Aplasies médullaires d'allure constitutionnelle

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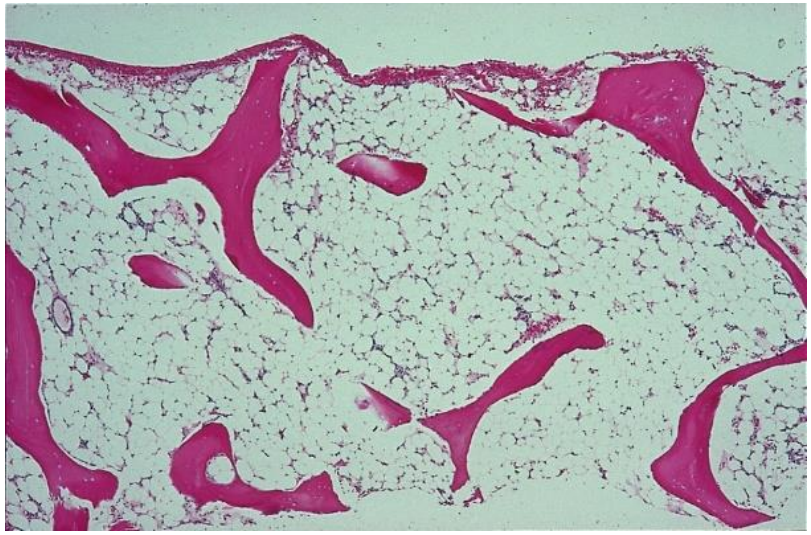
Bone marrow failure (BMF) syndromes



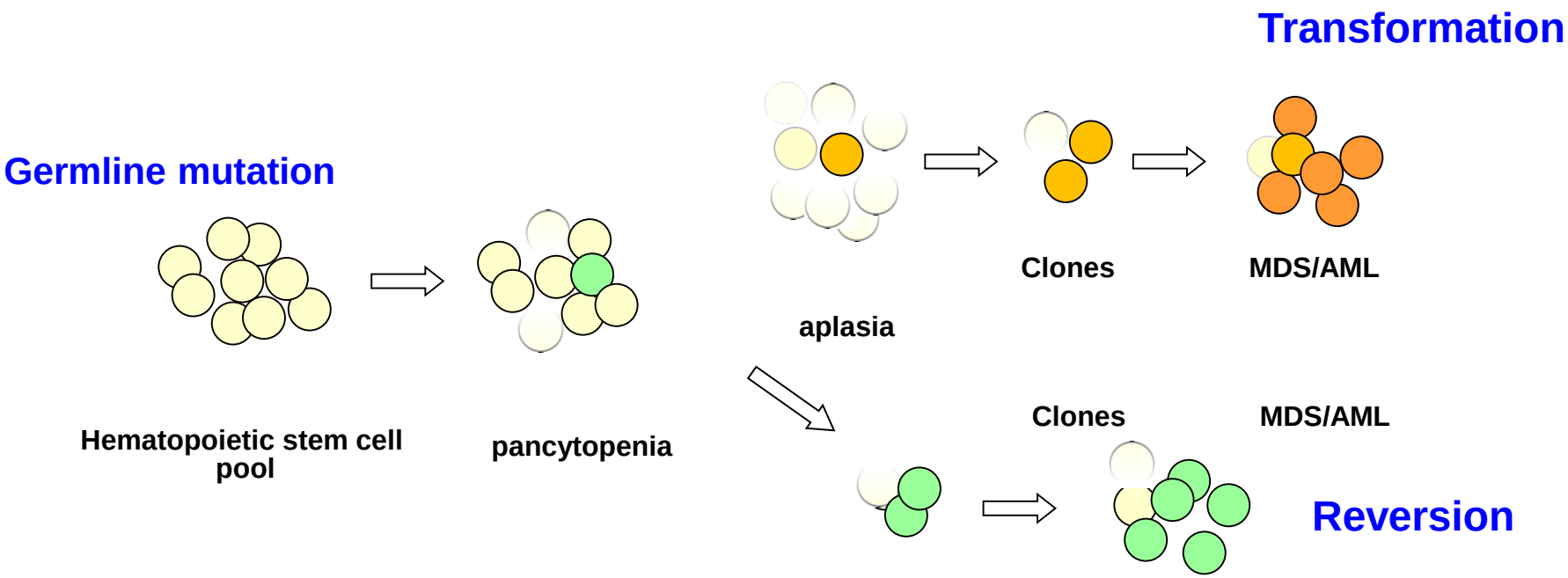
BMF

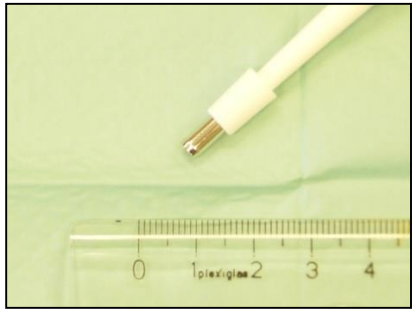
• Acquired: immune, viral, toxic

• **Genetic (Inherited BMF):** Fanconi anemia (FA), dyskeratosis congenita, *RUNX1*-deficiency, many others and emerging causes

An accurate diagnosis is crucial for BMF treatment (Immunosuppressive therapy or HSCT, donor choice, regimen), and family counseling, cancer screen, *etc.*

At diagnosis:
What is constitutive and what is somatic ?





Cultured skin fibroblast cells
« Germline » cells

The French Bone Marrow Failure Center at Saint-Louis and R. Debré Hospitals, Paris

Saint-Louis Hospital

Robert Debré Hospital

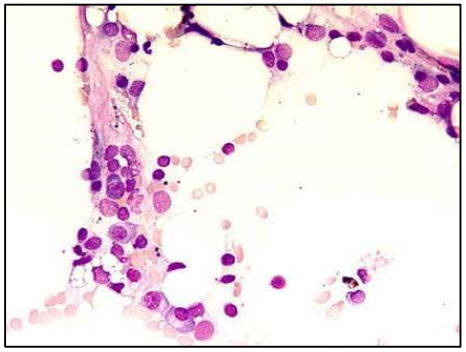
Institute of Hematology, IRSL St-Louis

Centre de Référence Maladies Rares Aplasie, filière MARIH

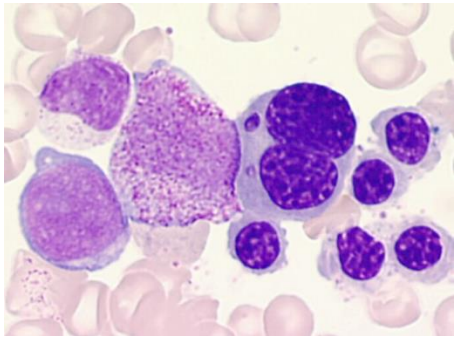
⇨ Clinical network and French cohort: R. Peffault de Latour, T. Leblanc, JH Dalle, F. Sicre, many physician
Centralized biological diagnosis (skin fibroblast cells, functional tests, NGS)
BM follow up for transformation and longitudinal sampling
Translational research

Fanconi anemia

Frequent congenital signs:
short size, FA face,
abnormal thumbs…



Cytopenia in childhood

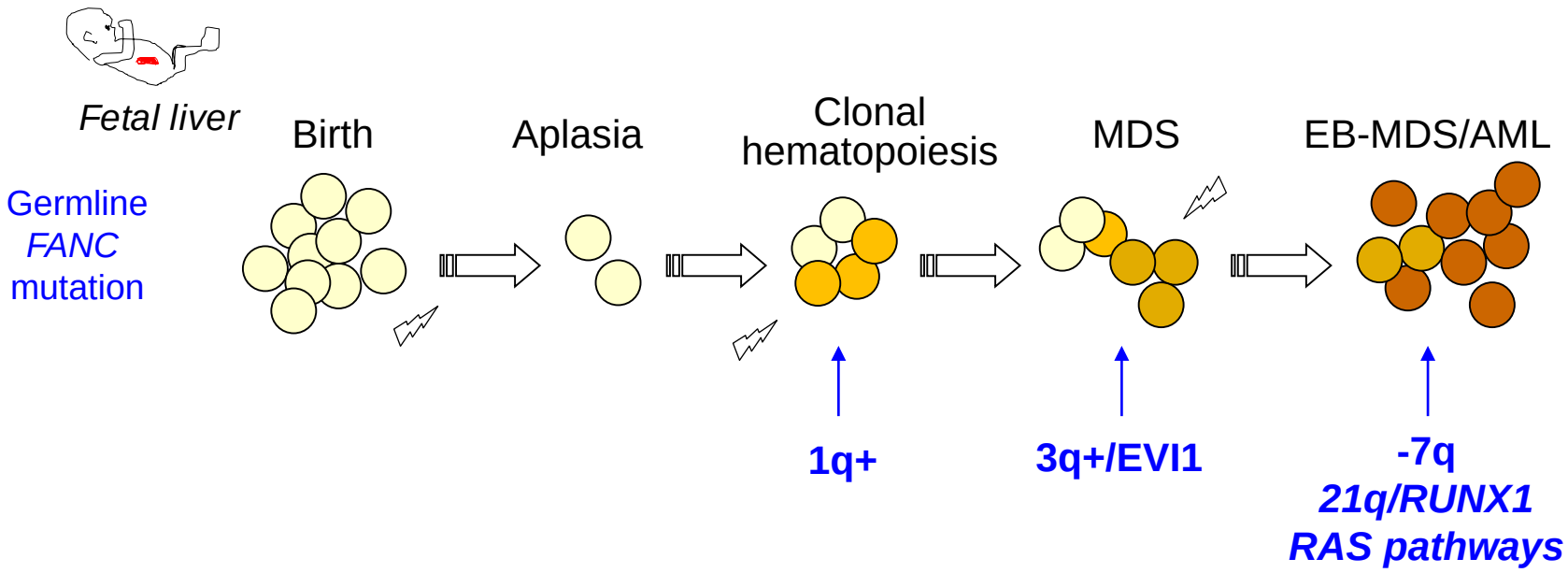


MDS/AML
Head&neck carcinoma

Hypersensitivity to
genotoxics: breaks, radials

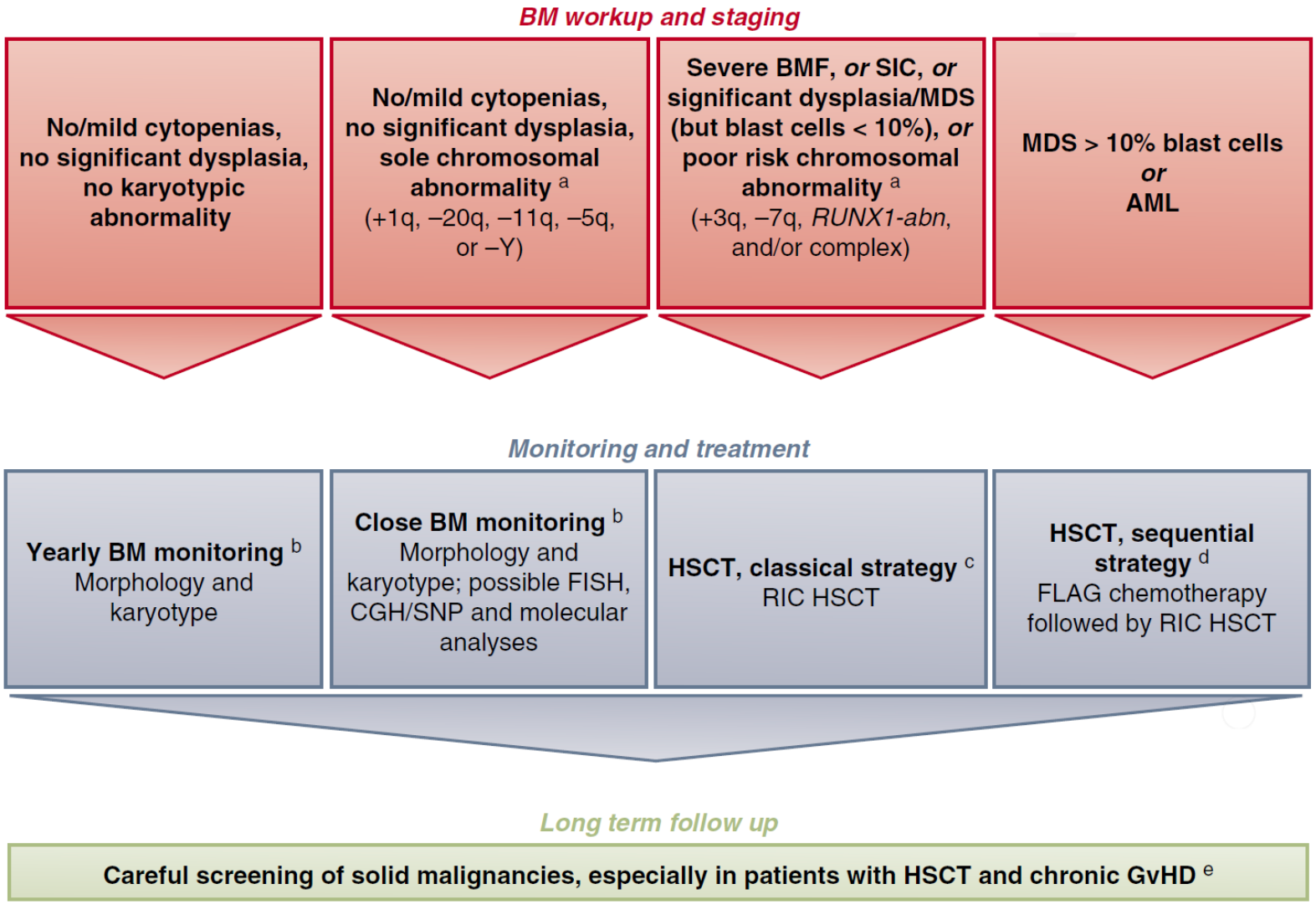
Biallelic mutations in one of the 22 *FANC* genes (2019),
FANCA+G+D2 representing 90% in France

A canonical model of BM progression in FA



Quentin et al. Blood 2011;Cecaldi et al. Cell Stem Cell 2012;
Peffault et al. Blood 2016; Sebert et al., in preparation

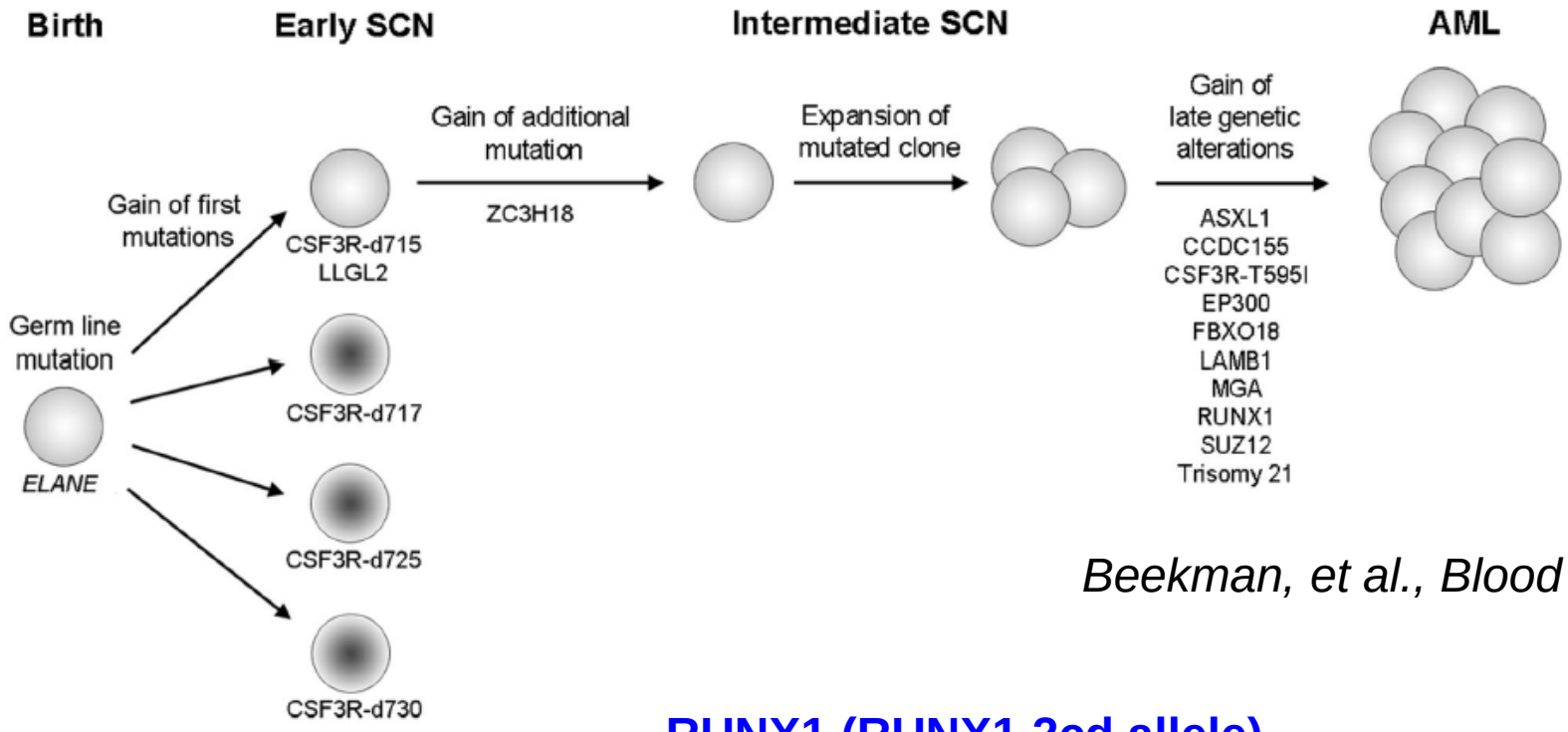
Staging criteria to help decision making in FA



R. Peffault de Latour & J. Soulier, Blood 2016

Clonal evolution in a case of Severe Congenital Neutropenia (SCN)

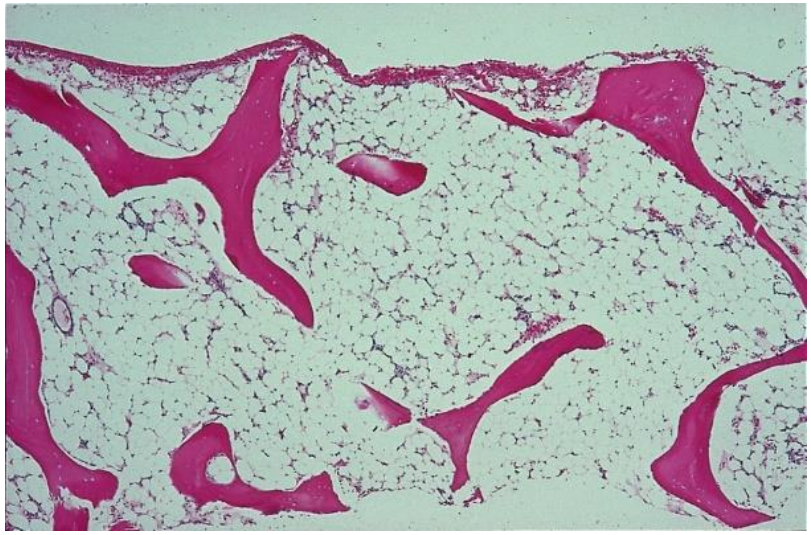
Exome sequencing, and deep-sequencing at several stages



Beekman, et al., Blood 2012

RUNX1 (RUNX1 2cd allele)
SDS (TP53, -7…)
Dyskeratosis congenital (-7)
…

Bone marrow failure (BMF) syndromes



BMF

• **Genetic (Inherited BMF):** Fanconi anemia (FA), dyskeratosis congenita, *RUNX1*-deficiency, many others and emerging causes

Unrecognized IBMF causes ?

Unrecognized genetic cases ?

Patients samples referred for assessment to the the **French Bone Marrow Failure Center Laboratory**
February 2002- June 2016

INCLUSION

- **BMF and low cellularity MDS patients**
  - Central origin cytopenias
  - Possible dysplasia (classified according to revised WHO 2008)

- **Likely-inherited,** based on at least one from:
  - Physical abnormalities
  - Family history of hematological disorders and/or consanguinity
  - Young age (≤ 2 years)

- **Fanconi anemia or well recognized causes at diagnosis: excluded**

OBJECTIVES, In a cohort of patients with an unresolved, likely-Inherited BMF :
To identify new IBMF/MDS causes; to draw a broad molecular portrait of this heterogeneous group of patients
N=179 patients from 173 unrelated families

Whole Exome Sequencing (WES) on skin fibroblast cell DNA

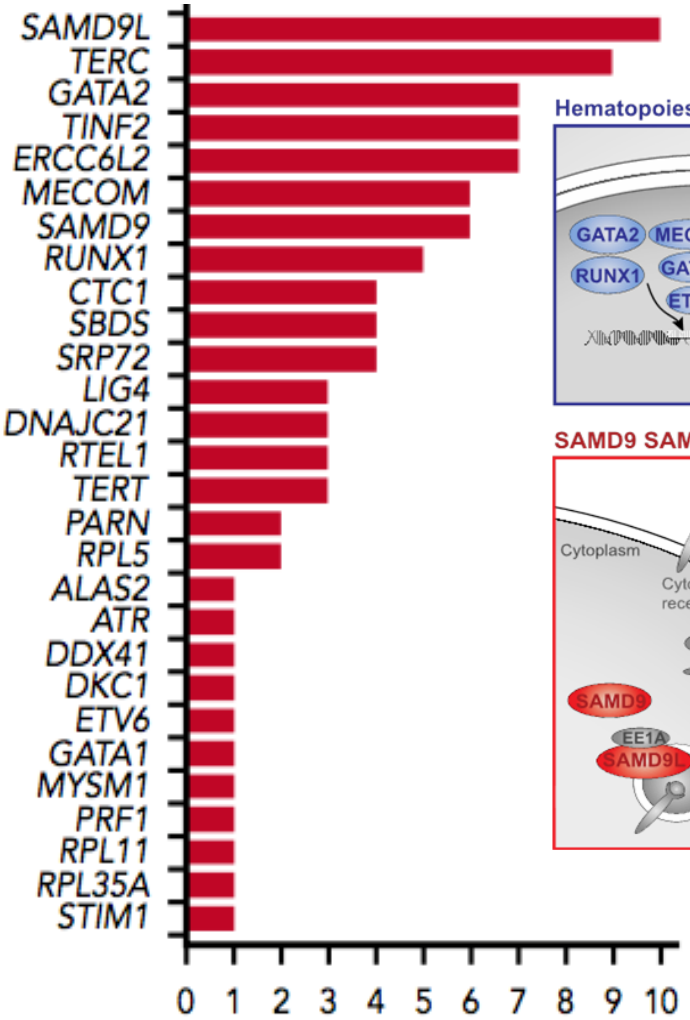
Table 1. Clinical characteristics of the 179 patients

Characteristic	Value*
Sex, no. (%)	
Male	96 (53.6)
Female	83 (46.4)
Age at skin biopsy, no. (%), y	
≤2	37 (20.7)
>2 and <18	76 (42.5)
≥18	66 (36.9)
Age of first hematological symptoms, median (range), y	8 (0-47)
Hematological characteristics	
Pancytopenia, no./total (%)	121/177 (68.4)
Cytopenia, 1 lineage, no./total (%)	32/177 (18.1)
Cytopenias, 2 lineages, no./total (%)	24/177 (13.6)
Anemia, no./total (%)†	158/178 (88.8)
Hb level, median (range), g/dL	9.5 (2.5-15)
MCV, median (range)	98 (68-117)
Thrombocytopenia, no./total (%), <150 × 10^9/L	147/178 (82.6)
Platelet count, median (range), × 10^9/L	45 (2-500)
Neutropenia, no./total (%), <1.5 × 10^9/L	138/177 (78.0)
Neutrophil count, median (range), × 10^9/L	0.87 (0-7)
BM dysplasia, no./total (%)	68/157 (43.3)
BM blast cell percentage, no./total (%)	
<5%	154/175 (88.0)
≥5, <10%‡	9/175 (5.1)
≥10%‡	12/175 (6.9)
Abnormal karyotype, no./total (%)§	45/161 (28.0)
Family history, no./total (%)	66/173 (38.2)
Family history of hematological disorders	50/173 (28.9)
Consanguinity‖	25/179 (14.0)
Physical abnormalities, no./total (%)	129/176 (73.3)

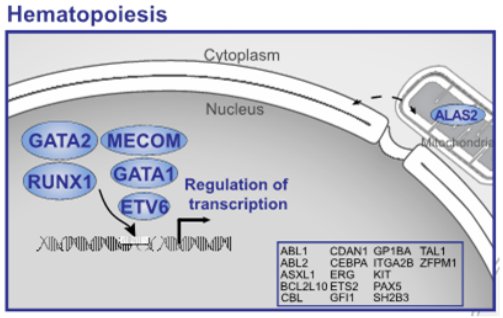
Bluteau, et al. Blood 2018

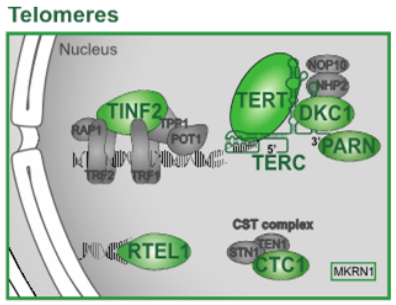
GL mutations define ‘Core’ BMF biological pathways

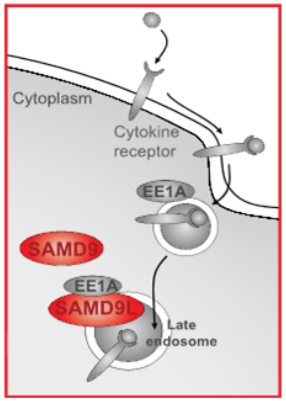
Molecular diagnosis: N=86 pts (48%)

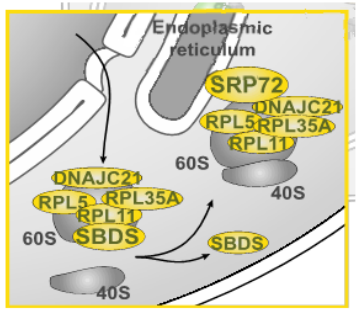


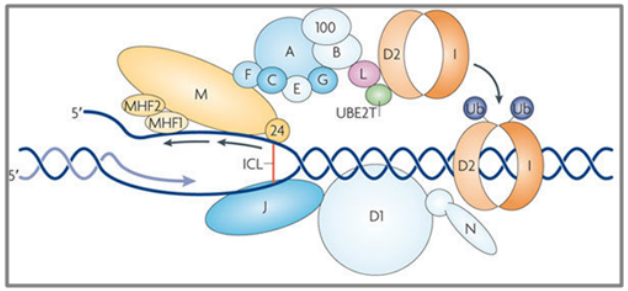
Number of patients with causal/very-likely causal variants

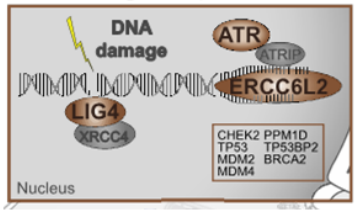






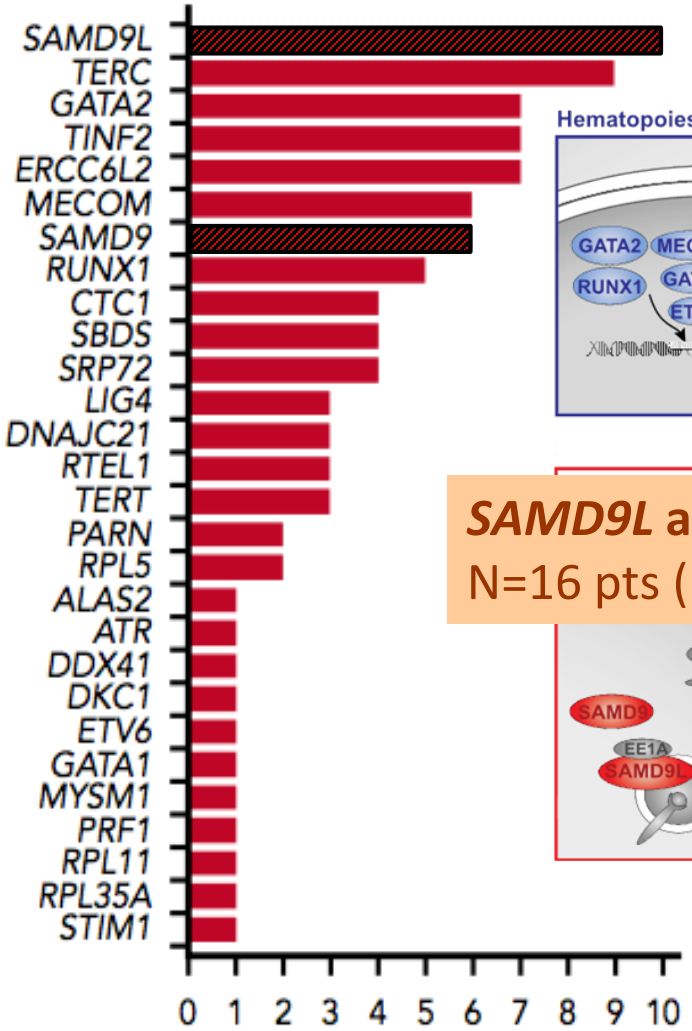






Bluteau, et al. Blood 2018

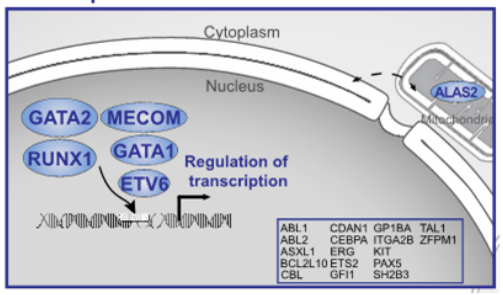
GL mutations define ‘Core’ BMF biological pathways



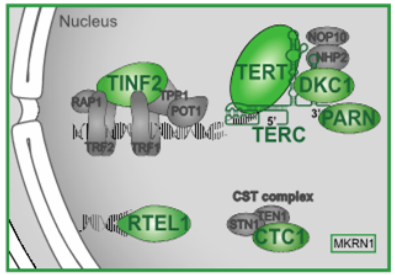
Number of patients with causal/very-likely causal variants

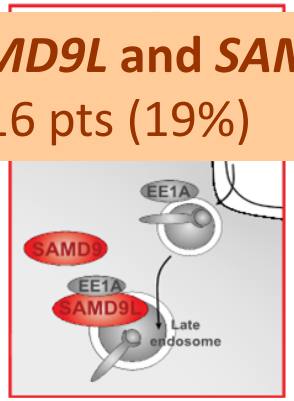
SAMD9L* and *SAMD9
N=16 pts (19%)

Hematopoiesis

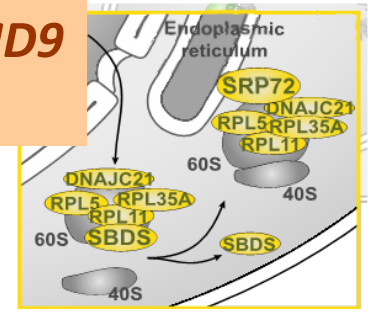


Telomeres

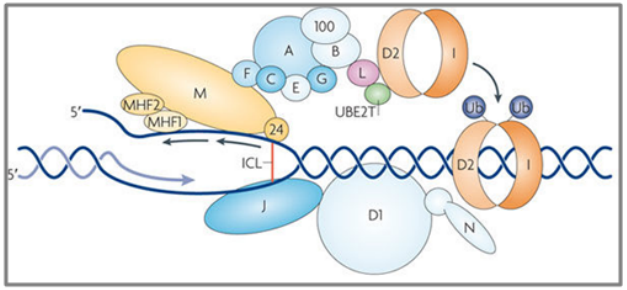




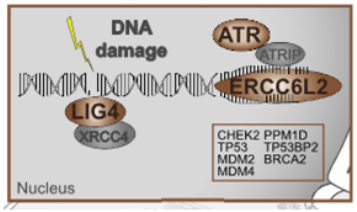
Ribosome



Fanconi pathway



DNA Damage Response



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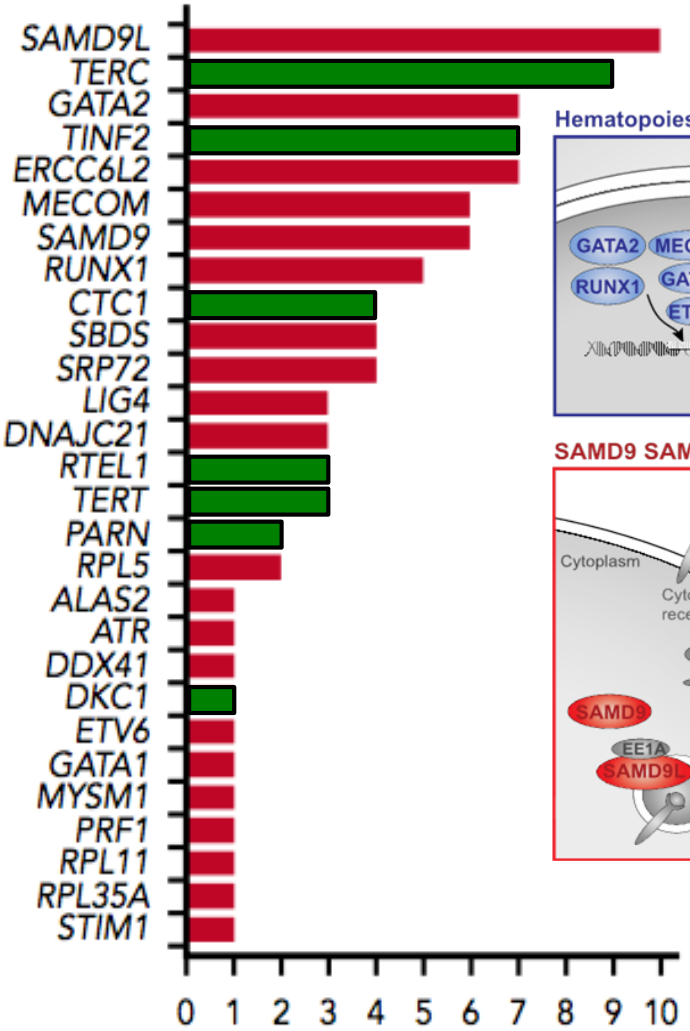

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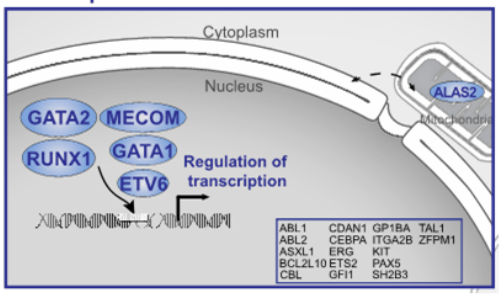
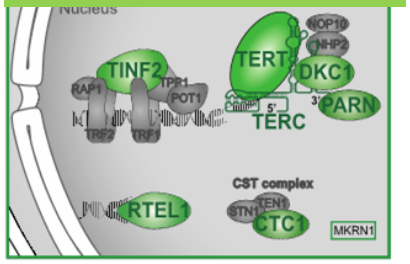
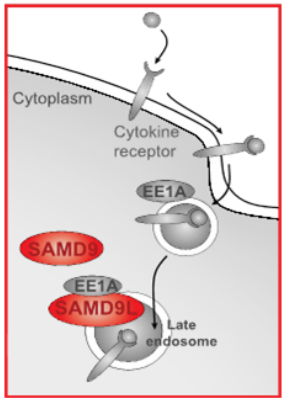


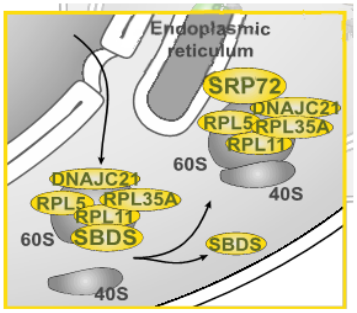
Telomere genes
N=29 pts (34%)



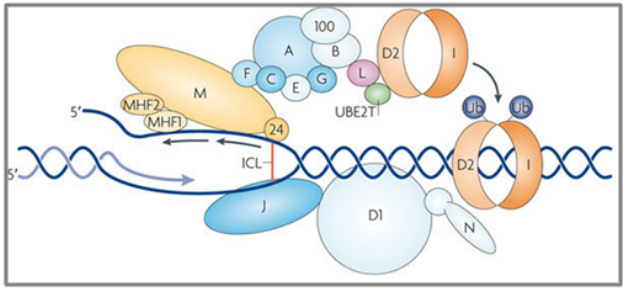
SAMD9 SAMD9L



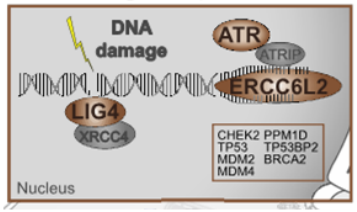
Ribosome



Fanconi pathway



DNA Damage Response



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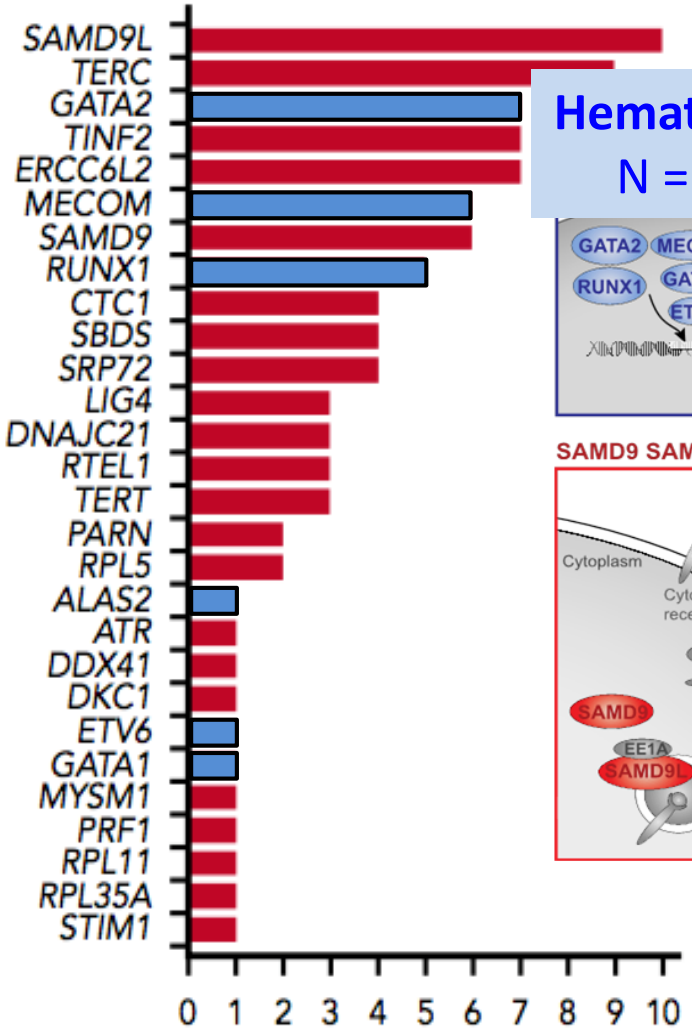
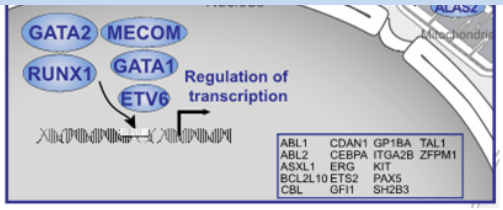
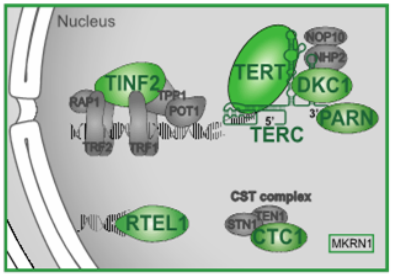


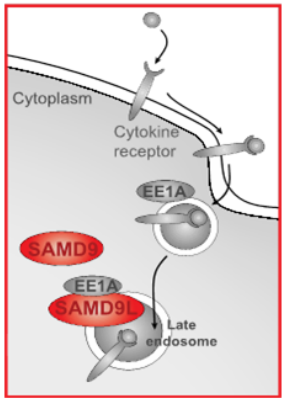
Hematopoietic genes
N = 21 pts (24%)



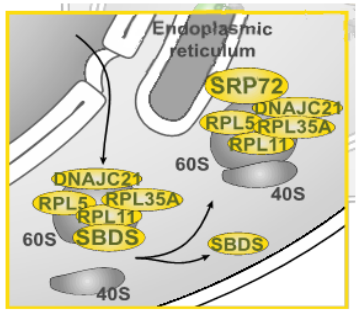
Telomeres



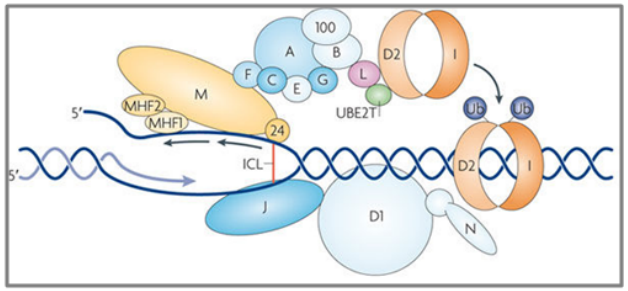
SAMD9 SAMD9L



Ribosome



Fanconi pathway



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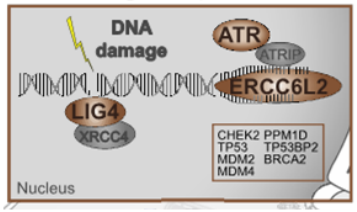

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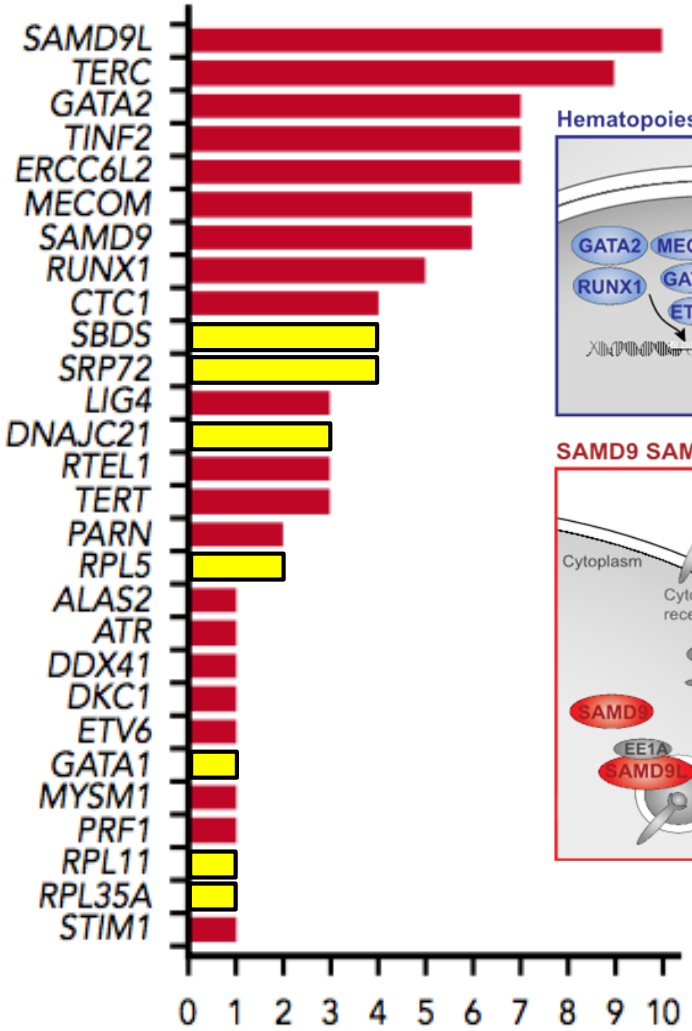

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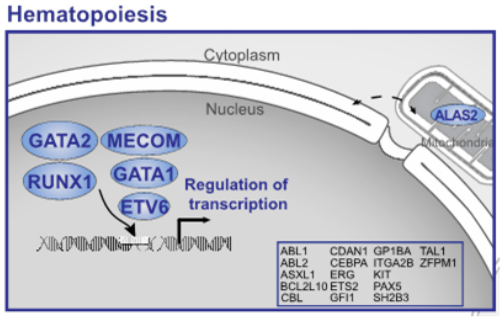
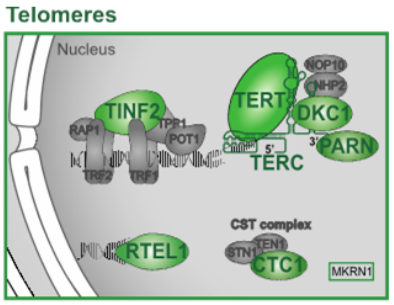
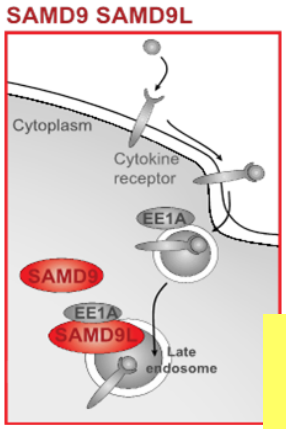
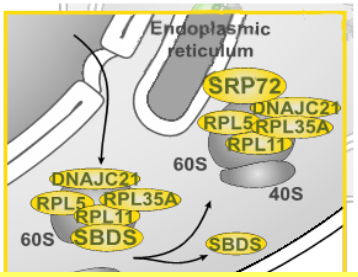
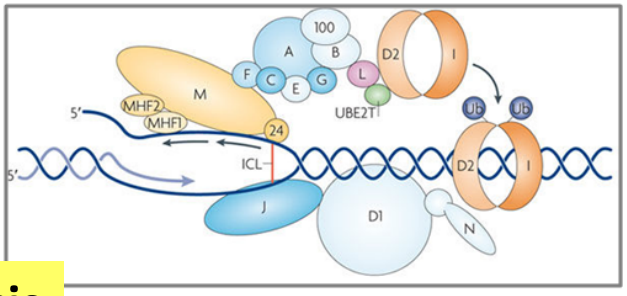


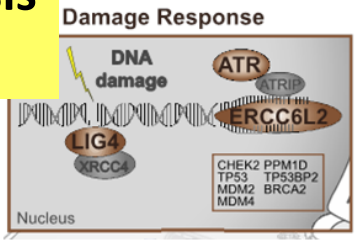








Ribosome biogenesis
N = 12 pts (14%)



Bluteau, et al. Blood 2018

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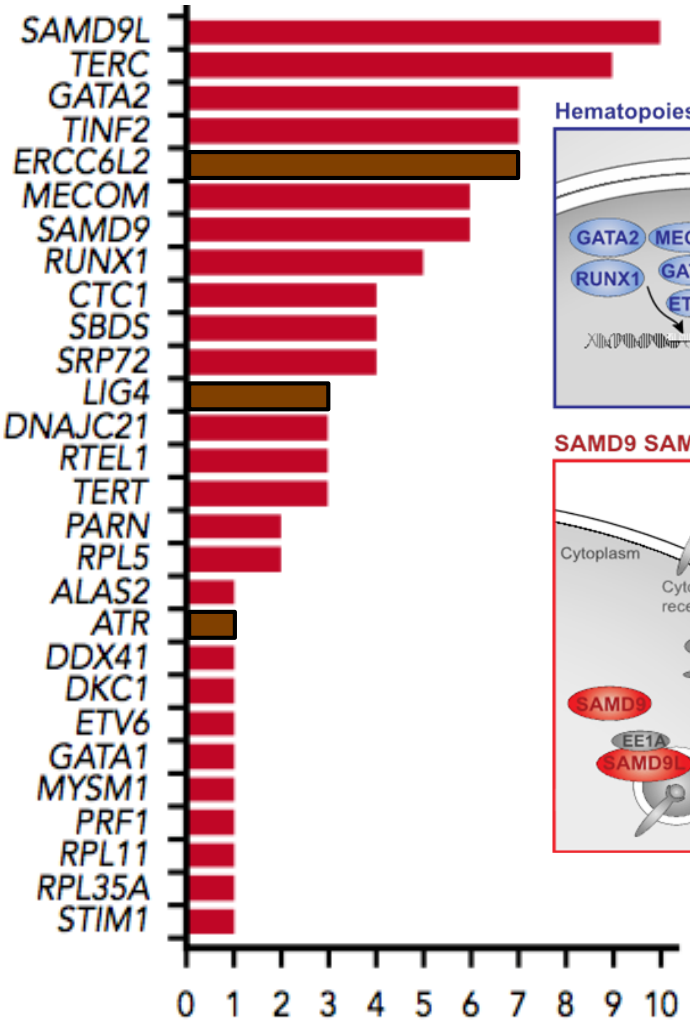
DNA damage: N=11 pts (13%)



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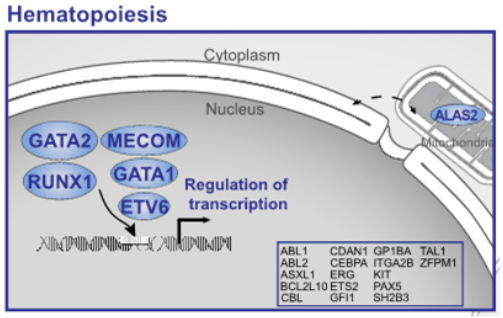
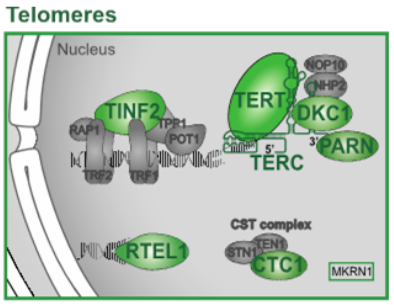
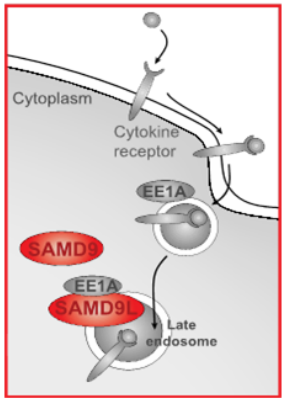
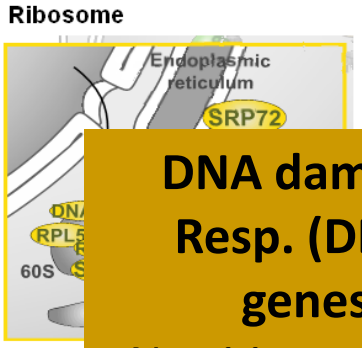
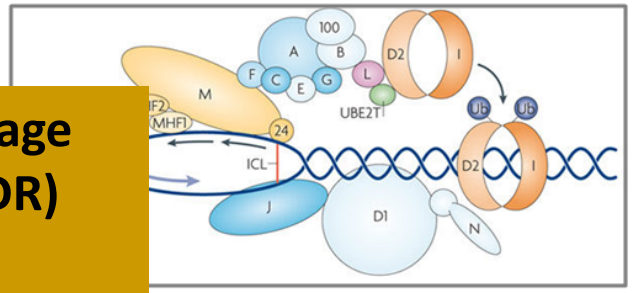


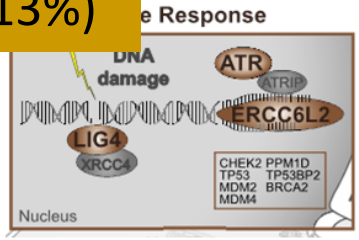








DNA damage Resp. (DDR) genes
N = 11 pts (13%)



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New or seldom reported IBMF syndromes

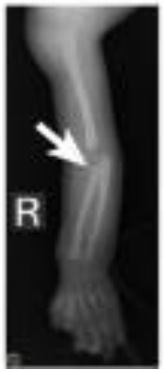
Each gene defines a clinical entity, more or less homogeneous and syndromic, of variable penetrance

Focus on three of them, new at that time or seldom reported

- *MECOM / EVI1 :* Severe neonatal BMF, *de novo*
- *ERCC6L2* (*autosomic recessive*): Mild BMF adolescent with MDS/AML risk
- *SAMD9* and *SAMD9L:* Familial aplasia with transient monosomy 7 in childhood

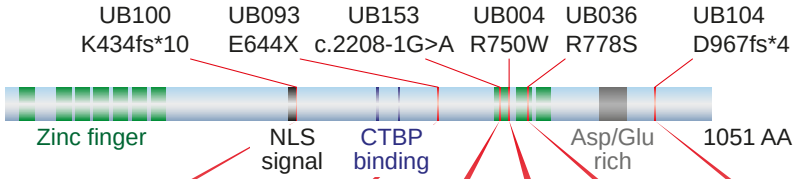
MECOM/EVI1-deficient disorder

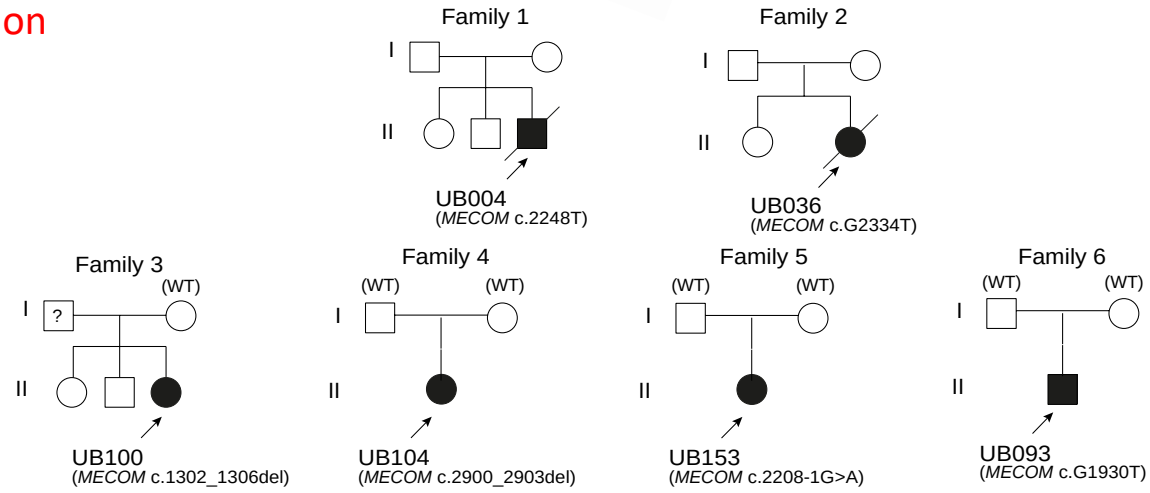
- Three reported patients with RUSAT (radio-ulnar synostosis with amegakaryocytic thrombocytopenia) syndrome *(Niihori, Am J Hum Genet. 2015)*



- **N=6 patients in our cohort**

Only one with ulnar abnormality
3 with cardiac abnormalities
All with severe neonatal aplastic anemia
All received HSCT before 3 yo
De novo, Heterozygous, inactivating, *MECOM/EVI1* Mutation





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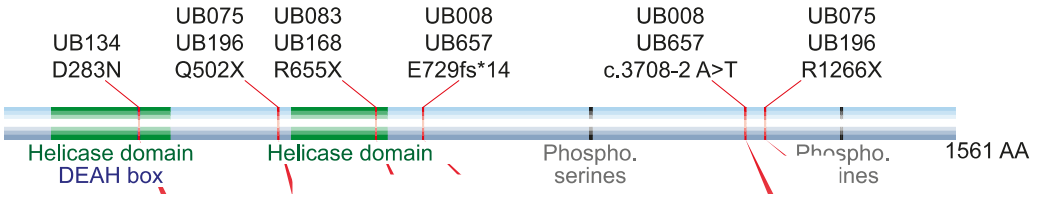
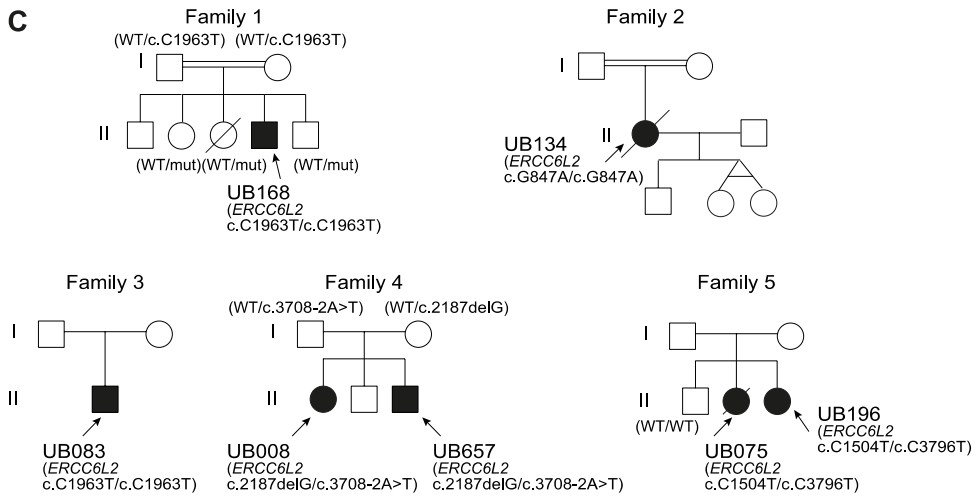
ERCC6L2-deficient disorder

- Helicase gene family
- Three patients reported with germline biallelic mutations, learning disabilities, microcephaly and BMF/MDS *(Tummala, Am J Hum Genet. 2014; Zhang, J Exp Med 2016))*



- **N=7 patients in our cohort**

Biallelic, inactivating *ERCC6L2* mutations
Median age 13 yo (child to young adult)
Only one with neurological signs
Mild cytopenia in all patients
MDS in 2 patients, -> AML in one 43 yo
Monosomy 7 in 2 patients



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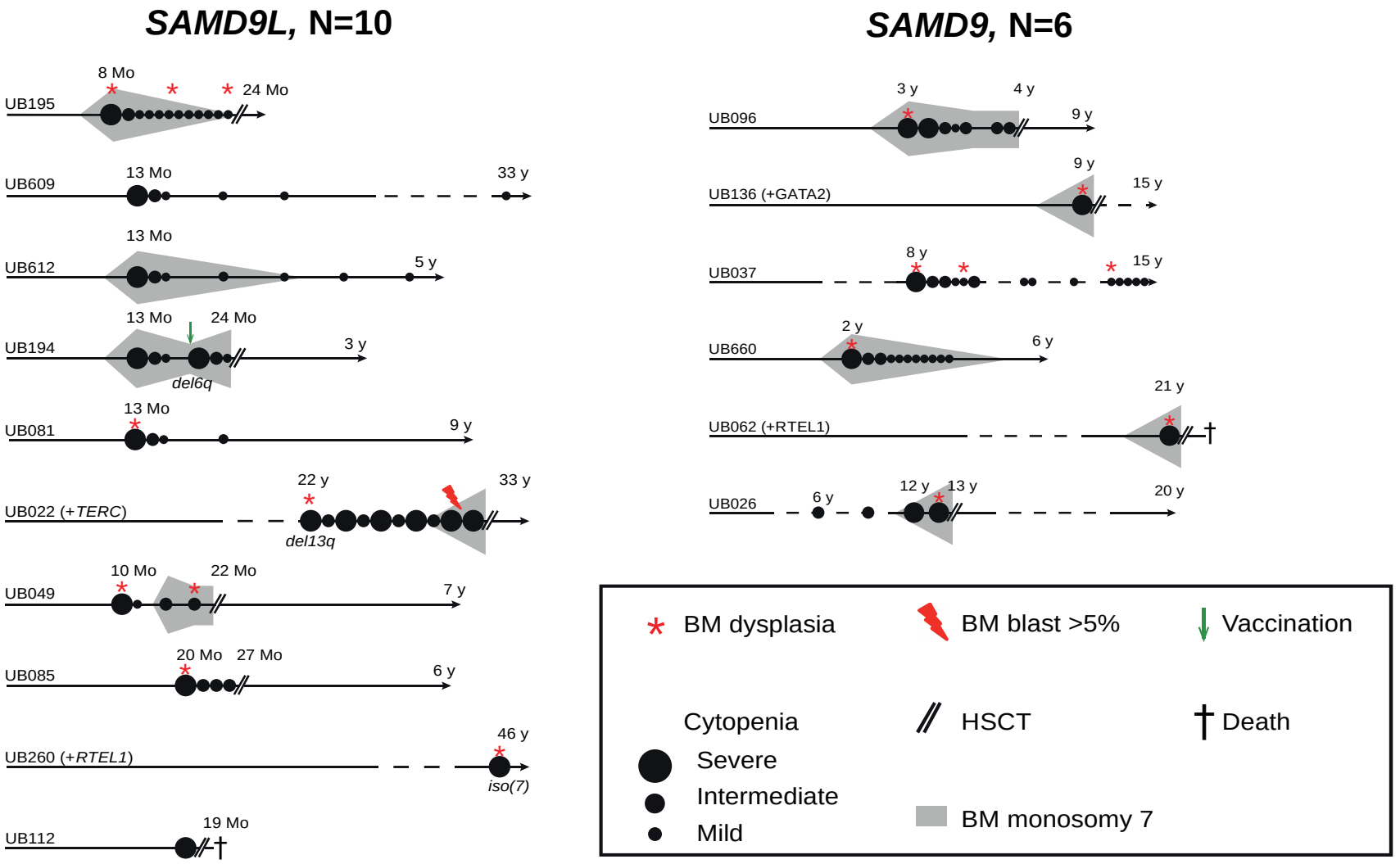
SAMD9/SAMD9L disorder



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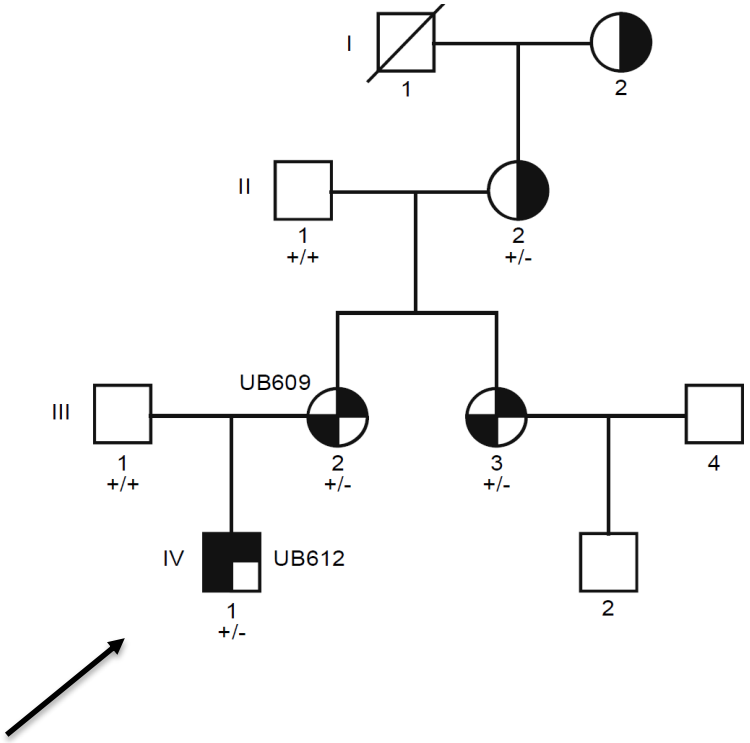
SAMD9/SAMD9L disorder

Ataxia-Pancytopenia Syndrome



SAMD9L c.C2956T
heterozygous mutation

Monosomy 7
Nystagmus
Transient pancytopenia
Ataxia and/or Cerebellar atrophia

13 mo boy
Severe aplasia with monosomy 7 (no dysplasia)
Improved spontaneously before HSCT; does well without treatment 7y later

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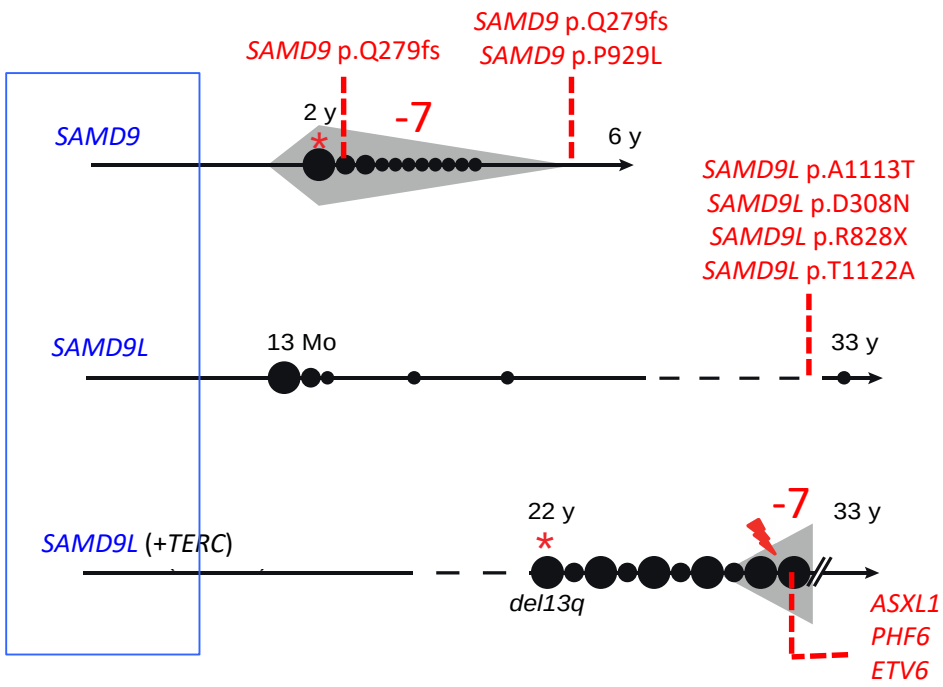
Somatic evolution in SAMD9/L disorder

- Spontaneous improvement in blood cell counts (N=11/16)
- MDS and monosomy 7 disappearance (N=5); HSCT planned and eventually cancelled (N=5)
- Evolution to excess of blast and AML (N=1)

Fibroblast DNA sequencing, all patients

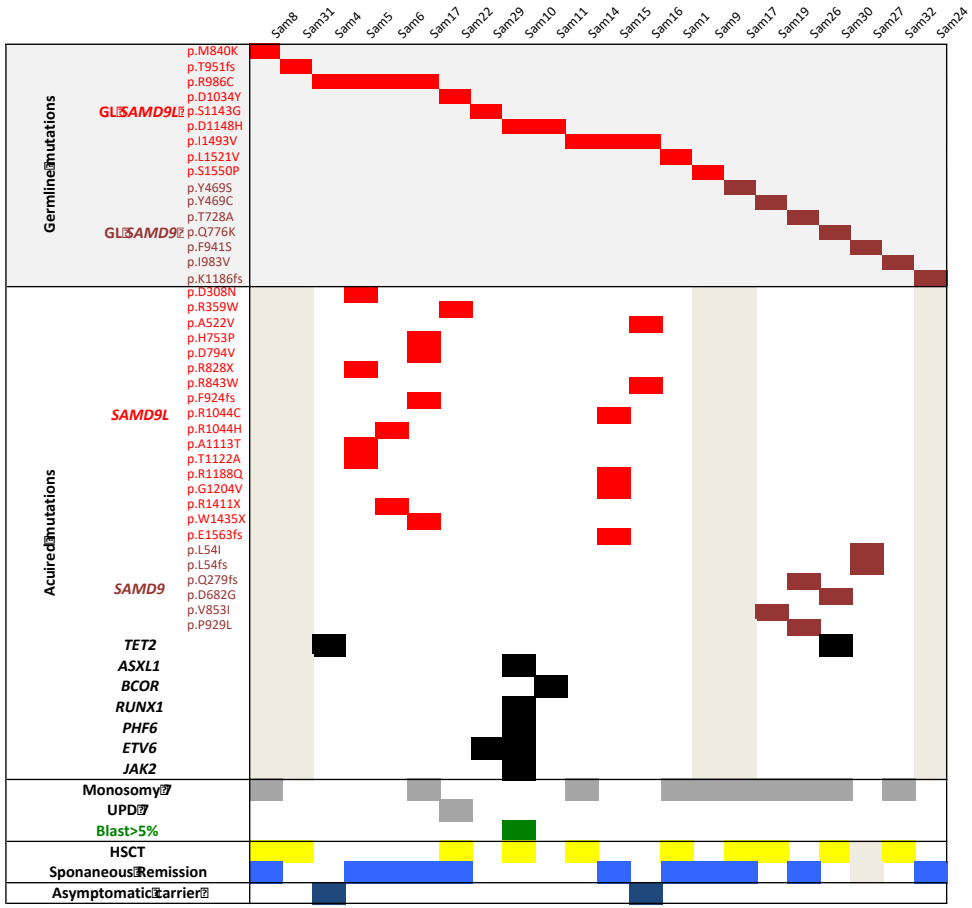
GERMLINE activating mutation



Blood and/or BM DNA sequencing, 17/22 updated patients

SOMATIC secondary (inactivating) mutations

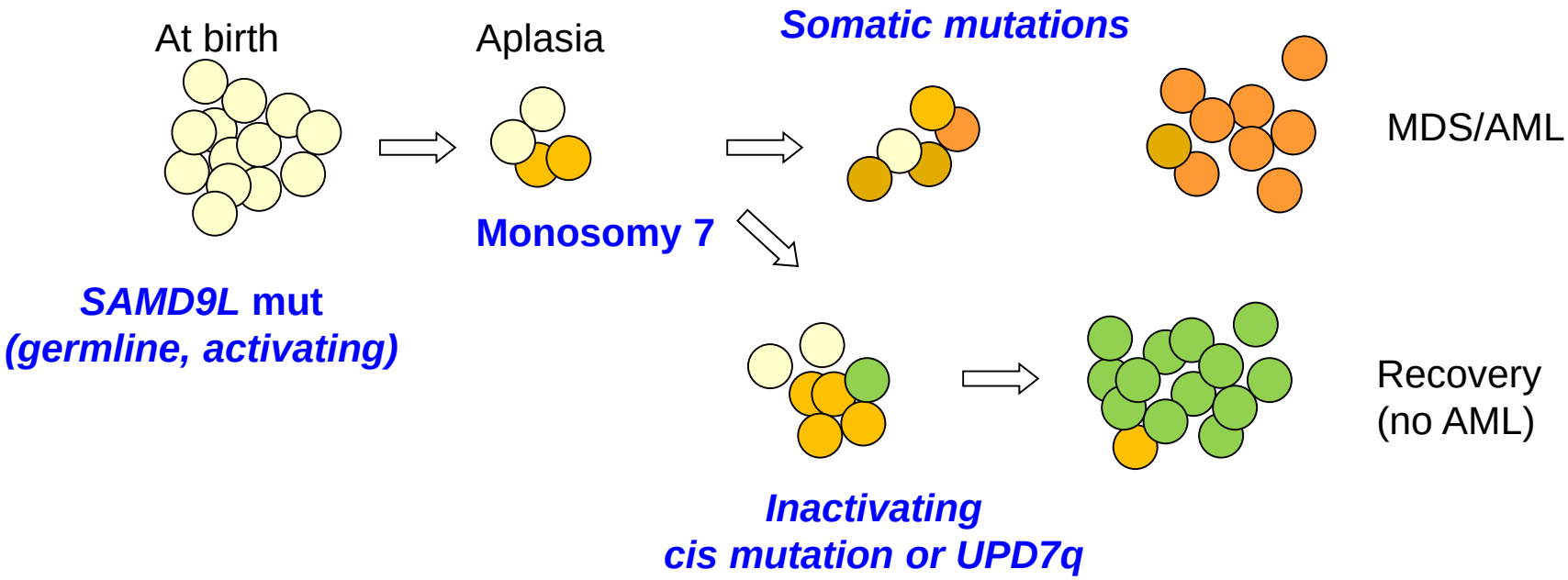
A cohort of 24 pts with *SAMD9/SAMD9L* disorder



- Patients could have several acquired *SAMD9/SAMD9L* mutations, associated with spontaneous remission
- Different mechanisms counteracting *SAMD9/SAMD9L* mutations coexist in the same patient
- Blastic evolution is associated with the acquisition of additional mutations

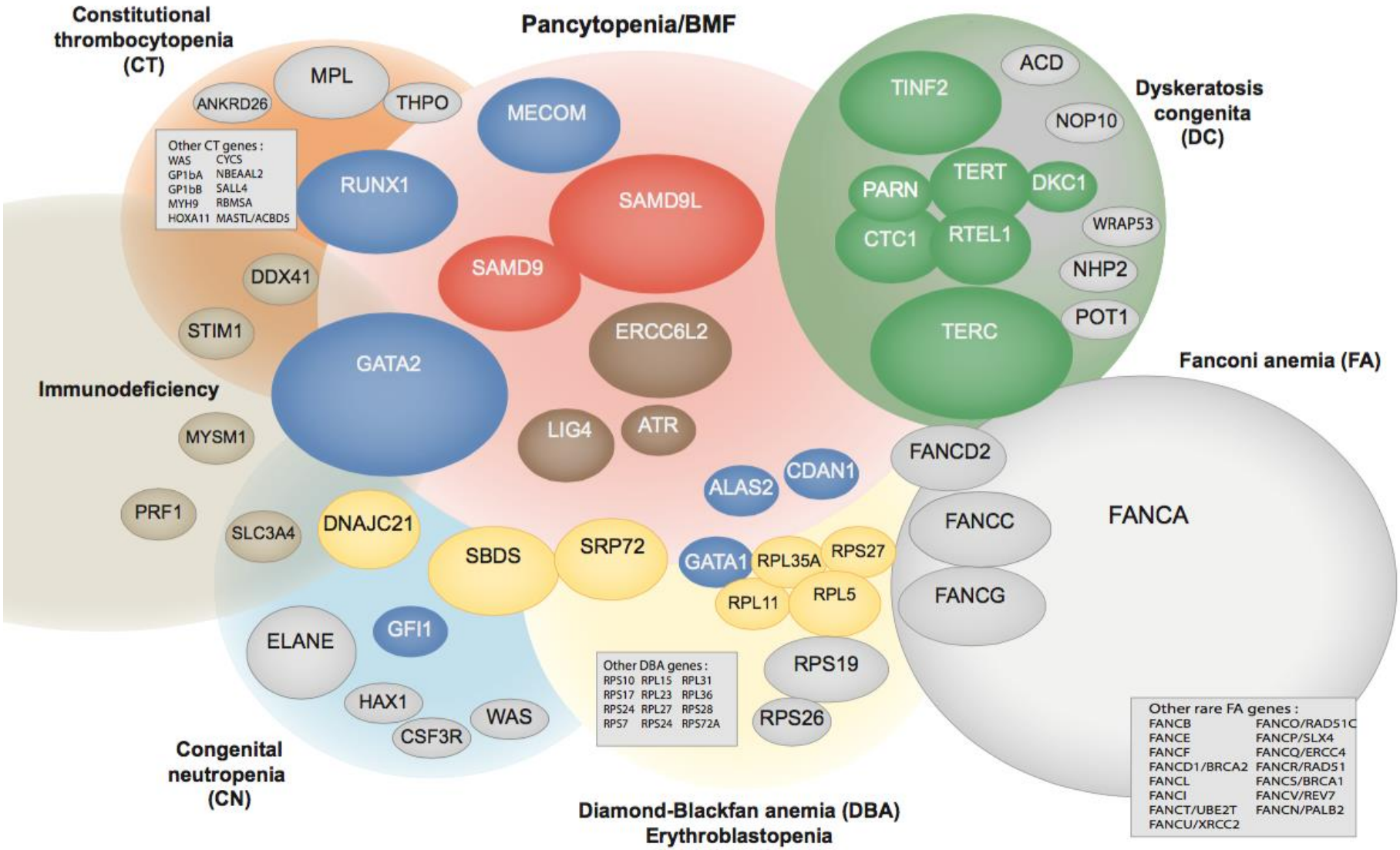
Sebert et al., SFH 2019

Natural history in SAMD9/*SAMD9L* disorder



Potential change in practice: careful wait-and-see policy before HSCT in children with aplasia/MDS, monosomy 7 and *SAMD9L* GL mutation

The expanding landscape of IBMF syndromes



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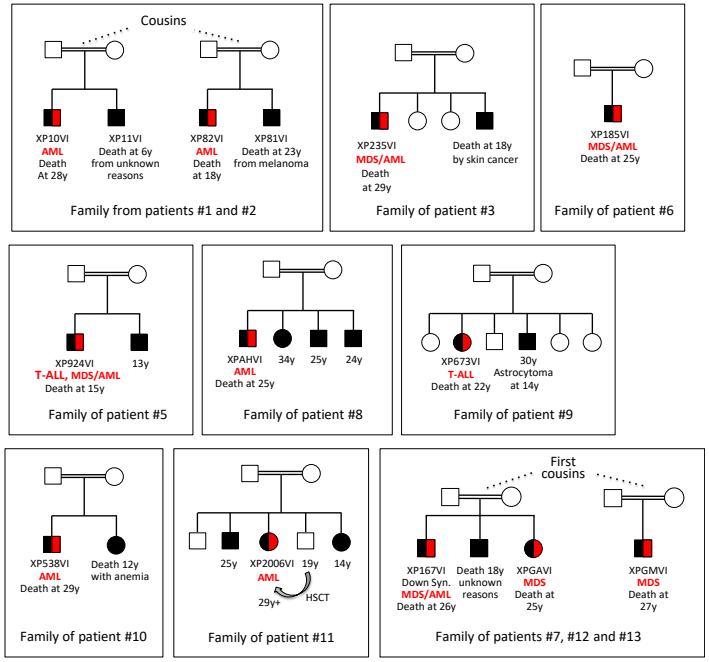
Still expanding landscape of genetic IBMF/MDS

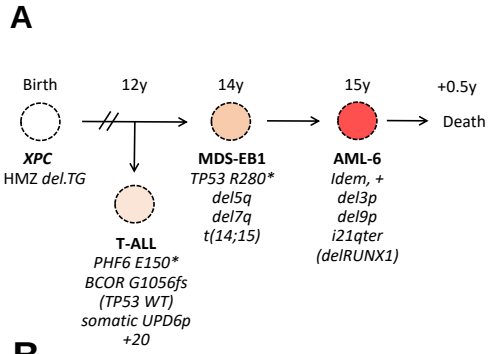
TO THE EDITOR:

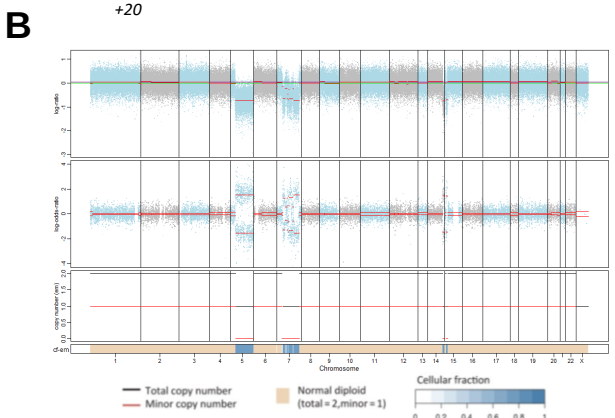
Familial predisposition to TP53/complex karyotype MDS and leukemia in DNA repair-deficient xeroderma pigmentosum

Alain Sarasin,[1] Samuel Quentin,[2-4] Nathalie Droin,[5,6] Mourad Sahbatou,[7] Véronique Saada,[8] Nathalie Auger,[8] Yannick Boursin,[9] Philippe Dessen,[9] Anna Raimbault,[2-4] Vahid Asnafi,[10] Jean-Luc Schmutz,[11] Alain Taïeb,[12] Carlos F. M. Menck,[13] Filippo Rosselli,[1] Laurianne Drieu La Rochelle,[14] Caroline Robert,[15] Flore Sicre de Fontbrune,[4,16] Marie Sébert,[4,17] Thierry Leblanc,[18] Patricia Kannouche,[1] Stéphane De Botton,[6] Eric Solary,[5,6] and Jean Soulier[2-4]

- 13 MDS or AML cases in a cohort of 160 XPC delTG patients from 142 consanguineous families originating from North Africa (Marocco, Tunisia) : 8.07% frequency, median age of 22 yo.
- Mutation TP53, del5q and 7q, complex karyotype are recurrent in the MDS/AML cells







Conclusions

- The GL landscape of IBMF/MDS patients includes many genes and is still expanding
- Many patients do not display a typical ‘syndromic’ or ‘familial’ phenotype (FA, DC and others)
- Systematic use of updated gene panels improves molecular diagnosis
- Genetic reversion (somatic mosaicism) can puzzle diagnosis – fibroblast cells are helpful
- Interpretation of genetic variants is often challenging and requires careful evaluation in the context of the patient's phenotype – Inconclusive situations are frequent
- BMF syndromes are cancer prone (each having its own evolution pattern): longitudinal follow up may be warranted, but when and how?
- Critical need of high-quality, multidisciplinar expertise and technologies to diagnose patients and families – time-consuming and expensive
- Ethic issues related to information and genetic screen in families, prenatal diagnosis, and cancer screen

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