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webinar

HEALTH PROFESSIONALS

EHA & EuroBloodNet Spotlight on Congenital BMF syndromes

Introduction to Congenital Bone Marrow Failure Syndromes

Pr. Thierry LEBLANC

Immunology and Hematology department. Hôpital Robert-Debré, Assistance Publique Hôpitaux de Paris & Pediatric site of the French reference center for Congenital & Acquired Aplastic Anemias, Paris, France

5 May 2025

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Conflicts of Interest

I have nothing to disclose

Plan

The landscape of IBMF & when to think to IBMF?

How to distinguish acquired aplastic anemia and IBMF

The challenge of somatic genetic rescue

The landscape of IBMF

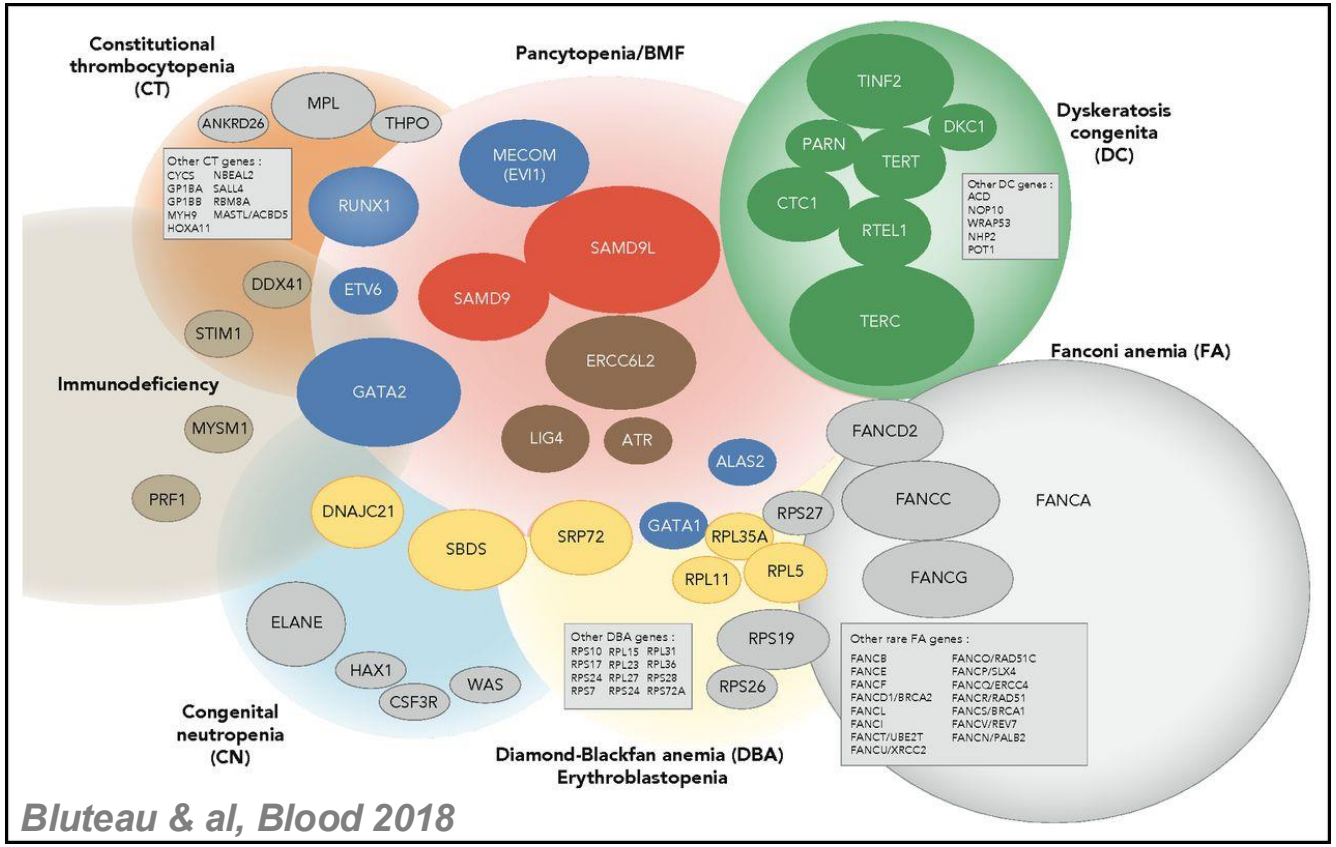
IBMFs are bone marrow failures due to germline mutations (transmitted or de novo). In addition to symptoms associated with aplastic anemia patients often have extra-hematological features more or less unique to each syndrome

Perimeter varies widely depending on authors

Focus on diseases associated with overt BMF: AA or multiple cytopenias

More and more diseases

Highly variable pathophysiology



Bluteau & al, Blood 2018

Age maters but IBMF may be diagnosed whatever the age

Age at IBMF:

Infants & toddlers	Children	AYA	Adults
MPL (amegacaryocytosis)	Fanconi	TBD: *DKC1*, *TERC*, *TERT* & *RTEL1*	*TERC* & *TERT*
MECOM	SDS	*THPO*	*DBAS*
Syndrome HH	*THPO*	*ERCC6L2*	
SAMD9 (MIRAGE)	*SAMD9*		
SAMD9L	*SAMD9L*		
DBAS			

Inheritance: may be tricky!

AR	(consanguinity but not in all pts!) (founding effect)	: Fanconi, *SBDS*, *DNAJC21*, *MPL*, *THPO*, *ERCC6L2*, *LIG4*,… + rare TBD* (*NOP10*, *NHP2*,…) and DBAS (*HEATR3)* subtypes
AD	(no consanguinity!)	: DBAS (40~45%)**, TBD*: *TERT*, *TERC*, *RTEL1* …, *SAMD9*/*SAMD9L*, …
X-linked	(boys)	: *DKC1*, rare DBAS subtype (*GATA1*…, *TRS2*), *FANCB*

<u>But also:</u>

De novo	(no familial history)	: *MECOM* (mostly), *TINF1* (mostly) *:* DBAS (55~60%)

*** For TBD some genes may be associated with both AR and AD inheritance…**
**** Parents with the variant may be w/o phenotype a first visit**

Extra-hematological phenotype may be helpful…

Some features are very suggestive:

Congenital anomalies: FA, DBAS
Horse shoe kidney: FA, DBAS

Microcephalia : LIG4 syndrome

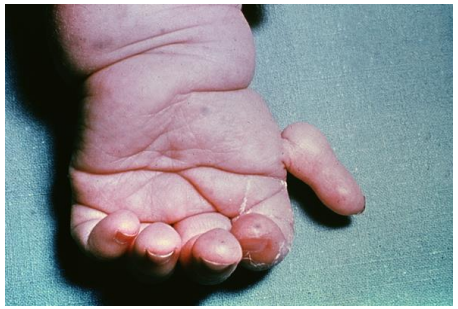
Cerebellar atrophy: HH syndrome

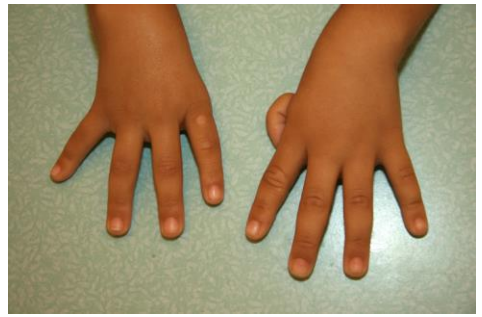
Nail dystrophy: TBD

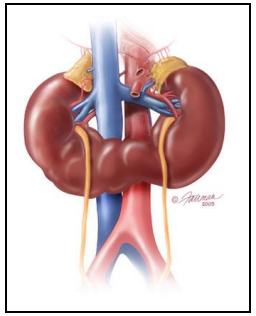
Fat-replaced pancreas (MRI): SBDS

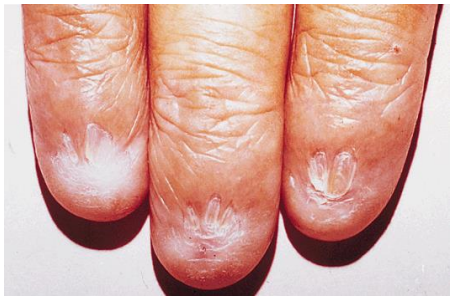
…/…

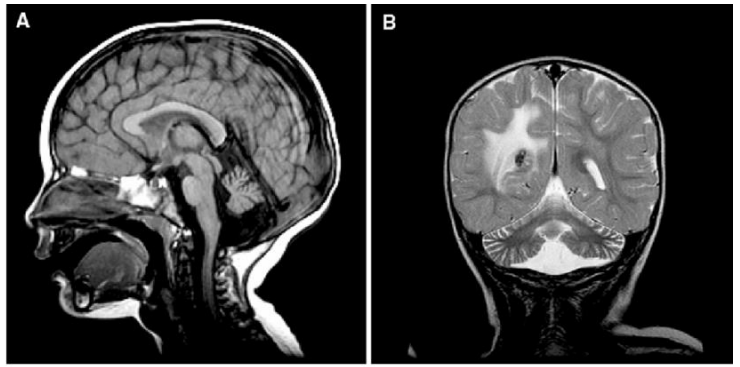
⇨ Clinical and radiological check-up

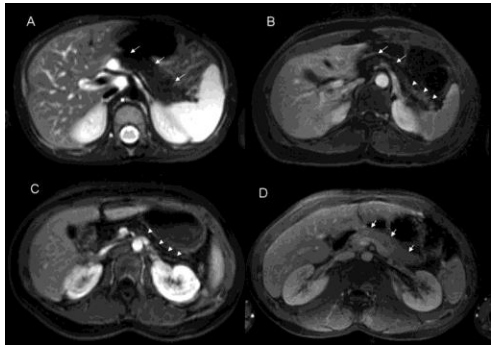








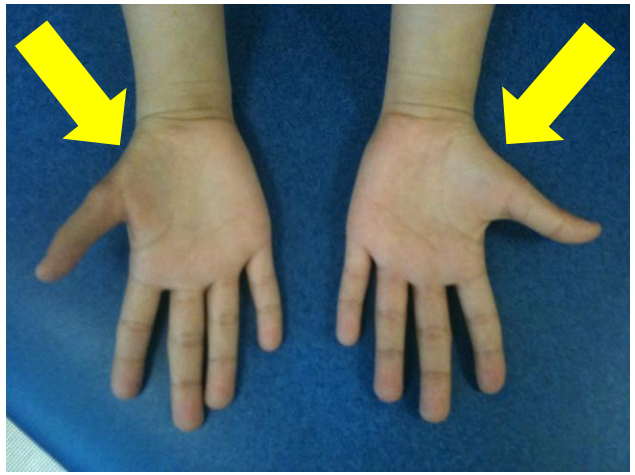




But whatever the syndrome extra-hematological phenotype may be absent or subtle!

Attenuated phenotype in some patients

Thenar eminence hypotrophy



Phenotype development over time +++:

- DNA instability: café-au-lait spots in FA ⇗ with time
- Telomere shortening: nail dystrophy & other TBD features ⇗ with time
- Parkinson-like disease: reported in older pts with *SAMD9L* variants

When to think to IBMF?

Children:

- Systematically in any case of central cytopenia (or macrocytosis!) or AA
± congenital anomalies
± extra-hematological phenotype

- MDS/AML: multilineage dysplasia, complex karyotype & specific anomalies

- Suggestive congenital anomalies or extra-hematological phénotype

Adult patients:

- Atypical PRCA: ☞ DBAS

- "MDS" in a "young" patient ++ if karyotype and myeloid NGS are normal: ☞ IBMF

- Atypical MDS with multilineage dysplasia, complex karyotype & specific anomalies

- Unexpected cancer: ex: head and neck squamous cell cancer in pt w/o alcohol or tabaco exposure

- Unexpected hematotoxicity post chemotherapy: ☞ IBMF mostly FA & DBAS

In children: 30% of AA are IBMF?

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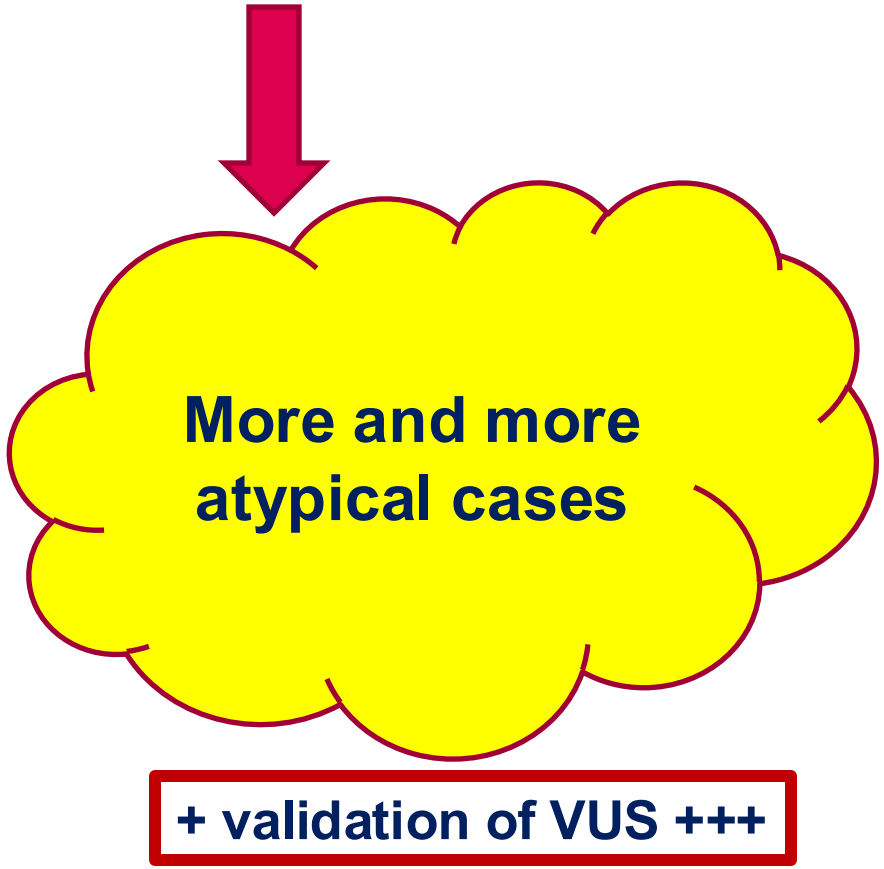
Good point: more and more diagnostic tools

- **Screening tests:**
  - HbF* : IBMF (not specific)
  - eADA: DBAS
  - Vitamin A & E: SBDS
  - AFP : FA*

  * Variable sensitivity according to the kit used (1)

- **Functional tests**
  - Chromosome breakage test: FA
  - Telomere length: TBD
  - TCRα directory bias : LIG4

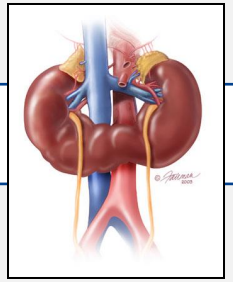
- **Genetic tests +++**



1: Cassinat & al, Clin Chem 2001

IBMF versus acquired APLASTIC ANEMIA

Hematologic profile * exception: SAMD9/9L	IBMF: progressive BMF* +++ (look for past CBC) : ± not-isolated: consanguinity, familial or personal history, extra-hematological phenotype, … aAA : acute presentation (± previous hepatitis ~ 10%)
Clinical examination	Growth retardation, congenital anomalies, extra-hematological phenotype, …
Imaging	Renal US, echocardiography, brain MRI, …
Fetal Hb	IBMF: suggestive if > 10% aAA: maybe a little high: 1-5%
PNH clone	IBMF: absent aAA: suggestive if > 1%
Other	6p CN-LOH Clonal TCR rearrangement



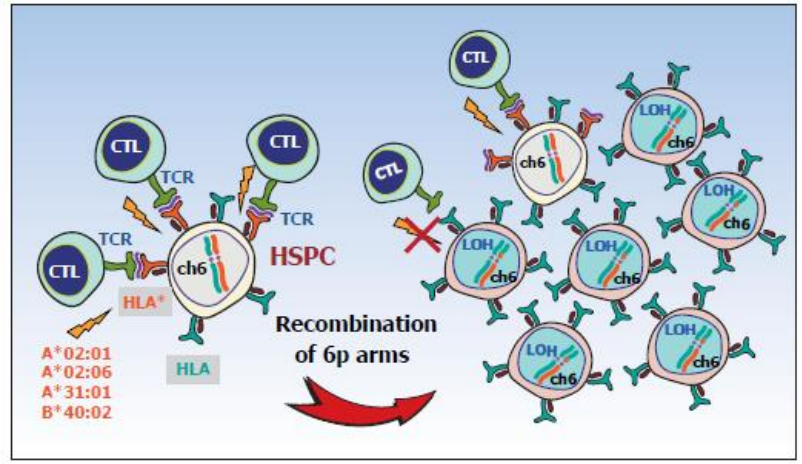
Childhood: 30% IBMF?

The predictive value of PNH clones, 6p CN-LOH, and clonal TCR gene rearrangement for aplastic anemia diagnosis

US study: 454 pts (children & adults)

Analysis:

- **PNH clone (immune escape)** ; threshold: > 0,05%
- **6p CN-LOH (immune escape)**
- **TCR gene rearrangement (auto-immune disease)**



Katagiri & al, Blood 2011

Table 2. The diagnostic value of PNH, acquired 6p CN-LOH, and clonal *TRG* rearrangement for the diagnosis of acquired AA

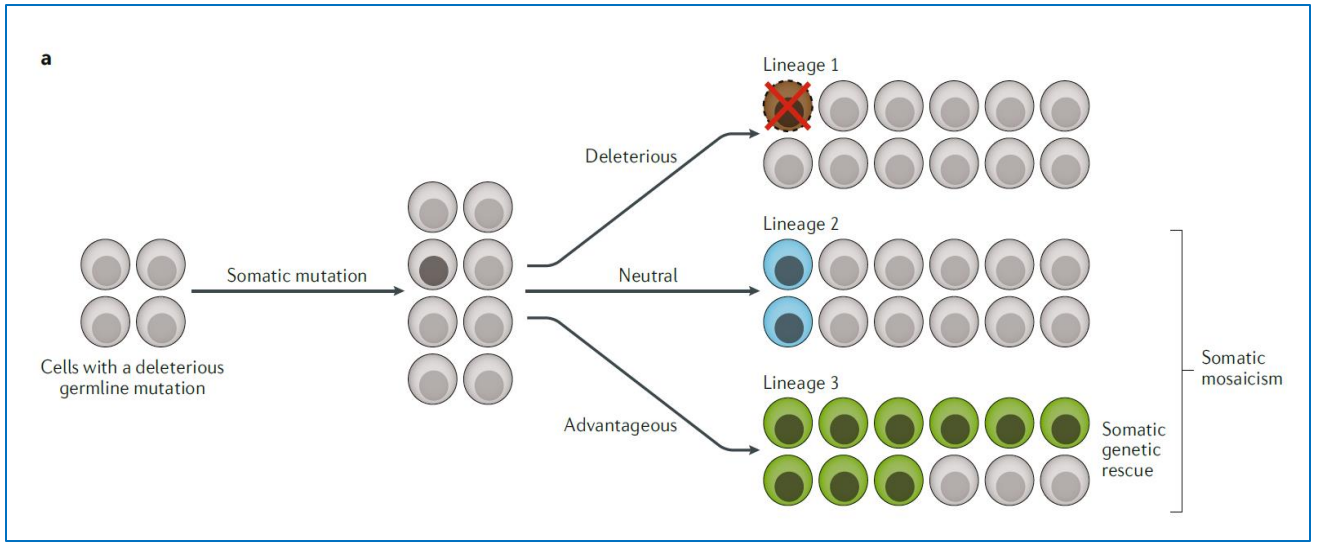
Laboratory test	Sensitivity, %	Specificity, %	PPV, %	NPV, %
PNH^{Gran}	46.0	100.0	100.0	48.5
Acquired 6p $CN\text{-}LOH^{MHC}$	11.4	100.0	100.0	63.2
Clonal *TRG* rearrangement PCR	29.2	63.4	50.0	41.7

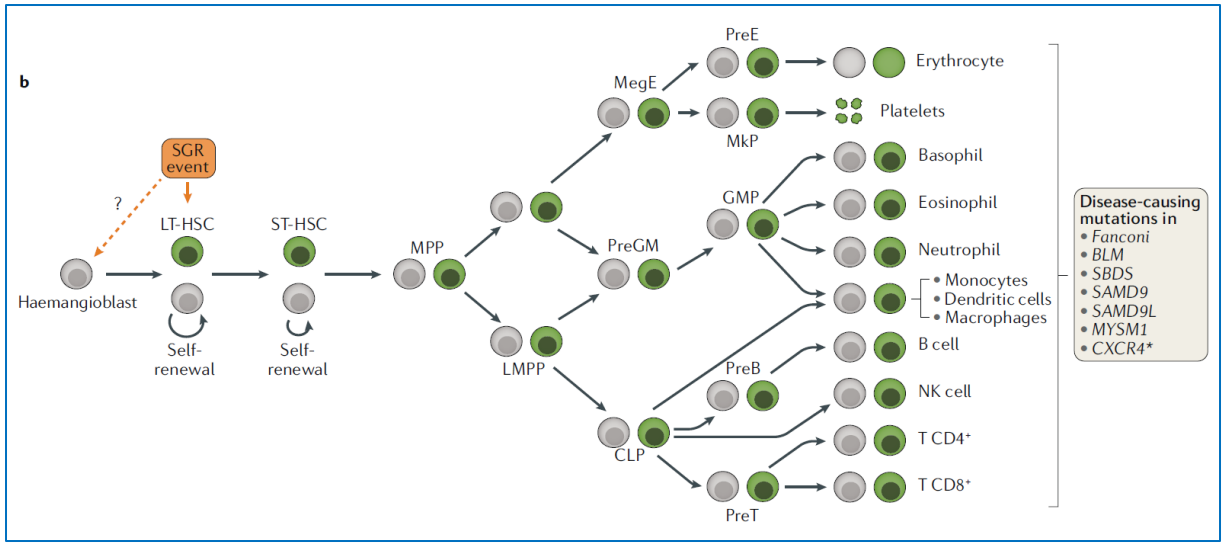
No IBMF work-up If PNH clone > 1%!

Shah & al, Blood Advances 2022

Somatic genetic rescue in Mendelian haematopoietic diseases

Patrick Revy [1,2], Caroline Kannengiesser[3,4] and Alain Fischer[2,5,6,7]*





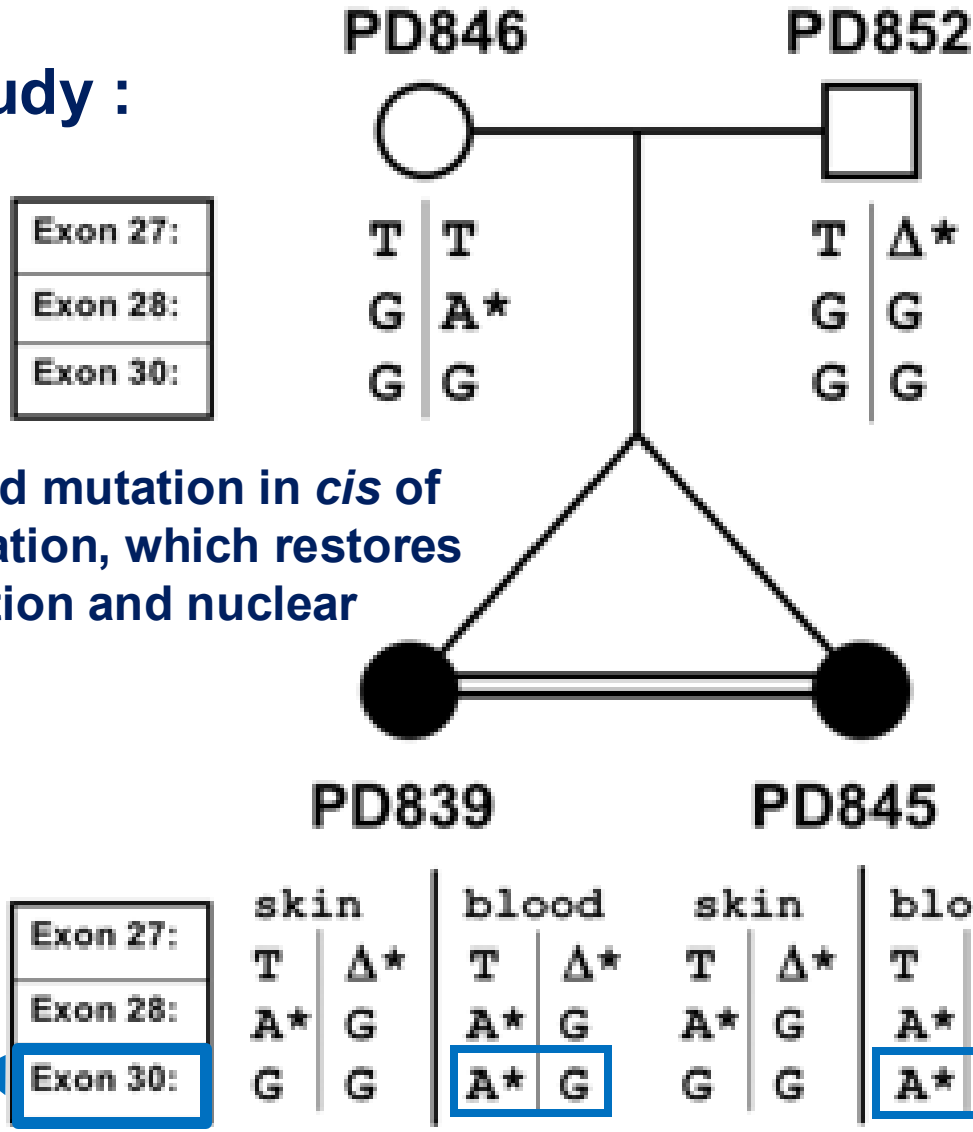
NB: SGR may also be indirect: other gene or locus

Nat Revy Genet 2019

Natural gene therapy in monozygotic twins with Fanconi

Mankad & al, Blood, 2004

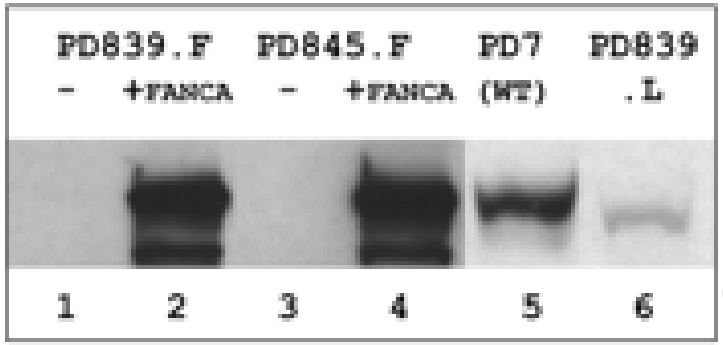
Age at study :
28 yr



New, acquired mutation in *cis* of exon 28 mutation, which restores FANCA function and nuclear localization

*** mutant allele:**

Exon 27; 2555 ΔT
Exon 28; 2670G>A; R880Q
Exon 30; 2927G>A; E966K



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SGR: take-home messages:

May explain "phenocopies": pts with extra-hematological features typical for an IBMF but with normal BCC

May explain diagnosis in adulthood

May explain variability of expression in one very family

Implies to analyse DNA on extra-hematological cells (fibroblasts)

May be helpful to classify a class 3 variant…

Man, 49 yr

- Surgery during childhood for left thumb malformation
- 49 yr: BMA for pancytopenia: AML FAB-M2
- Phenotype: small (162 cm), 1 café-au-lait spot, rigt kidney hypoplastic, peculiar face
- Caryotype: 46, XY, dic(1;15)(?p11;q2?5), -15 [8]
- CBS: 8 breaks/36 mitosis
- FancD2 test on fibroblasts: FA profile

Courtesy of Pr. Emmanuel RAFFOUX

Conclusion

An evolving world:

- More and more diseases
- More and more atypical cases including diagnosis in adult patients
- More and more unexpected results from genetic studies

☞ IBMF must be well-known by all hematologists (& also oncologists)

Thank you for your attention

thierry.leblanc@aphp.fr

MaRIH network: Reference centers for rare Immunological and hematological diseases

APLASIE MEDULLAIRE centre de référence

MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

Patients associations

AFMF
Association Française de la Maladie de Fanconi

AFMBD

Acknowledgments: Aplastic anemia & IBMF French group

- *Pediatric site: Mony FAHD, Jean-Hugues DALLE & Thierry LEBLANC*
- *Adult site: Flore SICRE de FONTBRUNE & Régis PEFFAULT DE LATOUR*
- *Hematology labs: Lise LARCHER, Jean SOULIER, Caroline KANNENGIESSER, Lydie DA COSTA*

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EHA&EuroBloodNet Spotlight on Congenital BMF syndromes

Diagnostic Challenges in IBMFS

Carlo DUFOUR, MD
G.Gaslini, Research Children ‘s Hospital , Genova ,Italy

5 May 2025

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Conflicts of Interest

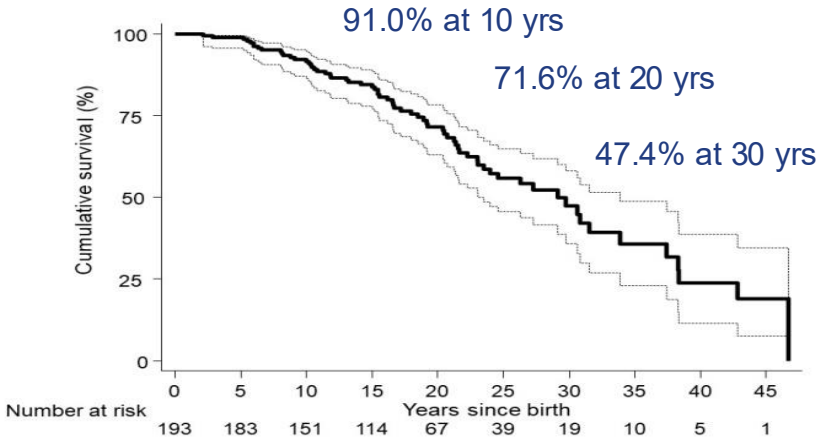
Consultancy	Gilead, Rockets
Conference fees	Pfizer
Advisory Comitee member	Biocryst, Novartis, Pfizer, Sobi

Content

- Illustrative case of FA
- Telomere Biology Diseases
- DADA2

Italian Registry of Fanconi Anemia

Median survival age: 29.1 years



Ricci E… Dufour C, et al. Am J Hematol 2025

162/193 pts = 84% aged ≥ 18 yrs

70% transplanted
30% non transplanted. Of them 1/3 alive

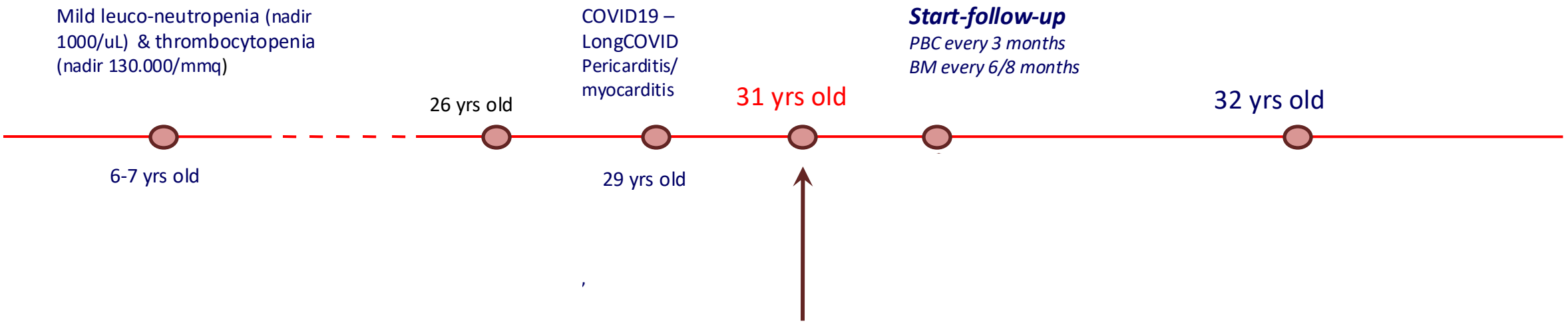
Chance for an adult hematologist to see an adult FA patient for diagnosis or pre- post transplant surveillance.

- Male, 32 yrs, silent non-hematological personal hystory.

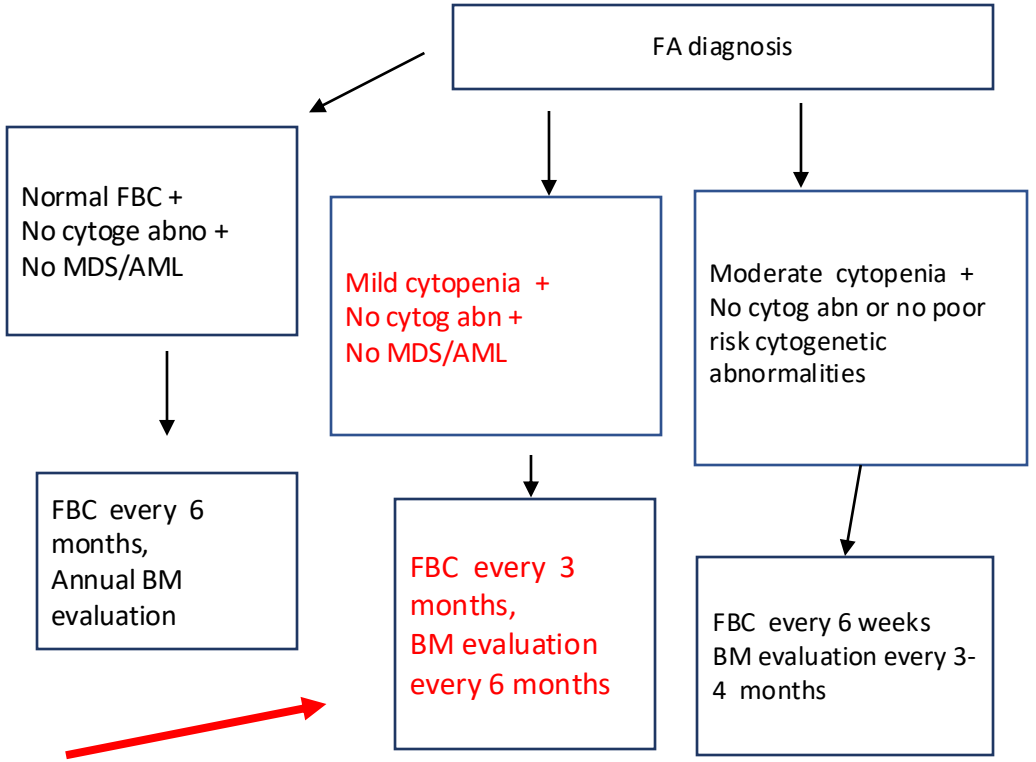
- Younger brother with mild pancytopenia

- Mild bilineage cytopenia (leukocytes and platelets) from infancy but stable over-time.
- Age 26 bone marrow cellularity reduced for age, no dysplastic features, no clonal abnormalities.

- Diagnosis of FANCG at age 31 yrs
- Start follow up. First marrow ok (morphology and cytogenetics).
- «Overwhelming» AML 8 months after BM.



Hematology
The American Society of Hematology Education Program



C Dufour, F Pierri. Hematology Am Society Hematol Educ Program 2022 Dec 9; 2022(1): 649-657.

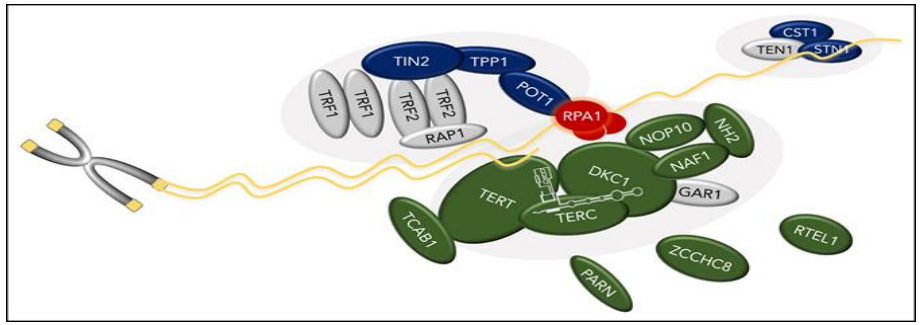
Content

- Illustrative case of FA
- Telomere Biology Diseases
- DADA2

TBD

- About 70% of patients has mutations in15 genes of shelterin-telomerase complex

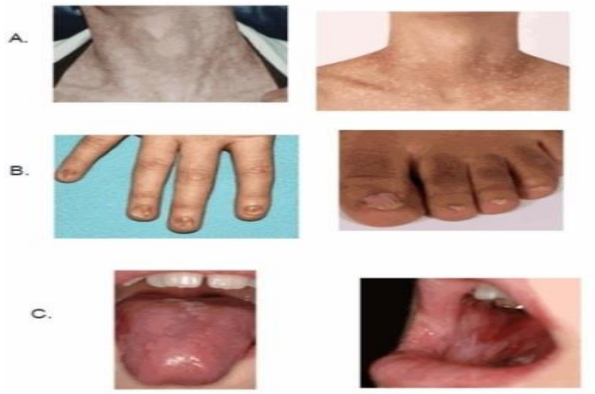
DKC1 (25%)
TNF2 (12%)
TERC (5%)
TERT (5%)
USB1 (2%)
R TEL (2%)
CTC1 (1%)
NOLA2 (<1%)
NOLA 3 (<1%)
T CAB1 (WRAP 53) (<1%)
TPP1 (ACD) (<1%)
PARN (<1%) (<1%)
POT1 (Apollo) (<1%)
RPA1 (<1%)
TYMS-ENOF-1 (<1%)



Skin dyspigmentation

Nail dystrophy

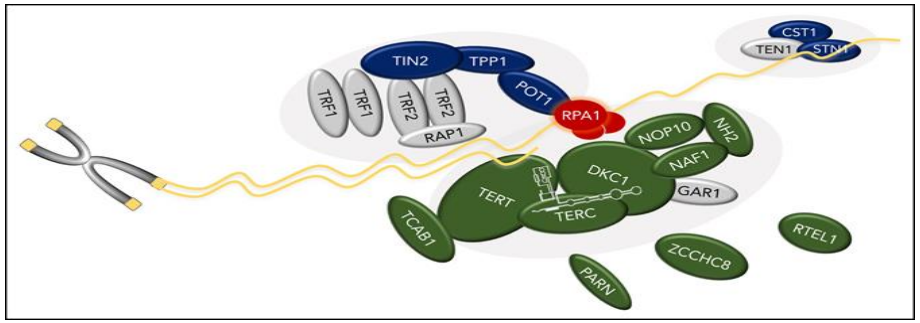
Leukoplakia



- X linked, autosomal dominant/recessive
- Remarkable shortening of the telomere

- Variabile penetrance
- Variable phenotype including marrow failure and increased risk of tumors

TBD

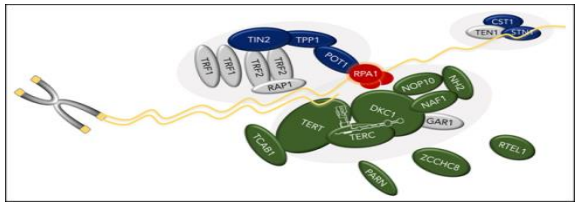


Some shelterin variants generates TBDs by telomere instability **without TL shortening**

(POT1, biallelic CTC1 and STN1. DCLRE1B acts with a diffrent mechanism).

Diagnosis: Clinical features,+ TL + genetics

TBD adults

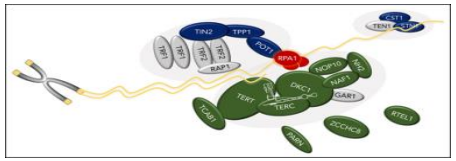


- Still severely underdiagnosed in adults
- Underdiagnosis has relevant impact on:

  prognosis,
  surveillance,
  treatment,
  management of complications
  appropriate family counseling

; Rolles B, et al. a Transfus Med Hemother. 2024; Tometten M, et al. Hemasphere. 2023; Niewisch MR, et al. Hematology Am Soc Hematol Educ Program. 2023

TBD adults



- Fairly different clinical phenotype as compared to children/ado.

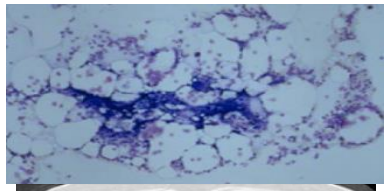
- AD inheritance is predominant.

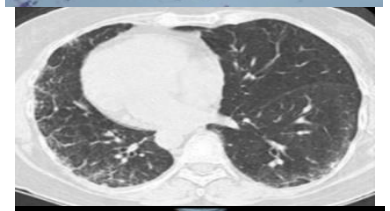
- Initial manifestation sometimes > age 40 years.

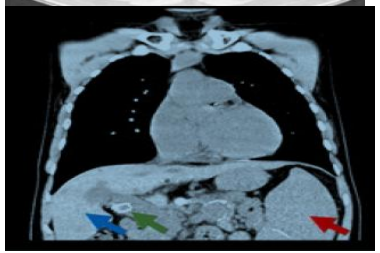
- Often mono- or oligo-symptomatic, often lacking a skin phenotype

  - AA
  - Early-onset sporadic PF or family history of PF
  - Unexplained liver disease and/or early-onset HNSCC

  → TL and genetics strongly recommended





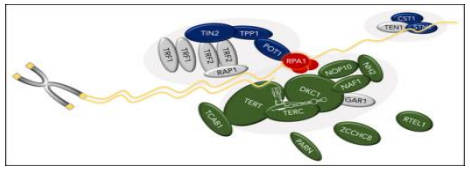


Look out! More frequent short (1-10th centile) than very short (<1st centile)
Restricted diagnostic window because of age related TL attrition

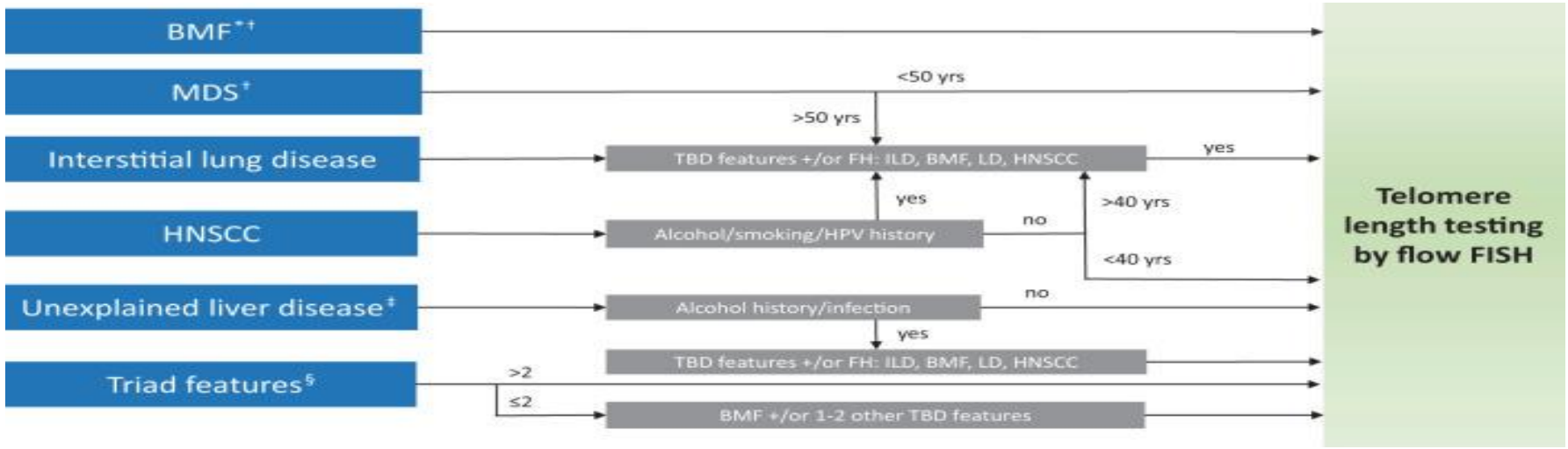
In age >40 yr abs shortage < 6,5 kb more specific than centile

Tometten M, Beier F, et al. Blood Adv. 2025; Rolles B, et al. a Transfus Med Hemother. 2024; Tometten M, et al. Hemasphere. 2023; Niewisch MR, et al. Hematology Am Soc Hematol Educ Program. 2023

TBD



- Some diagnostic tools available



Niewisch MR, et al. Hematology Am Soc Hematol Educ Program. 2023

Point-based algorithm (mutation, degree of telomere shortening, positive family history, TBD related clinical features) identified:

- proven,
- probable
- suspected-only TBD

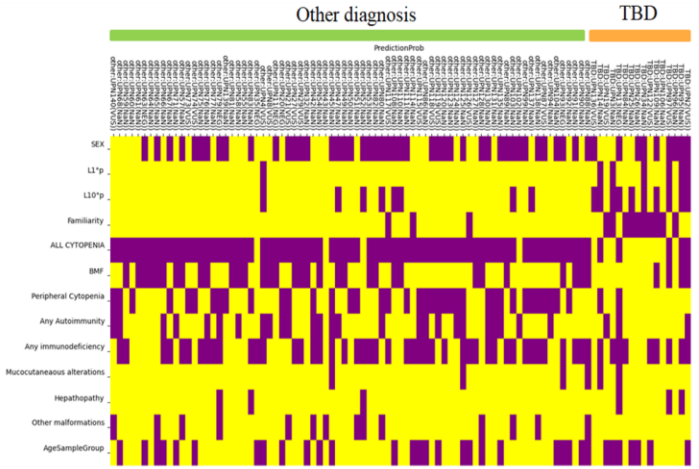
Tometten M, Beier F, et al. Blood Adv. 2025

but probably still need implementation with more data

ML in the diagnostic work-up of TBD

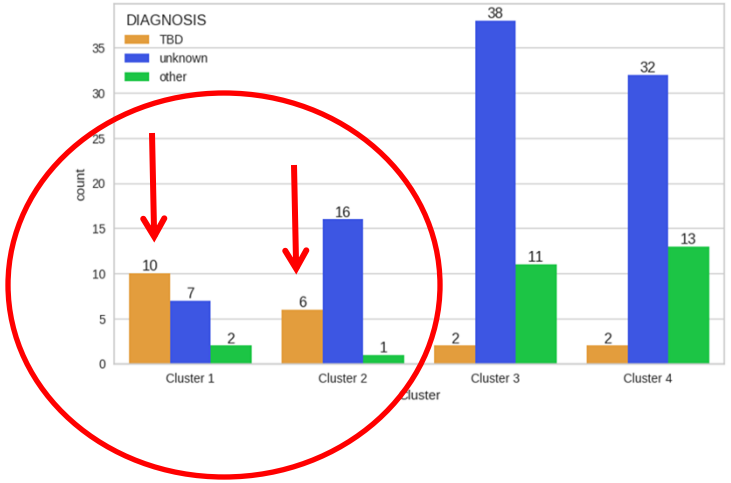
- Supervised analysis reallocated

  - 17.2% of Undefined Diagnosis patients to TBD
  - 82.7% of Undefined Diagnosis to other non-TBD molecular IBMF diagnoses.



- Unsupervised analysis identified 4 clusters

  In clusters 1 and 2 there was a strong prevalence of molecularly defined TBD (p=0.000001)



- All patients diagnosed as TBD by supervised analysis were in clusters 1 & 2 by unsupervised analysis, including 5/16 patients with a VUS on a TBD gene

- Need for validation on different, larger cohorts

Arcuri L, Massaccesi E… Dufour C, submitted

Content

- FA
- TBD
- DADA2

DADA 2

- ADA 2 expressed on myeloyd cells
- Binds adenosine receptors (not well defined) on T-cells
- Cytokine-like growth activity
- Down regulate inflammation

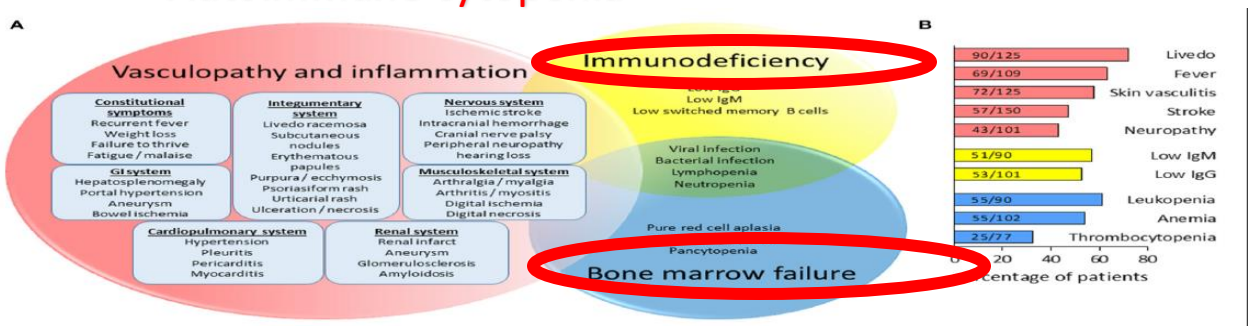
- Defiency of ADA2 polarizes macrophages to M1 inflammatory phenotype and activates neutrophils

ADA 2 deficiency

Multi faceted disorder

- Autoinflammation
- Vasculopaty
- Immune deficiency/autommunity
- Marrow failure

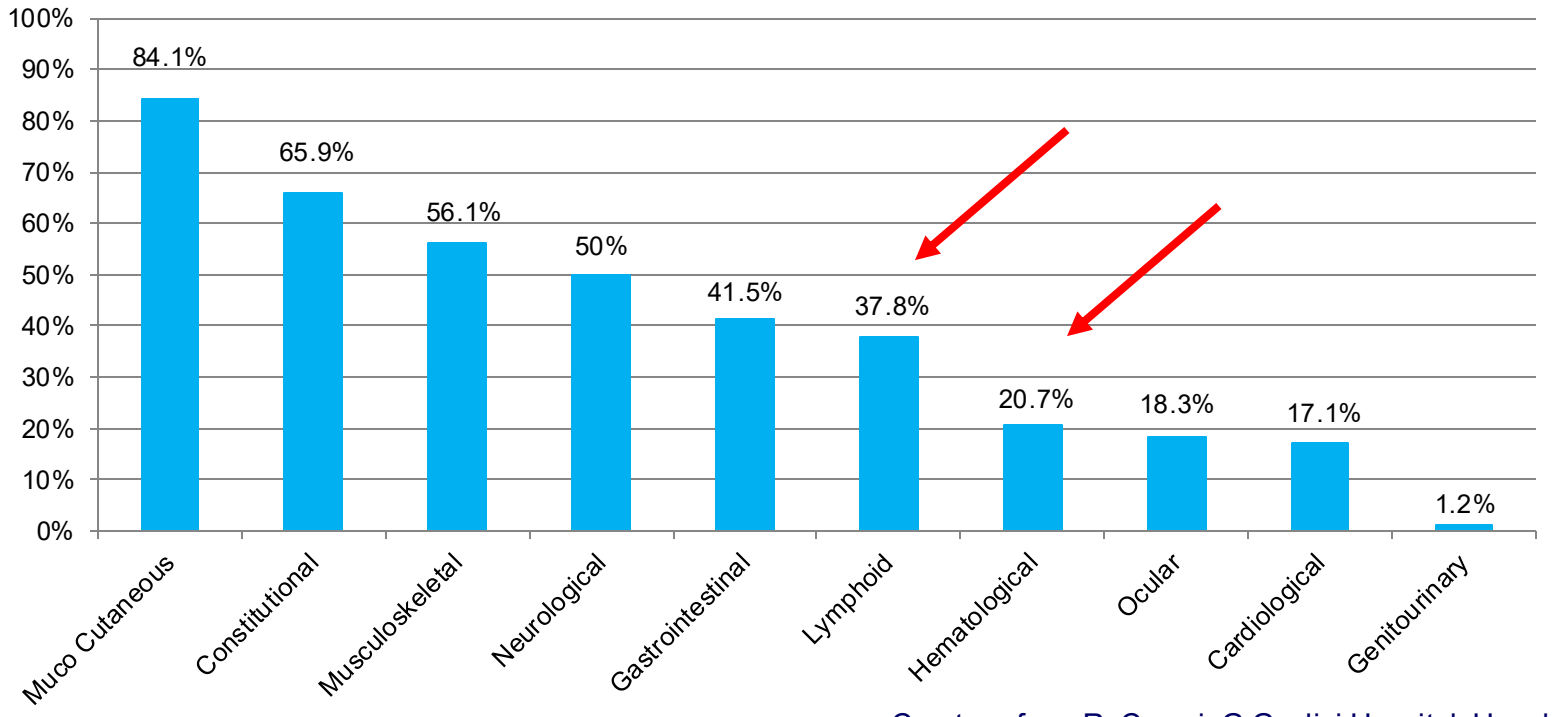
Autoimmune cytopenia



Pui Y Lee Frontiers in Pediatrics. Oct 2018

EUROFEVER REGISTRY-DADA 2-

Hematology- immunology



Courtesy from R. Caorsi, G.Gaslini Hospital. Unpublished. Please do not spot.

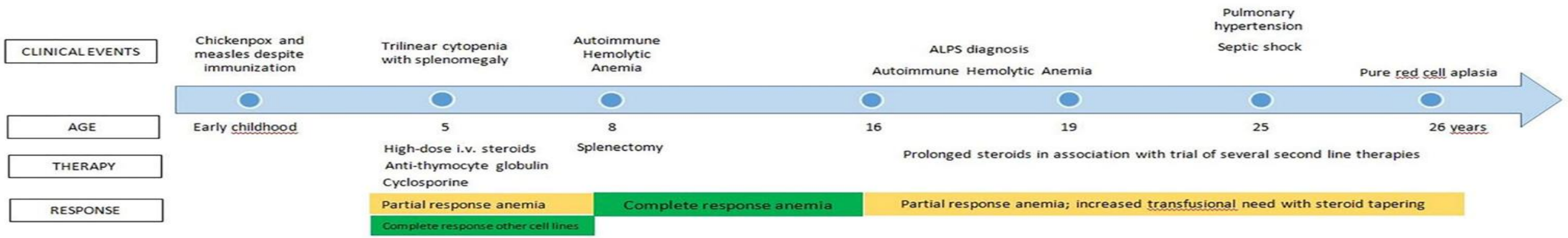
- Mono, bi, tri-lineage cytopenia
  - PRCA
  - Immune mediated neutropenia
  - Thrombocytopenia
  - Monocytopenia
  - Lymphopenia

- Diffuse lymphoadenopathy
- Low Ig G, A, M
- Low swithched memory B cells
- Low memory T cells
- Low NK

Differential Diagnosis

- ALPS and other immune cytopenias

26 yr old lady referred at our center after a 18 yr history of cytopenia, AIHA & PRCA



IGURE 1 | Clinical history previous to referral at our Center.

Dell'Orso et al. Frontiers in Immunology, 2021

Differential Diagnosis

- ALPS and other immune cytopenias
- PRCA
- DBA Syndrome

Ulirsch Jc et al Am J Hum Genet.2018 Dec 6;103(6):930-947

Diagnosis

- Plasma ADA2 activity
- Genetic testing

MLPA for CNV
(Multiple Ligation dependent Probe Amplification)

Take Home

- IBMF are difficult to diagnose.
- Many newcomers….make the scenario more crowded.
- Age ”per se” is not a diagnostic exclusion criteria.
- Genetics improved diagnostic accuracy but may not be conclusive.
- Need complementation with functional test and clinical findings.
- AI may be of support.

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info@ehaweb.org

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European Hematology Association (EHA)

European Hematology Association

@EHA_Hematology Youtube channel

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EHA&EuroBloodNet Spotlight on Congenital BMF syndromes

webinar

HEALTH PROFESSIONALS

Application of NGS in BMF

LYDIE DA COSTA

AP-HP, BICETRE HOSPITAL
PARIS SACLAY UNIVERSITY
INSERM UNIT, U1170 GUSTAVE ROUSSY INSTITUTE

5 May 2025

MaRIH

université PARIS-SACLAY

Hôpital Bicêtre AP-HP

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Conflicts of Interest

None

What is the NGS?

- NGS= Next generation sequencing, not anymore so next!
- Since 2008 (*Bentley et al., Nature, 2008; Ng.S.B et al., Nature 2009*) – really in hospital in 2015
- Sequencing machines and softwares able to analyze millions to billion of sequencing reactions from human genome simultaneously :

→ Large increase in the amount of informations

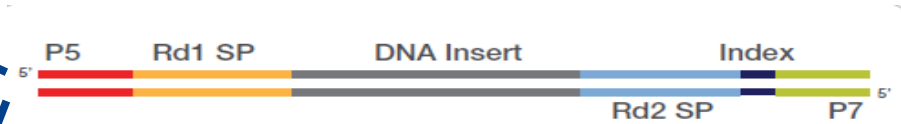
→ Saved time

→ Less expansive

- Various sequencing machines and softwares but there all share some steps :
  - Library to build
  - A sequencing
  - Some softwares, which allow the reading, the analysis of all the data

Capture sequencing technique

First glance, we see all the candies (the complete genome)



All the patients to screen (24 to 96)
The complete genomic DNA from these patients are fragmented and labeled with a specific index (bar-code)

Then, we want to see only the « watermelon » ones

We use capture probe to keep only the DNA fragments from gene sequences that we are interested (104 genes in our library)

The sequencing capture technique = targeting of DNA regions of interest

Like only « watermelon » candies

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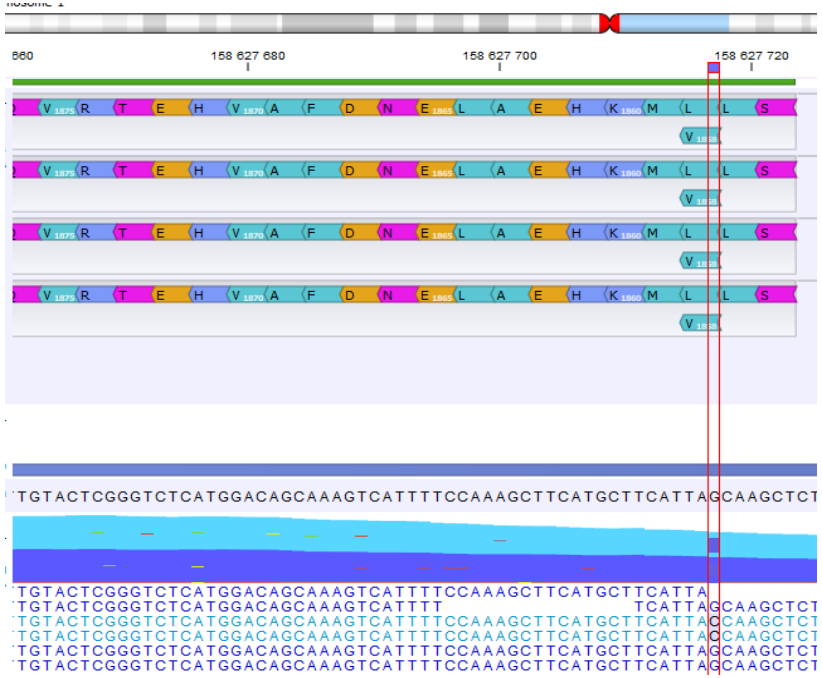
Duplication CAA

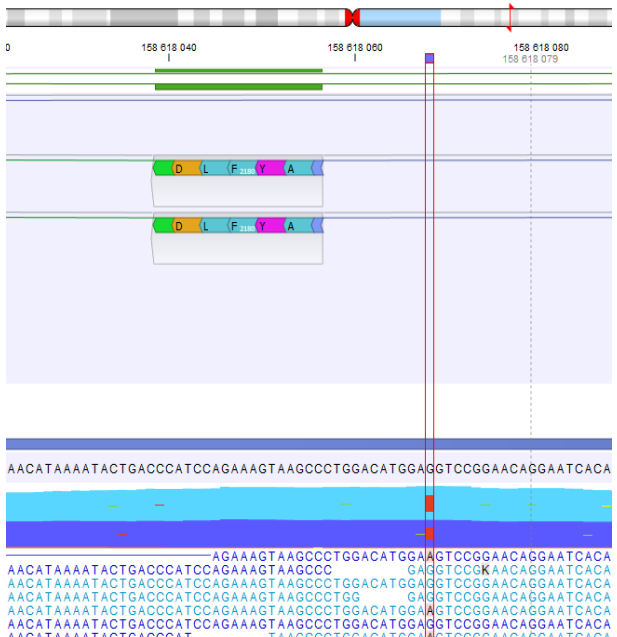
CLC Biomedical Workbench (Qiagen)

Read counting : nb of time that a nucleotide has been read
= mean 100X (minimum 30x)

Substitution C>G



Intronic variation



Annotation of the allelic variations

http://www.acgs.uk.com/media/1092626/uk_practice_guidelines_for_variant_classification_2017.pdf)

- **Recommandations from ACMG-AMP** (*Richards et al., Genet Med, 2015; Amendola et al., Am J Hum Genet 2016*)
- **The final characterization of the mutation is at the only assessment and responsibility of the biologist/geneticist**

- **The mutation analysis is always performed at a special time and depends on our knowledge at this time :**

- **The mutation analysis depends on arguments with a certain degree of importance:**
  - PVS= very strong / PS= strong / PM=moderate /PP= supporting criteria for pathogenicity
  - BA/BS = strong/weak criteria for benign mutation

- **At the end, we are able to classify the identified mutation in one of the 5 classes:**
  - **Class 1: benign variant**
  - **Class 2: likely benign variant**
  - **Class 3: unknown significance variant (additional functional experiments/data/family type segregation)**
  - **Class 4: likely pathogenic variant**
  - **Class 5: pathogenic variant**

- **Some examples:**

RPS19 Gene (NM_001022.3): c.184C>T p.(Arg62Trp) Pathogenic Variant (class 5)	*RPL35A* Gene (NM_000996.2) : c.227_228DelGGInsCCCAT p.(Arg76delinsProHis) Likely pathogenic variant (class 4)	*RPS26* Gene (NM_001029.3): c.1A>G p.(Met1Val) Pathogenic Variant (class 5)

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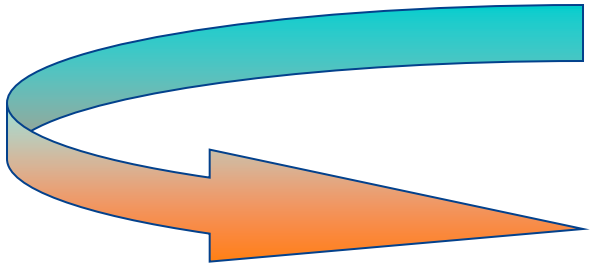
DBA mutation screening analysis

Targeted-NGS

Roche “NimbleGen SeqCap EZ” library and illumina flowcell (Flowcell standard 2*150) - Miseq

Hematology lab, Bicêtre hospital, Le Kremlin-Bicêtre, France

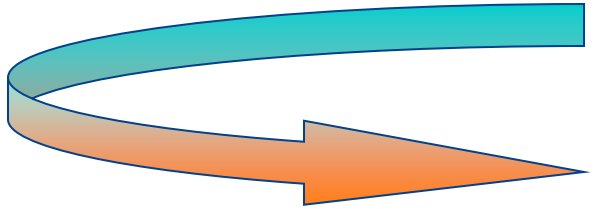


If no “DBA” genes have been identified

Large deletions (CGH/SNP array)

- HumanOmniExpress-12 v1.0 Analysis BeadChip Kit (>700 000 loci) - Genome studio software
- Custom G3 CGH Microarray 8x60K

Hematology lab, Bicêtre hospital, Le Kremlin-Bicêtre, France



If no “DBA” genes or large deleterious mutations have been identified

Exome/Genome Sequencing

SEQOIA platform, north part of France
AURAGEN platform, south part of France

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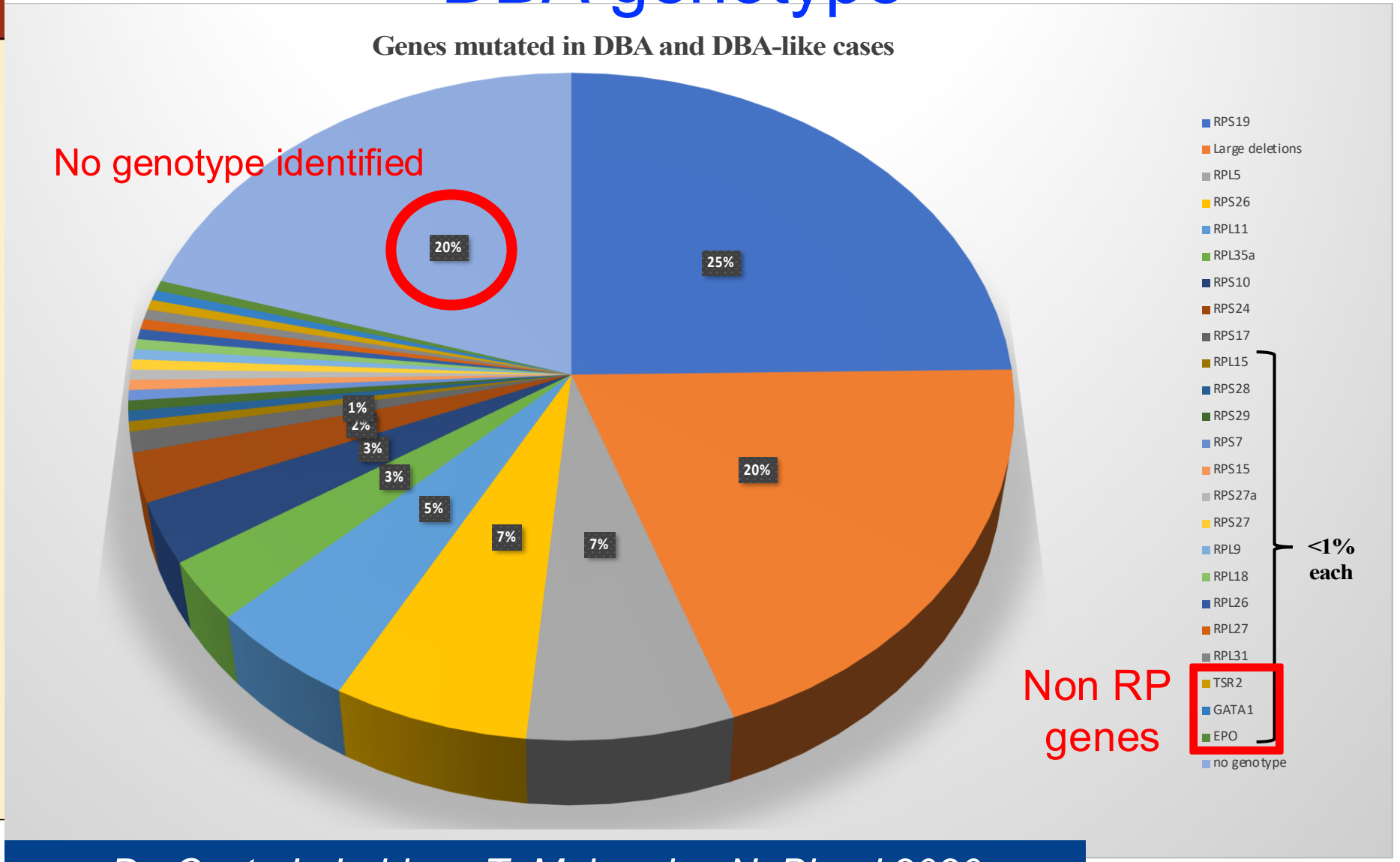
DBA genotype

Mutated gene	RP	Incidence in DBA population
Genes involved in DBA*		
RPS19	eS19	25%-30%
Large deletions		10%-20%
RPL5	uL18	7%-12%
RPS26	eS26	6.6%-9%
RPL11	uL5	5%-7%
RPL35a	eL33	2%-3%
RPS10	eS10	1%-3%
RPS24	eS24	2.4%-3%
RPS17	eS17	1%-3%
RPL15	eL15	1 case
		6 cases
RPS28	eS28	2 families
RPS29	uS14	2 families
RPS7	eS7	1 case
RPS15	uS19	1 case
RPS27a	eS31	1 case
RPS27	eS27	1 case
RPL9	uL6	1 case
RPL18	eL18	1 family
RPL26	uL24	1 case
RPL27	eL27	1 case
RPL31	eL31	1 case
TSR2 (X linked)†		1 family
Genes involved in DBA-like diseases		
GATA1 (X linked)‡		5 families
EPO		1 case
ADA2§		9 individuals



Da Costa L, Leblanc T, Mohandas N, Blood 2020

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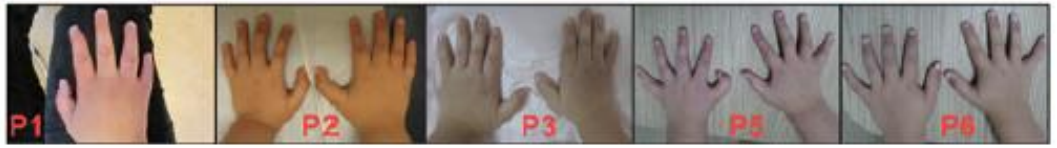
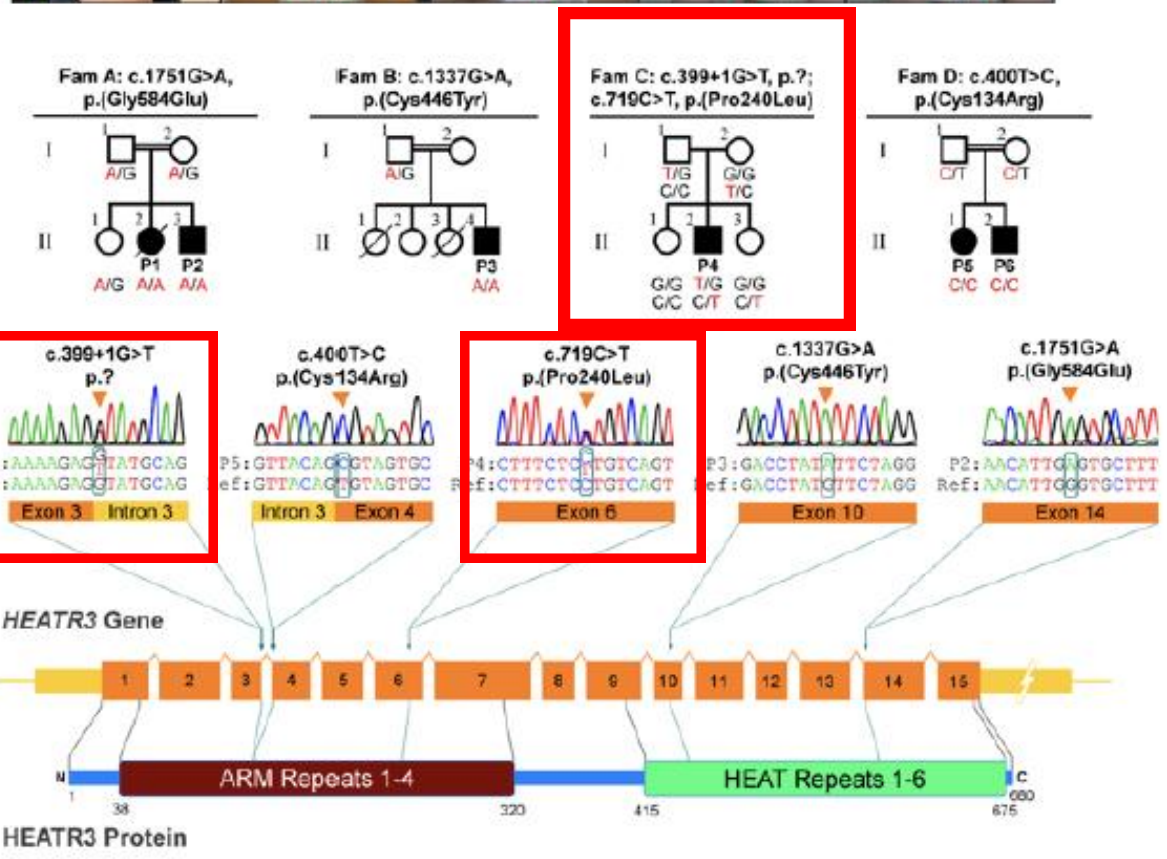
Identification of a new candidate gene, which is a chaperone of RPL5: *HEATR3*

A	homozygous	homozygous	compound heterozygous	homozygous
	anemia brachydactyly short stature mild intellectual disability P1 died of osteosarcoma	anemia brachydactyly short stature intellectual disability	Anemia short stature no intellectual disability	anemia, transient thrombocytopenia (P6 preaxial polydactyly, brachydactyly, mild intellectual disability (P5)



With parents' authorization



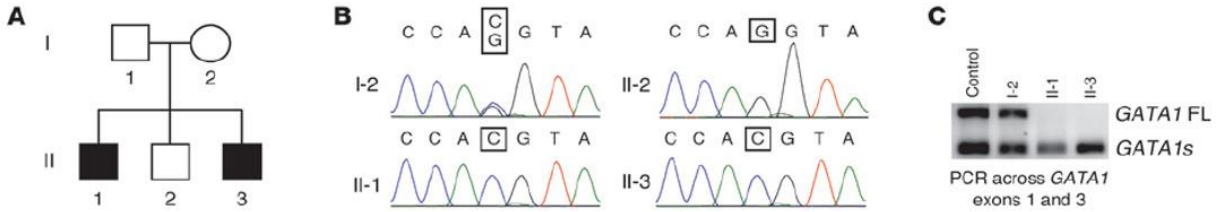
MF O'Donohue, L Da Costa*, Marco Lezzerini*, Sule Unal*, et al., Blood. 2022 May 26;139(21):3111-3126.*

DBA – like and borderline DBA cases

- *GATA-1 gene mutation:* X-linked

Sankaran et al., J Clin Invest, 2012
Weiss et al., J Clin Invest, 2012
Parella et al., Pediatr Blood cancer, 2014
Klar et al., Br J Hematol, 2014

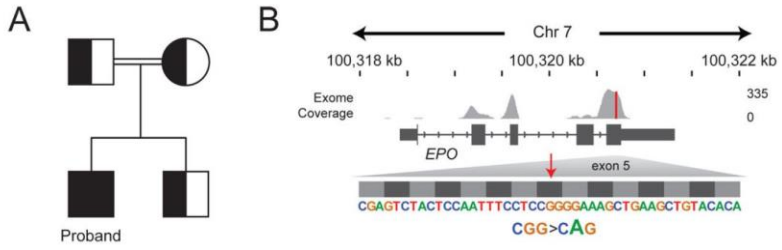
Mutation in exon 2:
c.220G>C ; p.(Leu74Val)



Loss of the 83 first aa
Loss of the long form of GATA1 (GATA1 FL)

- *EPO gene mutation: recessive inheritance*

KIM et al., Cell 2017

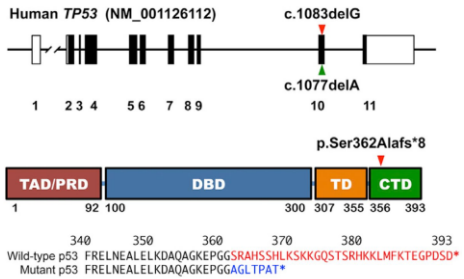


Mutation in exon 5:
g.100,320,704G>A
p.(Arg150Gln)

- *TP53 gene mutation:*

Toki et al., Am J Hum Genet, 2018

Borderline DBA/DKC?



Mutation in exon 10:
c.1083delG or c.1077delA
p.(Ser362Alafs*8)

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EUROPEAN HEMATOLOGY ASSOCIATION

Ferrata Storti Foundation

Recurring mutations in *RPL15* are linked to hydrops fetalis and treatment independence i Diamond-Blackfan anemia

Marcin W. Wlodarski,[1,2] Lydie Da Costa,[3,4,5,6] Marie-Françoise O'Donohue,[7] Marc Gastou,[3,4,8] Narjesse Karboul,[3,5] Nathalie Montel-Lehry,[7] Ina Hainman Dominika Danda,[1,9] Amina Szvetnik,[1] Victor Pastor,[1,10] Nahuel Paolini,[11] Franca M. di Summa,[11] Hannah Tamary,[12,13] Abed Abu Quider,[14] Anna Aspesi,[15] Riekelt H. Houtkooper,[16] Thierry Leblanc,[17] Charlotte Niemeyer,[1,2] Pierre-Emmanuel Gleizes[7] and Alyson W. MacInnes[16]

770–787 Nucleic Acids Research, 2020, Vol. 48, No. 2 Published online 4 December 2019
doi: 10.1093/nar/gkz1042

Ribosomal protein gene *RPL9* variants can differentially impair ribosome function and cellular metabolism

Marco Lezzerini[1,†], Marianna Penzo[2,†], Marie-Françoise O'Donohue[3,†], Carolina Marques dos Santos Vieira[4,†], Manon Saby[5,†], Hyung L. Elfrink[1,6], Illja J. Diets[7], Anne-Marie Hesse[8], Yohann Couté[8], Marc Gastou[9,10,11], Alexandra Nin-Velez[12], Peter G.J. Nikkels[13], Alexandra N. Olson[4], Evelien Zonneveld-Huijssoon[14,15], Marjolijn C.J. Jongmans[14,16], GuangJun Zhang[12], Michel van Weeghel[6], Riekelt H. Houtkooper[1], Marcin W. Wlodarski[17,18], Roland P. Kuiper[14], Marc B. Bierings[16], Jutte van der Werff ten Bosch[19], Thierry Leblanc[20], Lorenzo Montanaro[2], Jonathan D. Dinman[4], Lydie Da Costa[5,9,10,21], Pierre-Emmanuel Gleizes[3] and Alyson W. MacInnes[1,*]

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ARTICLE | VOLUME 103, ISSUE 6, P930-947, DECEMBER 06, 2018

The Genetic Landscape of Diamond-Blackfan Anemia

Jacob C. Ulirsch • Jeffrey M. Verboon • Shideh Kazerounian • ... Ron Do • Vijay G. Sankaran [18] • Hanna T. Gazda [18] • Show all authors • Show less • Show footnotes

Open Archive • Published: November 29, 2018 • DOI: https://doi.org/10.1016/j.ajhg.2018.10.027 •

AJHG ASHG Supports open access

REPORT | VOLUME 105, ISSUE 5, P1040-1047, NOVEMBER 07, 2019

RPL13 Variants Cause Spondyloepimetaphyseal Dysplasia with Severe Short Stature

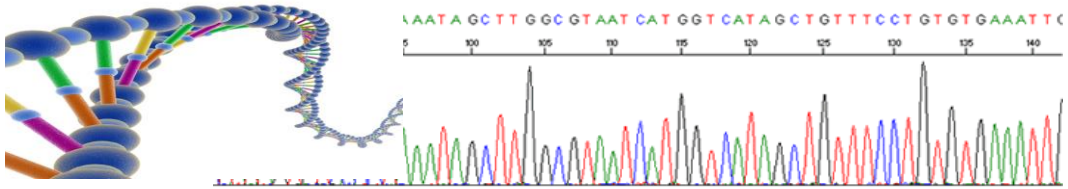
Cedric Le Caignec [21] • Benjamin Ory [21] • François Lamoureux [21] • ... Pierre-Emmanuel Gleizes [22] • Marc Baud'huin [22] • Bertrand Isidor [22] • Show all authors • Show less • Show footnotes

genes MDPI

Article

GATA-1 Defects in Diamond–Blackfan Anemia: Phenotypic Characterization Points to a Specific Subset of Disease

Birgit van Dooijeweert [1,2], Sima Kheradmand Kia [3,4], Niklas Dahl [5], Odile Fenneteau [6], Roos Leguit [7], Edward Nieuwenhuis [8], Wouter van Solinge [1], Richard van Wijk [1], Lydie Da Costa [6] and Marije Bartels [2,8,*]



JCI insight 2024

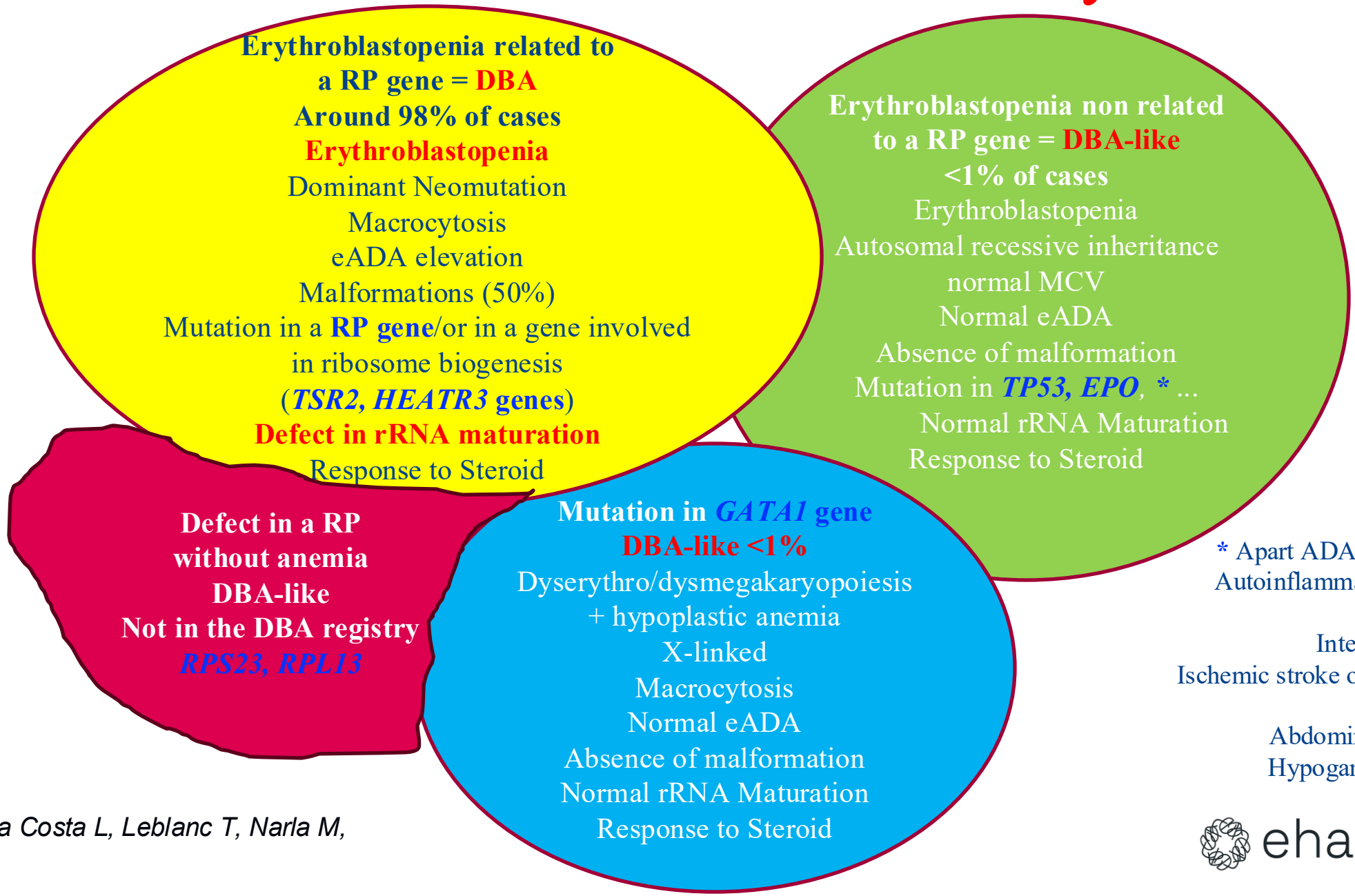
An atypical form of 60S ribosomal subunit in Diamond-Blackfan anemia linked to *RPL17* variants

Florence Fellmann, … , Erica E. Davis, Pierre-Emmanuel Gleizes

Vanlerberghe C, …Da Costa L, Petit F.
RPL26 variants: a rare cause of Diamond-Blackfan Anemia Syndrome with multiple congenital anomalies at the forefront. Genet Med. 2024 **2024**

New definition

DBA+DBA-like = DBA syndrome



* Apart ADA2 deficiency :
Autoinflammatory disorder
Vasculitis
Intermittent fever
Ischemic stroke or hemorrhage
Arthralgia
Abdominal pain crisis
Hypogammaglobulins

Modified from Da Costa L, Leblanc T, Narla M, Blood, 2020

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TAKE HOME MESSAGE

- In general in all the diseases and also in IBMFS, targeted-NGS / Whole exome sequencing (WES) / Whole genome sequencing (WGS) have revolutionized the genetics:

- screening of a large amount of genes
- easier molecular diagnosis
- faster molecular screening
- cheaper molecular screening – to modulate

- DBA molecular diagnosis with NGS is now easier compared to the 2010s (all the 24 RP genes and other related genes screened at once)
- Easier genetic counseling (parents and relatives screened)
- Prenatal diagnosis, Pre-implantation diagnosis
- A DBA definition more and more complex based on molecular diagnosis = DBA syndrome
- Importance of the functional tests to validate the unsignificant variation

Hôpital Bicêtre AP-HP

AP-HP. Université Paris-Saclay

CLUB DU GLOBULE ROUGE ET DU FER CGRF

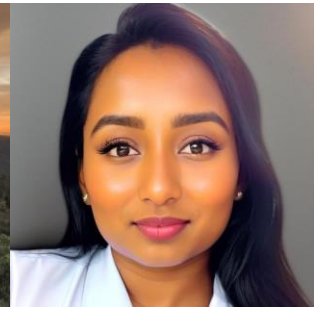
Pr Thierry Leblanc
Isabelle Marie
Ludivine David Nguyen
Dorin David-Ponn

Association Française de la Maladie de Blackfan-Diamond AFMBD

RIBOeurope
DBAGenCure

euro DBA consortium



Pierre-Emmanuel Gleizes, Marie-Françoise O'Donohue
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Hanna Tamary
Paola Quarello, Irma Dianzani, Ugo Ramenghi
Dagmar Pospisilova
Katarzyna Albrecht
Sule Unal, Nurten Akarsu, Arda Cetinkaya
Denis Lafontaine
Kaan Boztugn, Leo Krager
Riekelt Houtkooper
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Dr Virginie Penard-Lacronique
Pr Olivier Bernard

MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

Pr Régis Peffault de la Tour
Dr Flore Sicre de Fontbrune
MDs, nurses who take care of the patients
The patients and their families

filière de santé maladies rares
Reconnue par le Ministère de la Santé

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