere le piastrinopenie congenite da quelle acquisite per evitare trattamenti inutili o dannosi

- Considerare che il rischio emorragico spontaneo è normale o basso nella maggior parte delle condizioni

- Considerare che le piastrinopenie congenite possono associarsi 1) a patologie di altri organi o apparati 2) ad aumentato rischio di patologie ematologiche maligne

Piastrinopenie Congenite

Gestione del Rischio Emorragico negli Interventi Chirurgici e in Gravidanza

Inherited Platelet Disorders (IPD)

Available treatments to prevent bleeding during surgery
(but…poor evidence…)

- Platelet transfusions
- Antifibrinolytic agents
- Desmopressin (DDAVP)
- Recombinant activated FVII (FVIIa)

Available treatments to increase platelet count
(poor evidence…)

- Platelet transfusions
- Thrombopoietin mimetics

Gestione delle Procedure Invasive/Chirurgiche nei Pazienti con Piastrinopenie

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Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Management of bleeding and of invasive procedures in patients with platelet disorders and/or thrombocytopenia: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET)

A. Tosetto [h,*], C.L. Balduini [a], M. Cattaneo [b], E. De Candia [c], G. Mariani [d], A.C. Molinari [e], E. Rossi [f], S. Siragusa [g]

bjh review

A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO

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Evidence from Large Studies on Defined Platelet Disorders

- SPATA study: surgery in inherited platelet function and platelet number disorders (423 patients)

- Pregnancies and inherited thrombocytopenia (181 women)

EUROPEAN HEMATOLOGY ASSOCIATION

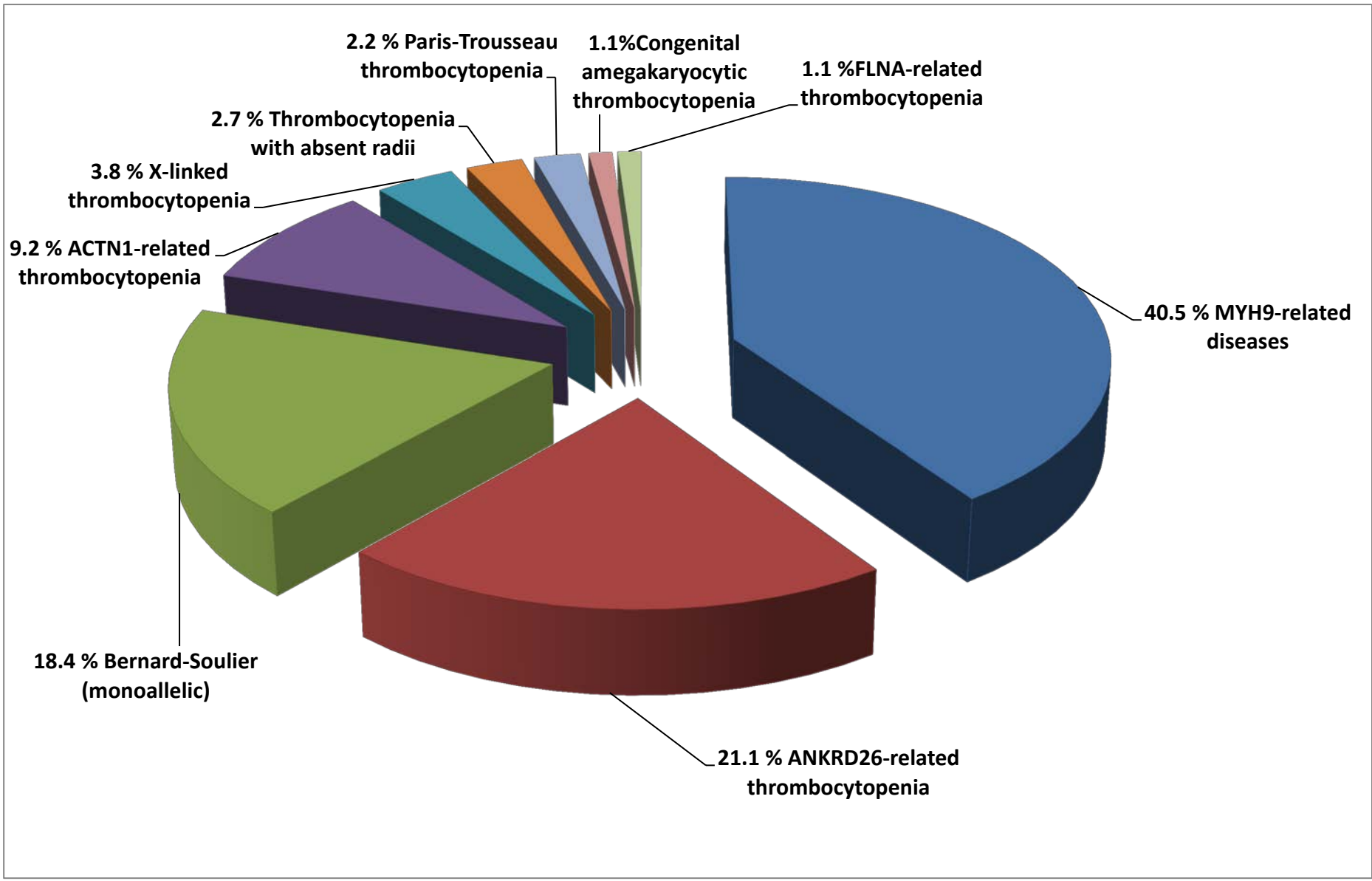
Ferrata Storti Foundation

SPATA (Surgery in Platelet disorders And Therapeutic Approach) Study

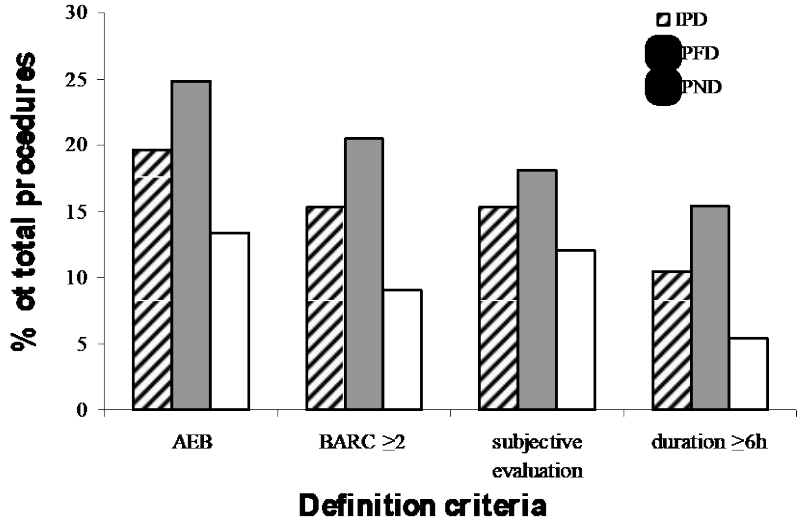
Worldwide, multicentric, retrospective study promoted by the Scientific Working Group on Thrombocytopenia and Platelet Function Disorders of European Hematology Association

Outcome of 829 surgical procedures carried out in 238 patients with platelet function disorders and 185 patients with platelet number disorders from 49 centers and 17 countries

Diagnosis of IPNDs in SPATA study



Post-surgical Bleeding in IPD



Supplemental Figure 2. Post-surgical bleeding in IPD.

Percentage of total procedures (IPD=829; IPFD=455; IPND=374) followed by excessive bleeding according to the different definition criteria: AEB= any excessive bleeding; BARC≥2= any bleeding to which a BARC≥2 was assigned; subjective evaluation= bleeding classified as "excessive" or "normal" based on a subjective evaluation by the surgeon or when this was not available by the patient; duration ≥6h= a bleeding with a duration ≥ 6 hours.

Bleeding and Type of Disease

Supplemental Table 3. Incidence of bleeding according to definition and diagnosis

IPFD	AEB	BARC									Subjective evaluation	Duration >6h
Diagnosis	**AEB/total (% of total)**	**0**	**1**	**2**	**3a**	**3b**	**4**	**5a**	**5b**	**% >=2**	**N (% of total)**	**N (% of total)**
Defect of thromboxane A2 receptor	4/5 (80)	2	0	1	2	0	0	0	0	60	3 (60)	5 (60)
Platelet-type Von Willebrand Disease	4/5 (80)	1	0	2	2	0	0	0	0	80	3 (60)	5 (40)
CalDAG-related platelet disorder	1/2 (50)	0	1	1	0	0	0	0	0	50	1 (50)	2 (50)
Bernard-Soulier Syndrome (biallelic)*	16/36 (44)	15	9	11	1	0	0	0	0	33.3	7 (19.4)	36 (41.7)
Familial platelet disorder and predisposition to acute myelogenous leukemia*	4/13 (30.8)	8	3	2	0	0	0	0	0	15.4	4 (30.8)	13 (15.4)
Glanzmann thrombasthenia*	53/182 (29.1)	102	34	19	19	5	2	0	0	24.7	37 (20.3)	167 (15)
Hermansky–Pudlak syndrome*	6/22 (27.3)	13	3	3	1	2	0	0	0	27.3	5 (22.7)	21 (19)
Gray platelet syndrome*	4/17 (23.5)	12	2	2	1	0	0	0	0	17.6	2 (11.7)	17 (0)
Autosomal dominant GT-variant*	5/22 (22.7)	15	2	2	2	0	0	0	0	18.2	5 (22.7)	19 (10.5)
Defects in α2-adrenergic receptor	2/9 (22.2)	7	0	1	0	1	0	0	0	22.2	2 (12.5)	16 (0)
Defects in collagen receptors*	2/16 (12.5)	13	2	1	0	0	0	0	0	6.2	2 (22.2)	9 (22.2)
Delta granule deficiency*	4/36 (11.1)	29	3	2	1	0	0	0	0	8.3	4 (11.1)	36 (11.1)
Primary secretion defect*	8/76 (10.5)	66	3	5	1	1	0	0	0	9.2	7 (9.2)	76 (9.2)
Combined alpha-delta granule deficiency	0/2 (0)	2	0	0	0	0	0	0	0	0	0 (0)	2 (0)
P2Y12 deficiency	0/9 (0)	8	0	0	0	0	0	0	0	0	0 (0)	9 (0)
Scott syndrome	0/3 (0)	3	0	0	0	0	0	0	0	0	0 (0)	3 (0)
TOTAL	**113 (24.8)**	**296**	**62**	**52**	**30**	**9**	**2**	**0**	**0**	**20.4**	**82 (18)**	**436 (15.4)**

IPND	AEB/total (% of total)	BARC									Subjective evaluation	Duration >6h
Diagnosis	**N (% of total)**	**0**	**1**	**2**	**3a**	**3b**	**4**	**5a**	**5b**	**% >=2**	**N (% of total)**	**N (% of total)**
FLNA-related thrombocytopenia	1/2 (50)	1	1	0	0	0	0	0	0	0	1/2 (50)	1/2 (50)
X-linked thrombocytopenia	2/92 (22.2)	5	2	1	0	0	0	0	0	11.1	2/92 (22.2)	2/92 (22.2)
Paris-Trousseau thrombocytopenia	1/5 (20)	4	0	0	1	0	0	0	0	20	1/5 (20)	1/5 (20)
MYH9-related disease*	23/148 (15.5)	119	13	11	3	0	0	0	1	10.1	20/148 (13.5)	3/148 (2.1)
ACTN1-related thrombocytopenia*	5/39 (12.8)	34	1	3	0	1	0	0	0	10.3	5/39 (12.8)	2/39 (5.1)
ANKRD26-related thrombocytopenia*	10/89 (11.2)	74	5	7	1	0	0	0	0	9	10/89 (11.2)	7/89 (7.9)
Bernard-Soulier Syndrome (monoallelic) *	8/74 (10.8)	65	4	3	1	1	0	0	0	6.7	6/74 (8.1)	4/74 (5.4)
Congenital amegakaryocytic thrombocytopenia	0/2 (0)	1	1	0	0	0	0	0	0	0	0/2 (0)	0/2 (0)
Thrombocytopenia with absent radii	0/6 (0)	4	2	0	0	0	0	0	0	0	0/6 (0)	0/6 (0)
TOTAL	**50 (13.4)**	**307**	**29**	**25**	**6**	**2**	**0**	**0**	**1**	**9.1**	**45 (12)**	**370 (5.4)**

*Disorders with more than 10 procedures

Bleeding and Type of Surgery

Table 5. Incidence of bleeding in the different inherited platelet disorder populations according to the type of surgery.

Procedure	IPD N (% AEB)	IPFD N (% AEB)	IPND N (% AEB)	IPFD *vs.* IPND 2 *P*
DENTAL PROCEDURES	233 (13.3)	134 (15.7)	99 (10.1)	
MINOR SURGERY:				
Cyst/abscess drainage	5 (60)	3 (66.7)	2 (50)	ns
Central catheter placement	11 (36.4)	9 (44.4)	2 (0)	ns
Hemorrhoidectomy	8 (25)	3 (33.3)	5 (20)	ns
Invasive procedure	25 (20)	15 (26.7)	10 (10)	ns
Colonoscopy	25 (20)	21 (23.8)	4 (0)	ns
Gastroscopy	11 (18.2)	10 (20)	1 (0)	ns
Biopsy	17 (17.6)	13 (23.1)	4 (0)	ns
TOTAL minor surgery	102 (23.5)	74 (28.4)	28 (10.7)	ns
MAJOR SURGERY:				
Thoracic surgery	2 (50)	2 (50)		ns
Cardiovascular surgery	17 (47.1)	9 (77.8)	8 (12.5)	0.02
Urological surgery	38 (34.2)	24 (37.5)	14 (28.6)	ns
Neurological surgery	7 (28.6)	5 (20)	2 (50)	ns
Gynecological surgery	56 (26.8)	31 (35.5)	25 (16)	ns
Otorinolaringological surgery	106 (24.5)	49 (24.5)	57 (24.6)	ns
Plastic surgery	14 (21.4)	4 (25)	10 (20)	ns
Eye surgery	25 (20)	12 (41.7)	13 (0)	0.03
Abdominal surgery	126 (19.8)	52 (30.8)	74 (12.2)	0.01
Orthopedic surgery	56 (12.5)	30 (16.7)	26 (7.7)	ns
Breast surgery	13 (7.7)	7 (14.3)	6 (0)	ns
Dermatologic surgery	34 (5.9)	22 (9.1)	12 (0)	ns
TOTAL major surgery	494 (21.9)	247 (28.7)	247 (15)	0.0003
TOTAL	829 (19.7)	455 (24.8)	374 (13.4)	0.0001

IPD: inherited platelet disorder; IPFD: inherited platelet function; IPND: inherited platelet number disorder; *vs.*: *versus*; N: number: AEB: any excessive bleeding; ns: not significant.

Efficacy of Prophylactic Treatments

IPFDs

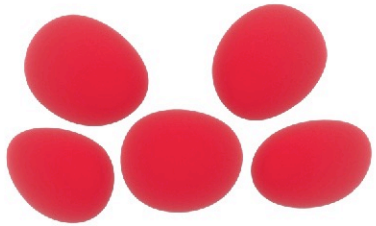
- IPDS have significant reduction of bleedings when receive prophylaxis
- significant reduction upon DDAVP and a combination of DDAVP+ antifibrinolyitic agents
- Platelet transfusions alone seem not to reduce significantly bleedings
- rFVIIa is effctive in reducing bleedings

IPNDs

- Prophylaxis did not modify surgical bleedings
- Antifibrinolyitic agents gave some reduction of surgical bleedings

Main Conclusions of the SPATA Study

Surgery-associated bleeding risk is high in inherited platelet disorders, especially in inherited platelet function disorders, and varies according to diagnosis and procedure



829 Surgical procedures assesment

- bleeding complications of surgery
- preventive and therapeutic approaches adopted
- efficacy

Frequency of surgical bleeding

423 Patients with inherited platelet disorders — 19.7%

238 Inherited platelet **function** disorders — 24.8%

185 Inherited platelet **number** disorders — 13.4%

Frequency of bleeding

- the type of inherited platelet disorders
  biallelic Bernard Soulier syndrome (44.4%)
- the type of surgery
  cardiovascular and urologic
- female gender

Orsini *et al.*, Haematologica, 2017

Prophylaxis is effective in reducing surgical bleedings in IPFDs, not in IPNDs

Analysis of 339 pregnancies in 181 women with 13 different forms of inherited thrombocytopenia

Patrizia Noris,[1] Nicole Schlegel,[2] Catherine Klersy,[3] Paula G. Heller,[4] Elisa Civaschi,[1] Nuria Pujol-Moix,[5] Fabrizio Fabris,[6] Remi Favier,[7,8] Paolo Gresele,[9] Véronique Latger-Cannard,[10,11] Adam Cuker,[12] Paquita Nurden,[13] Andreas Greinacher,[14] Marco Cattaneo,[15] Erica De Candia,[16] Alessandro Pecci,[1] Marie-Françoise Hurtaud-Roux,[2] Ana C. Glembotsky,[4] Eduardo Muñiz-Diaz,[17] Maria Luigia Randi,[6] Nathalie Trillot,[18] Loredana Bury,[9] Thomas Lecompte,[19,20] Caterina Marconi,[21] Anna Savoia,[22,23] and Carlo L. Balduini[1] on behalf of the European Hematology Association – Scientific Working Group on Thrombocytopenias and Platelet Function Disorders

Main conclusions of the study

- Gestation of IT mothers was similar to that of general population
- The risk of abnormal blood loss was increased in IT mothers (6.4-14.2%) with respect to normal population
- No death, no hysterectomy in mothers
- 7 of 156 affected thrombocytopenic newborns had delivery-related bleedings, 2 died of cerebral hemorrhage
- Higher bleeding of mothers was correlated with bleeding score before pregnancy and with plt count $<50 \times 10^9/L$

Inherited Platelet Disorders (IPD)

Available treatments to prevent bleeding during surgery

- Platelet transfusions
- Antifibrinolytic agents
- Desmopressin (DDAVP)
- Recombinant activated FVII (FVIIa)

Available treatments to increase platelet count

- Platelet transfusions
- Thrombopoietin mimetics

TPO Mimetics and Inherited Thrombocytopenias

Which future?

Which IT?

Which platelet parameter?

Eltrombopag for the treatment of the inherited thrombocytopenia deriving from *MYH9* mutations

Alessandro Pecci,[1] Paolo Gresele,[2] Catherine Klersy,[1] Anna Savoia,[3] Patrizia Noris,[1] Tiziana Fierro,[2] Valeria Bozzi,[1] Anna Maria Mezzasoma,[2] Federica Melazzini,[1] and Carlo L. Balduini[1]

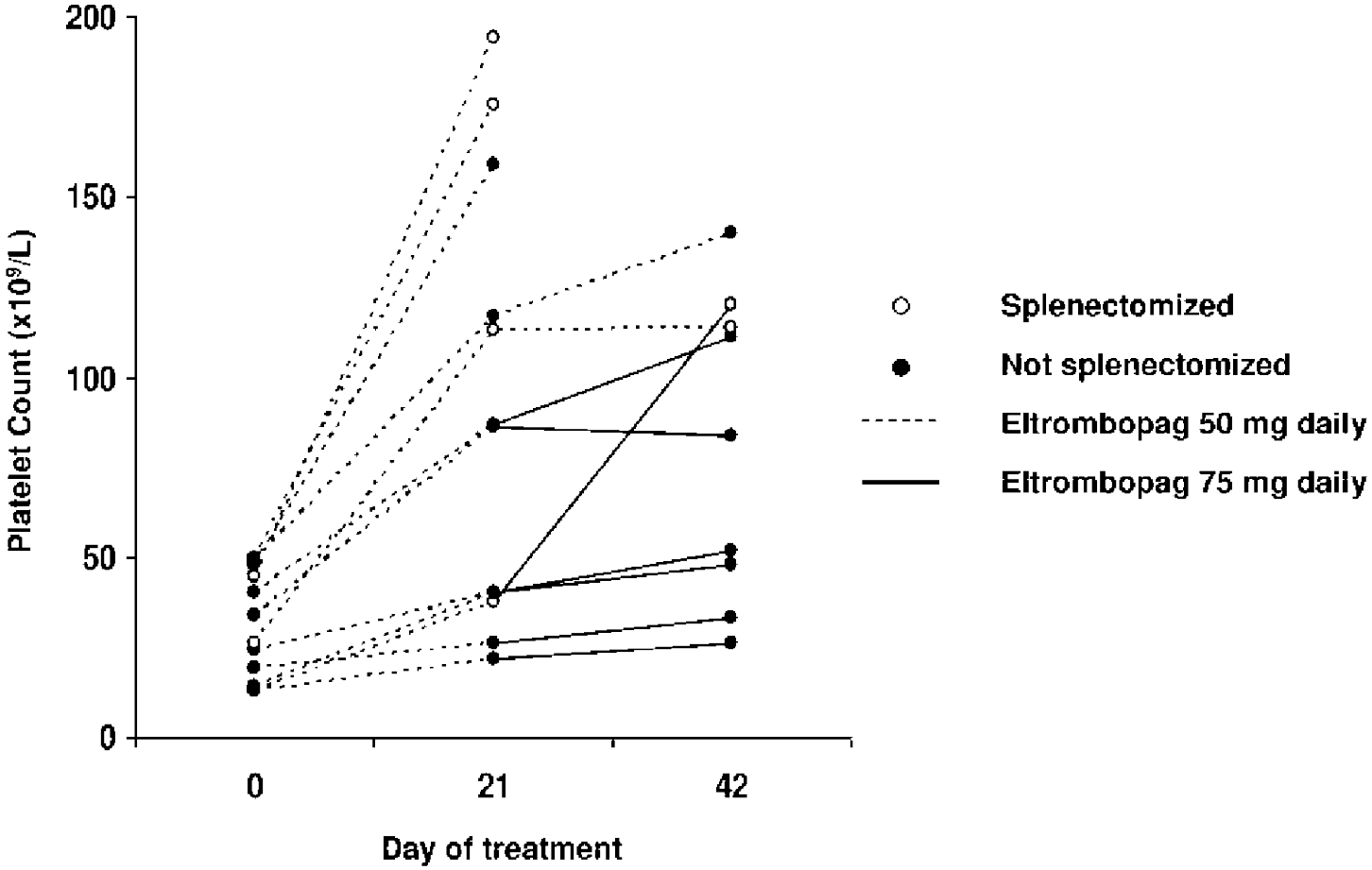
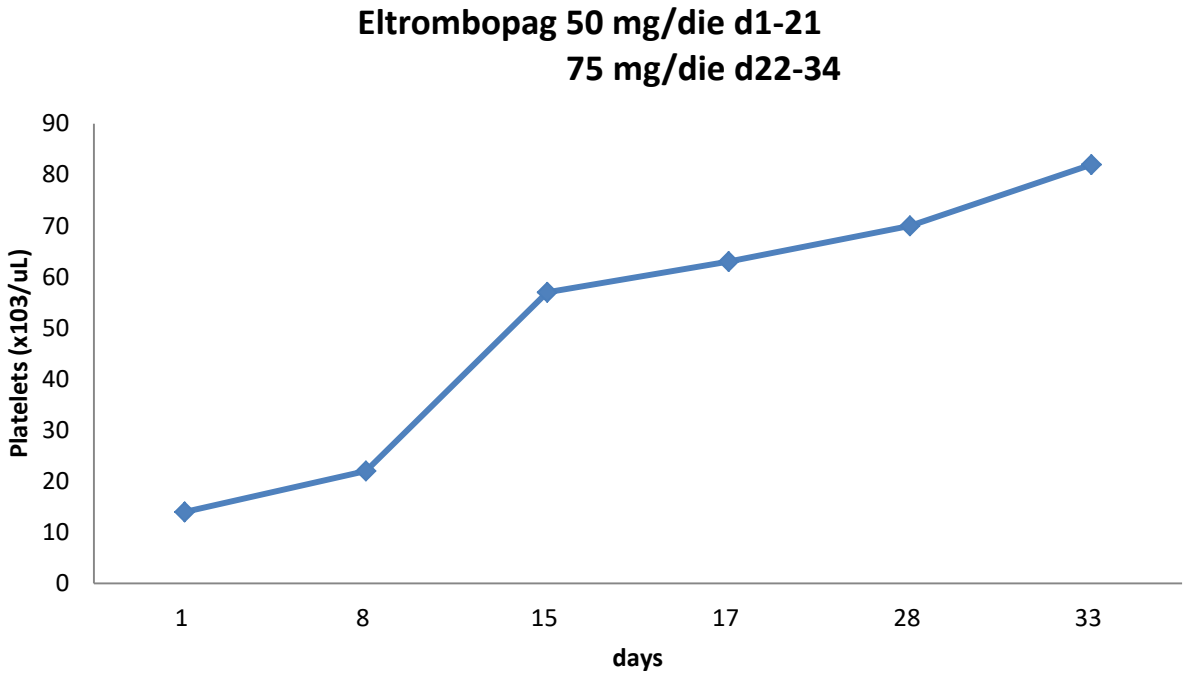


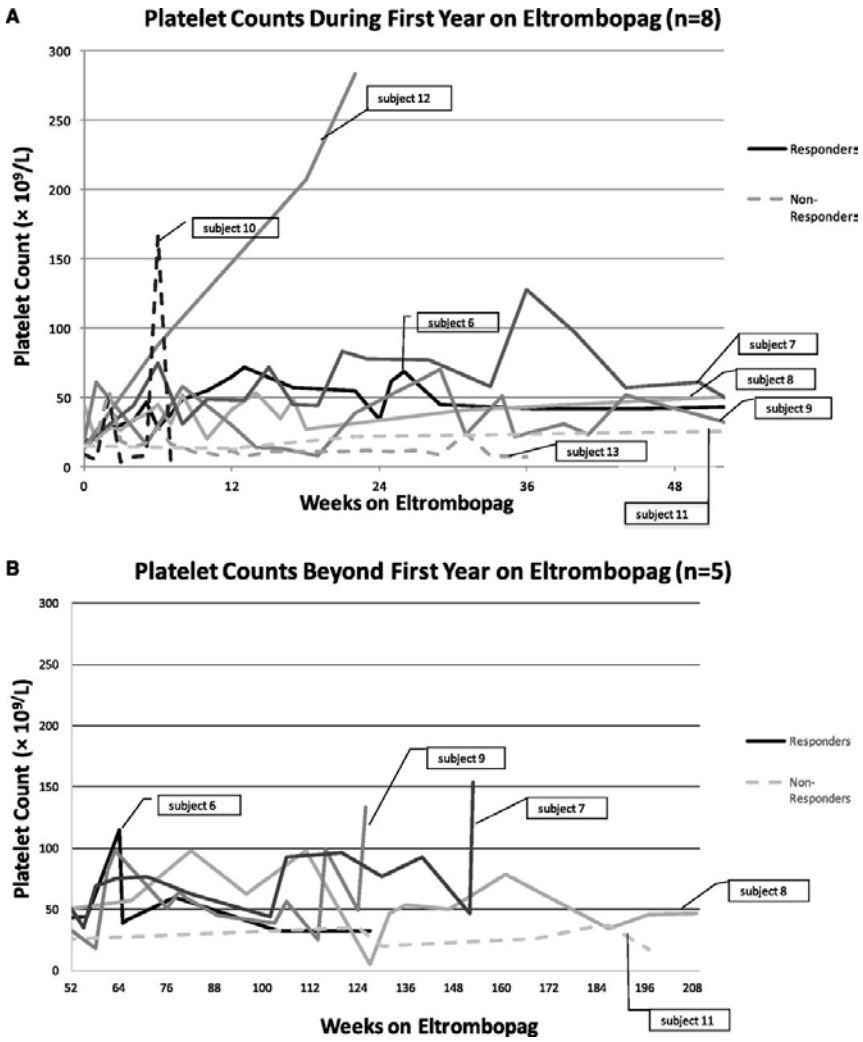
Figure 1. Time course of platelet count evaluated microscopically in the 12 *MYH9*-RD patients treated with eltrombopag. The dosage of eltrombopag is described, as well the splenectomized or not splenectomized state.

Eltrombopag Effect on Platelet Count in Fetchner Syndrome Before Surgery

(personal observation)



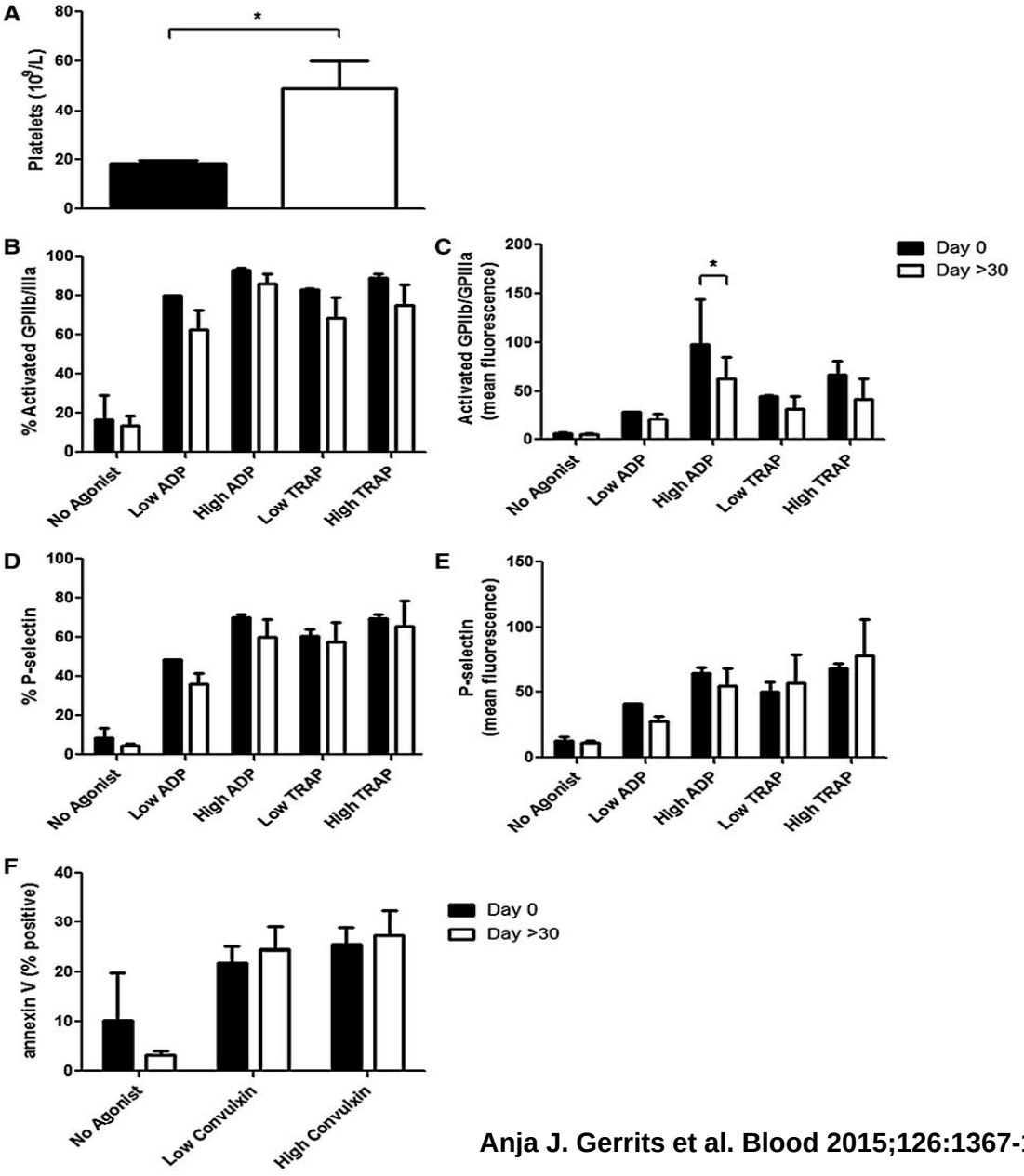
Platelet counts of WAS/XLT patients (n = 8) during treatment with eltrombopag.



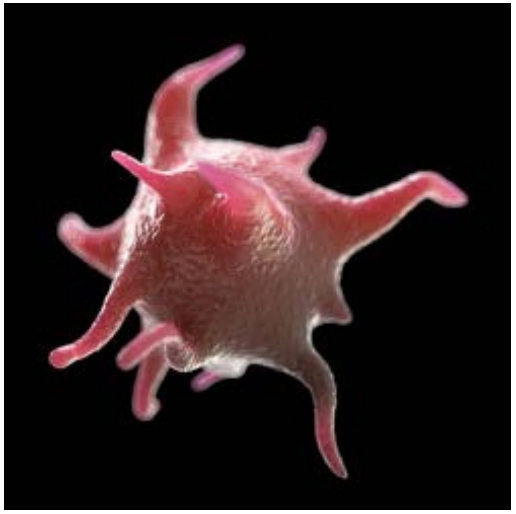
Eltrombopag doses varied by patient and ranged from 9 mg to 75 mg daily. Patients were considered responders if at least one platelet count increased to ≥50 × 10^9/L, was double the baseline count, and bleeding was reduced. The temporary rise in platelet count at week 6 to >160 × 10^9/L in subject 10 (a nonresponder) was the result of a platelet transfusion (A). Five patients continued treatment past 52 weeks (B).

Anja J. Gerrits et al. Blood 2015;126:1367-1378

Platelet markers in WAS/XLT patients at day 0 and >30 days of eltrombopag treatment.



Anja J. Gerrits et al. Blood 2015;126:1367-1378



Grazie per l'attenzione!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