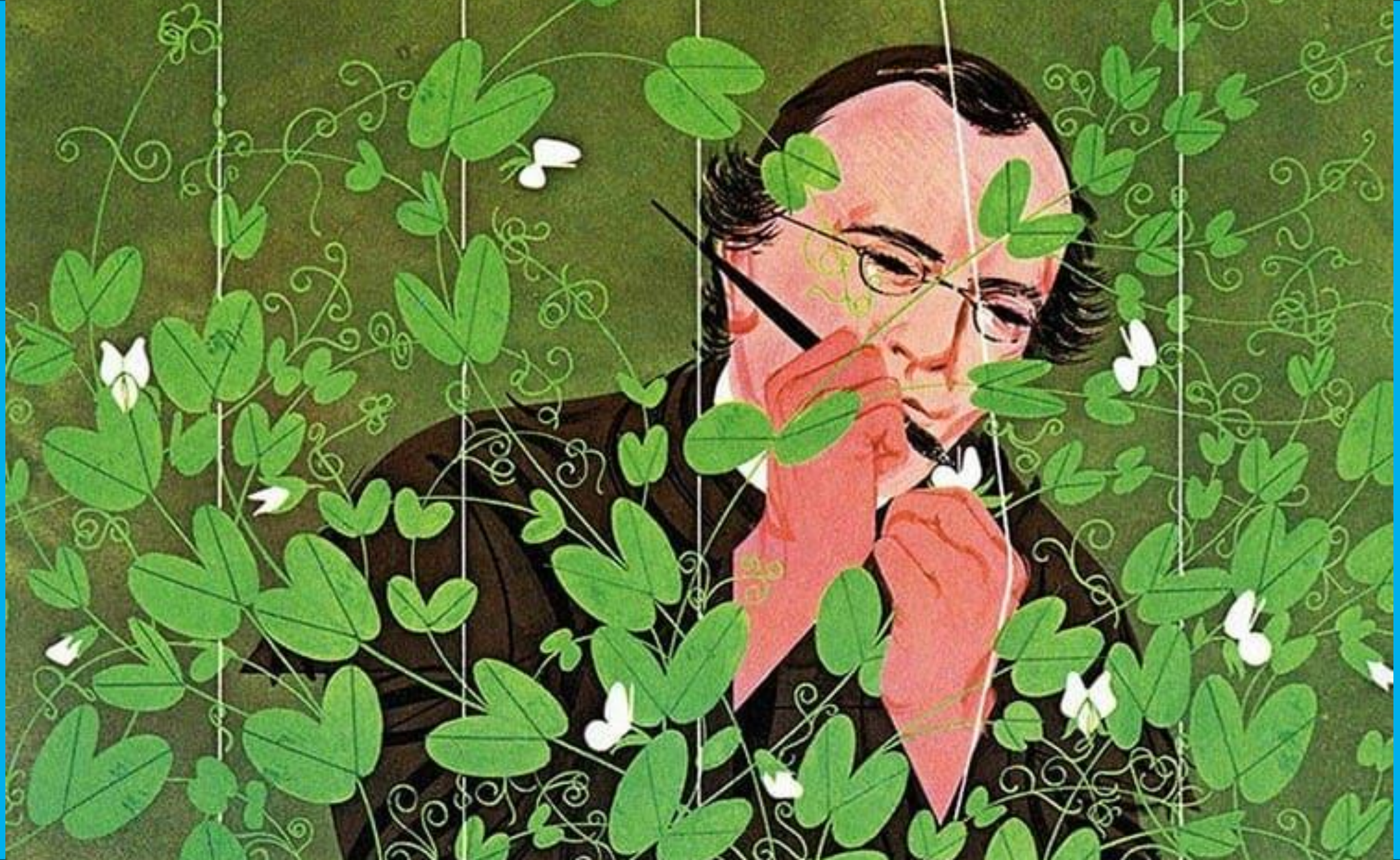


La familiarità in oncoematologia

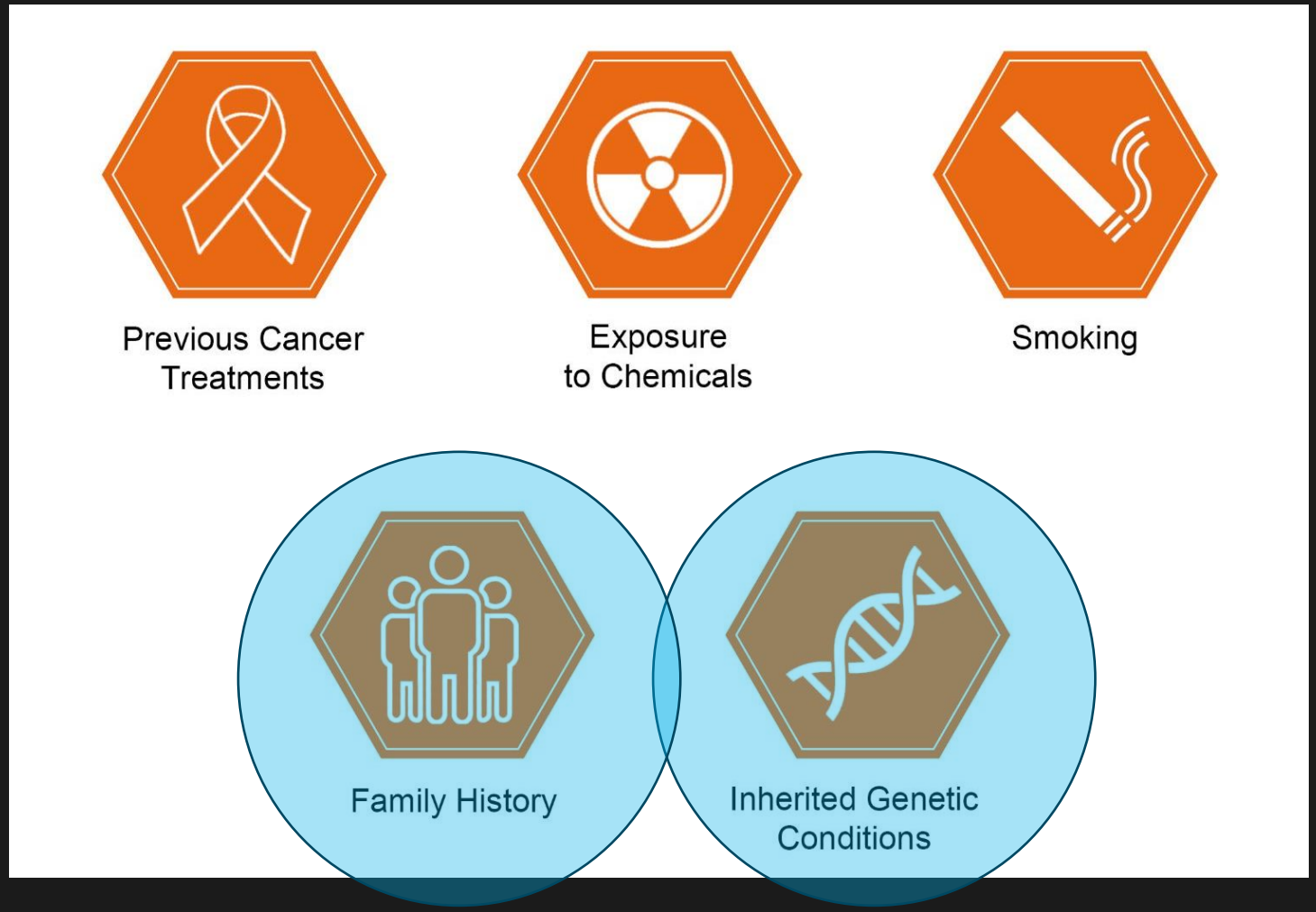
Dr.ssa Simona Bernardi

AGENDA

- Definition of «Familiarity»
- The case of CLL and related involved genes
- The WHO classification of AML/MDS with germline predisposition
- Focus on DDX41 gene
- The familiarity in MPNs

The risk factors for leukemia

Inherited genetic conditions are the bases of familiarity



What does familiarity mean?

High incidence of cases of leukemias and/or solid tumors in family members within 3° grade.

Different from LFS.

The malignancies are associated with genetic predisposition related with rare germline mutations.

Commonly, the inheritance is AD.

As more patients and families with predisposing conditions are identified, it is increasingly important for the practicing physician to have a working knowledge of the approach to evaluation and management of hematologic malignancies predisposition.

It is more common that we think and less known that it needs to be

In Italy, the counselling may be managed by Haematologists

Germline hematopoietic malignancy risk gene

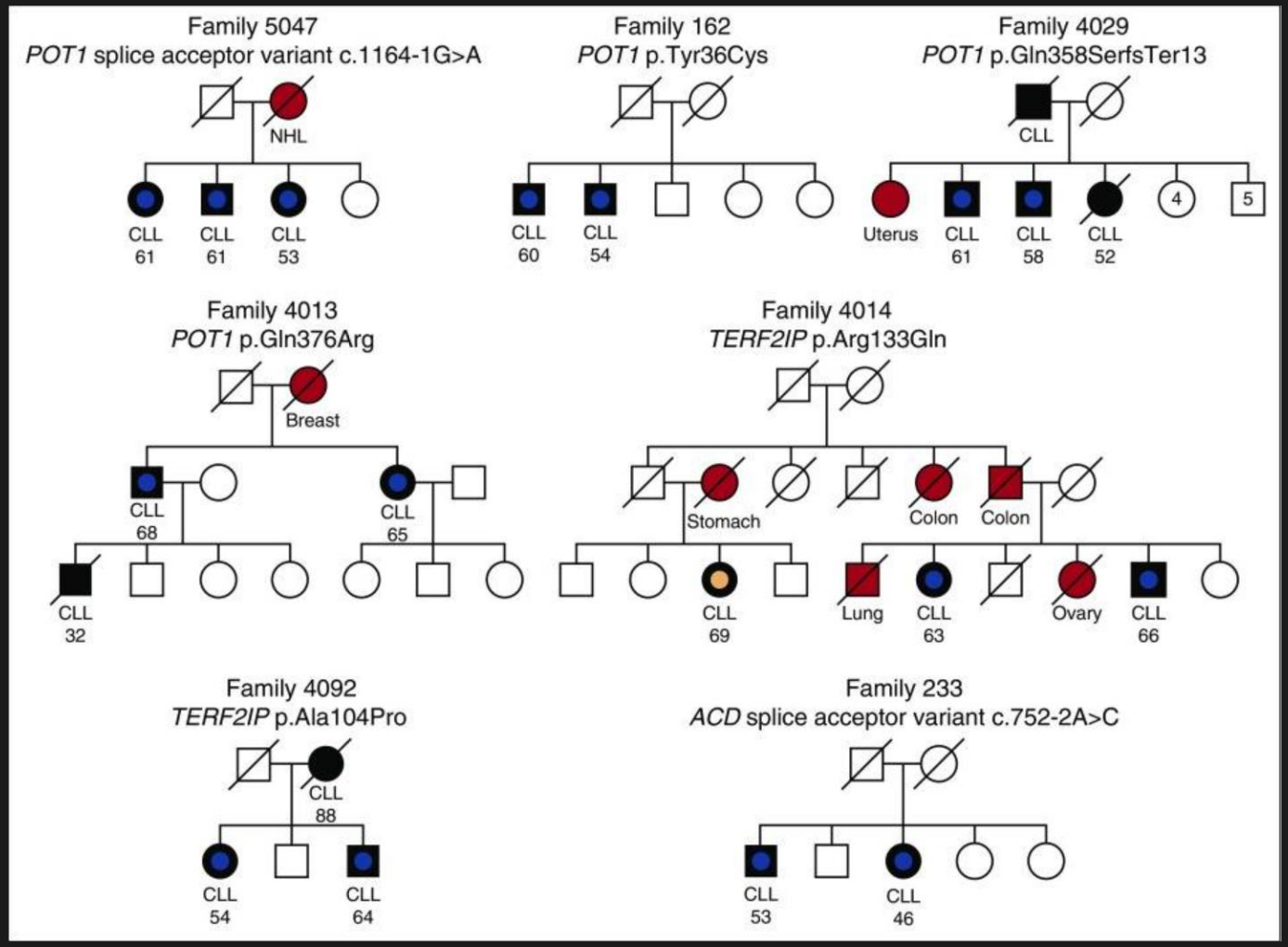
Risk for myeloid malignancies	Risk for lymphoid malignancies or immunodeficiency	Risk for hematopoietic malignancies	Risk for hematopoietic and non-hematopoietic malignancies
ANKRD26, CBL, CEBPA, DNAJC21, EFL1, ERCC6L2, GATA2, JAK2, MECOM/EVI1, MPL, NAF1, NPM1, RBBP6, RBM8A, RTEL1, SAMD9, SAMD9L, SBDS, SRP72	*APOA1, APOA2, ARID1A, BTK, CARD11, CASP10, CD27, CD40LG, CD70, CST3, CTLA4, CTPS1, DIS3, DOCK8, FGA, GSN, IKZF1, ITK, KDM1A, LYZ, MAGT1, MALT1, MRTFA, NPAT, PAX5, PGM3, PIK3CDG, RASGRP1, STAT3, TTR, UNC13D, USP45 TNFRSF9, ZNF431*	*CSF3R, DDX41, ETV6, RUNX1, TET2, trisomy 21*	*ATM, BLM, BRCA1, BRCA2, CHEK2, MBD4, NBN, NF1, POT1, PTEN, PTPN11, RECQL4, SH2B3, TP53, WAS,* BMF/DKC*, FA*, HBOC*, LS*

* DKC, dyskeratosis congenita; FA, Fanconi anemia; HBOC, hereditary breast and ovarian cancer; LS, Lynch syndrome

Godley, ESH conference, 2023

Familial Chronic Lynphocytic Leukemia (LLC)

- CLL has one of the highest familial risks of any cancer, with risk being increased eightfold in relatives of patients
- The familiarity in CLL has been recognized more than 30 years ago



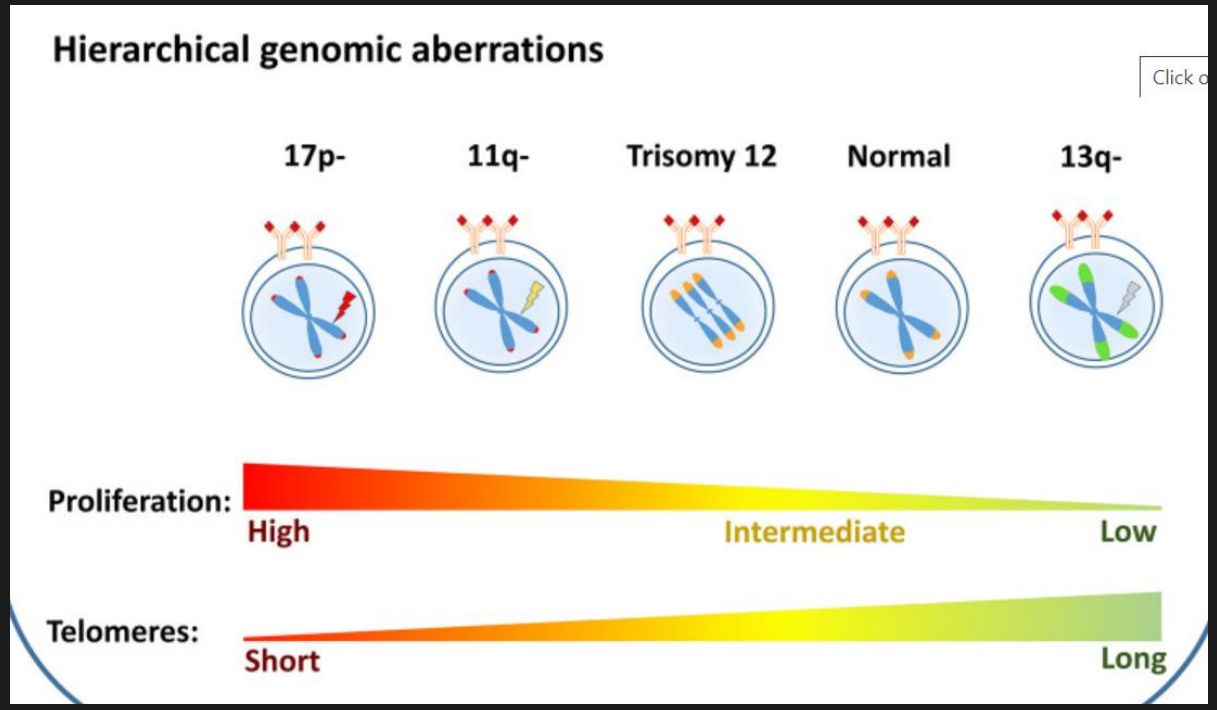
Speedy HE at al, Blood 2016

Shelter proteins

The Shelterin protein complex has a fundamental role in modulating the telomere replication process, in safeguarding the latter from degradation processes and aberrant recombinations, and in regulating telomerase activity.

Telomere length is one of the main element affected in CLL.

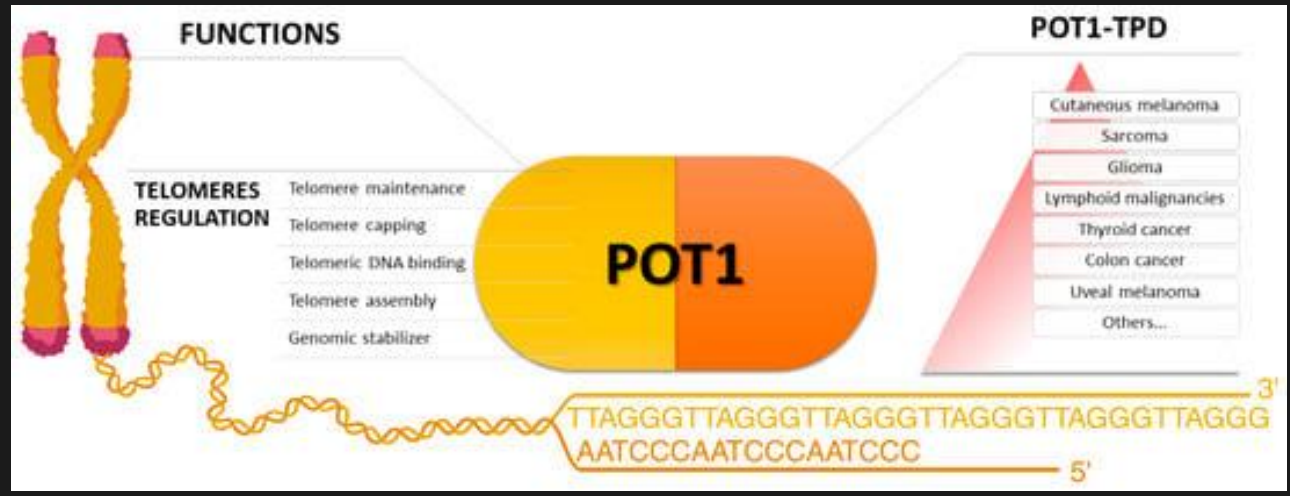
The shorter are the telomere, the higher is the proliferation rate and the aggressiveness of the disease.



POT1, TERT, ACD, and TERF are known to be germline mutated in familial CLL and are involved in the mantenance of telomere lenght.

POT1 mut and familial predisposition in CLL

- *POT1* tumor predisposition (*POT1*-TPD) is associated with an increased risk for multiple cutaneous melanomas, chronic lymphocytic leukemia (CLL), angiosarcoma (particularly cardiac angiosarcomas), and gliomas.
- A 3.6-fold increased risk for CLL was reported for individuals with POT1 germline variant p.Gln376Arg. This cohort also exhibited a younger average age of diagnosis than in sporadic CLL (59 years vs 70 years).



Henry ML et al, GeneRev, 2022

POT1 mut and familial predisposition in CLL

Limited data suggest that a germline POT1 variant occurs in up to 6% of families with familial CLL, while the penetrance is known to be underestimated.

Recommended Surveillance for Individuals with POT1 Tumor Predisposition

- CBC w/differential → Annually beginning at age 18 yrs
- Comprehensive physical exam incl lymph nodes → Annually
- Evaluate results of whole-body MRI for enlarged lymph nodes → When imaging is performed (e.g., in families fulfilling LFL criteria 1)

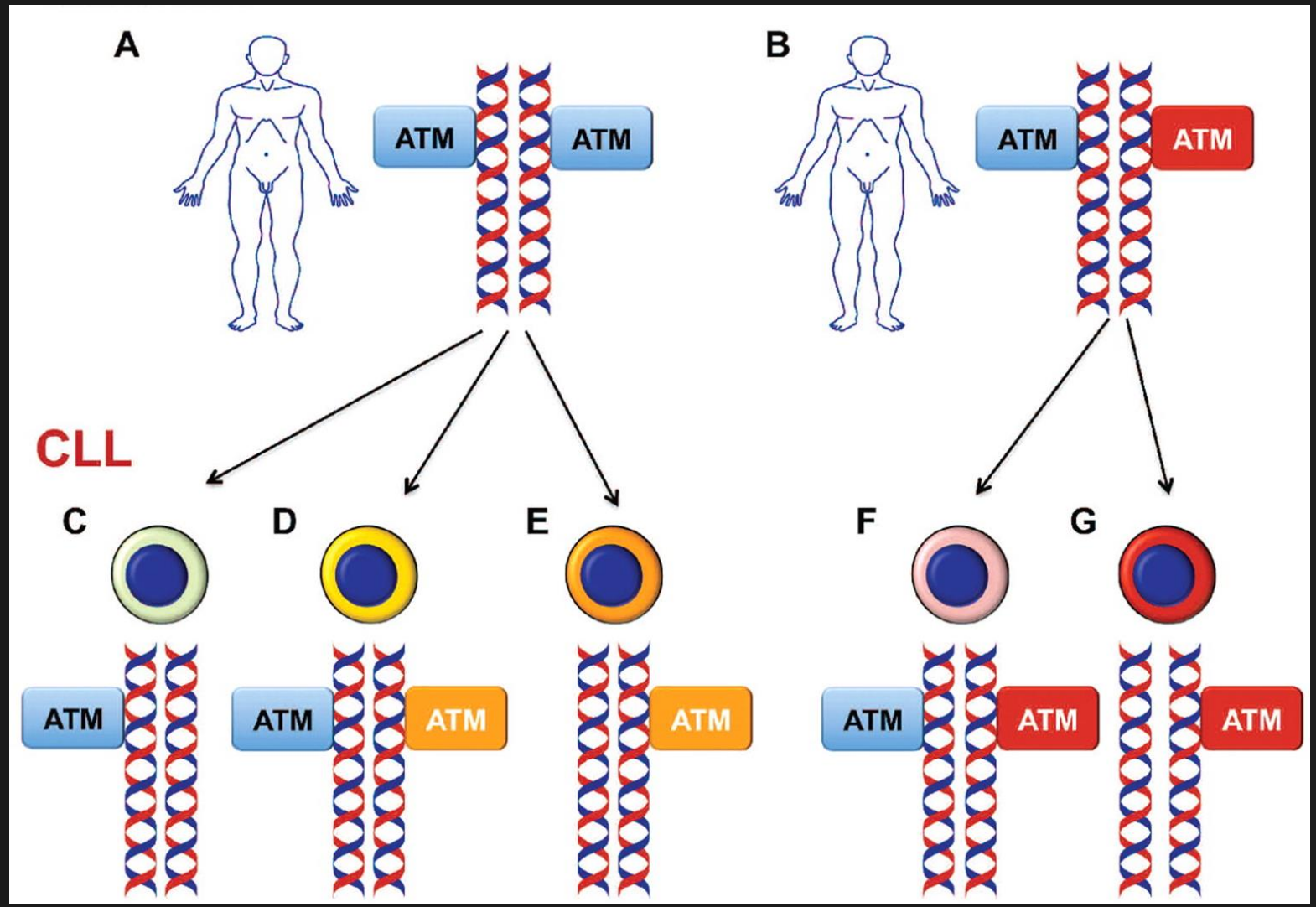
Henry ML et al, GeneRev, 2022

ATM mut and familial predisposition in CLL

- Rare germline *ATM* variants are present in 24% of patients with familial CLL, significantly greater than that in patients with other lymphoid malignancies (16% prevalence), myeloid disease (15%), or no hematologic neoplasm (14%). Patients with CLL with germline *ATM* variants are younger at diagnosis and twice as likely to have 11q deletion.
- The *ATM* variant p.L2307F is present in 3% of patients with CLL, is associated with a three-fold increase in rates of somatic 11q deletion, and is a hypomorph in cell-based assays.
- **Conclusion:** Germline *ATM* variants cluster within CLL and affect the phenotype of CLL that develops, implying that some of these variants (such as *ATM* p.L2307F) have functional significance and should not be ignored.

Lampson BL et al, JCO, 2023

ATM mut and familial predisposition in CLL



Different option of ATM involvement on the basis of germline/somatic variants and 11q deletion

Germline predisposition to myeloid malignancies

WHO Classification (2016)

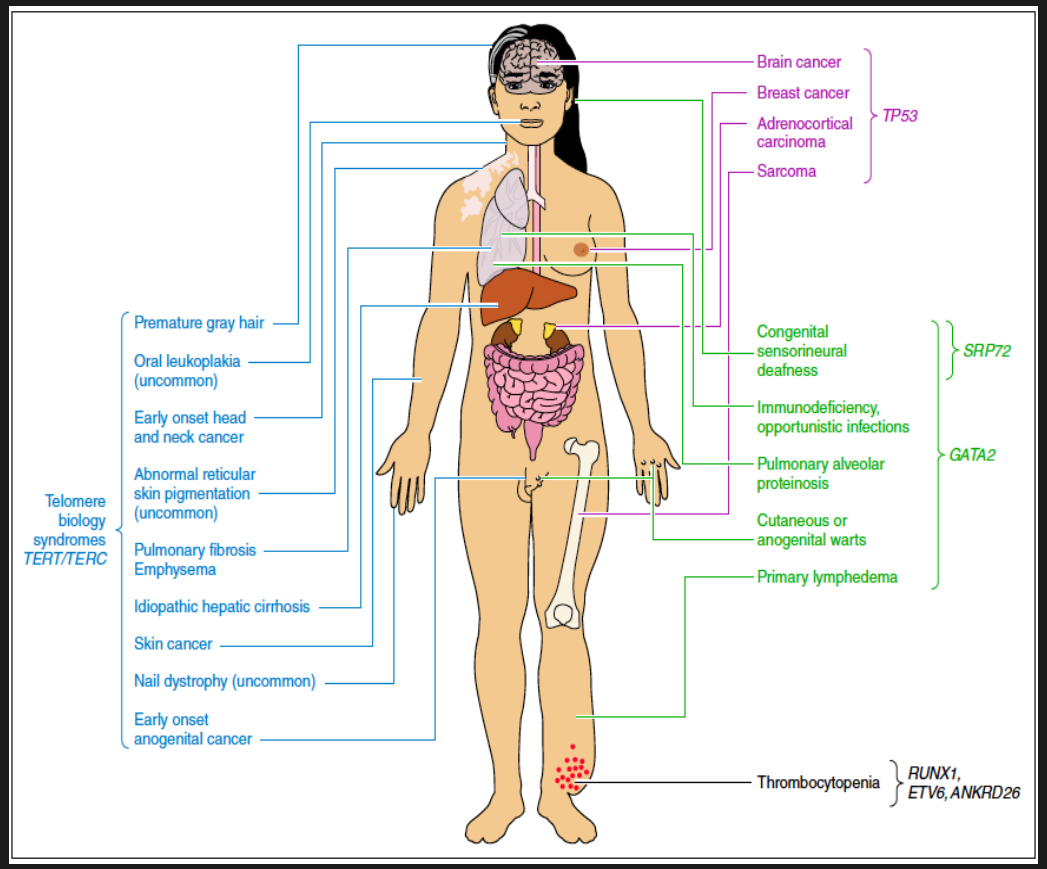
Myeloid neoplasm with germline predisposition without preexisting disorder or organ dysfunction
• CEBPA mutation
1. DDX41 mutation
Myeloid neoplasm with germline predisposition and preexisting platelet disorders
1. RUNX1 mutation
2. ANKRD26 mutation
3. ETV6 mutation
Myeloid neoplasm with germline predisposition and other organ dysfunction
1. GATA2 mutations
2. Telomere biology disorders
• BMFS (Fanconi anemia, dyskeratosis congenital, severe congenital neutropenia, Swachman-Diamond syndrome, Blackan-Diamond syndrome)

CEBPA
DDX41
RUNX1
ANKRD26
ETV6
GATA2
TERT
TERC

Features of proband suspected to be affected by AML/MDSs

- a first- or second-degree family member who has a diagnosis of acute leukemia (AML or ALL), MDSs or other myeloid neoplasms;
- a first- or second-degree family member who has a diagnosis of other hematologic neoplasms;
- a first- or second-degree family member who has a diagnosis of solid tumor that has arisen in age < 40 years;
- presence of signs, symptoms or laboratory tests compatible with one of the known syndromes with germinal susceptibility to AML/MDSs, for example:
  - > History of thrombocytopenia and/or bleeding tendency (as seen in cases with germline mutations of RUNX1, ANKRD26 or ETV6)
  - > cutaneous pigmentation anomalies, oral leukoplakia, nail dystrophy, idiopathic pulmonary fibrosis, idiopathic liver cirrhosis (as seen in cases with germline mutations of TERT and TERC)
  - > Lymphedema, infections by atypical bacteria, immunodeficiency (as seen in cases with germline mutations of GATA2)

The red flags

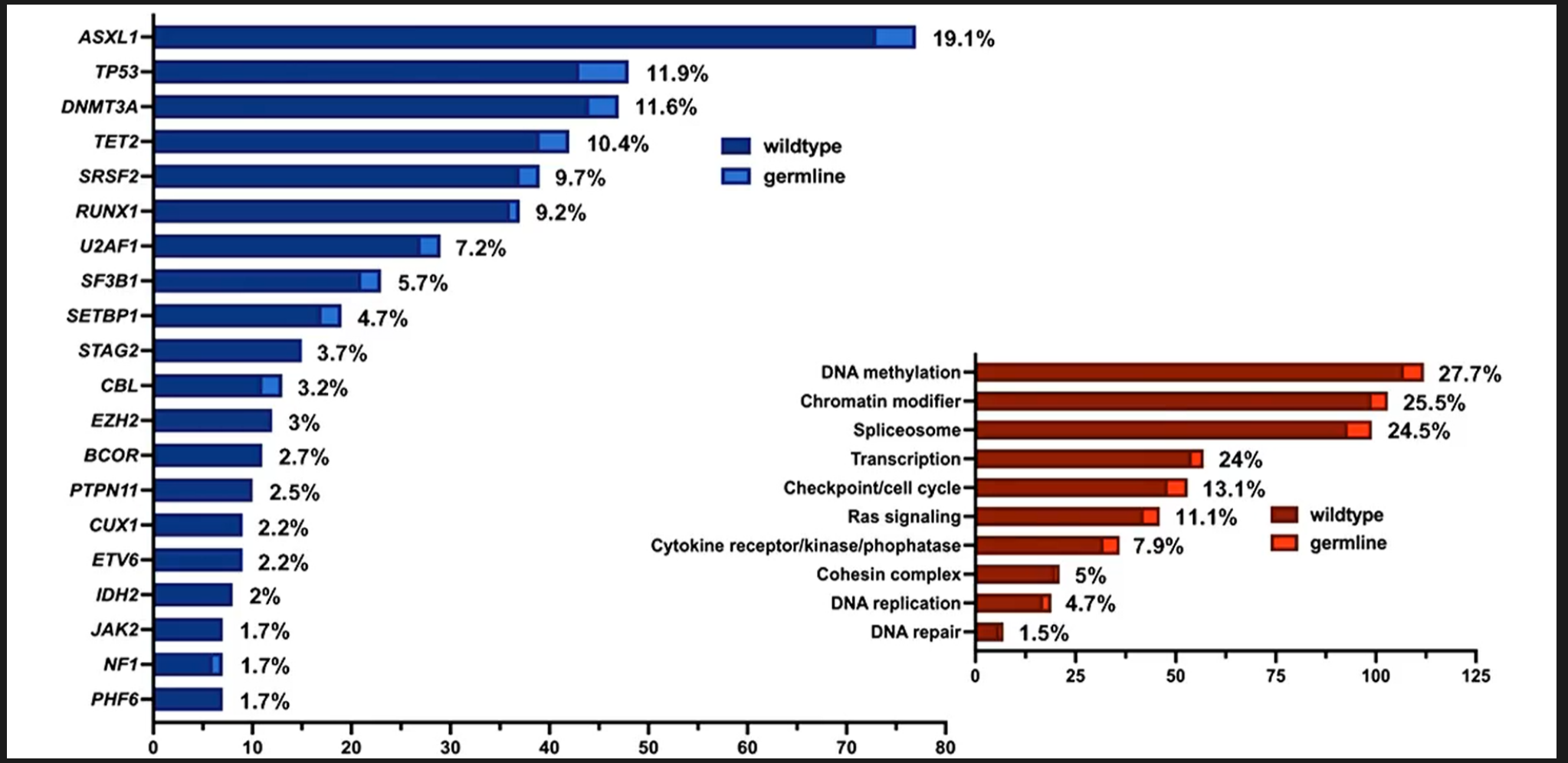


- History of thrombocytopenia and/or clinical bleeding propensity (as in *RUNX1*, *ANKRD26* or *ETV6* germline mutations)

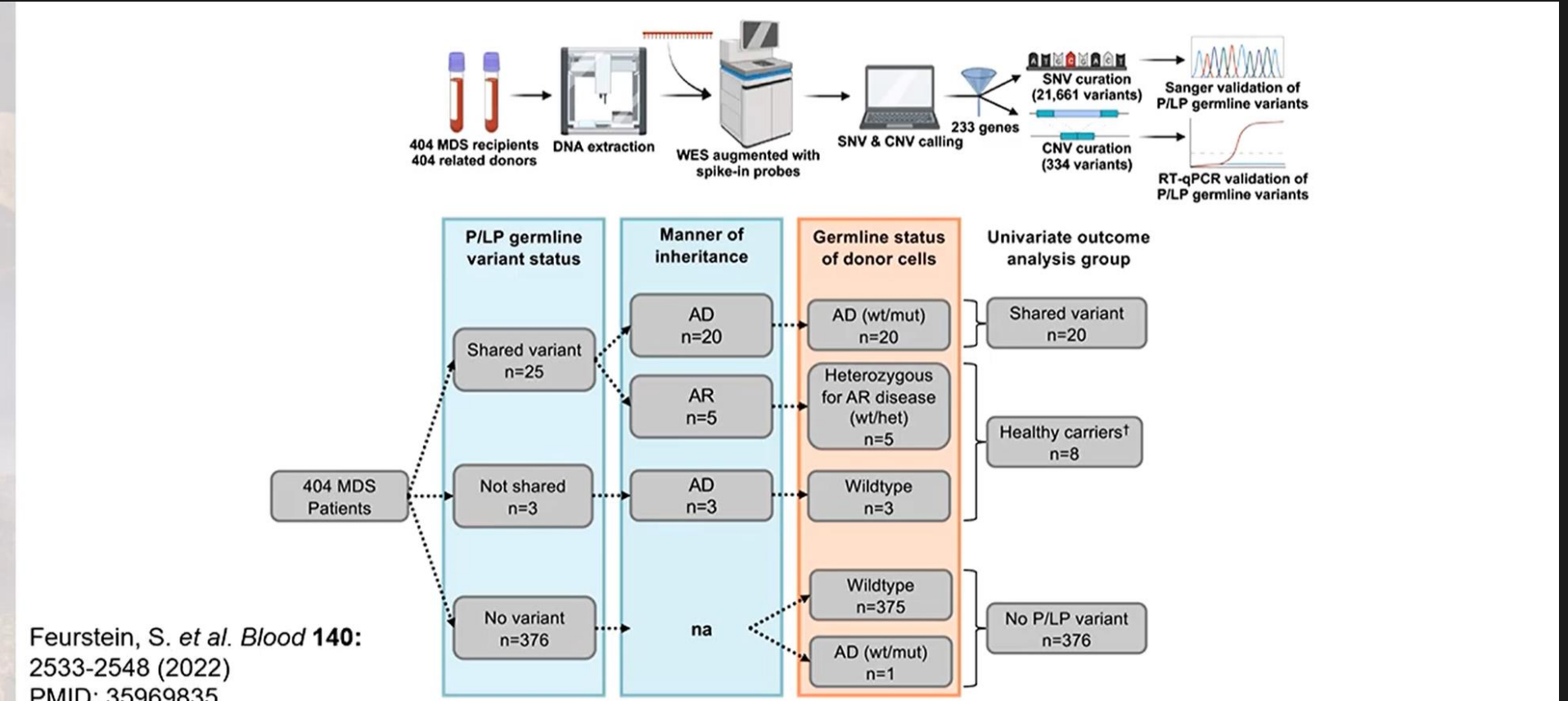
- Abnormal nails or skin pigmentation, oral leukoplakia, idiopathic pulmonary fibrosis, unexplained liver disease (as in *TERT* and *TERC* germline mutations)

- Lymphedema, atypical infections, immune deficiencies (as in *GATA2* germline mutations)

Somatic mutation spectrum is the same that of *de novo* MDS/AML

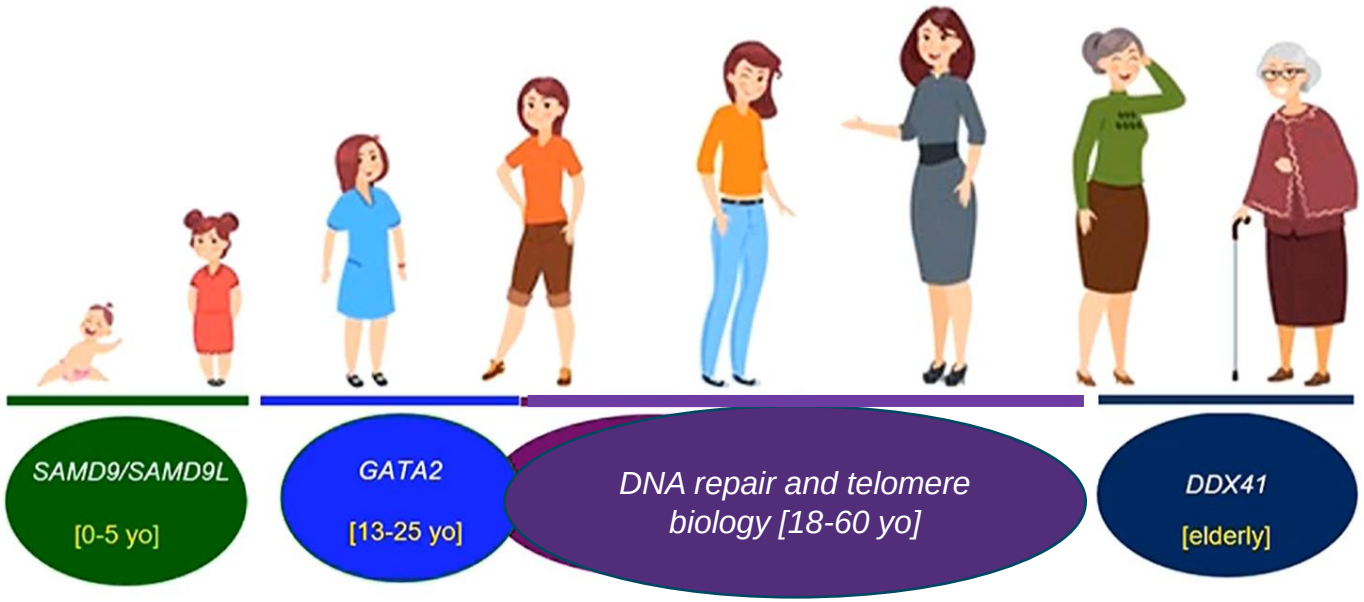


Determining the frequency of deleterious germline variants in MDS



Feurstein, S. *et al*. *Blood* **140:** 2533-2548 (2022)
PMID: 35969835

Age of presentation is a surrogate for the biological pathway



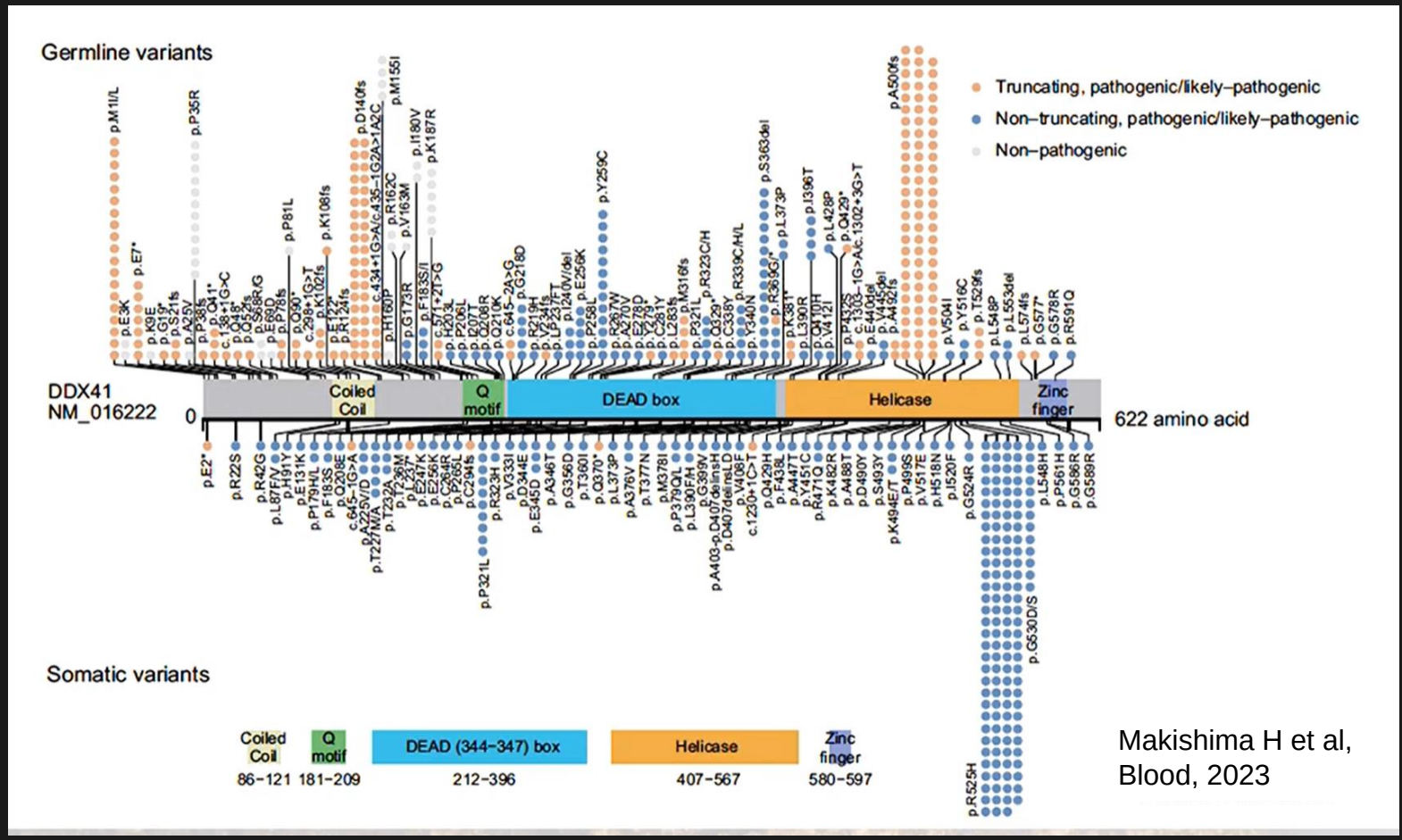
Feurstein, S. *et al. Leukemia* **35:** 2439-2444 (2021)
PMID: 33510405

The strange case of DDX41

DDX41 on 5q35.3 encodes a DEAD/H-Box helicase

Protein involved in the pre-mRNA splicing, translation initiation, ribosome and spliceosome assembly, and in the innate immunity.

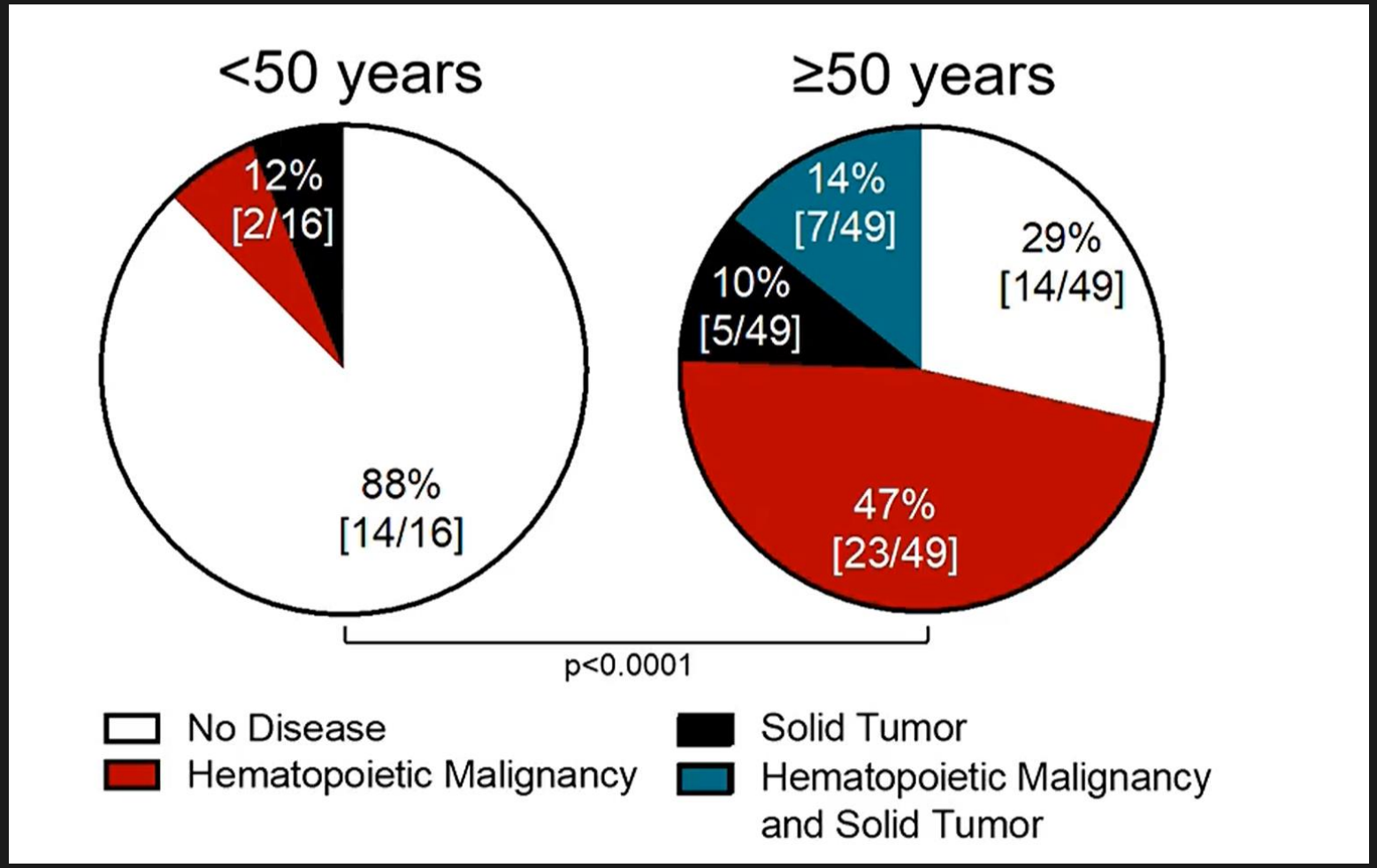
Some members of the DEAD box protein family are believed to be involved in embryogenesis, spermatogenesis, and cellular growth and division.



Makishima H et al, Blood, 2023

Godley, ESH conference, 2023

Germline DDX41$_{mut}$ predispose to late-onset malignancies



Godley, ESH conference, 2023

Clinical Description

- DDX41-associated familial myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) is characterized by an increased risk of myeloid neoplasms, lymphoid neoplasms, adult-onset single- or multiple-lineage cytopenias, male predominance, and red blood cell macrocytosis. To date, more than 200 individuals have been identified with a confirmed or presumed germline disease-causing heterozygous variant in DDX41.
- Prevalence: Approximately 1.5%-6.1% of individuals presenting with MDS/AML have been found to have a germline DDX41 pathogenic variant.
- Penetrance: Only 27%-39% of individuals with a myeloid malignancy and a germline DDX41 variant have a family history of hematologic malignancies.

Churpek JE et al, GeneRev, 2021

Suggestive Findings

Clinical findings

Important info from medical history

Suggestive Findings

Clinical findings

- Myeloid neoplasms. Most common types are MDS, AML, therapy-related myeloid neoplasms, with age of onset typically in the sixth decade.
- Less common myeloid neoplasms include chronic myelomonocytic leukemia, chronic myeloid leukemia, and myeloproliferative neoplasms.
- Lymphoid neoplasms (less common). Types include non-Hodgkin lymphoma (follicular lymphoma most frequent), Hodgkin lymphoma, multiple myeloma, chronic lymphocytic leukemia, and acute lymphoblastic leukemia, with age of onset typically in adulthood.
- Aplastic anemia (rare)

Churpek JE et al, GeneRev, 2021

Suggestive Findings

Clinical findings

Important info from medical history

Laboratory findings

Typical (not absolute!!) characteristic in terms of blood counts and genetic/cytogenetic analysis

Suggestive Findings

Laboratory findings

- Unexplained blood count abnormalities including mild single- or multiple-lineage cytopenias and/or macrocytosis (in 40%-66%)
- In individuals with MDS/AML:
  - Bone marrow hypocellularity
  - Previous history of cytopenia
  - Personal history of hematologic malignancy (including lymphoid) or solid cancer
  - Prominent erythroid dysplasia, in some instances resulting in a French-American-British Cooperative Group AML Classification subtype M6 or erythroleukemia morphology
  - Normal karyotype (in 59%-85%)
  - One or more DDX41 pathogenic variant(s) identified in DNA from malignant myeloid cells. This pattern of a germline variant and a second, acquired variant in DDX41 in malignant myeloid cells occurs in 50%-88% of individuals with MDS/AML who have DDX41-associated familial MDS/AML.

Suggestive Findings

Clinical findings	Laboratory findings	Familiar findings
Important info from medical history	Typical (not absolute!!) characteristic in terms of blood counts and genetic/cytogenetic analysis	Inheritance, penetrance and incidence

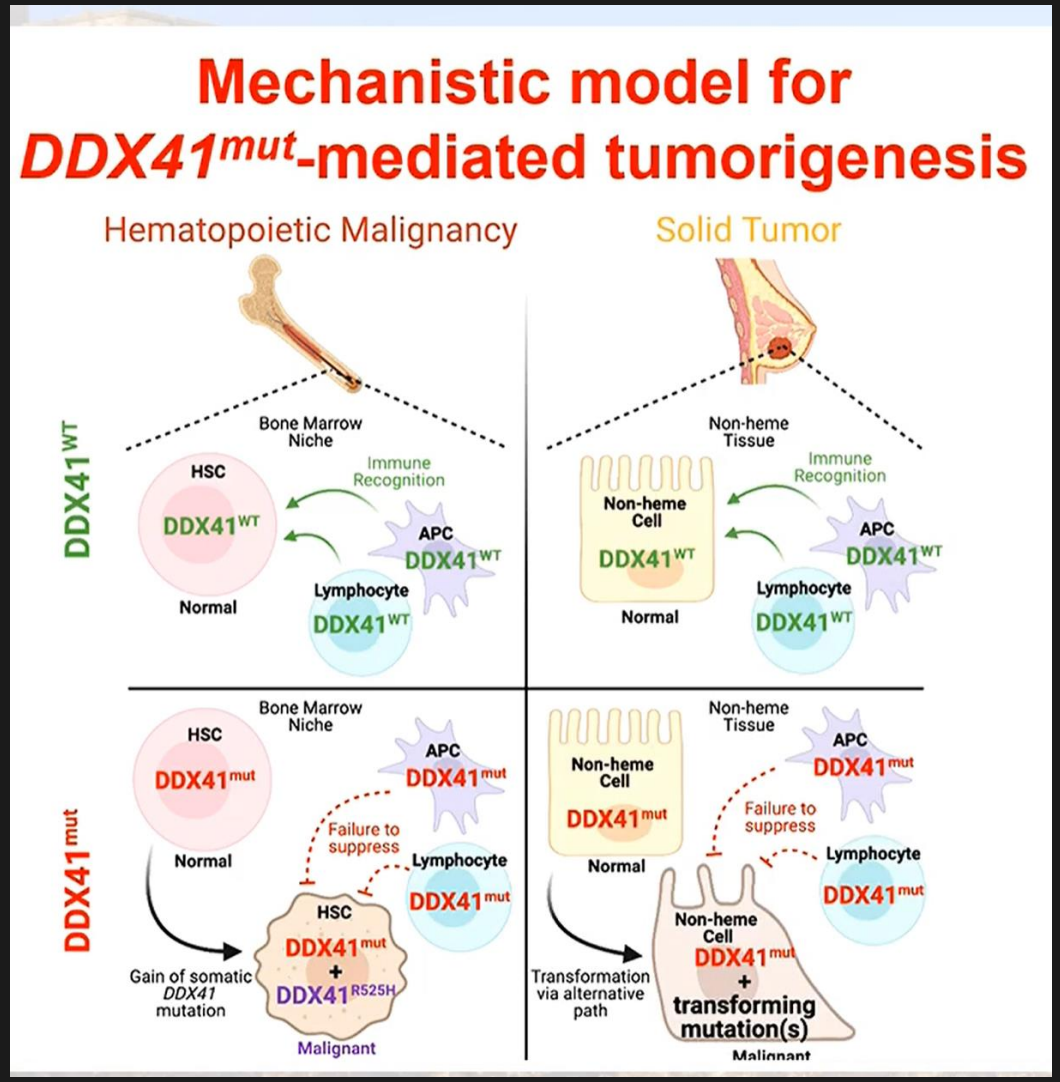
Suggestive Findings

Family history

- It is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations) of hematologic malignancies (especially MDS/AML), unexplained cytopenias, and/or macrocytosis.
- Absence of a known family history does not preclude the diagnosis: only 27%-39% of individuals with a germline DDX41 pathogenic variant have a family history of hematologic malignancies.
- Penetrance of hematologic malignancies appears higher in males than females (3:1) which may result in a male-predominant familial hematologic malignancy pattern

Churpek JE et al, GeneRev, 2021

Mechanistic model for DDX41$_{mut}$-mediated tumorigenesis



Patients with germline DDX41mut present a higher rate of aGVHD when compared with controls

Inflammation?

The impact of the mutations in the trasplant

Some poor outcomes at transplant arise from germline predisposition alleles in the patient/donor

- Severe GVHD [*DDX41*]; effect is ameliorated with post-transplant cyclophosphamide
- Graft failure [*RUNX1, CEBPA*]
- Donor derived leukemias

Therefore, it is important to know the germline mutation status of BOTH the patient/donor!

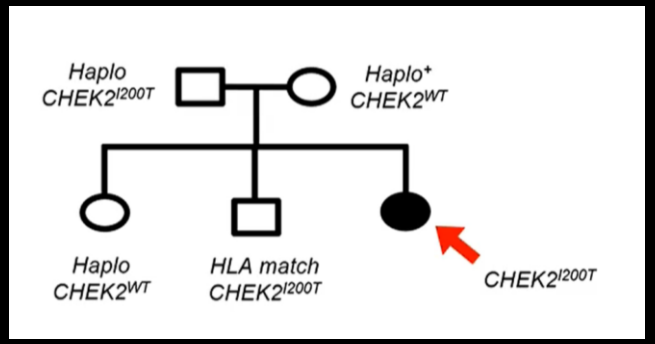
- What are the outcomes of autologous transplants when stem cells with germline mutations are used?

Higher risk of therapy-related leukemias?
Higher risk of relapse?

A clinical case

How old is the patient? 11y old

A new variant identified:



The challenges regarding donor selection...

Familial MPNs

It exists germline variants that can favour the initiation of the disease or may affect its phenotype.

- First, they can be common risk alleles, which correspond to frequent single nucleotide variants present in control population and that contribute to the development of either sporadic or familial MPN.

- Second, some variants predispose to the onset of MPN with a higher penetrance and lead to familial clustering of MPN.

- Finally, some extremely rare genetic variants can induce MPN-like hereditary disease.

Familial MPNs

Familial MPNs often lead to multiple cases of PMF, ET, or PV within the same family. They occur when a specific inherited mutation is passed down from parent to child. About 7% of MPNs are familial MPNs.

Researchers have identified two general types of familial MPNs.

In one type, the condition occurs later in life. People with this disorder have inherited mutations that increase the likelihood of developing the same acquired mutations seen in most other cases of MPNs (mutations in the JAK2, MPL, and CALR genes). Experts aren't always sure which gene mutations cause familial MPNs, but these predisposition factors or pathways could also be involved in the initiation of sporadic cases or other hematological malignancies.

Bellanné-Chantelot C et al, Blood Rev, 2020

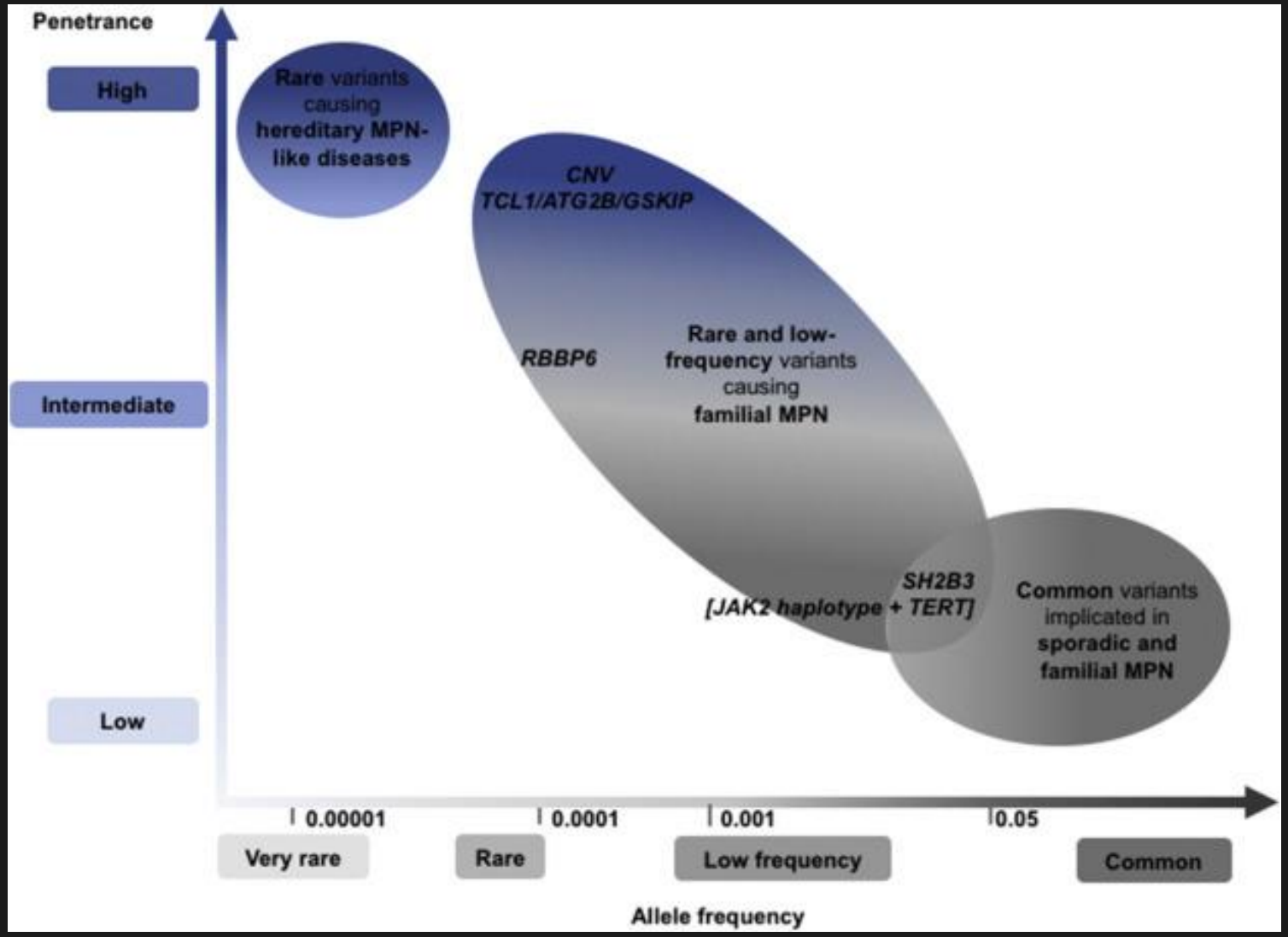
Familial MPNs

In another type of familial MPN, an MPN develops soon after birth or during the early part of a person’s childhood.

Germline Mendelian variants can be responsible for the development of MPN-like diseases transmitted through a complete penetrance. These families correspond to hereditary diseases that are extremely rare and that affect only one myeloid lineage leading to hereditary thrombocytosis, erythrocytosis or neutrophilia and present a polyclonal hematopoiesis contrary to familial MPN. They are generally of good prognosis and not associated with myeloid transformation.

Bellanné-Chantelot C et al, Blood Rev, 2020

Familial MPNs



The genetic test is not required since syntoms, reponse to treatment and disease development are superimposable with ones of sporadic MPNs.

To note that healty relatives of MPNs patients suspected to have a familial MPNs present an 8 fold increased risk to develop an MPNs.

Bellanné-Chantelot C et al, Blood Rev, 2020

Rare germline variants high-risk	Variants	Type of disease(s)
TCL1A/ATG2B/GSKIP	14q32.13-q32.2 700 kb CNV (g.96,163,103_96,857,129dup)	6 families with ET mainly and other hematological myeloid malignancies (PMF, AML, LMMC, MDS)
	14q32 700kb CNV encompassing TCL1A	1 family with 7 cases with PMF, de novo AML and MDS (RARS-T and RCMD-RS)
	14q32 1.8 Mb CNV (chr14:94,387,112_96,219,286dup)	1 family with 4 cases of lymphoma, PMF, de novo and secondary AML and MDS (RS-MLD-RS)
RBBP6	p.R1569H, p.E1654G, p.R1451T	PMF families, associated with JAK2 haplotype and TERT rs2736100
ZXDC, ATN1 and LRRC3 (potential candidates)	ZXDC (p.P644R), ATN1 (p.R234Q) and LRRC3 (p.R234Q)	One PV family
Extremely rare germline variant causing MPN-like hereditary diseases	**Variants**	**Type of disease(s)**
EGLN1 (PHD2) (AD)	p.P317R ; More than 25 mutations	Hereditary erythrocytosis
EPAS1 (HIF2A) (AD)	Around 10 mutations	Hereditary erythrocytosis
EPO (AD)	p.W11fs and p.P7fs EPO (AD) p.W11fs and p.P7fs	Hereditary erythrocytosis
EPOR (AD)	More than 20 truncating mutations	Hereditary erythrocytosis
SH2B3 (LNK)	p.E208Q, p.E400K	Hereditary erythrocytosis
VHL (AR)	p.R200W + more than 15 other mutations	Hereditary erythrocytosis
	Complex splicing defects (new pseudo-exon 1) and in exon 2 (Synonymous variant)	Hereditary erythrocytosis
JAK2 (AD)	p.T108A, p.L393V	Hereditary erythrocytosis and thrombocytosis
	p.R564Q	Hereditary thrombocytosis
	p.H608N	Hereditary thrombocytosis
	p.L611S	Congenital thrombocytosis
	p.V617I	Hereditary thrombocytosis
	p.S755R, p.R867Q, p.R938Q	Hereditary thrombocytosis
	p.R867Q	Hereditary thrombocytosis with PV progression
	p.E846D, p.R1063H	Hereditary erythrocytosis and thrombocytosis
MPL (AD, AR)	Homozygous p.K39N (Baltimore polymorphism)	Hereditary thrombocytosis
	Heterozygous p.R102P	Hereditary thrombocytosis
	Homozygous p.P106L	Hereditary thrombocytosis
	Heterozygous p.S505N	Hereditary thrombocytosis
	Heterozygous p.W515R	Hereditary thrombocytosis
THPO (AD)	5’UTR and variants affecting donor splice site of exons 2 and 3	Hereditary thrombocytosis
CSF3R (AD)	p.T640N	Hereditary neutrophilia