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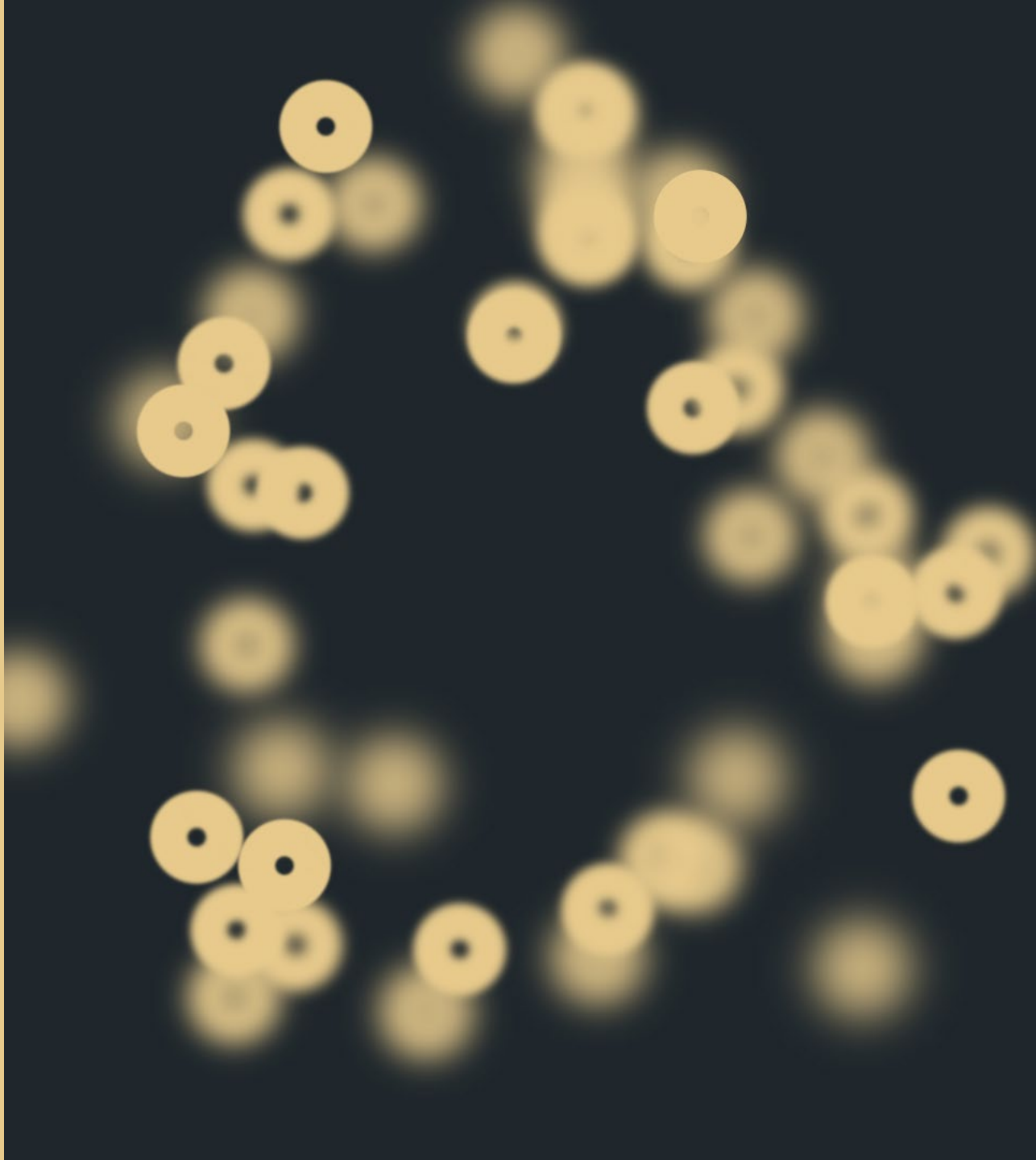
EHA-SWG Scientific Meeting on Recent Advances in the Pathogenesis and Treatment of Secondary Acute Myeloid Leukemias

Berlin, Germany
April 25-26, 2025



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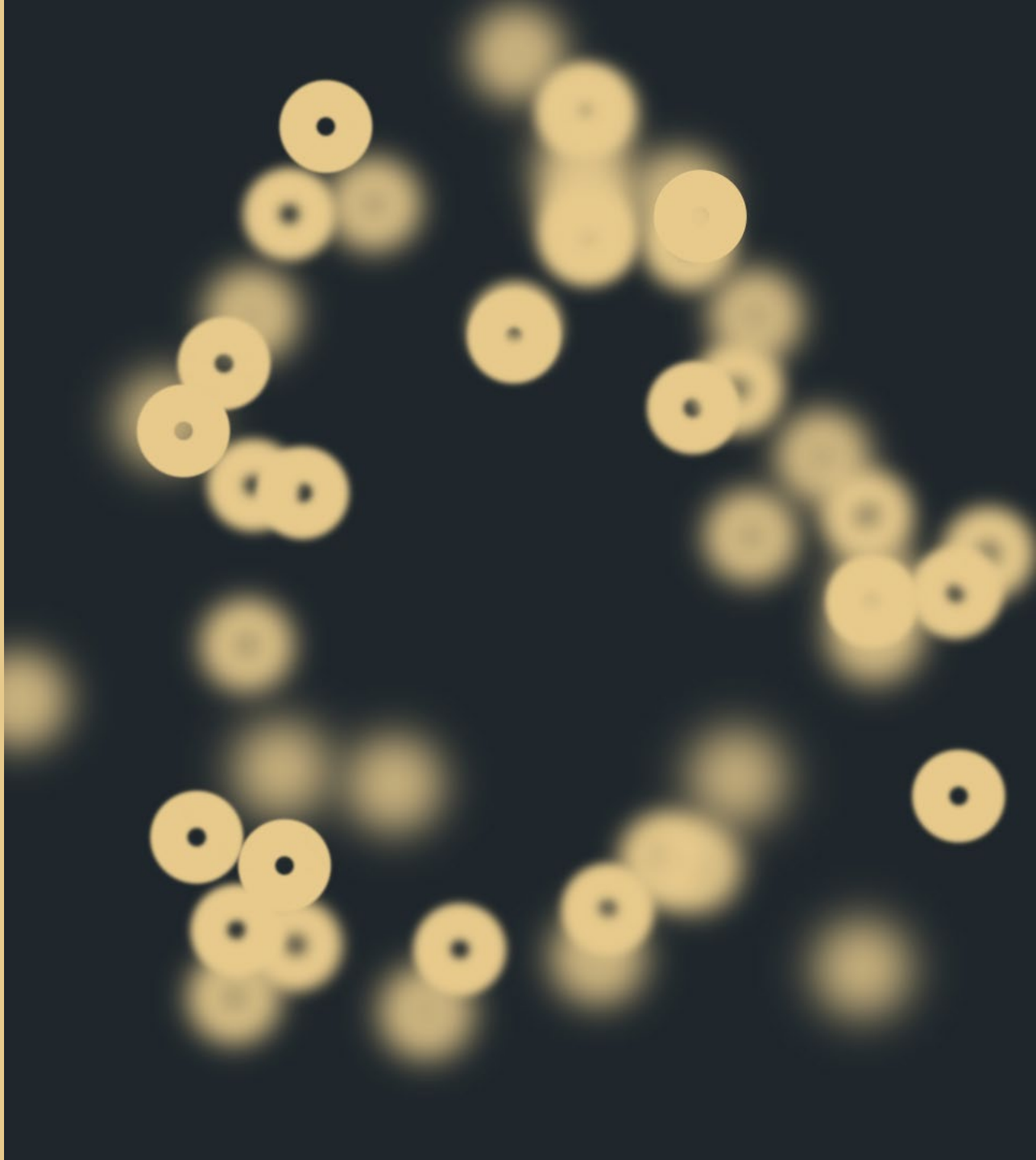
DDX41 and other susceptibility genes

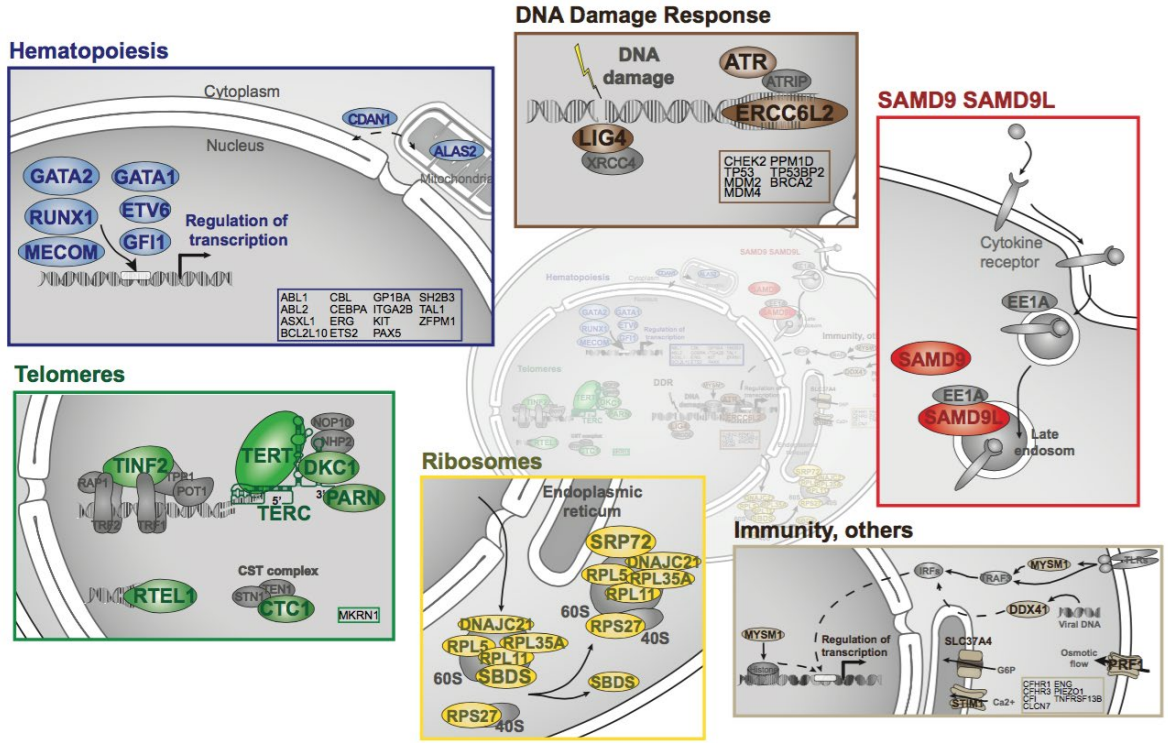
Marie Sébert, MD, PhD
Saint-Louis Hospital, Paris

INSTITUT DE LA LEUCÉMIE PARIS SAINT-LOUIS

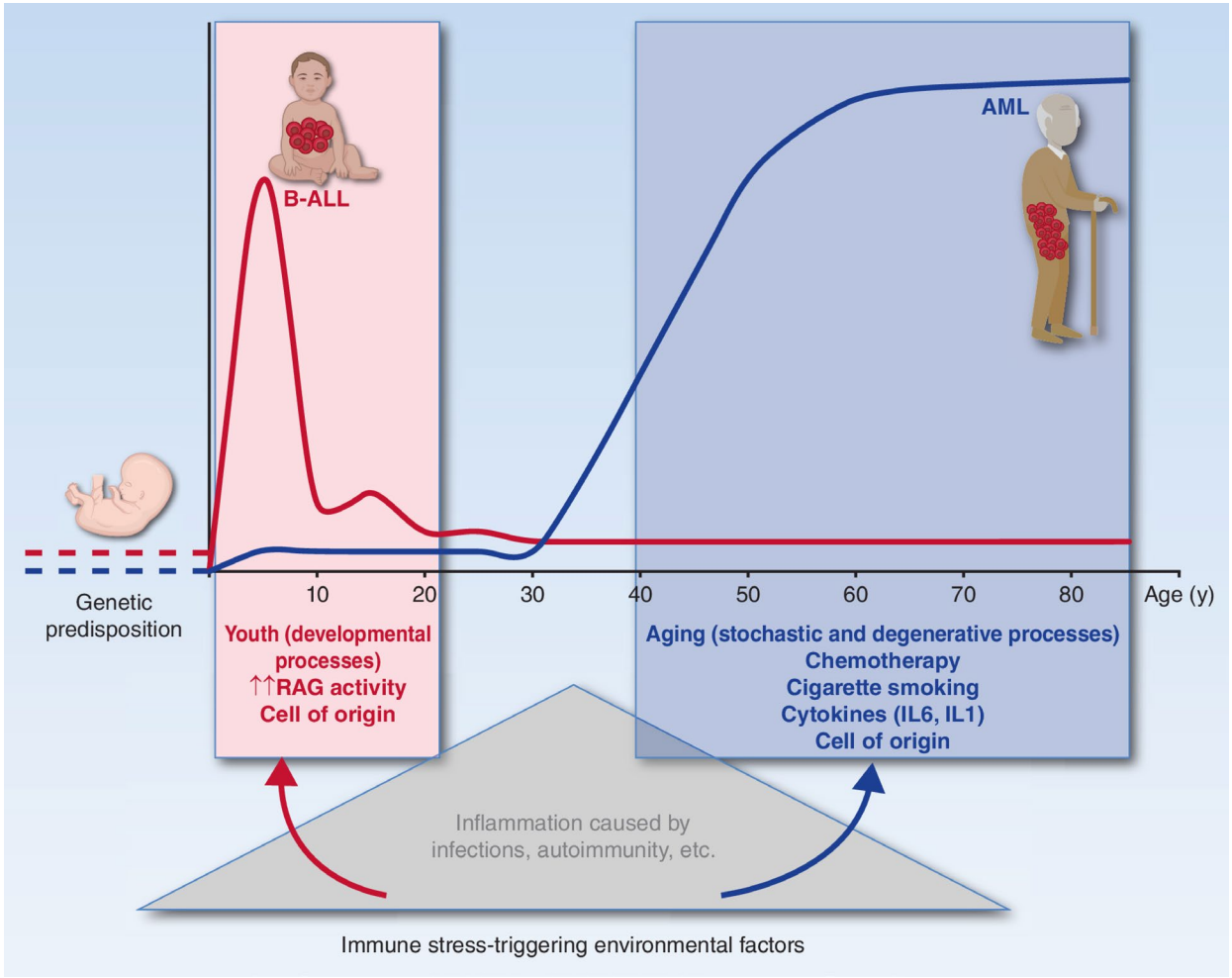


Biological background for hematopoiesis and clonal evolution

Biological pathways and hematopoiesis Related to the genetic predisposition



Age based microenvironment



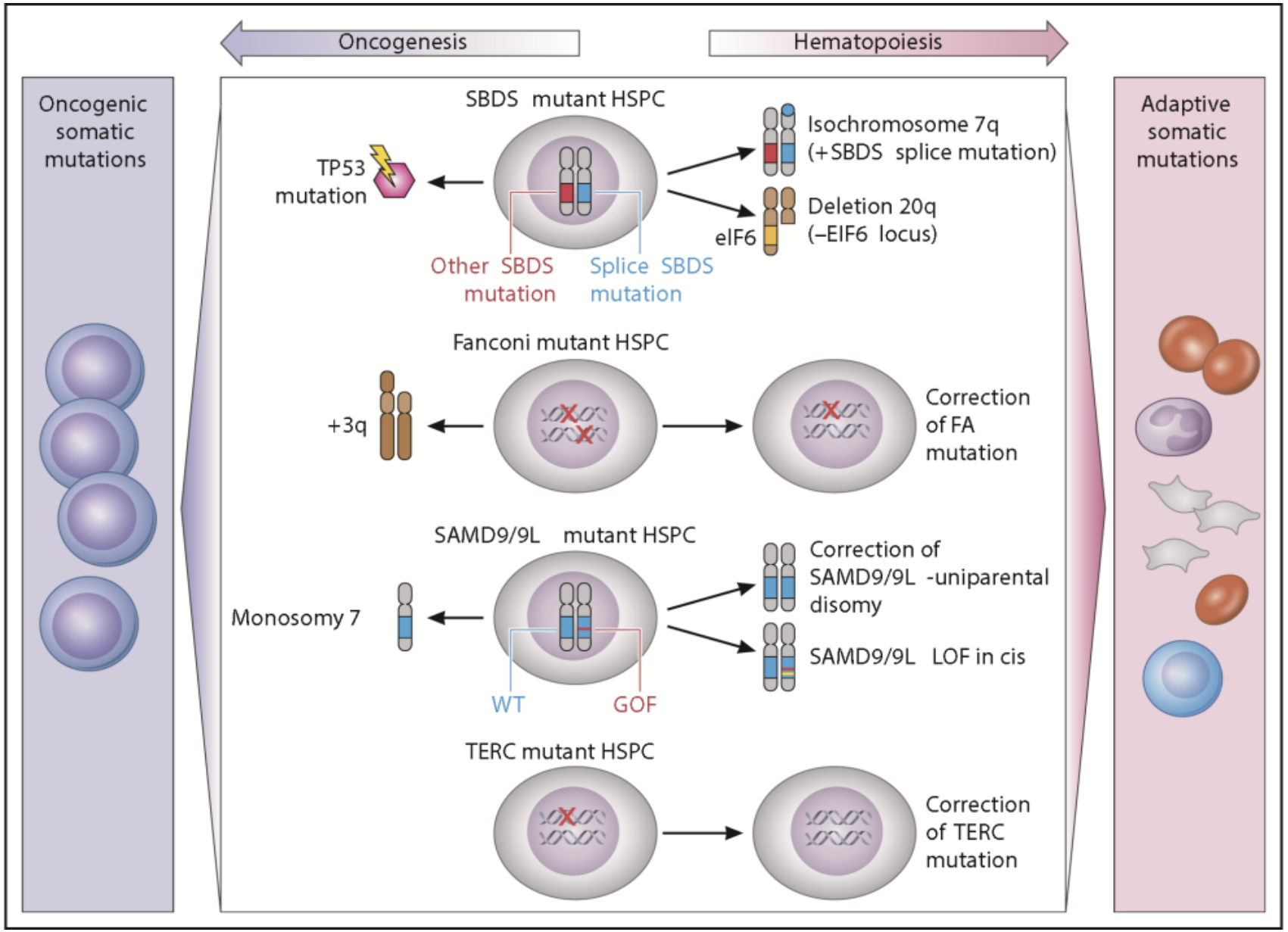
Bluteau et al. Blood 2018

Cobaleda et al. Cancer discovery 2024

Susceptibility genes, between rescue and disease

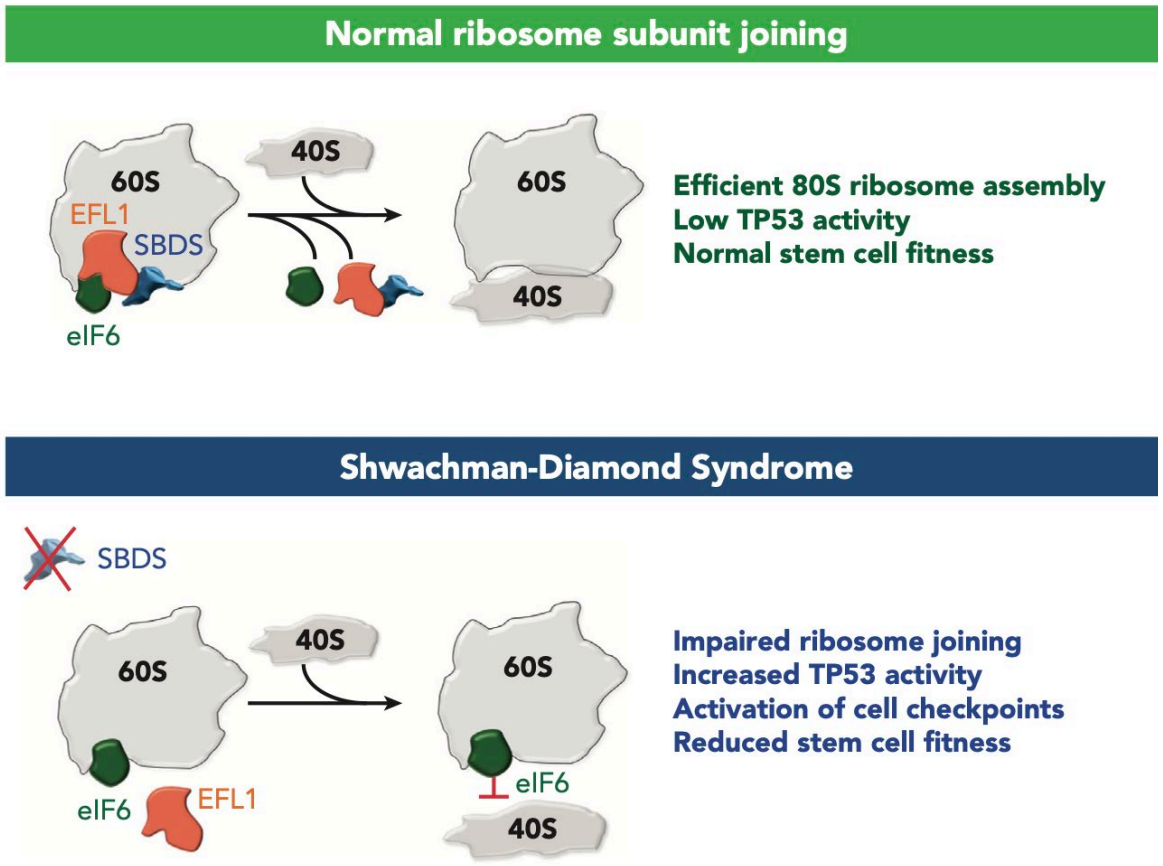
- *SBDS*
- Fanconi anemia
- *SAMD9/SAMD9L* syndrome
- Short telomere syndrome

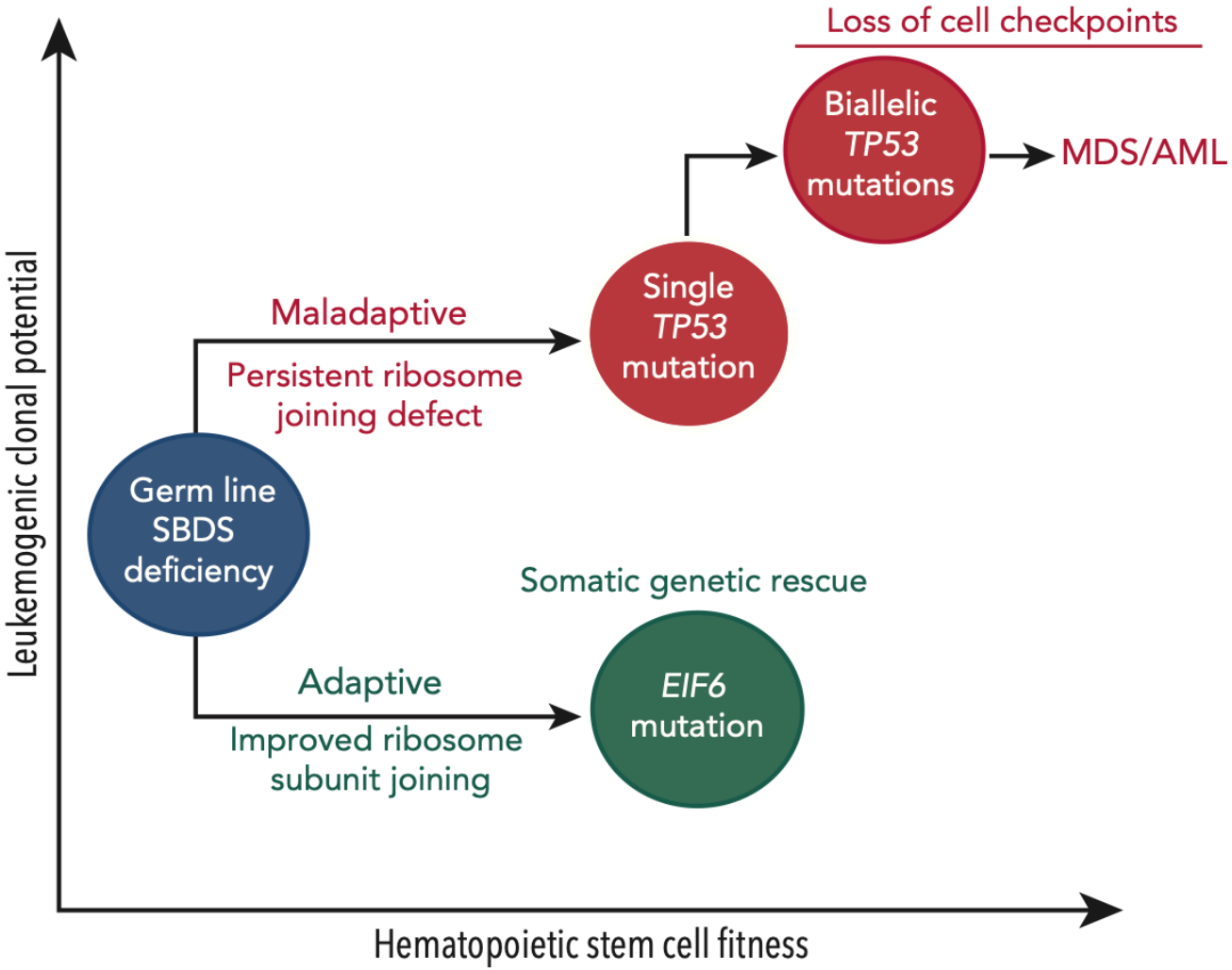
Clonal hematopoiesis: adaptation or pathology?



Alyssa L. Kennedy and Akiko Shimamura, Blood 2019

Schwachman syndrome





Christopher R. Reilly and Akiko Shimamura, Blood 2023

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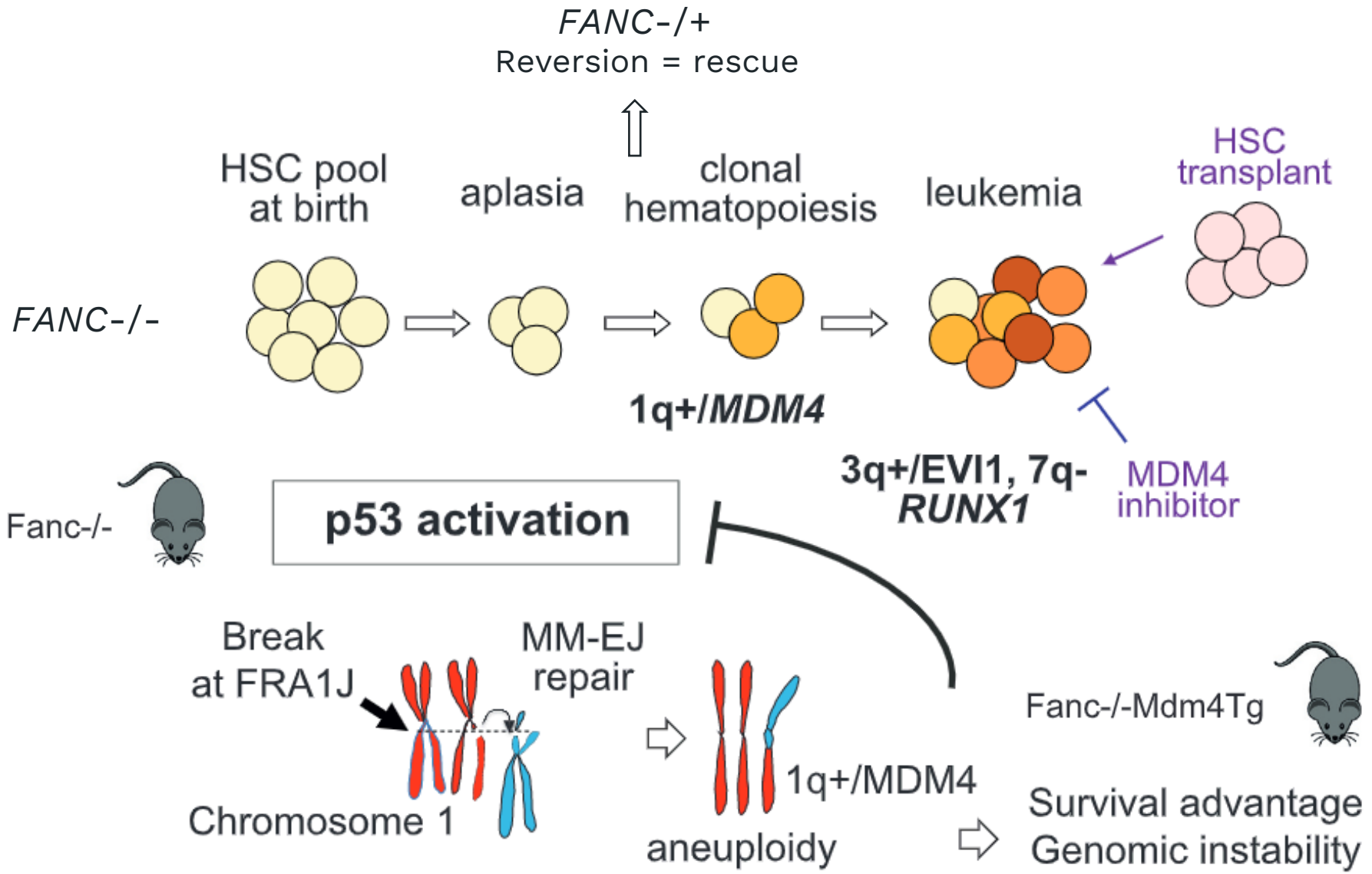
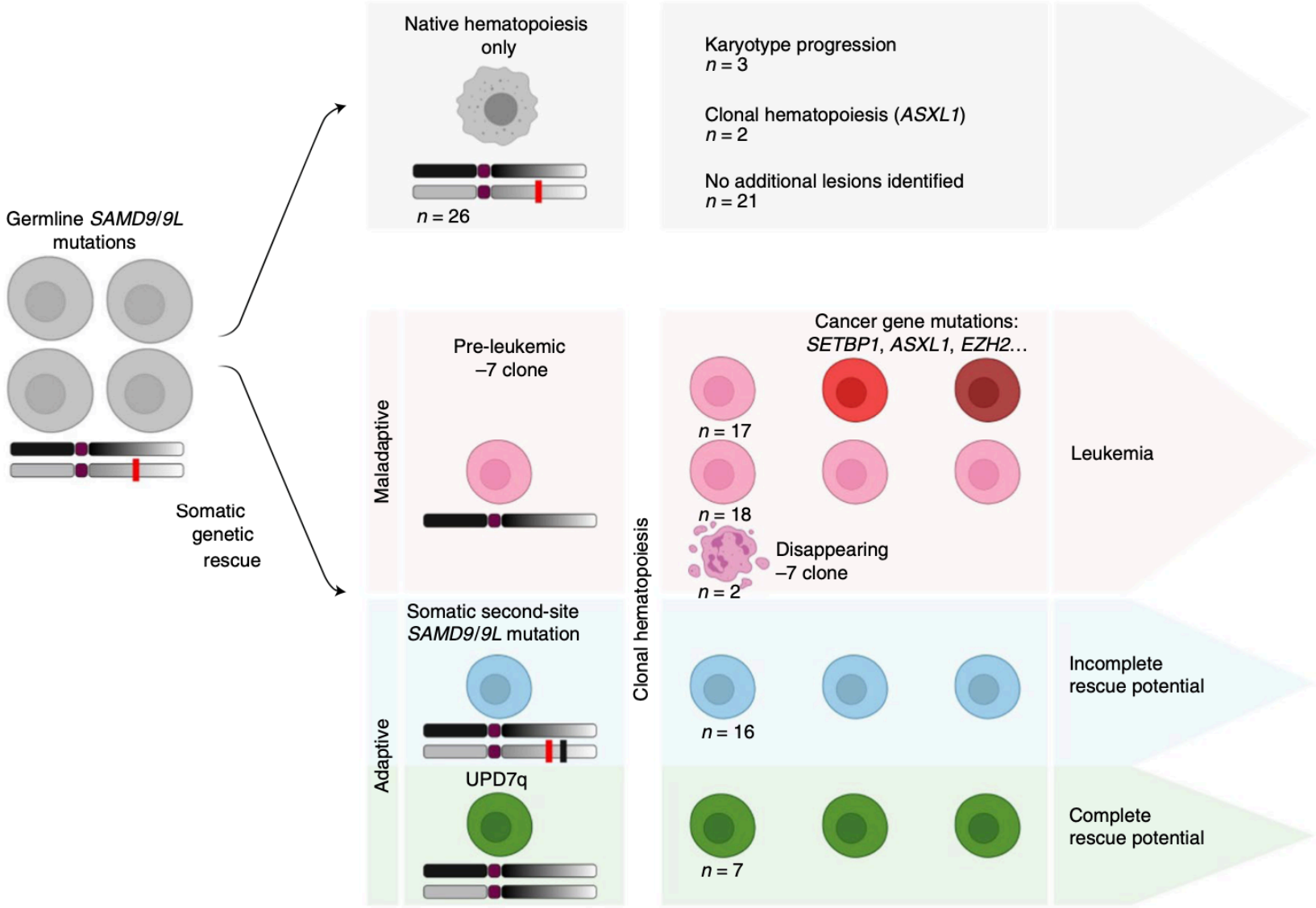
Fanconi anemia



Sébert et al. Cell stem Cell 2023

SAMD9/SAMD9L syndromes



ESahoo et al., Nat med 2021

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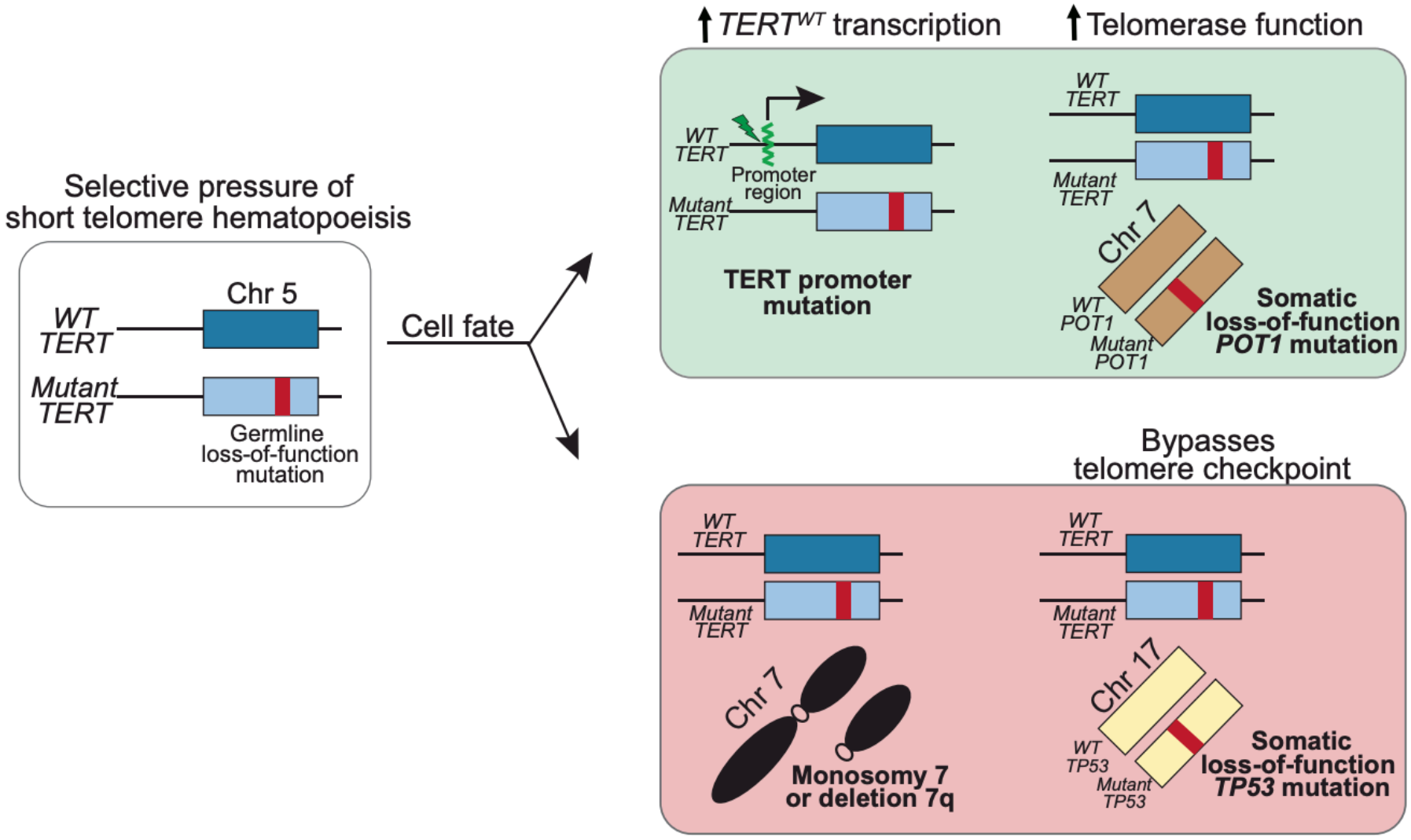
Short telomere syndrome



E.A. Schratz., Am Soc Hematol Educ Program 2023

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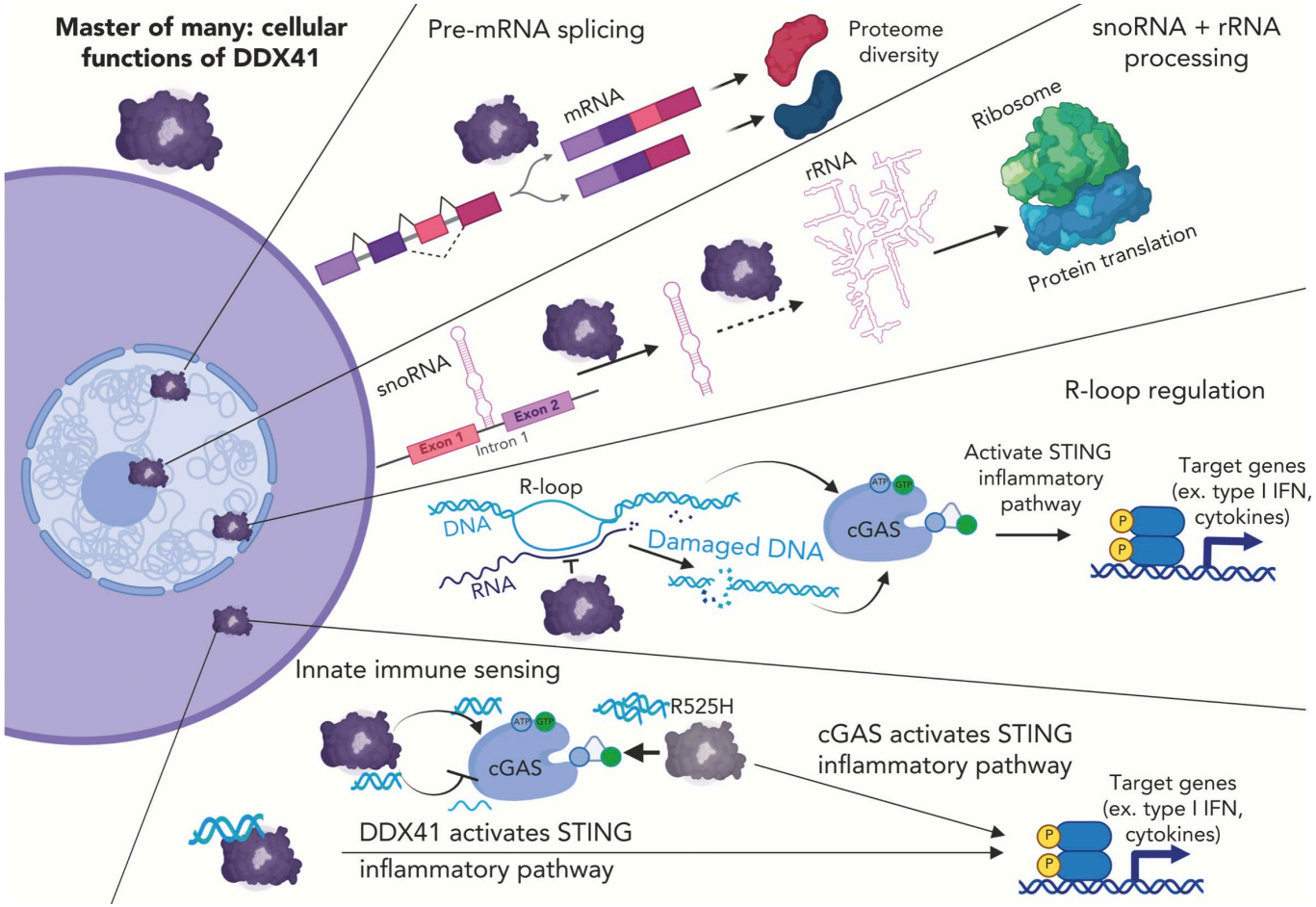
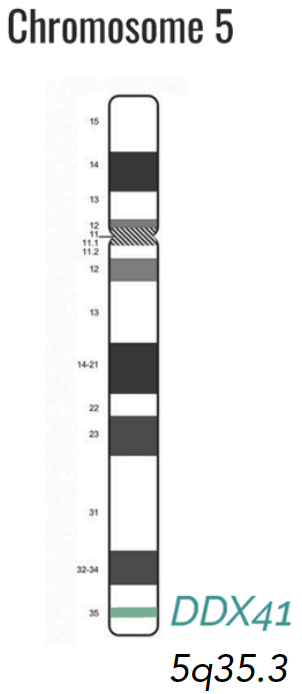
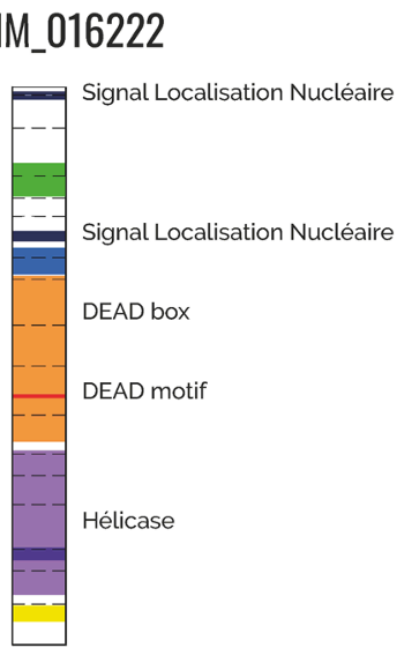
DDX41-related hematological malignancies

- Clonal evolution
- Penetrance
- Drug sensibility
- Prognosis
- Specific model of relapse?

DEAD-box helicase 41 (DDX41)



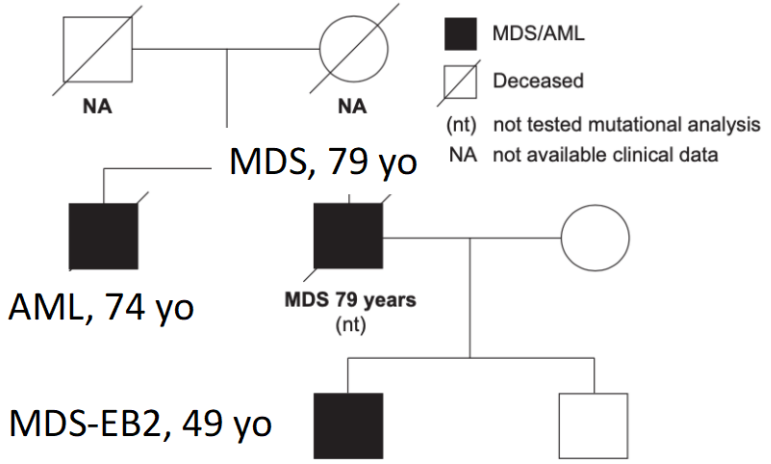




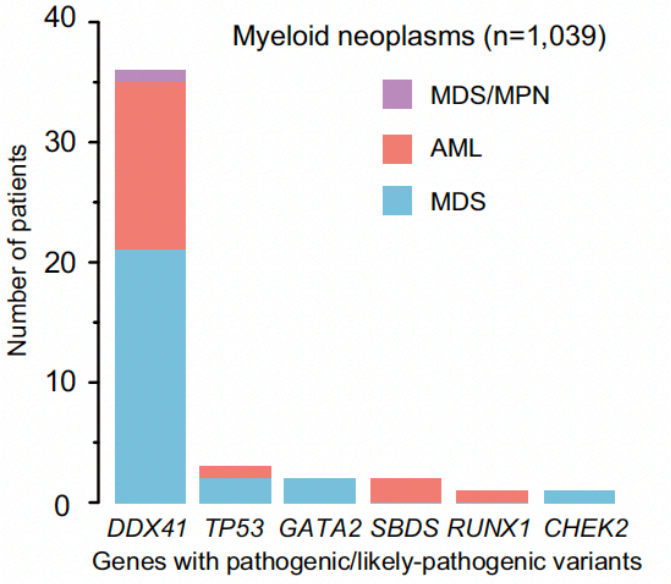
Makishima et al. Blood 2023

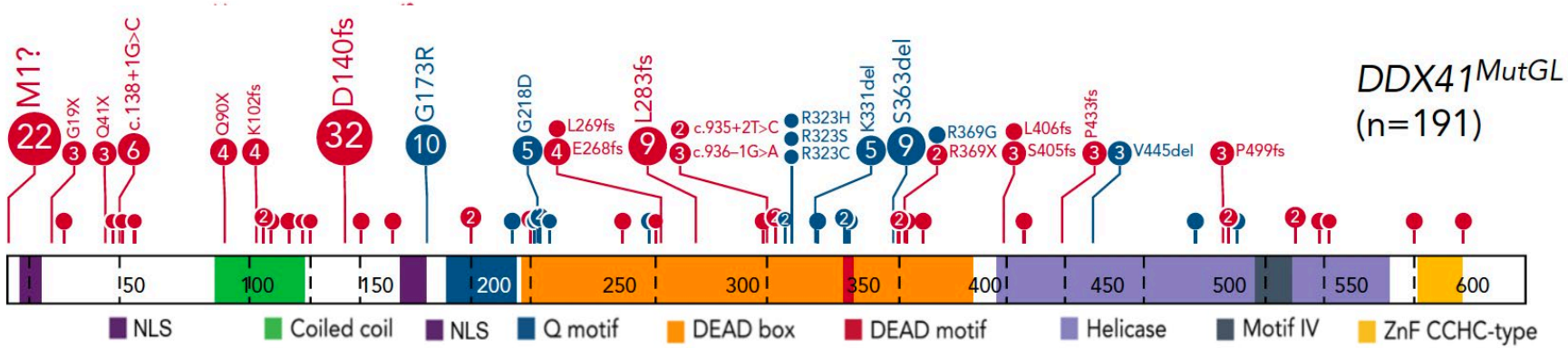
DDX41 as a genetic predisposition to hematological malignancies

- Transmission: Autosomal dominant
- Represent about 3% of all myeloid malignancies
- Is the most frequent predisposition to MDS/AML



Polprasert et al. Cancer Cell. 2015





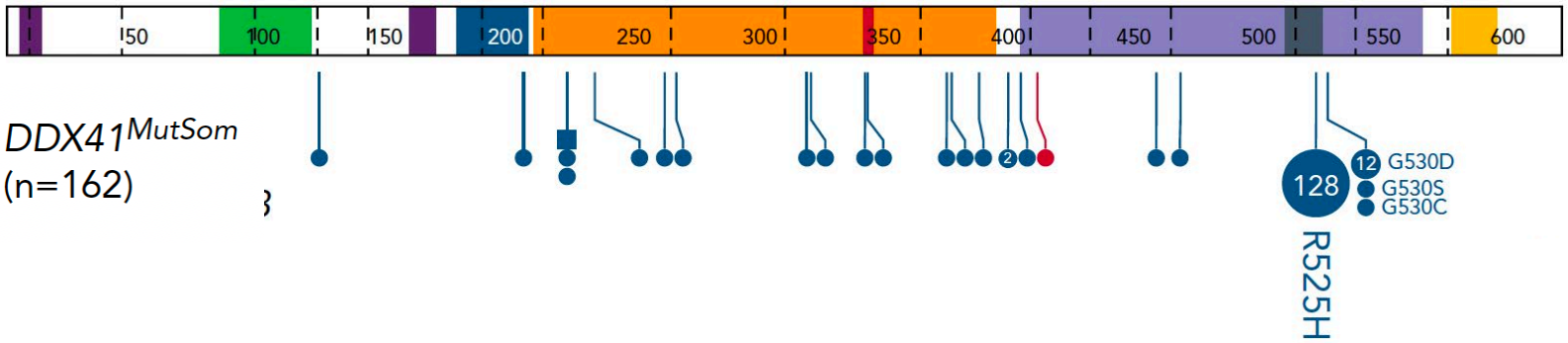
DDX41 5q35.3

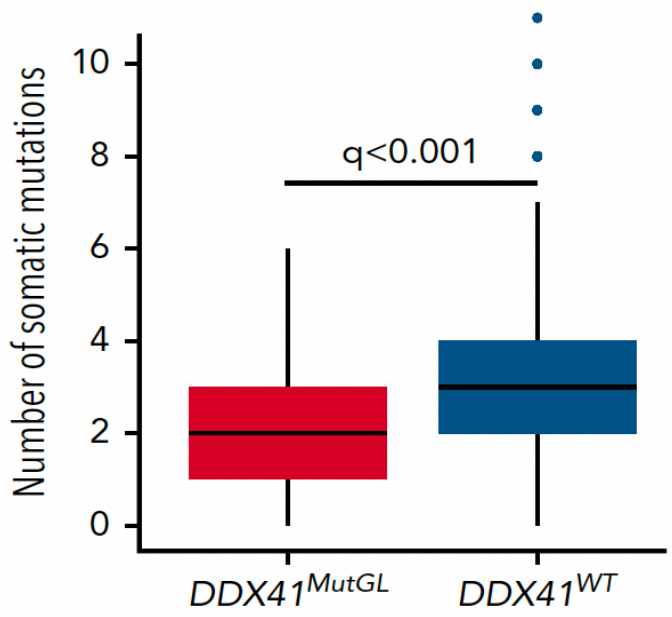
Makishima et al. Blood 2022

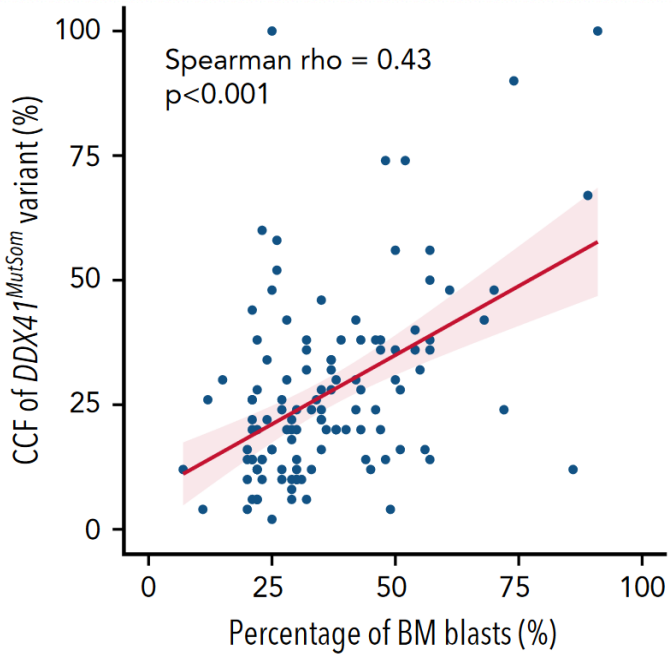
Duployez et al. Blood 2022

Clonal evolution in DDX41-related MDS/AML

- Normal karyotype
- Fewer oncogenetics events compared to DDX41wt
- Acquisition of a somatic *DDX41m*, one hotspot, correlated with blastic progression



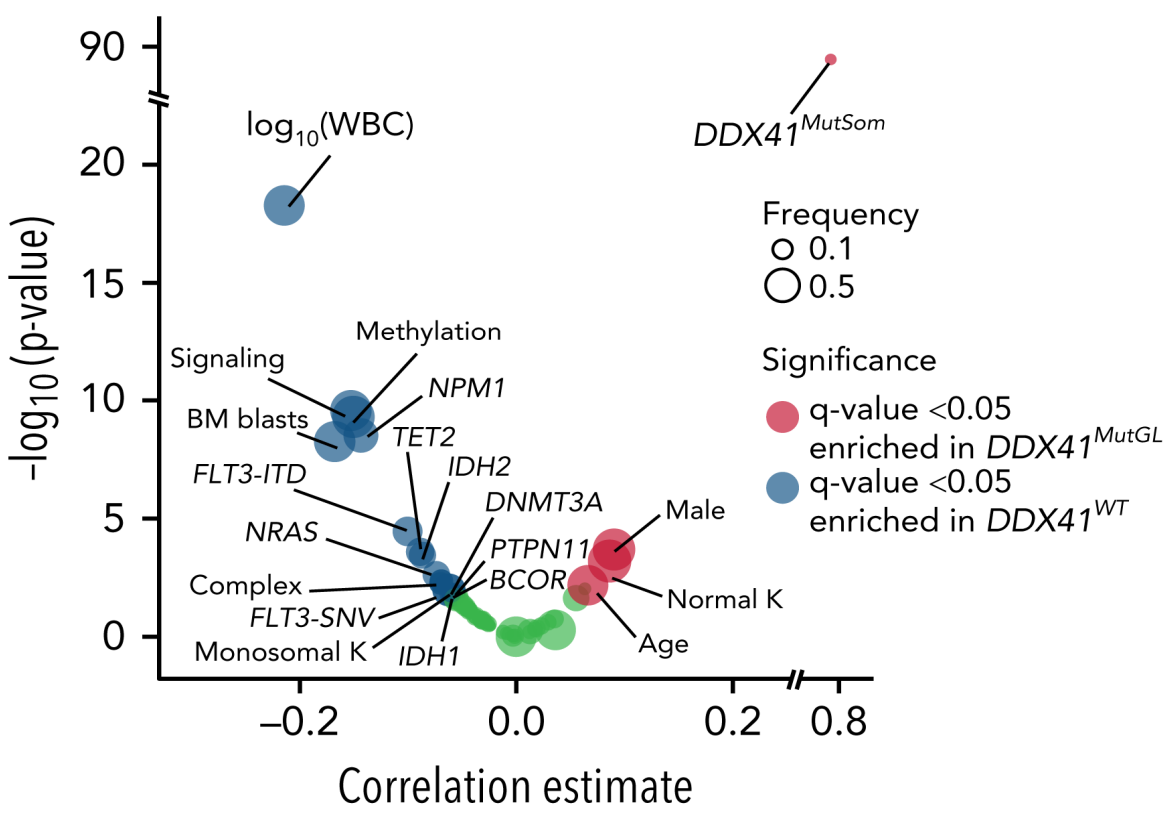




Sébert et al. Blood 2019; *Duployez et al. Blood 2022*

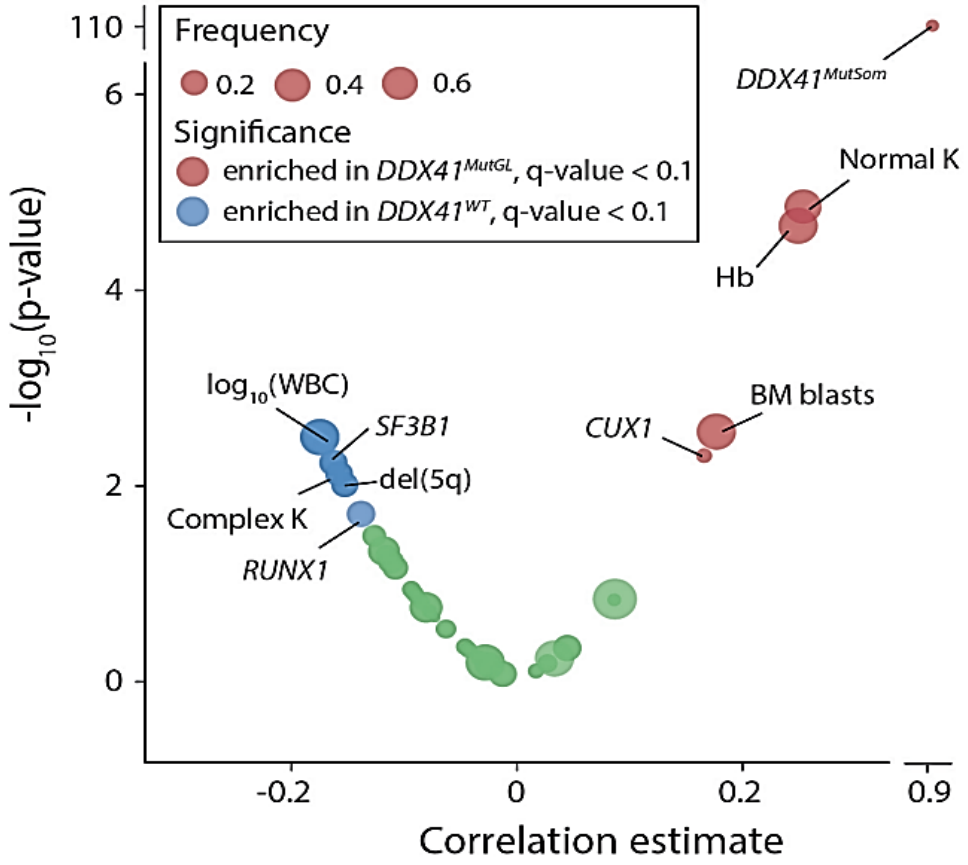
Somatic DDX41 mutation : a founder event ?

AML patients



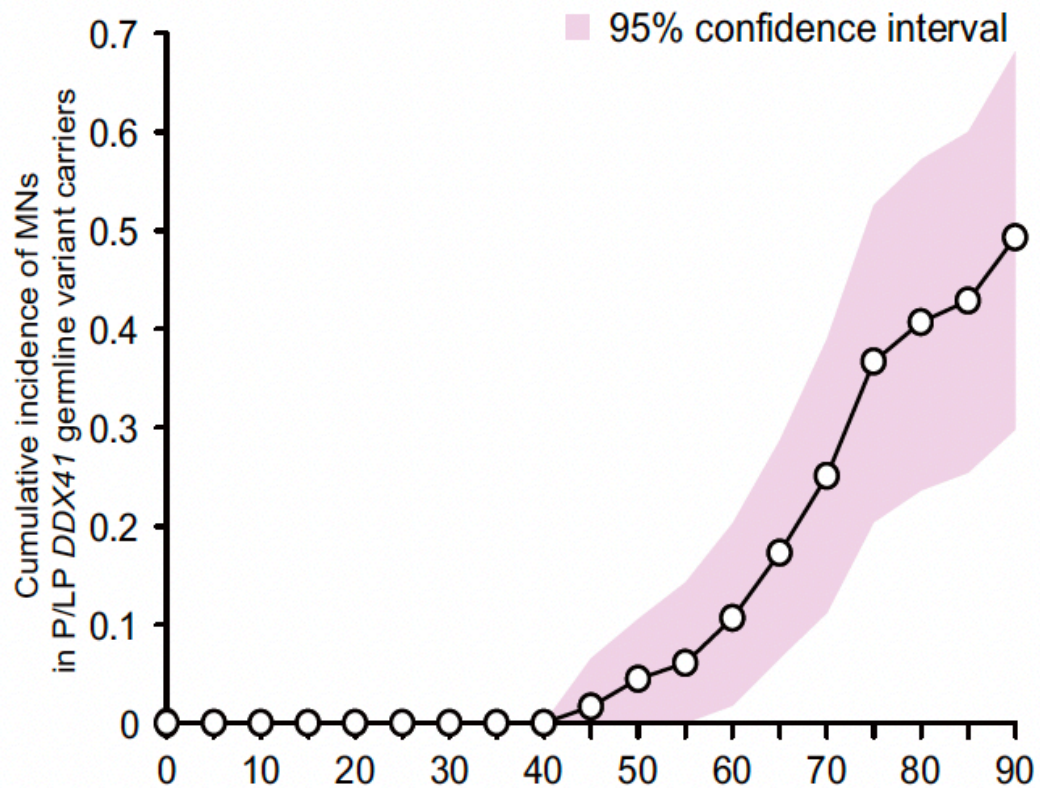
Duployez et al., Blood 2022

MDS patients

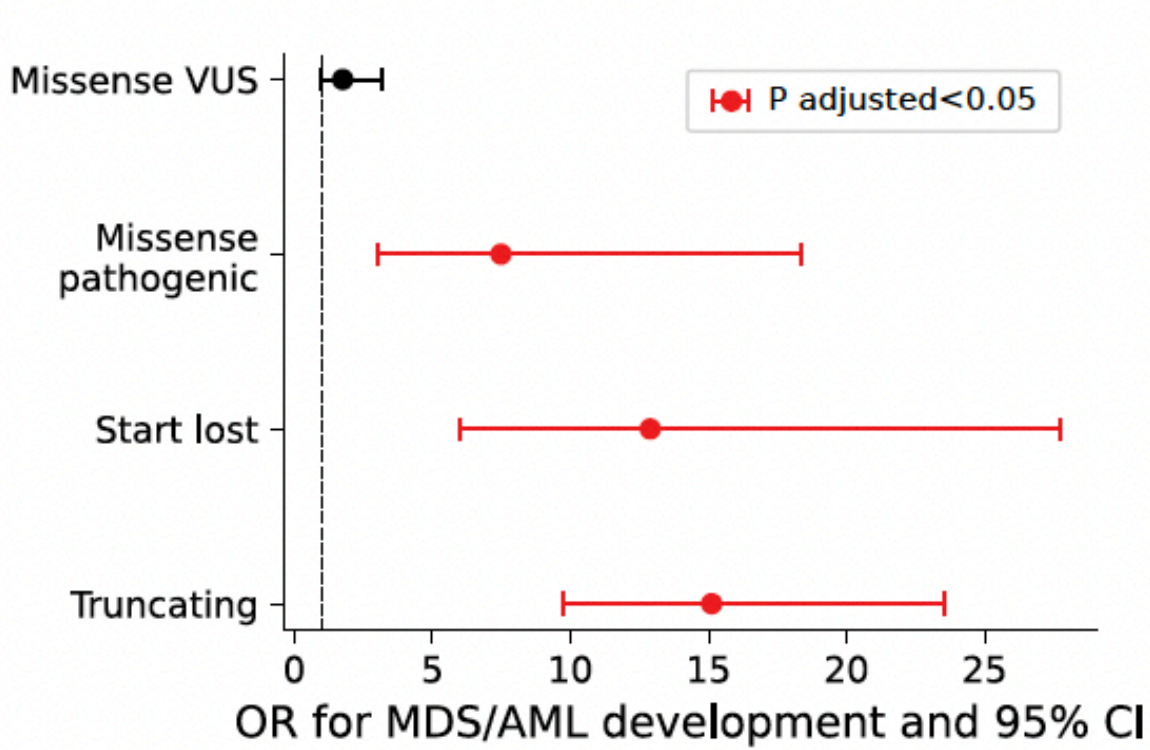


Sébert et al., Leukemia 2024

Penetrance



Makishima et al. Blood 2023

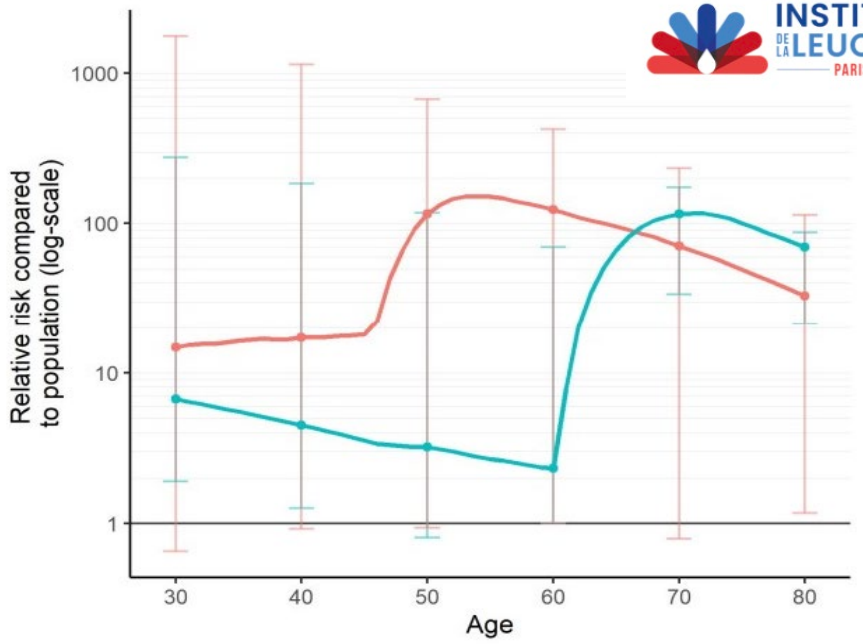


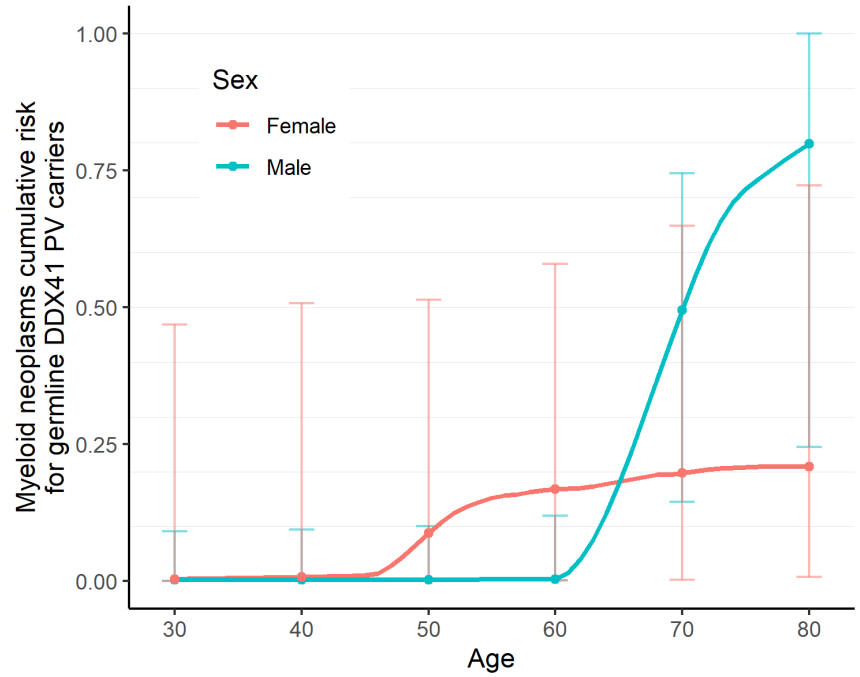
SC Kovilakam et al., Blood 2023

Penetrance

- 63 probands with DDX41-related MDS/AML
- 160 genotyped relatives
- Genotype-Restricted-Likelihood (GRL) approach

Age (years)	Absolute cumulative risks (95%CI)		Relative risks (95%CI)	
	Males	Females	Males	Females
30	0.2% (0.1–9.1)	0.4% (0–46.8)	6.7 (1.9–275)	14.7 (0.7–1770)
35	0.2% (0.1–9.3)	0.6% (0–49.3)	5.5 (1.6–226)	16.3 (0.8–1447)
40	0.2% (0.1–9.4)	0.8% (0–50.7)	4.5 (1.3–184)	17.1 (0.9–1145)
45	0.2% (0.1–10)	1.0% (0.1–51.2)	3.5 (1.0–155)	18.0 (1.0–881)
50	0.3% (0.1–10)	8.8% (0.1–51.4)	3.2 (0.8–118)	115.4 (0.9–673)
55	0.3% (0.1–10.1)	15.2% (0.1–53.1)	2.7 (0.8–86)	150.5 (1.0–527)
60	0.4% (0.2–11.9)	16.8% (0.1–57.9)	2.3 (1.0–69)	123.7 (1.0–426)
65	17.7% (6.1–32.1)	18.2% (0.1–60.6)	66.9 (23–121)	95.3 (0.8–318)
70	49.5% (14.5–74.4)	19.8% (0.2–64.9)	115.2 (34–173)	70.7 (0.8–232)
75	71.6% (23.0–100.0)	20.8% (0.4–70.9)	100.7 (32–141)	49.4 (1.0–168)
80	79.9% (24.5–100.0)	21.0% (0.7–72.2)	69.5 (21–87)	33.0 (1.2–114)

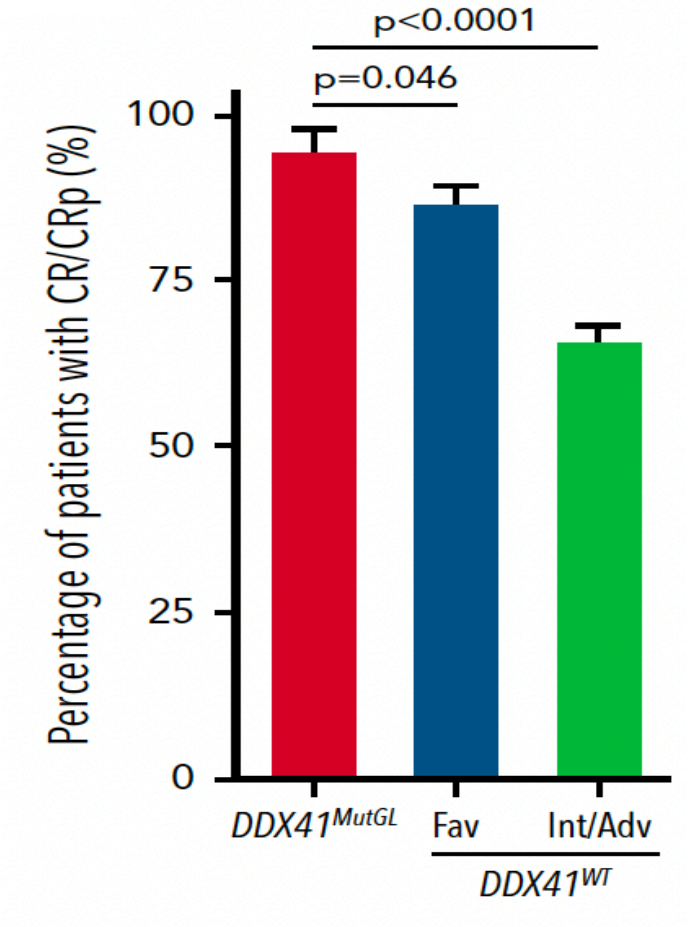




Villy et al. under revision

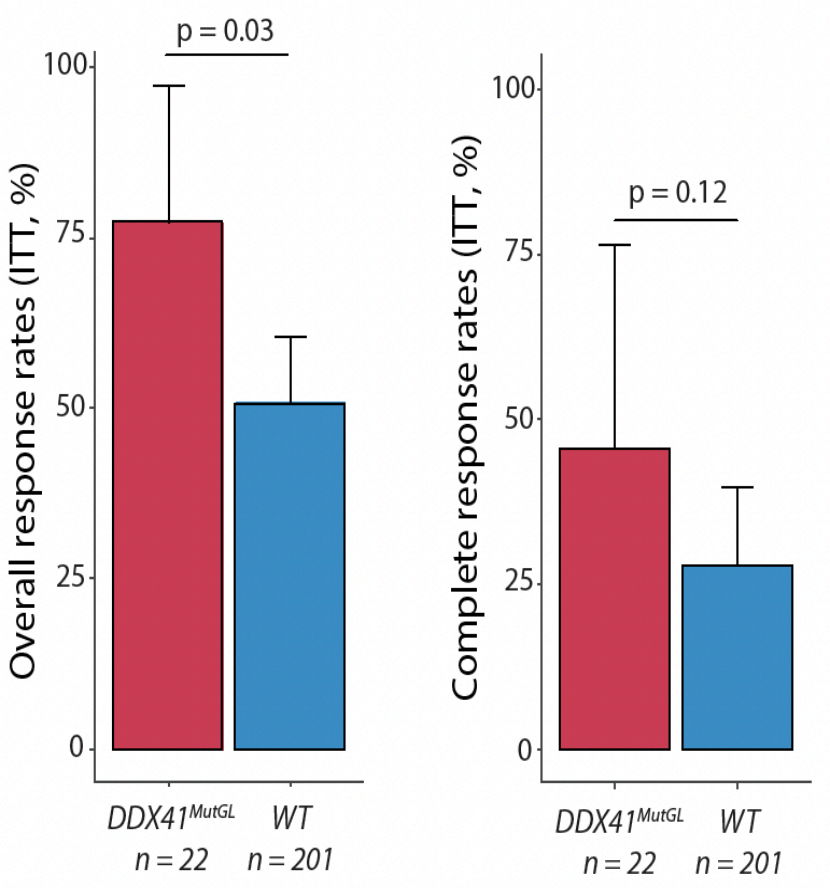
Drug sensitivity

To Intensive chemotherapy



Duployez et al. Blood 2022

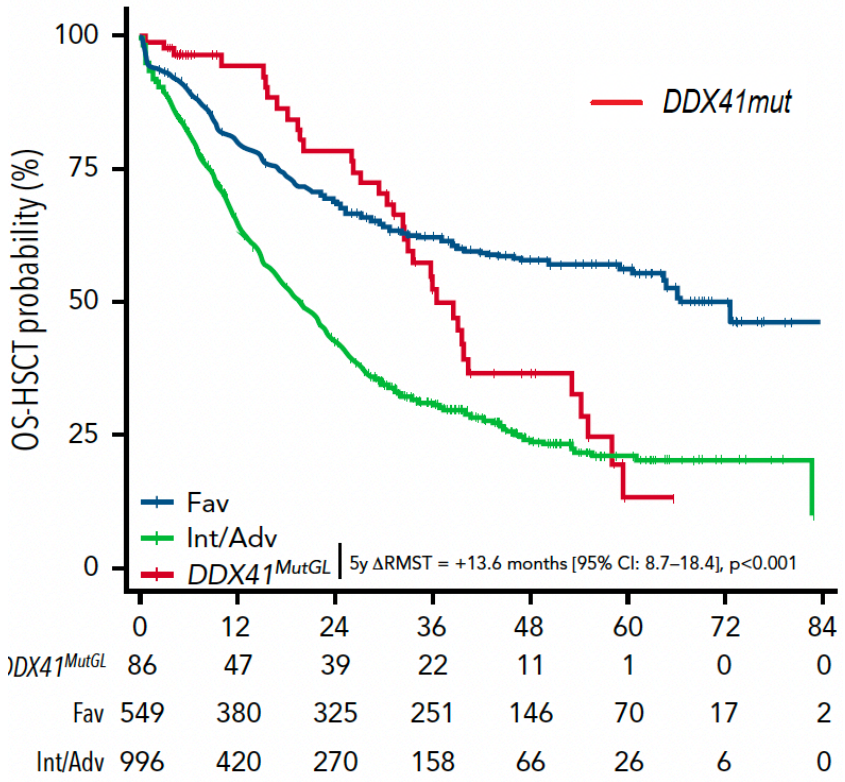
To Azacitidine-based regimen



Sébert et al. Leukemia 2024

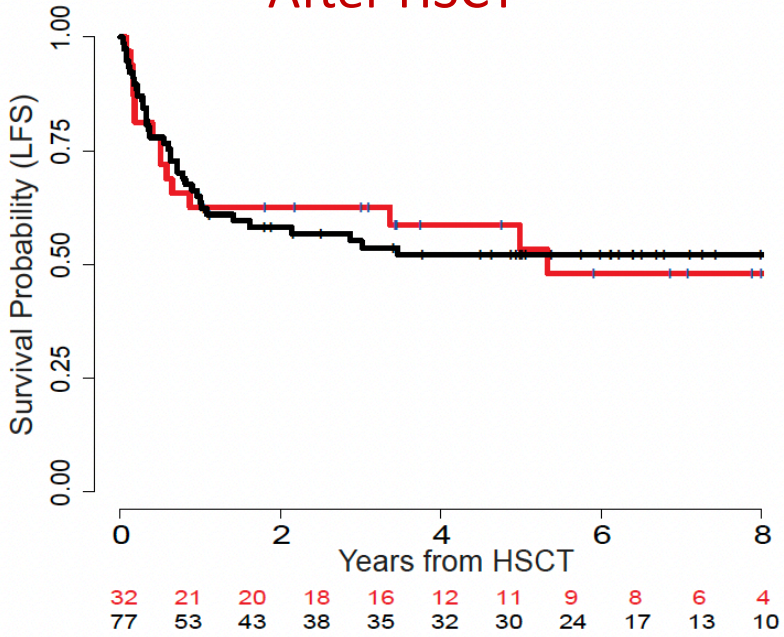
Prognosis

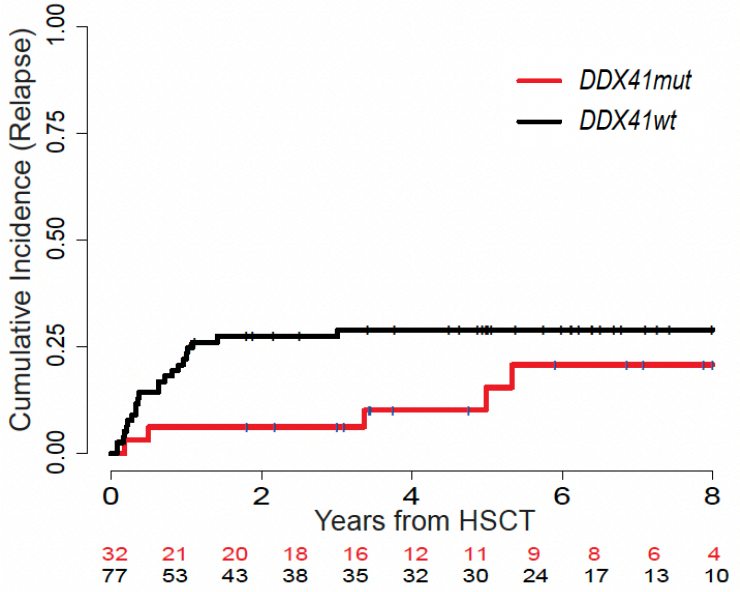
AML After Intensive chemotherapy



Duployez et al. Blood 2022

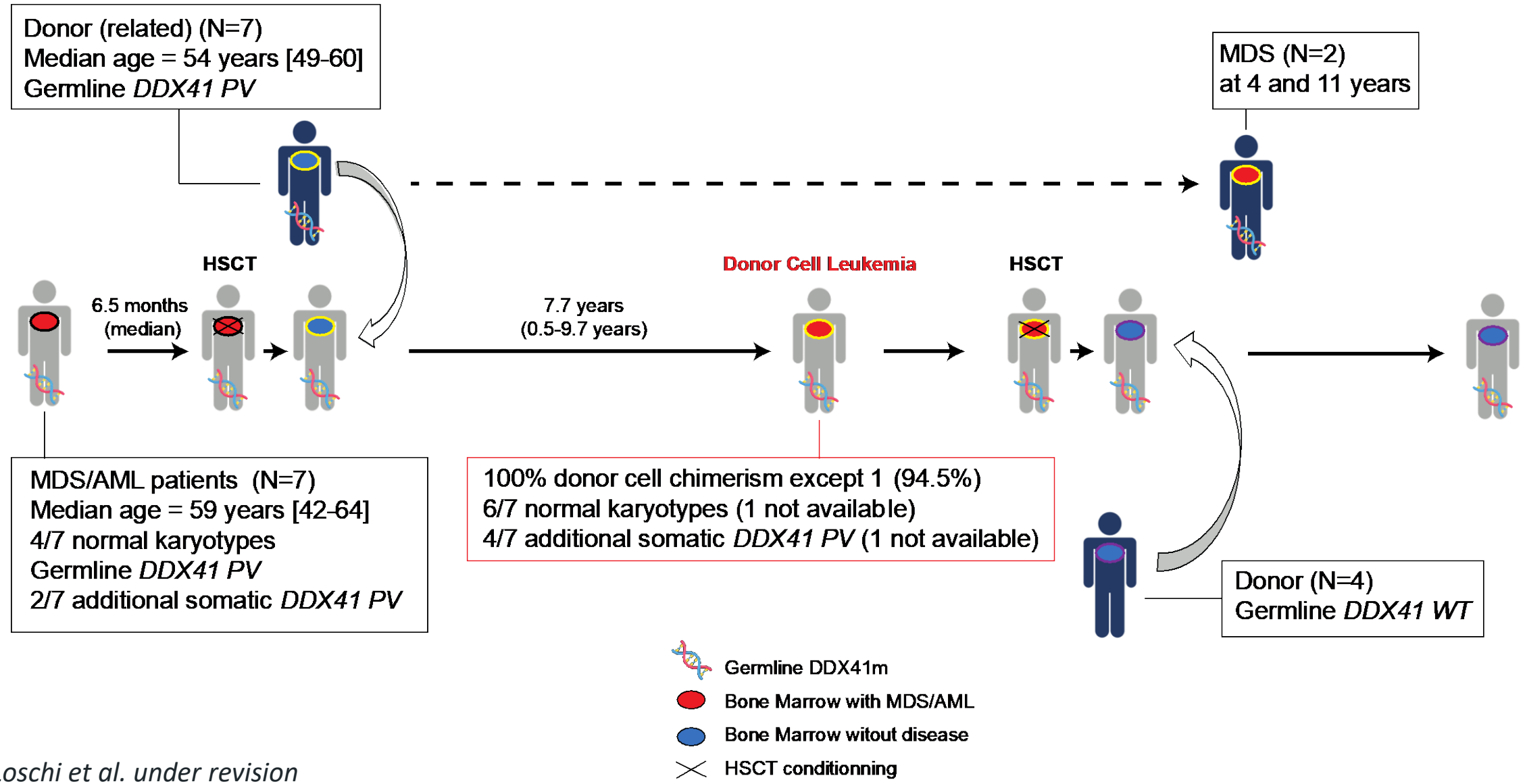
After HSCT





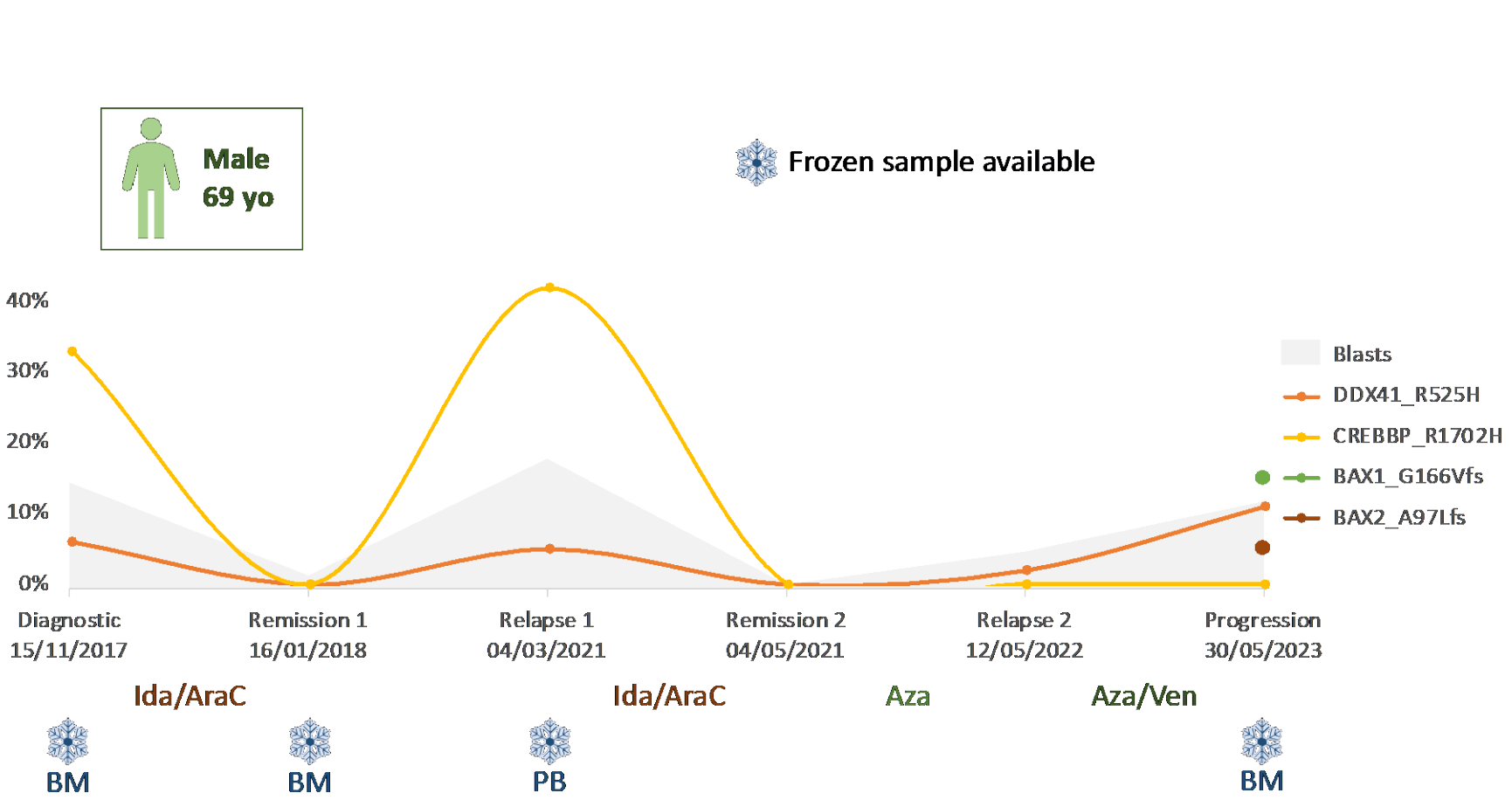
Loschi et al. under revision

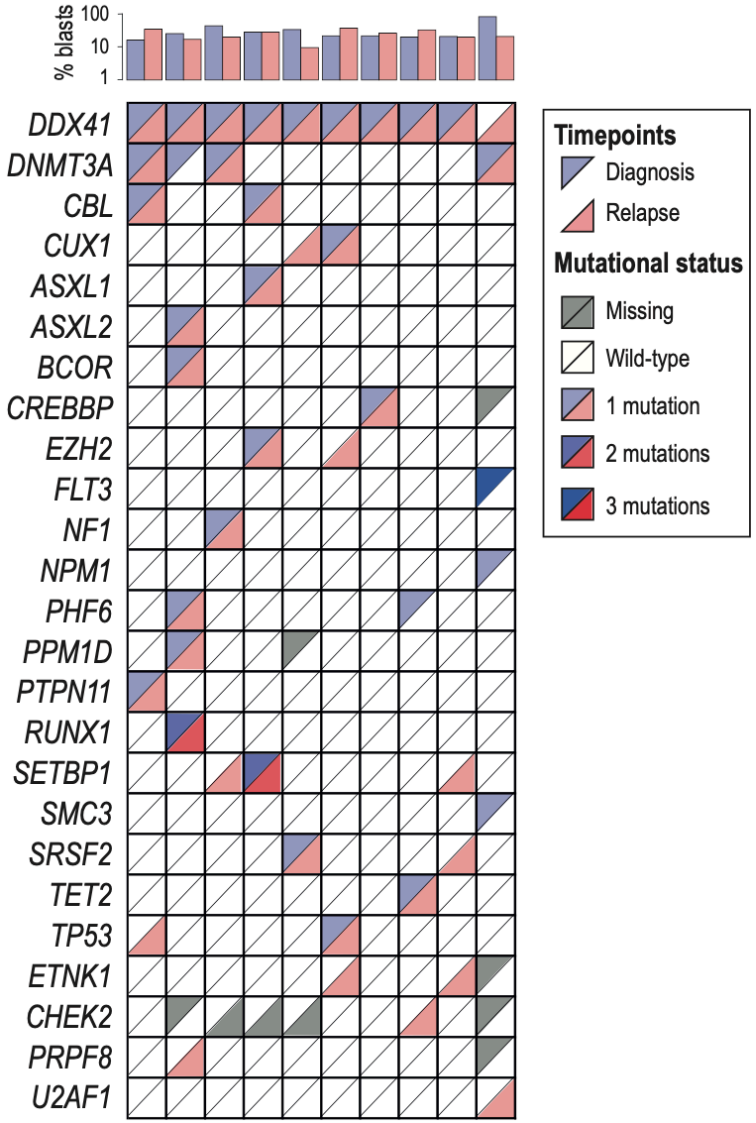
Focus on donor cell leukemias



Loschi et al. under revision

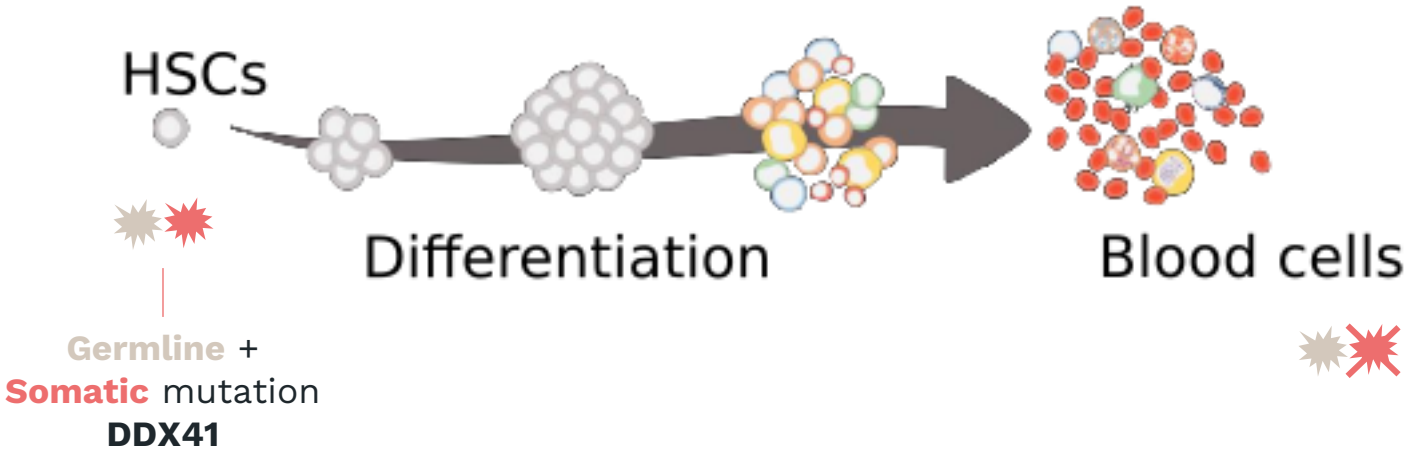
Natural history of relapse





Mathematical model and hypothesis

Dr. Carine Legrand,
Prof. Vincent Bansaye,
CMAP Polytechnique
Lisa Crépin &
Robinson Le-Bihan,
MSV Polytechnique

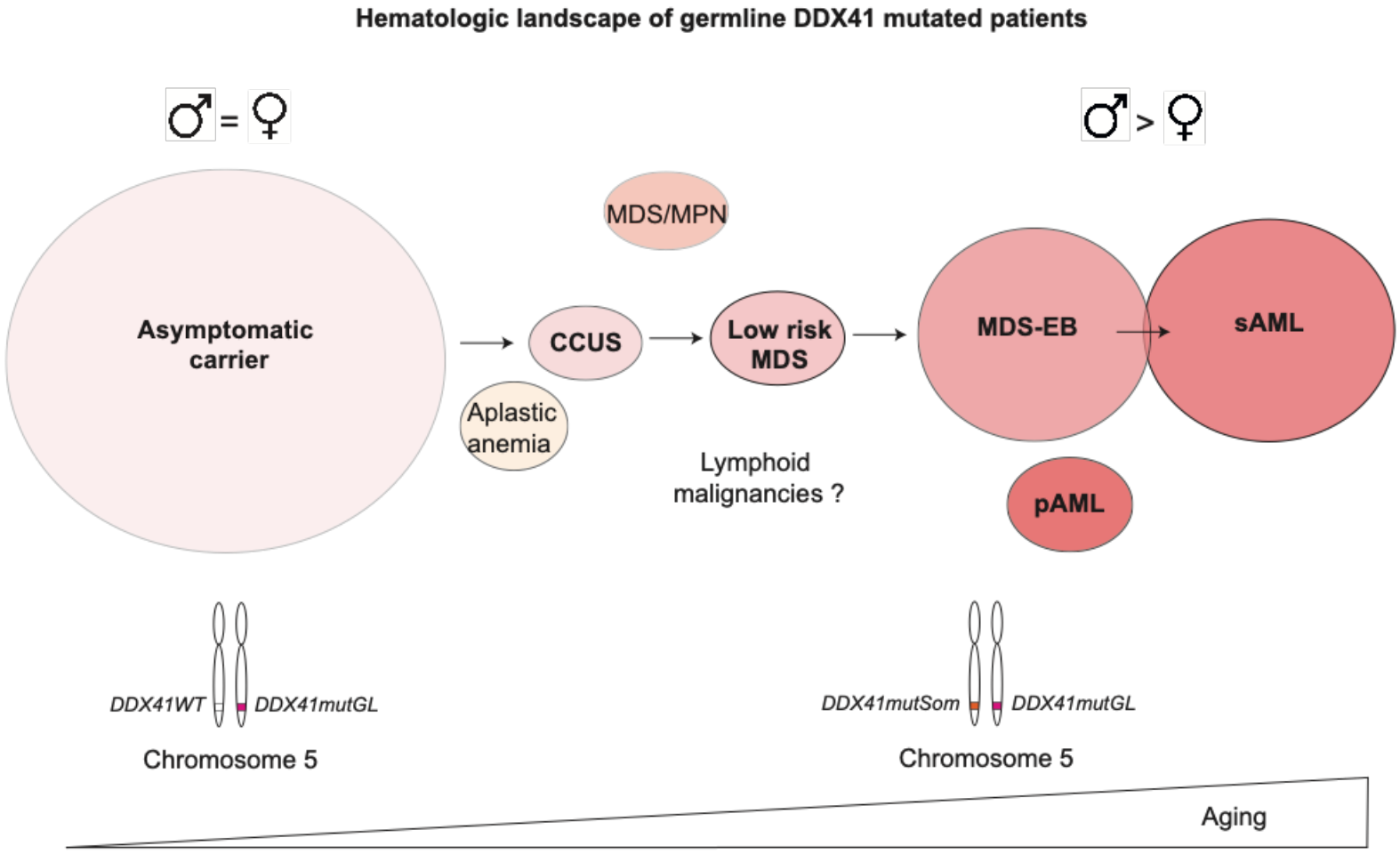


➡ Probabilistic model for cellular differentiation during hematopoiesis

Method	Markov Chain : successive states, linked by transition probabilities for renewal / differenciation / death
Hypothesis	➢ Selection disadvantage during differentiation ? ➢ De-differentiation (of somatic-mutated lineage) ?

DDX41-related MN, conclusions

- 5% of sporadic MDS/AML
- Autosomal dominant
- Variable penetrance, sex and age-driven
- Leukemogenesis associated with somatic *DDX41m*
- Associated with drug sensitivity
- Good prognosis
- Relapse
- Donor cell leukemia
- Rescue?



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Bone Marrow Failure Department, Hôpital St-Louis and Robert Debré, Paris - French Reference Center "Bone marrow failure "

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