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Cytogenetics in the management of hematologic neoplasms with germline predisposition: guidelines from the Groupe Francophone de Cytogénétique Hématologique (GFCH)

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ABSTRACT

The number of predisposing genes is continuously growing with the widespread availability of DNA sequencing, increasing the prevalence of hematologic malignancies with germline predisposition. Cytogenetic analyses provide an effective approach for the recognition of these malignancies with germline predisposition, which is critical for proper diagnosis, optimal treatment and genetic counseling.

Based on the World Health Organization and the international consensus classifications as well as the European LeukemiaNet recommendations, this review first presents an advanced classification of neoplasms with germline predisposition focused on the acquired cytogenetic alterations during leukemogenesis.

The various genetic rescue mechanisms and the progression to transformation are then explained. The review also outlines the specific constitutional and somatic cytogenetic aberrations indicative of germline predisposition disorders in B-acute lymphoblastic leukemia (ALL), T-ALL, bone marrow failure syndrome and myeloid neoplasms. An emphasis is made on monosomy 7 in the predisposition field, its frequency and diagnosis impact as well as its various circumstances of occurrence. Lastly, we propose cytogenetic technical recommendations and guidelines for clinical reporting of these specific aberrations.

Introduction

Hematologic cells can harbor two kinds of genetic abnormalities: first of all, the germline abnormalities from parental germ cells present in every cell of the body, also called constitutional abnormalities, some of which being responsible for inherited germline predisposition to hematopoietic malignancies and secondly, the somatic abnormalities appearing mainly during the cancer development as secondary events restricted to the hematological lineage, as acquired genetic alterations. These germinal and somatic abnormalities can be cytogenetic abnormalities (CA) such as +21 or gene abnormalities, also called pathogenic variants [1].

Although considered rare and restricted to pediatric patients, familial hematologic cancers have long been known. However, the widespread availability of high throughput sequencing has revealed new predisposing genes, primarily *DDX41* in the elderly population with a prevalence of 3 % among all myeloid neoplasms (MN). Germline predisposition to hematologic malignancies is a recent concept poorly integrated into current practice for many reasons, such as the large age spectrum at time of onset, the complex landscape of germline variants, heterogeneous clinical presentation from syndromic disorders to pure hematologic malignancy or the lack of consensus recommendations for most of the predispositions. Moreover, the majority of germinal predisposition genes are often involved in oncogenic process with acquired somatic alterations of important diagnostic and prognostic value. In addition, DNA sequencing in the molecular genetic assays is now a routine procedure and the most frequent germinal predisposition genes are included in the design of genetic panels for somatic mutation analysis.

Germinal predisposition impacts the management of both the patients and their families. For the patient, germinal predisposition identification results in a proper diagnosis, the most suitable follow-up and an appropriate treatment in case of increased toxicities due to the germinal predisposition. When hematopoietic stem cell transplantation (HSCT) is proposed, germinal predisposition could affect the conditioning regimens and the donor selection. For their relatives, germinal predisposition identification allows the genetic counselling and the identification of high-risk families.

To date, as new genes are continuously reported, knowledge of their location is crucial for cytogenetic analysis in regard to the existence of some alterations too large to be detected by sequencing analysis or the possibility of somatic cytogenetic rescue (Fig. 1).

Classifications of germline predispositions for hematological neoplasms

Hematologic neoplasms related to germinal predisposition are mainly MN including myelodysplastic neoplasms (MDS) and acute myeloid leukemia (AML) and in a lesser extent acute lymphoblastic leukemia (ALL) mainly with a B-cell phenotype (B-ALL). About 5 to 15 % patients with MDS or acute leukemia may have a germinal predisposition to MN. The percentage may be lower for lymphoid diseases [2–6]. A

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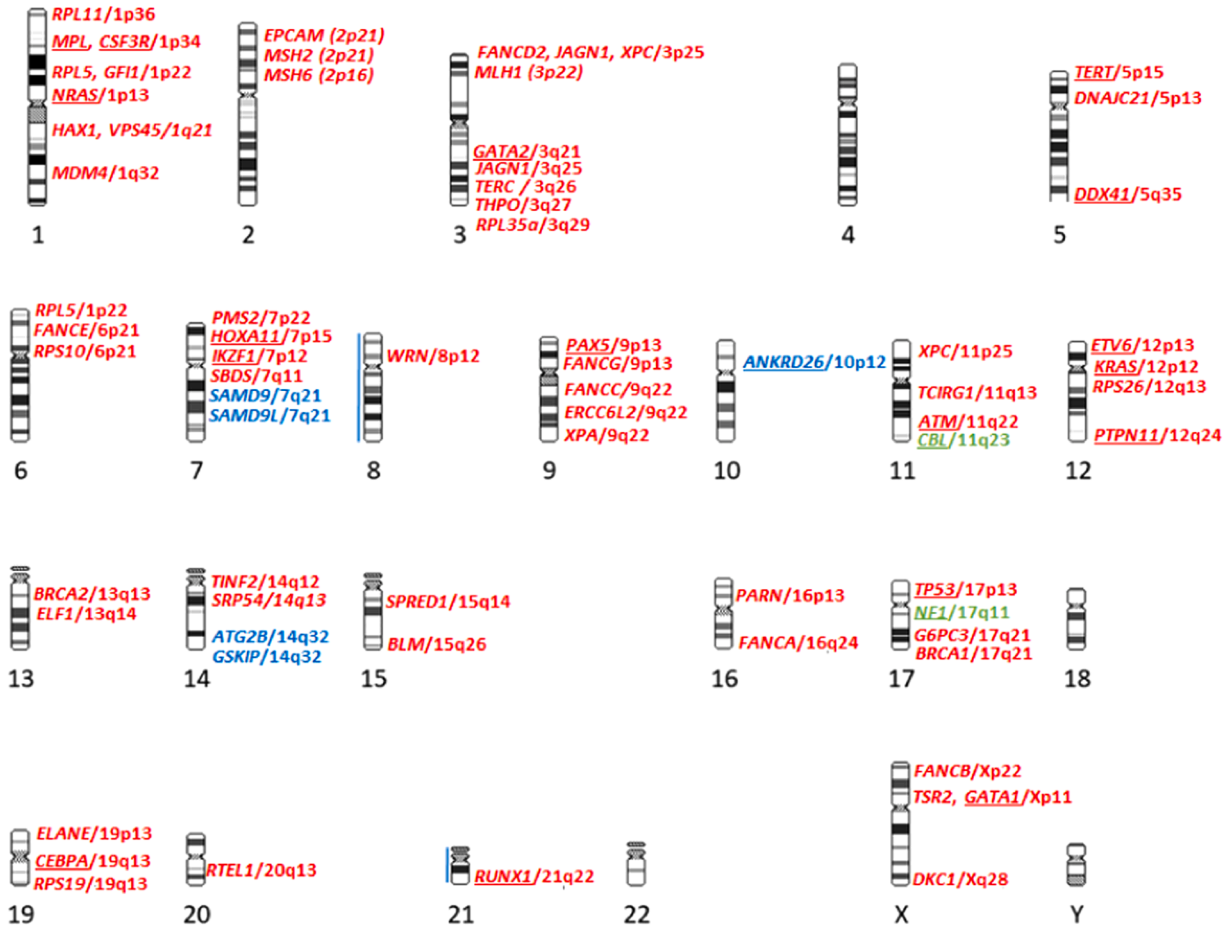

Fig. 1. Chromosomal location of main genes associated with germline predisposition for hematologic neoplasms based on Schlegelberger et al. 2021 [4], red: genes with loss of function, blue: genes with gain of function, green: genes frequently reported with uniparental disomy (UPD), blue lines represent total, partial or mosaic trisomy, underlined genes also present somatic mutations in hematological neoplasms.

large amount of published data has led to the MN with germinal predisposition being integrated as a distinct entity in the 2016 WHO revision of the classification of tumors of hematopoietic and lymphoid tissues [7].

MN with germinal predisposition can be split into three subgroups according to clinical and biological presentation observed before the occurrence of the hemopathy: the first group comprises the MN with germline predisposition without any preexisting disorder. In this case, only the family history can suggest a genetic disorder, as there are no personal clinical or pathological clues. This group comprises the germline variants of *CEBPA* and *DDX41*. The second group corresponds to the familial thrombocytopenias and contains the germline variants of *RUNX1, ANKDR26* and *ETV6*. The third group consists of genetic diseases with multiorgan dysfunction, including GATA2 deficiency, inherited bone marrow failure syndromes (IBMFS), telomeropathies, RASopathies and Down syndrome (DS). In this last group, the germline genetic abnormality is most frequently identified before the onset of the hematological malignancy, which allows the follow-up of patients and an early neoplasm diagnosis. This extended monitoring of patients led to propose some models of leukemic transformation such as in Fanconi anemia (FA) [8].

In the latest World Health Organization (WHO) 2022 classification (5th WHO edition), the chapter of MN with germline disposition was moved into the new subgroup of secondary MN [9]. This edition also spotlights the genetic diseases by using the widely used germline variant term instead of germline mutation and specifying the genetic disease instead of neoplasms. Specifically, the Li Fraumeni syndrome (LFS), despite predisposing to multiple cancers, is added to the first group because some patients present *de novo* acute leukemia without any history of solid tumors and the LFS diagnosis is established during leukemia therapy [10]. Furthermore, in the third group, the 2022 WHO edition emphasizes on IBMFS, adding the severe congenital neutropenia, Shwachman-Diamond syndrome (SDS) and FA and adds three new genetic disorders: SAMD9 and SAMD9L syndromes and Bloom syndrome.

Beside the WHO classification, other groups have made their own proposals on hematological neoplasms with germline predisposition. In the International Consensus Classification (ICC) of MN and acute leukemia, Arber et al. emphasizes that germinal predisposition is not only restricted to the myeloid lineage, but can involve the lymphoid one too, consequently both are specified in their classification [11]. This classification specifies the existence of hematological abnormalities linked to the germline disease apart from any neoplasia. These baseline changes overlap with genetic and morphologic features of malignant transformations, such as dysplasia. They are typical of SDS with incomplete nuclear segmentation of neutrophils or megakaryocytes and monoallelic *TP53* inactivation whereas *TP53* biallelic mutation in this context is associated to MN. The European LeukemiaNet group, in agreement with the WHO proposals, discusses two new subtypes of MN with germline predisposition: first, those with a gene predisposing to multiple cancer types including MN and second, emerging disorders not yet classified because of the limited number of published cases [12].

Finally, there are some other not yet classified neoplasms with germinal predisposition because of recent or unclarified reported data such as predisposition familial myeloproliferative neoplams (MPN) [11, 13]. Indeed, familial predisposition to MPN is a complex concept. Familial MPN occurs when one or several MPN affect different relatives of

the same family. The germline variants are responsible for a phenotypic diversity in MPN within the same family and can be classified into three different groups: the first one contains frequent single nucleotide variants (SNV) present in control population with a low risk to the development of MPN by promoting *JAK2 V617F* or *CALR* mutation. These common variants are implicated in sporadic and familial MPN at low frequency [14]. The second group contains rare predisposing germline variants with a higher penetrance. The chromosome 14q32 duplication is the most well documented with 9 described familial MPN [15]. The last group contains extremely rare variants responsible for non-clonal MPN-like diseases such as hereditary erythrocytosis with germline variants of *EPO, EPOR* or *SH2B3* (see [14] for review).

Integrating all of these concepts into Table 1, this article proposes a list of predisposition genes in familial neoplasms grouped by categories of the resulting neoplasms, subcategorized by the main feature of the genetic disease and including cytogenetic alterations acquired during leukemogenesis as well as clinical phenotypes and inheritance pattern.

Cytogenetic abnormalities in hematological neoplasms with germline predisposition

Cytogenetic analyses provide an effective approach for the detection and monitoring of patients in several circumstances:

- Among somatic CA evidenced by chromosomal banding analysis, constitutional abnormalities can also be detected, in particular some predisposing to hematological malignancies such as +21.
- Certain types of acquired abnormality are strongly associated with germinal predisposition syndromes.
- Some acquired abnormalities can reveal a rescue mechanism. Indeed, a spontaneous additional somatic mutation can repair or compensate the causal inherited mutation. In FA, 20 % of patients appear to benefit from genetic instability since the latter also increases the chance of somatic reversions of their germline mutations [16]. This natural self-correction is sometimes visible in cytogenetic analyses.
- Cytogenetic analyses can more rarely detect co-occurring somatic second allele inactivation of the predisposing gene. In those cases, the second somatic hit is only detectable in cytogenetic analyses.
- Cytogenetic analyses are often very useful for the detection of sequential or multiple somatic abnormalities associated with progression. In many neoplasms with germinal predisposition, a complex karyotype (CK) is associated with AML transformation.
- During the monitoring following allogeneic HSCT, the identification of new CA contributes to the differential diagnosis between relapse and donor cell leukemia, especially when the predisposition was unknown in the donor at the time of the transplantation.

Germline predisposition with constitutional cytogenetic abnormalities

To our knowledge, among CA evidenced by chromosomal banding analysis, only constitutional CA involving chromosomes 21 and 8 can constitute a predisposing factor for hematological malignancies.

Constitutional trisomy 21 (Down syndrome)

Children with Down syndrome (DS) due to constitutional +21 have an increased risk of developing AML (especially megakaryoblastic differentiation AML (AMKL)) or B-ALL (150-fold and 33-fold respectively) [17,18].

About 25 % of DS newborns present a transient abnormal myelopoiesis (TAM) characterized by an acquired *GATA1* mutation, which can evolve in 10 % of cases into an AMKL occurring before the age of 5 years. These AML are referred in the 5th WHO classification as “myeloid leukemia associated with Down syndrome” [9]. They are associated with a good prognosis [19]. Among patients presenting AMKL or TAM, the frequency of mosaicism and other atypical rearrangements of chromosome 21 is found to be high [20]. Thus, the occurrence of AMKL with *GATA1* mutations may lead to the detection of previously unknown constitutional mosaicism for +21 in patients with normal phenotypes [21–23]. Based on these results, it is suggested that constitutional studies be performed for all patients with AMKL/TAM with *GATA1* mutation [21,23] in search of mosaicism or other atypical chromosome 21 rearrangements.

In contrast, DS-ALL have a poorer prognosis due to specific cytogenetic features and increased toxicity of therapies. The overwhelming majority of DS-ALL are of B lineage. As compared to non-DS-ALL, they present a lower frequency of good risk CAs such as high hyperdiploidy and *ETV6::RUNX1* fusion (11 % and 10 %, respectively) and of poor risk CAs such as *KMT2A* rearrangements and *BCR::ABL1* fusion [24]. Conversely, a higher frequency (40 %) of normal karyotypes (no other CA in addition to the constitutional +21) and cryptic *CRLF2* rearrangements (60 % of cases vs 10 % in non-DS ALL) are frequently associated with *JAK2* mutation as Ph-like JAK-STAT type ALL, with frequent *IKZF1* and *PAX5* deletion [25] (for review [26]).

Robertsonian translocations involving chromosome 21 and constitutional ring 21

Apart from DS, other constitutional abnormalities involving chromosome 21 are associated with a high risk B-ALL subtype, B-ALL with intrachromosomal amplification of chromosome 21 (iAMP21) because they can initiate the formation of chromothripsis leading to iAMP21 (see joint dedicated ALL article) [27,28]. iAMP21 is defined as greater than or equal to three extra copies of the *RUNX1* gene on a single abnormal chromosome 21. There are unusual cases of iAMP21 where the extra *RUNX1* copies are either less numerous or located on another abnormal chromosome [28]. iAMP21 corresponds to a complex structure of one copy of chromosome 21q comprising multiple regions of gain, amplification, inversion or deletion. This abnormality is detectable by cytogenetic analysis, fluorescence in situ hybridization (FISH), molecular analyses (CGH or NGS) or optical genome mapping technology.

- **Robertsonian translocations:** (rob) they can occur between short arms of acrocentric chromosomes 13, 14 or 15 and chromosome 21 or 22 leading to whole-arm chromosomal translocations (Fig. 2A) [27]. The rob(13;14)(q10;q10), is the most common, comprising about 74 % of them. In contrast, the rob(15;21)(q10;q10) is rare: about 0.5–1 % with an incidence of 1 per 100,000 to 200,000 births [28]. In an international study, out of 530 cases of B-ALL with iAMP21, 4 cases (0.8 %) of rob(15;21) were identified [29]. For rob (15;21), the increased risk of developing B-ALL with iAMP21 was estimated to be approximately 2700-fold. Of note, 2 cases of rob (14;21) were also identified in this study but the abnormal rob (14;21) chromosome was not involved in the mechanism of iAMP21.
- **Ring of chromosome 21** or r(21)c was identified in 3/530 cases, i.e. 0,6 % of the above-mentioned international study but this incidence is difficult to evaluate in the general population because many carriers of a ring 21 are asymptomatic. Indeed, this structural abnormality leads to a fragility of the abnormal chromosome 21, derivative 21 or der(21), which will undergo successive break-fusion-bridge phenomena that can lead to chromothripsis of the long arm of chromosome 21 [27].

Constitutional trisomy 8 mosaicism

Constitutional trisomy 8 mosaicism (mos +8c) occurs in around 1:25,000 newborns whereas the complete +8 remains even less frequent because it is not usually compatible with life [30]. Several cases of AML and MDS appearing in patients with a mos +8c have been described in the literature. Hence, mos+8c is suspected to be a predisposing factor for cancer ([31,32] for review). The main difficulty is the distinction between a constitutional mosaic form and an acquired +8. Indeed, +8 is one of the most frequent secondary CA found in MN (for more details, see joint dedicated article on Clonal Chromosomal Abnormalities of undetermined Significance). Acquired +8 is restricted to the malignant cells whereas constitutional +8 can be seen as a mosaic in blood, in bone

Table 1
Germline syndromes predisposing to hematological malignancies.

Gene (localization) / Syndrome name	Acquired cytogenetic alterations during leukemogenesis	Hematologic pathologic features (less frequent or sporadically reported)	Inheritance Penetrance of neoplasm (level or%)	Age of hematologic neoplasm onset (median) (years)	Clinical features	Refs.
1 - Myeloid neoplasms with germline predisposition						
1.1 - Hematologic neoplasms with germline predisposition without a preexisting platelet disorder or organ dysfunction						
* *DDX41* (5q35.3) / **Familial AML with *DDX41* mutation** (OMIM #616871)	Normal karyotype (75 %) or +8, −5/del(5q), −7/del (7q), del(20q), CK	AML generally hypocellular or with erythroleukemia or high-grade MDS with prominent erythroid dysplasia; CMML, CML, MDS/MPN, lymphoproliferative disorders, frequently second somatic DDX41 mutation (R525H); Potentially non-hematopoietic neoplasms	AD High	6–93 (66)	Long latency, male predominance, gradual cytopenia	[6,12, 62,72]
* *CEBPA* (19q13.1) / **Familial AML with *CEBPA* mutation** (OMIM #601626)	Normal karyotype, −7 (1–5 %)	AML (FAB M1/2), Auer rods seen in blasts, aberrant CD7 expression, CEBPA biallelic mutation, somatic mutations reported (GATA2, WT1, EZH2, TET2, NRAS); Favorable long-term outcome with 10-year OS of 67 %; Without allogeneic HCT possibilities of additional malignancies	AD Almost 100 % for germline 5′-end variant, lower for 3′-end variants	2–46 (25)	No predisposition to other cancers	[6,12, 57,62, 69,72, 73]
1.2 - Hematologic neoplasms with germline predisposition with pre-existing platelet disorder						
* *RUNX1* (21q22.1) / **FPD/AML** (OMIM #601399)	Normal karyotype, +21; AML: clonal with +8 (50 %), rarely −7	Bone marrow premalignancy with dysmegakaryopoiesis; MDS, AML with blast with Auer rods and CD7 aberrant expression, T-ALL, HCL, CMML	AD 35–50 %	5–77 (33)	Preceding thrombocytopenia, qualitative platelet defects	[6,12, 72–74]
* *ANKRD26* (10p12.1) / **Thrombopenia 2** (OMIM #188000)	Not reported	AML,MDS (CML, CLL)	AD <10 %	20–70	Moderate thrombopenia (normal platelet size), megakaryocytic dysplasia, increased plasma thrombopoietine, platelet dysfunction, mild spontaneous bleeding	[6,12, 69,75]
1.3 - Hematologic neoplams with germline predisposition and potential organ disorder						
* *GATA2* (3q21.3) / **GATA2 haploinsufficiency syndrome**	−7, +8, der(1;7) (q10;p10), +21, del (20q)	MDS (75 %), AML (20 %), CMML (3 %), B-ALL	AD 90 %	0.4–78 (20)	Overlapping phenotypes: - Emberger syndrome (OMIM#614038), lymphedema and monosomy 7) - MonoMAC syndrome (OMIM#614172), monocytopenia and Mycobacterium avium complex infection or DCML, dendritic cell, monocyte, B and natural killer (NK) lymphoid deficiency) - Familial MDS/AML (OMIM#601626), bone marrow failure, Thrombosis, recurrent bacterial, fungal and viral infections	[6,12, 59,62, 66,69, 76]
* *SAMD9* (7q21.2) / **MDS and leukemia syndrome with monosomy 7** (OMIM#252270), SAMD9 syndrome	−7 (possibly transient), del(7q), UPD(7q), CK	Transient cytopenia, pancytopenia, clonal hematopoiesis with monosomy 7, MDS, AML	AD 70 %	Childhood (1)	Mirage syndrome (OMIM#617053), infection, restriction of growth, adrenal hypoplasia, genital phenotypes, enteropathy	[5,61, 62,64, 77,78]
* *SAMD9L* (7q21.2) / **MDS and leukemia syndrome with monosomy 7** (OMIM#252270)				Childhood (1)	Ataxia pancytopenia syndrome (OMIM#159550), cerebral calcifications, systemic autoinflammatory disease	

(*continued on next page*)

Table 1 (*continued*)

Gene (localization) / Syndrome name	Acquired cytogenetic alterations during leukemogenesis	Hematologic pathologic features (less frequent or sporadically reported)	Inheritance Penetrance of neoplasm (level or%)	Age of hematologic neoplasm onset (median) (years)	Clinical features	Refs.
1.3.1 - Inherited bone marrow failure syndromes						
* FANC A-W (22 genes including *FANCA (16q24.3), FANCC (9q22.3), FANCG* (9p13.3), *FANCD2* (3p25.3), BRCA1 (17q21.3), BRCA2 (13q13.1)) / **Fanconi anemia** (OMIM#227650)	+1q, del(6p), del (20q); MDS/AML: +3q, del (7q), CK, *RUNX1* alteration	Bone marrow failure, clonal hematopoiesis, MDS, AML	AR, AD, XL BMF: 80 % by age 10 years MDS/AML: 10–30 %	0,1–49 (13)	Pancytopenia, congenital abnormalities (abnormal thumbs), chromosome breakage, cancers(squamous cell carcinoma), sensitivity to genotoxic agents	[12,13, 50]
* 30 genes including ***ELANE*** (19p13.3), *G6PC3* (17q21.3), *GFI1* (1p22.1), *HAX1* (1q21.3), *JAGN1* (3p25.3), *TCIRG1* (11q13.2), *SRP54* (14q13.2), *CSF3R* (1p34.3), *VPS45* (1q21.2)/ **severe congenital neutropenia**	−7, del(7q), +21	Preceding neutropenia; MDS, AML (except for SRP74 and CSF3R when biallelic variants); MM, ALL (*CSF3R*)	AD, AR (*HAX1, G6PC3, CSF3R*)	2–49 (12)	Sever opportunistic infections without growth factor support, lymphopenia and immunodeficiency (GIF1), osteopenia (ELANE), seizures and other neurologic disorders (HAX1), congenital cardiac malformations and genitourinary abnormalities (G6PC3)	[5,12, 62,79]
** **ribosomal protein genes**: all RPL et RPS genes (including *RPS19* (19q13.2), *RPL5* (1p22.1), *RPS26* (12q13.2), *RPL11* (1p36.1), *RPL35a* (3q29), *RPS10* (6p21.31) and others genes (*GATA1* (Xp11.23), *TSR2* (Xp11.23)) / **Diamond-Blackfan anemia** (OMIM#105650)	Not described	Early-onset aregenerative macrocytic anemia: normocellular bone marrow with erythroid hypoplasia; MDS, AML (HL, NLH, ALL)	AD, X-linked (*TSR2*)	2–24	Short stature, failure to thrive, abnormal facies, abnormal thumb, limb abnormalities, cardiac structural abnormalities, genitourinary abnormalities, hypogammaglobulinemia, lymphopenia, solid cancer (soft tissue sarcomas), elevated Hemoglobin F, elevation of erythrocyte adenosine deaminase enzyme	[5,80]
* ***SBDS*** (7q11.21) **(95 %)**, *DNAJC21* (5p13.2), *ELF1* (13q14.1), *SRP54* (14q13.2) / **Shwachman-Diamond syndrome** (OMIM#260400)	iso7q, −7, del(20q) without prognosis value	Pancytopenia, MSD, AML; no reports for ELF1 or SRP54	AR, AD (*SPR54*)	Childhood>adult 5–42 (18)	Short Stature, exocrine pancreas dysfunction, variable cytopenias, skeletal dysplasia, hepatomegaly and transaminitis in early childhood, may present as non-syndromic or MDS/AML	[12,52, 53,67]
* *DKC1* (Xq28), *RTEL1* (20q13.33), *TERC (3q26.2), TERT* (5p15.33), *TINF2* (14q12), *PARN* (16p13.12), *MDM4* (1q32.1) (and others / **Telomere biology disorders** and **Dyskeratosis congenita** (OMIM#127550)	-Y, del(13q), −7, CK	Pancytopenia (BMF), macrocytosis; MDS/AML (30 %)	AD, AR,XL	19–61 (35)	Dyskeratosis congenita: nail dystrophy, oral leukoplakia, skin pigmentation, pulmonary fibrosis, liver fibrosis, short telomeres, cancer predisposition	[3, 81–84]
** ***MPL*** (1p34), *THPO* (3q27.1), *HOXA11* (7p15.2)/ **Congenital amegakaryocytic thrombocytopenia** (OMIM#604498)	Normal karyotype; Progression (aplastic anemia, MDS): increased accumulation of chromosomal aberrations	Aplastic anemia, rarely MDS	AR	Childhood, mainly <5	Absent radii, amegakaryocytic thrombocytopenia, high level of thrombopoietin serum, nystagmus or strabismus most likely secondary to intracranial bleeding	[5,85, 86]
1.3.2 - Rasopathies						
* *CBL* (11q23.3) / **CBL syndrome** (OMIM#613563)	UPD(11q)	JMML	AD	0.1–3,6 (1.1)	Developmental delay, cryptorchidism and impaired growth (CBL),	[5,12, 62,87]
* *PTPN11* (12q24.13), *NRAS* (1p13.2), *KRAS* (12p12.1) / **Noonan syndrome** (OMIM#163950)	−7	JMML mostly (high rate spontaneous regression), AML, MPN, B-ALL	AD	Early childhood	Non hematologic cancers, facial dysmorphism, growth retardation, skin lesions, cardiopathy, hygroma	[62,88, 89]
* *NF1* (17q11.2), *SPRED1* (15q14) / **Neurofibromatosis type I** (OMIM#162200)	−7	MDS, JMML	AD	Childhood> adult	"café au lait" spots, neurofibromas, gliomas, Noonan syndrome like disorder	[12,13, 62]
1.3.3 - DNA repair syndromes						
* *BLM* (15q26.1) / **Bloom syndrome** (OMIM#210900)	−7, del(7q), CK	MDS, AML, ALL, B-NHL	AR	Childhood> adult	Short stature, Microcephaly, High pitched voice, mild immunodeficiency, type 2	[5,12, 90]

(*continued on next page*)

Table 1 (*continued*)

Gene (localization) / Syndrome name	Acquired cytogenetic alterations during leukemogenesis	Hematologic pathologic features (less frequent or sporadically reported)	Inheritance Penetrance of neoplasm (level or%)	Age of hematologic neoplasm onset (median) (years)	Clinical features	Refs.
					diabetes mellitus, hypogonadism, light sensibility, solid tumors (carcinomas)	
** *ERCC6L2* (9q22.3) / **Bone marrow failure syndrome** (OMIM#615667)	AML: CK, hypoploid, mainly −7, +20, −5/del(5q), +8	BMF,MDS, AML (mainly M6)	AR	14–65 (38)	DNA repair syndrome (neurological symptoms)	[62,78,91]
XPC (3p25.1) and *XP* genes / **Xeroderma pigmentosum** (OMIM#278700) and others	del(5q), CK, rarely −7	MDS, AML (adult)	AR	7–29 (25)	Xeroderma pigmentosum and variants: extreme UV hypersensitivity, skin lesions and cancers	[62,92]
WRN (8p12) / **Werner syndrome** (OMIM#277700)	CK, rarely −7	MDS, AML (adult)	AR	Adult	Short stature, premature aging: graying or loss of air, cataracts, skin atrophy, thyroid cancer	[93]
1.3.4 - Cancer predisposition syndromes						
* Total or partial +21 / **Down syndrome** (OMIM#190685)	+8, +11, quadrisomy 21, del (6q), del(7p), del (16q) and dup(1p)	Transient abnormal myelopoiesis with *GATA1* somatic mutation; Acute megakaryoblastic leukemia, ALL	De novo (95 %), Translocation (5 %)	1–4	Mental retardation, cardiac abnormalities, facial dysmorphism, multiple congenital anomalies	[22,26,94,95]
mos +8c	del(5q), del(11q), del(20q), −7, del (7q), der(17q)	MDS, AML (ALL, CML, MPN)	De novo	1–49	Multiple congenital abnormalities, mental retardation, solid cancer	[30–33]
2- ALL with germline predisposition						
*** *IKZF1* (7p12.2) / **IKZF1-associated immunodeficiency** (OMIM#603023)	Not described	B-ALL, less commonly T-ALL	AD 10–30 %	2–15	Immunodeficiency, autoimmunity; If microdeletion 7p12: facial dysmorphism intellectual disability	[6,13,96]
*** *PAX5* (9p13.2) / **Familial ALL** (OMIM#615545)	iso(9q), dic(9;V) (acquired loss of the second copy)	B-ALL	AD 50 %	1–25		[13,39–41]
* *ETV6* (12p13.2) / **Thrombopenia 5 (**OMIM #616216)	High hyperdiploid B-ALL (>50), + 21, +8	Mostly B-ALL, AML, MDS, rarely DLBCL and MM	AD 20- 40 %	8–82	Preceding thrombocytopenia, platelet function abnormalities, inconstantly, red cell macrocytosis, potentially non-hematopoietic neoplasm (skin, colon cancers)	[3,69,97]
2.1 - Cancer predisposition syndromes						
* *TP53* (17p13.1) / **Li-Fraumeni syndrome** (OMIM #151623)	B-ALL: low hypodiploidy B ALL (or masked hypoploidy due to the tendency of aneuploid genome duplication); AML: −7, CK	B-ALL,T-ALL (early precursor), post-cytotoxic AML/MDS, lymphoma	AD 2–4 %	Wide age range (12 for ALL)	High risk of cancer beginning in infancy: sarcoma, premenopausal breast cancer, adrenocortical carcinoma, osteosarcoma and soft-tissue sarcomas, brain tumors and many others, occurring at ages earlier than expected	[10,12,72,98]
** *MLH1* (3p22.2), *MSH2* (2p21), *MSH6* (2p16.3), *PMS2* (7p22.1), 3′ deletion *EPCAM* (2p21) / **CMMRD** (OMIM#276300)	CK, rarely −7	T-NHL, T -ALL (B- ALL, AML)	AR	0.4–30(6)	CMMRD: brain, gastro intestinal, ovarian, endometrial cancer, “café au lait” spots, skin hypo or hyperpigmentation	[5,99]
2.2 - Constitutional aberrations						
rob(15;21), r(21)c	iAMP21	B-ALL	de novo			[27–29]
3 - Lymphoma with germline predisposition: specific inherited immune deficiency syndrome						
ATM (11q22.3) / **Ataxia telangiectasia** (OMIM#208900)	Structural rearrangements of *TCR* (7p13, 7q35, 14q11) and *IG* (14q32, 2p12, 22q11), presence of tri- or tetraradial chromosomes	Lymphomas, ALL	AR	Early childhood	Ataxia telangiectasia t(7;14): cerebellar ataxia, telangiectasia, immunodeficiency, cancer, radiation sensitivity	[72]
4 - MPN with germline predisposition						
ATG2B/GSKIP (14q32.2) / **chromosome 14q32 duplication syndrome** (OMIM#616604)	−7, CK during the progression	MPN: mostly essential thrombocythemia, myelofibrosis with high risk of transformation and frequently associated with TET2 mutation; AML	AD High (>80 %)	18–74 (41)	Earlier age of MPN onset in comparison to sporadic cases (41 years versus >60 years)	[15,48,100]

AD, autosomal dominant; AR: autosomal recessive; XL :X-linked; UPD, uniparental disomy; CK, complex karyotype; mos+8c, constitutional trisomy 8 mosaicism; iAMP21, intrachromosomal amplification of chromosome 21; rob, Robertsonian translocation; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMF, bone marrow failure; CML, chronic myeloid leukemia; CMMRD, constitutional mismatch repair deficiency; CMML, chronic myelomonocytic leukemia; CLL, chronic lymphocytic leukemia; FDP/AML, familial platelet disorder with associated myeloid malignancies; HCL, hairy cell leukemia; HL, Hodgkin lymphoma; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndromes; NHL, non-Hodgkin lymphoma; HCT, hematopoietic cell transplantation; OS, overall survival.

[*] present in 2022 WHO classification of myeloid neoplasm with germline predisposition.

[**] only present in 2022 ELN recommendations.

[***] only present in 2022 ICC classification.

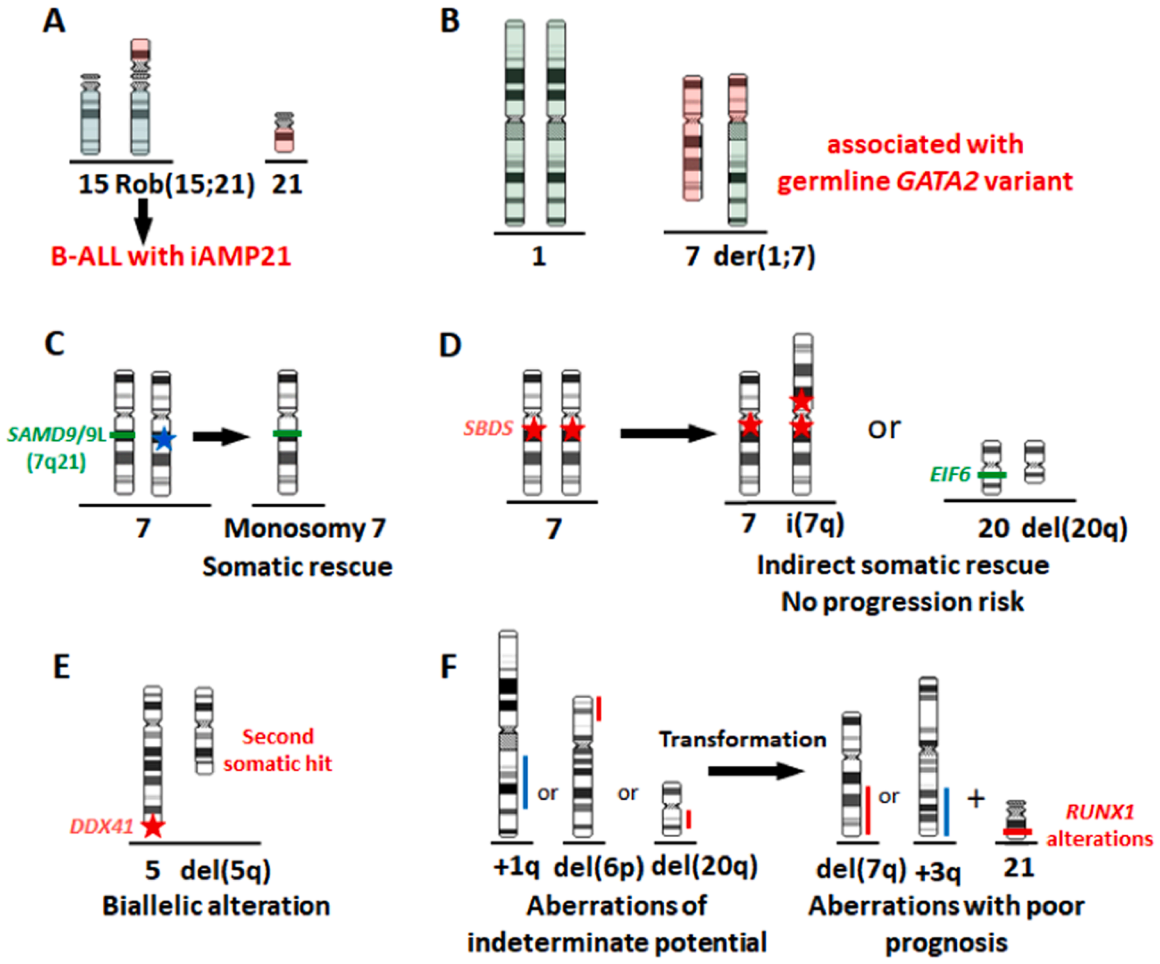

Fig. 2. Examples of cytogenetic abnormalities useful in the diagnosis and monitoring of hematologic disorders associated with germline predisposition: A. The constitutional Robertsonian translocation, rob(15;21)(q10;q10), implicating the long arm of chromosome 15 and 21, is associated with a high risk of iAMP21 B-acute lymphoblastic leukemia [29]. B. The rare unbalanced whole-arm translocation der(1;7)(q10;p10) leading to gain of 1q and 7q deletion is strongly associated with germline *GATA2* variant [65]. C. In autosomal dominant with SAMD9/9L syndromes, monosomy 7 eliminating the pathogenic allele (7q11) is a mechanism of somatic rescue [62]. D. In the recessive Shwachman-Diamond syndrome, isochromosome 7q, i(7q), and deletion of the long arm of chromosome 20, del(20q), are recurrent acquired cytogenetic abnormalities: i(7q) results in duplication of one of the mutated *SBDS* gene (located at 7q11) whereas del(20q) deletes the *EIF6* locus leading to an *EIF6* haploinsufficiency and to an indirect somatic rescue [53]. E. A deletion of chromosome 5 long arm (5q-) can constitute the second hit on the *DDX41* locus [55]. F. CGH array data. In Fanconi anemia, due to the genetic instability, the natural evolution of the disease allows some clonal aberrations of indeterminate potential. However, the progression to myeloblastic acute leukemia is associated with the sequential appearance of specific poor prognosis aberrations, the *RUNX1* alterations representing the latest events of the clonal evolution [50,51]. A blue star represents germline variant with gain of function; a red star, germline variant with loss of function. Green crossbars represent the normal allele. Red crossbar represent somatic genetic *RUNX1* alterations (translocation, deletion or mutations). Red lines and blue lines represent common regions of deletions and gains respectively.

marrow and in skin fibroblasts. Moreover, the phenotype of the mos+8c is very heterogeneous from profound disability (including mental retardation and dysmorphic features) to near normal and thus can be missed. In 2002, Maserati et al. showed that around 15–20 % of the patients with a MN and *a* +8 did in fact present a mos +8c [33]. These cases might be underdiagnosed in current practice and could be ruled out by analyzing non-hematopoietic cells or CD3+ lymphocytes [34]. The existence of both acquired and mos +8c cases developing malignancy suggests a role of +8 in the oncogenesis. However, the specific oncogenic mechanism by which the +8 would increase the risk of AML and SMD remains unknown. A study shows a promotion of progenitor cell proliferation and expansion stimulated by the bone marrow stromal cells while another highlights the potential role of defective +8 NK cells in the expansion of neoplastic cells [35].

Acquired chromosomal abnormalities suggesting a germline predisposition

In B-ALL

- **the diagnosis of iAMP21 should evoke the presence of a constitutional abnormality of 21** (see above and joint dedicated B-ALL article)

According to the previously described strong association of constitutional abnormalities of chromosome 21 and B-ALL subtype with iAMP21, the detection of iAMP21 in B-ALL should prompt the search for a constitutional structural abnormality of 21 (and more particularly rob (15; 21)). Indeed, the presence of such a chromosomal abnormality in a bone marrow karyotype at the time of disease remission suggests a constitutional origin. If such an abnormality remains during remission, a constitutional karyotype must be performed, allowed by the genetic counselling. If the constitutional abnormality is confirmed in the patient, a genetic counselling will be subsequently offered to healthy family members at risk. The unexpected detection of such a constitutional abnormality in the patient relatives results in a high risk of B iAMP21 ALL for all the carriers, including healthy people, but also in a risk of miscarriage or congenital malformations in the offsprings of the carriers. It also affects the choice of the donor in the context of an intrafamilial allograft.

- **the diagnosis of low hypodiploidy should suggest the presence of a germline *TP53* variant** (see joint dedicated B-ALL article)

TP53 alteration was found in 91 % of childhood low-hypodiploid (30–39 chromosomes) ALL but only in 8 % of non-low-hypodiploid cases ALL [36]. The hypoploidy clone can often undergo a genomic endoreplication leading to a near triploid clone that is frequently predominant at diagnosis, masking the low-hypoploidy one. In hypodiploid B-ALL, the examination of germline *TP53* pathogenic variant in the diagnostic bone marrow sample and then in remission blood sample is recommended to refer the patient for a genetic counselling if a variant is present in both samples.

- **Chromosomal aberrations of chromosome 9 in B-ALL with germline *PAX5* variant**

Somatic alterations of the lymphoid transcription factor gene *PAX5* are a hallmark of B-ALL observed in approximately 30 % of sporadic B-ALL [37]. Germline *PAX5* variants are rare, identified in less than 1 % in pediatric B-ALL leukemia [38]. Three different heterozygous specific germline variants in *PAX5* were observed in familial children B-ALL with autosomal dominant transmission [38–41]. These cases are characterized by chromosomal aberrations of chromosome 9: i(9)(q10) or dic(9;v) leading to 9p deletion [38,39,41], deletion or translocations leading to a loss of heterozygosity of the region 9p21 [40]. All these 9p alterations involved the second wild copy of *PAX5* suggesting that bi-allelic inactivation of *PAX5* is required for leukemogenesis [40,41].

- **High hyperploidy ALL and germline *ETV6* variant with thrombopenia history**

ETV6 is a transcriptional repressor that belongs to the ETS family and is essential for hematopoiesis, particularly thrombopoiesis. *ETV6* is involved in the most common somatic translocation t(12;21)(p13;q22) in childhood B-ALL, present in up to 25 % of cases, resulting in the chimeric fusion protein *ETV6*::*RUNX1* [42]. The second allele is often deleted subsequent to the translocation [37]. Germline *ETV6* variants are responsible for type 5 familial thrombocytopenia and predispose to MDS and acute leukemia including AML and B-ALL.

Germline *ETV6* variants are predominantly found in B-ALL (78 %) and 80 % of cases occurred before 15 years [43]. The high hyperdiploid karyotype (51–65 chromosomes in ALL blasts) is present in 70 % of ALL cases harboring germline *ETV6* variants (despite their older age) compared to the wildtype group. In contrast, the frequency of t(12;21) (*ETV6::RUNX1* fusion) is low (about 7 %) [42]. This group is characterized by RAS pathway mutations with recurrent mutations in *NRAS, KRAS* and *PTPN11*. In the remaining 30 % cases of childhood ALL with germline *ETV6* variants, there is a normal diploid karyotype very frequently associated with somatic focal deletion of *PAX5* and *ETV6* and to a lesser degree of *IKZF1*. The gene expression pattern of the latter group is strikingly similar to that of ALL with somatic *ETV6::RUNX1* fusion [44].

In T-ALL

The presence of tri- or tetraradial images and especially clonal and non-clonal structural abnormalities involving the *TCR* and/or *IG* genes should evoke a bi-allelic constitutional *ATM* (Ataxia telangiectasia) variant. It can be revealed at diagnosis, especially in attenuated forms of the disease, which may pose a therapeutic problem due to the extreme sensitivity of these patients to radiation and chemotherapy [45].

At the diagnosis of T-ALL, bone marrow karyotype can find these abnormalities and evoke the diagnosis. The karyotype of these T-ALL is most often complex with a pattern of chromothripsis, which mainly affects chromosome 14 [46].

In myeloid malignancies

- **14q32 duplication**

This germline heterozygous duplication, located upstream of the *IGH* genes, varies from 700 kb to 1,8Mb and can be partially overlapping. It can be detected with Copy Number Variations (CNV) in Single Nucleotide Polymorphism (SNP) arrays and Next Generation Sequencing (NGS) when the corresponding genes are included in the panel and optical genome mapping technology. This duplication implicates *ATG2B* and *GSKIP* genes, which play a synergistic role in megakaryopoiesis [47]. This genetic duplication is responsible of a broad spectrum of myeloid malignancies, including MPN as well as MDS and AML. It was initially described in two large families from French West Indies [48]. The intra-familial phenotype is heterogeneous, with MPN (mostly essential thrombocytemia with a high propensity to transformation) and more rarely, AML, MDS and chronic myelomonocytic leukemia [15]. The mutation landscape of these patients with MPN is atypical, as no triple negative patients (for *JAK2, CALR* or *MPL*) were found and an unexpected number of coexisting acquired mutations are detected in the MPN stage. The delay of transformation of essential thrombocytemia was highly variable. However, these families with a duplication of *ATG2B* and *GSKIP* show a very poor prognosis, mostly due to a rapid progression to AML associated with an unexpectedly high frequency of gene mutations [48]. During progression, the karyotype often presents a −7 or a CK and is associated with a mutation of *TET2* or *IDH1/2*.

- **Cytogenetic abnormalities suggestive of Fanconi anemia**

The myeloid clonal evolution of FA is driven by cumulated genetic events, including unbalanced translocations leading to gains or losses of chromosomes. These gene alterations do not occur randomly and are associated with different stages of disease progression. In particular, several abnormalities are visible on the karyotype and predict the time of AML transformation. Gain of chromosome 1q (+1q), the most common abnormality in FA, del(20q) and/or del(6p) can occur without transformation. In contrast, gain of chromosome 3q (+3q), del(7q) and/or −7, which occur after one or more of the previous three abnormalities, are associated with a poor prognosis and AML transformation with elevated blast count [49]. As latest events, genetic alterations of locus *RUNX1* (21q22) also occurred, such as unbalanced translocations, deletions in addition to *RUNX1* mutations [49]. The early detection of

sequential somatic CA associated with clonal progression allows for a timely allogenic transplantation decision [50,51]. Therefore, the non-random association of such abnormalities (e.g. +1q, del(7q) or +3q which is rare outside of FA), should evoke a previously unknown FA (Fig. 2F).

- **Del(20q) in Shwachman-Diamond syndrome as an indirect rescue mechanism**

This somatic interstitial deletion of the long arm of chromosome 20, del(20q), is a recurrent event in SDS with constitutional mutation of *SBDS* gene [52]. The resulting SBDS deficiency impairs the maturation of ribosome with a defect of ribosome subunit joining due to the inability to remove eIF6 from the nascent 60S subunit [53]. Variable in size from 1.7 to 26.9 Mb, the del(20q) results systematically in the deletion of *EIF6* gene located in 20q11 (Fig. 2D). This abnormality could be an indirect adaptive mechanism of rescue by reducing eIF6 dosage or eIF6 binding to the 60S subunit and finally conferring a selective advantage over non-modified cells. Therefore, in SDS, the del(20q) should not be associated with a risk of progression to malignancy. Balanced translocation with chromosome 20, t(16;20)(q24;q12) resulting in the disruption of *EIF6*, is also described [53]. The identification of del(20q) in karyotype for aplasia evaluation can lead to a suspicion of SDS.

- **Del(5q) in *DDX41* neoplasms as co-occurring somatic events**

Germline *DDX41* variants are the most common mutations predisposing to myeloid neoplasms in adults [54]. Somatic mutation of the second *DDX41* allele occurs in almost half of the reported cases. This second somatic alteration is sometimes visible on the karyotype and consists in an unusual del(5q) deleting the subtelomeric DDX41 locus (5q35.3). This deletion of chromosome 5 is present in 6 % of *DDX41* neoplasms and leads to haploinsufficient *DDX41* expression (Fig. 2E) [55].

- **Chromosome 7 abnormalities**

Monosomy for all or part of chromosome 7, as −7/del(7q), is a recurrent karyotype abnormality in the progression of MDS and AML and frequently associated with post-cytotoxic therapy MN and IBMFS. Chromosome 7 abnormalities also have a special place in the germline predisposition field because of their frequency and their diagnosis impact. In MDS, −7/del(7q) is more frequent in children than in adults (30–40 % and 10 %, respectively) [56]. Moreover, in pediatric MDS, monosomy 7, along with other chromosome 7 alterations mainly leading to del(7q) (−7, del(7q) and der(1;7)(q10;p10)), are frequently associated with germline predisposition, mainly *GATA2* or *SAMD9/SAMD9L* [57]. Indeed, Wlodarski et al. showed that 72 % of adolescents with MDS and −7 carry an underlying GATA2 deficiency [58,59]. In contrast, in a large series of adult MDS/AML with −7/del(7q), only 12 % were associated with germline predisposition, mainly FA or other DNA repair genes with no cases of germline *GATA2* or *SAMD9* variant [60]. Monosomy 7 and del(7q) can also reveal *SAMD9/9L* germline variant mostly in children and young adults but can represent either a progression mechanism towards MDS or a somatic rescue phenomenon as a loss of the mutated allele that can be followed by a uniparental disomy, UPD(7q) [61]. Chromosome 7 abnormalities can be constructed following 4 different situations which explain the different prognosis values [62]:

1. **A somatic maladaptive rescue**, in the case of *SAMD9/9L* diseases (see joint dedicated BMF article). Monosomy 7/del(7q) results from an aneuploidy adaptive mechanism by the non-random loss of chromosome 7q region containing the mutated allele, leading to the disappearance of germline *SAMD9/9L* variant in hematopoietic cells and hematopoietic rescue (Fig. 2C). This loss makes the variant difficult to detect, as the variation allele frequency (VAF) is fewer than 45 %, even as low as 5 %. Thus, non-hematopoietic tissue, unaffected by the rescue, can be tested for the presence of the pathogenic variant. On the other hand, large deletions or −7 are involved in the leukemic transformation because of the loss of several myeloid tumor suppressor genes such as *CUX1, DOCK4, EZH2* and *MLL3* and the gain of additional cancer mutations [63]. Molecular rescue can also occur with two other mechanisms: an incomplete rescue associated with somatic *SAMD9/9L* mutations or a complete genetic rescue resulting in uniparental isodisomy 7q containing the normal allele [61]. Although maladaptive rescue is the most frequent one, all three rescues coexist, allowing −7 clones to be replaced by clones with uniparental isodisomy of 7q. This reversion model explains the transient −7 in this pathology [64].
2. A **preferential relationship between chromosome 7 abnormalities and GATA2 deficiency** (see joint dedicated BMF article). The most common cytogenetic alterations associated with *GATA2* variant are −7 and der(1;7)(q10;p10). The latter, corresponding to an unbalanced whole-arm chromosomal translocation resulting in trisomy 1q and deletion 7q, is a rare abnormality more strongly associated with *GATA2* variant (Fig. 2B) [62,65]. Secondly, karyotypes of leukemic transformation may also display secondary somatic events like +8 (up to 40 %) and less frequently +21.
3. **An isochromosome 7q as favorable clonal evolution in Shwachman Diamond syndrome.** Clonal abnormalities are often found in SDS and the most frequent alteration is the isochromosome for the long arm of chromosome 7, i(7)(q10) [66]. As rarely reported in myeloid neoplasms, i(7)(q10) is quite characteristic of SDS. This alteration results in duplication of the mutated *SBDS* gene and allows the production of a scant amount of functional protein. Similar to del (20q), i(7q) is not associated with an increased risk of progression to malignancy [67].
4. **Secondary events associated with clonal evolution**. This concerns several germline predispositions: neurofibromatosis, LFS, SDS (others than i7q), familial MDS/AML with germline *DDX41* variant, Bloom syndrome, familial AML with germline *CEBPA* variant, severe congenital neutropenia, RASopathies (Table 1) [57]. In these germline predispositions, −7/del(7q) are secondary events associated with clonal evolution and may contribute to the progression of the disease from isolated cytopenia to MDS or from MDS to AML [13,68,69]. Others germline disorders dot not have specific association with −7: telomere disorders, Diamond-Backfan anemia, disorders with germline variants of *ANKRD26, ETV6, ATM* and *MPL* [57].

Cytogenetic technical recommendations for hematologic neoplasms with germline predisposition

For the samples

- Bone marrow samples are the preferred samples for the identification of acquired CA.
- The cytogenetic blood analysis can be done in ALL or AML with peripheral blasts ≥ 1 G/L [70].

For the time of analysis

- Cytogenetic analysis of bone marrow must be done at diagnosis and during the survey of predisposition syndrome when bone marrow test is planned. An annual bone marrow cytogenetic analysis for screening for high risk CA (−7) is recommended [71].

For the karyotype

- The recommended culture times is overnight (24 h) for ALL and at least 24 h for MN.

- In case of poor samples, several culture times can be used, 24 and 48 h for IBMFS, MDS/AML or even 72 h when adding G-CSF to avoid karyotype failure.
- Samples must be unstimulated (without PHA or others lymphoid mitogens) because stimulation can mask cells with monosomy 7 [57].
- Analysis must be of a minimum of 20 metaphases in order to detect a maximum of secondary abnormalities including CK, or > 20 to ensure normal karyotype.

For FISH analysis

- The chromosome 7 FISH analysis is recommended for AML, in case of karyotype failure and for patients treated with steroids, which inhibit the growth of cells in culture and can mask the cytogenetic aberrations [57].
- For children and young adults, when −7 is found isolated, FISH is recommended for copy number changes or translocations involving chromosome 7 and other relevant changes in other chromosomes including 1, 3, 5, 8, 17 and 20 [57].
- The chromosome 7 centromeric probe (cen7) is used to assess monosomy and the specific locus probes to assess others 7q abnormalities: 7q22 (*CUX1, RELN, KMT2E*), 7q31 (D7S486, D7S522, *MET*), 7q34 (*BRAF*), 7q36 (*CUL1, EZH2*).
- When a der(1;7) is found, FISH 1q is recommended for the assessment of cell percentage, because der(1;7) can be accompanied by other cytogenetic lesions implicating the chromosome 7 that affect the same clone.
- FISH analysis is preferred when performing longitudinal assessment of clonal percentage [57].
- For GATA2 syndrome, SAMD9/SAMD9L syndrome, FA, Telomere biology disorders/dyskeratosis congenita, Diamond-Blackfan anemia, SDS, congenital amegakaryocytic thrombocytopenia, see joint dedicated BMFS article for the FISH recommendations.
- Some germline variants are associated with large deletions on the second allele, sometimes unseen with DNA sequencing. This second allele loss generates high VAFs on DNA sequencing (greater than 50 %). It is therefore recommended to perform a locus-specific FISH to verify the presence of large deletions that could explain this high VAF. This is for example possible for *TP53* or *RUNX1* variants as *TP53* or *RUNX1* FISH is part of the standard probe panel. For the small deletion into the second allele, CGH/SNP array or WGS would be useful.

For other techniques

- CGH/SNP array, whole genome or exome sequencing (WGS/WES) is recommended to detect small rearrangements (dup14q, disomy 11q). Yet in validating process, Optical Genome Mapping can be useful for abnormal ploidy (low hypoploidy and iAMP21) and small or complex abnormalities (chromothripsis of the long arm of chromosome 21).
- Recommendations for surveillance of children and young adults with leukemia predisposing conditions including cytogenetic analysis (chromosome banding analysis and FISH) were established by the AACR childhood cancer predisposition workshop in 2017. All children with pediatric MDS/AML with −7, del 7q der(1;7) and probably all adults with MDS before the age of 50 should be tested with constitutional panel genes for hematologic predisposition on non-hematological samples (hair follicles or skin fibroblasts) [2].

Clinical report guidelines for hematologic neoplasms with germline predisposition

To inform the physicians about a potential germline predisposition, Table 2 summarizes the proposed guidelines for the clinical report.

Table 2
Clinical report guidelines for hematological neoplasms with germline predisposition.

Cytogenetic abnormalities	Recommendations for the clinical report
iAMP21 in B-ALL	- mention the possibility of the existence of a constitutional abnormality of 21 (Robertsonian translocation rob(15; 21) or a ring of 21) - request a control karyotype - when the abnormality is found at the remission stage, request a control of the constitutional karyotype after genetic counselling
chromosome 9p rearrangement (iso(9q), dic(9;v)) in B-ALL	- recommend the examination of germline *PAX5* variant as part of genetic counselling
hypodiploid B-ALL	- request the examination of germline *TP53* pathogenic variant in the diagnostic bone marrow sample and in remission blood sample to refer the patient for a genetic counselling if a variant is present in both samples
presence of tri- or tetraradial images	- mention the suspicion of underlying ataxia telangiectasia - request a genetic counselling to perform a constitutional karyotype and especially a germline *ATM* variant search
association of +1q, +3q and/or del (7q)/−7	- mention the suspicion of underlying Fanconi anemia
- 7, del 7q der(1;7) in children and young adults with myeloid malignancies	- mention the suspicion of germline predisposition - request a research of germline pathogenic variants on non-hematological tissues as part of genetic counselling -when the abnormality is found isolated, recommend a molecular testing for somatic pathogenic variants in *SETBP1, ASXL1, RUNX1* and *RAS* pathway genes [57]

iAMP21, intrachromosomal amplification of chromosome 21; ALL, acute lymphoblastic leukemia.

Conclusion

Over the last decade, the spectrum of predisposition genes in hematological disorders has rapidly expanded. Timely recognition of hereditary predisposition syndromes is critical to ensure a proper diagnosis and a suitable management, especially for therapeutic conditioning and stem cell transplantation. Cytogenetic analyses can be helpful to reveal abnormalities suggestive of germline predisposition and more often, to detect the emergence of clonal hematopoiesis and secondary abnormalities associated with progression. Some cytogenetic abnormalities are involved in somatic rescue of hematopoietic cells, such as the indirect rescue mechanism of del(20q). Notably, chromosome 7 abnormalities hold a special place in inherited malignancies, whether in diagnosis, rescue mechanism or somatic clonal evolution. Technical recommendations are therefore proposed to ensure an optimal surveillance of these pathologies, ultimately refining patient management.

CRediT authorship contribution statement

Nathalie Gachard: Writing – original draft, Validation, Conceptualization. **Marina Lafage-Pochitaloff:** Validation, Writing – original draft. **Julie Quessada:** Writing – original draft. **Nathalie Auger:** Writing – original draft. **Marie-Agnès Collonge-Rame:** Writing – original draft, Validation.

Declaration of Competing Interest

Undeclared.

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