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Review Article

Genetic Predisposition to Hematologic Malignancies in Childhood and Adolescence

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Abstract. Advances in molecular biology and genetic testing have greatly improved our understanding of the genetic basis of hematologic malignancies and have enabled the identification of new cancer predisposition syndromes. Recognizing a germline mutation in a patient affected by a hematologic malignancy allows for a tailored treatment approach to minimize toxicities. It informs the donor selection, the timing, and the conditioning strategy for hematopoietic stem cell transplantation, as well as the comorbidities evaluation and surveillance strategies.
This review provides an overview of germline mutations that predispose to hematologic malignancies, focusing on those most common during childhood and adolescence, based on the new International Consensus Classification of Myeloid and Lymphoid Neoplasms.

Keywords: Gilteritinib; Acute myeloid leukemia (A.M.L.); Early access; Real-life data; Response; Prognosis.

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Introduction. Advances in molecular biology and genetic technologies have significantly improved our knowledge about the genetic landscape of major cancer types in children and adults.[1] Aside from offering valuable diagnostic and prognostic insights from somatic alterations, assessing non-tumor or germline material using comprehensive sequencing techniques has revolutionized our understanding of how germline mutation affects cancer development. According to several large-scale studies involving pediatric cancer patients, the frequency of potentially harmful germline mutations was estimated to be around 8.5%.[2,3]

Hematologic malignancies represent the most frequent neoplasm affecting children and adolescents, with acute lymphoblastic leukemia (ALL) being the most common type of childhood cancer.[4] In hematologic malignancies, most efforts have focused on identifying acquired genetic alterations to guide prognostic stratification and tailored treatment strategies.[5,6] Although the role of germline genetic alterations in the development of hematologic malignancies has for a long time been underestimated, the inclusion of the category "Myeloid neoplasms with germline predisposition" in the fourth edition of the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues has underscored the utmost importance of germline assessment in patients with myeloid tumors.[7] Furthermore, it is becoming increasingly clear that these observations can now be extended to lymphoid malignancies, as demonstrated by the recent International Consensus Classification (ICC) of Myeloid and Lymphoid Neoplasms.[8] Thus, the title is changed from "myeloid neoplasms" to "hematologic neoplasms" with germline predisposition.

Even though many patients lack a family history consistent with a cancer predisposition syndrome,[3] some clues can help us suspect a germline mutation in patients with a hematologic malignancy (**Figure 1**).[6] In particular, several associated clinical features may point toward specific syndromes (**Table 1**).[6]

The discovery of a germline mutation in a patient affected by a hematologic malignancy has significant

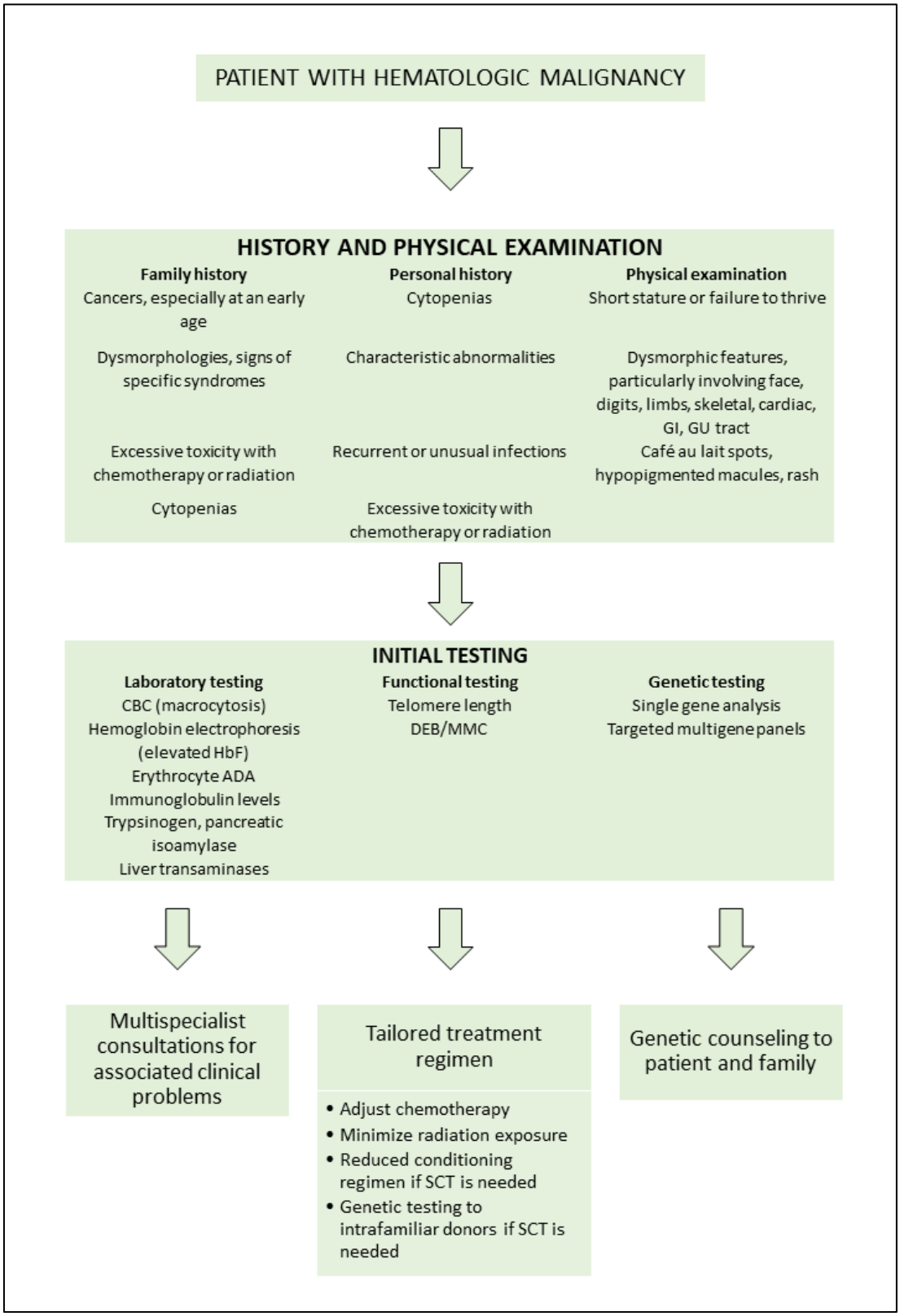

Figure 1. The diagnostic algorithm we propose in the detection of germline mutations in patients with hematologic malignancies. **ADA**, adenosine deaminase; **CBC**, complete blood count; **DEB**, diepoxybutane; **FISH**, fluorescence in situ hybridization; **GI**, gastrointestinal; **GU**, genitourinary; **MMC**, mitomycin C; **SCT**, stem cell transplantation.

implications, impacting the patient's psychosocial well-being and family relationships, and may lead to important decisions regarding reproductive planning and genetic counseling. Furthermore, it may influence the type and intensity of treatment and the risk of recurrence and secondary cancers. In fact, several of these conditions carry an increased risk of severe toxicity with standard chemotherapy or radiation dosages. Such toxicity can result in prolonged or permanent cytopenias, organ damage, or significant mucositis; thus, early

Table 1. Comparison of somatic abnormalities found in germline predisposition syndromes to hematologic malignancies.

	FA	*DC*	*SDS*	*DBA*	*ELANE*	*RASopathies*	*Bloom*	*AT*	*NBS*	*GATA2*	*SAMD9/SAMD9L*	*DS*	*CMMRD*
Growth	X	X	X	X	X	X	X	X	X		X	X	
Facial	X			X		X					X	X	
Skeletal	X	X	X	X									
Skin	X	X	X		X		X			X	X		X
Limb	X			X								X	
Renal	X	X		X						X	X		
Heart	X	X	X	X		X						X	
Lung		X								X		X	
Exocrine pancreas			X										
Mucosa		X											
Neurologic	X	X	X			X		X	X	X	X	X	X
Vascular		X					X	X		X			
Dental	X	X	X										
Hair		X											

AT, ataxia telangiectasia; **CMMRD**, constitutional mismatch repair disorder; **DBA**, Diamond Blackfan anemia; **DC**, dyskeratosis congenita; **DS**, Down syndrome; **FA**, Fanconi anemia; **NBS**, Nijmegen breakage syndrome; **SDS**, Shwachman Diamond Syndrome.

detection of such patients enables tailored treatment using less intense regimens.[6,9] Finally, discovering an inherited mutation in a patient with a hematologic malignancy inevitably impacts the selection of a donor when hematopoietic stem cell transplantation (SCT) is indicated. Even though HLA-matched sibling donors are usually the preferred donors, they may share the same mutation with the affected individual.

Consequently, screening must be performed even if the sibling appears asymptomatic. Several questions also arise regarding the ideal timing for performing SCT as well as the intensity of the conditioning regimen to be preferred, which must be evaluated on a case-by-case basis considering the specific disease.[10] For example, in patients with germline mutations carrying a high penetrance of leukemia, a preemptive SCT may represent a wise option; on the other hand, in cases with a lower probability of developing leukemia, a watch-and-wait strategy may be preferred. Similarly, a reduced-intensity conditioning regimen may benefit patients at high risk of transplant-related toxicities, such as syndromic conditions characterized by numerous comorbidities.

This review provides an overview of genetic mutations predisposing to hematologic malignancies, focusing on those most common among children and young adults. For convenience, we have grouped genes according to the new ICC (**Table 2**), which includes 4 major subgroups with new entities added in comparison with the 2016 WHO classification: hematologic neoplasms with germline predisposition without a constitutional disorder, including CEBPA, DDX41, and TP53 alterations; those associated with thrombocytopenia or platelet dysfunction including RUNX1, ANKRD26, and ETV6 alterations; those associated with constitutional disorders affecting multiple organ systems including GATA2, SAMD9, and SAMD9L mutations, inherited genetic mutations associated with classic bone marrow failure (BMF) syndromes and juvenile myelomonocytic leukemia (JMML), and Down syndrome; ALL with germline predisposition. These classifications should not be considered rigid as they can sometimes overlap; for example, Down syndrome and germline mutations in ETV6 or TP53 predispose to ALL.

Hematologic neoplasms with germline predisposition without a constitutional disorder affecting multiple organ systems.

Myeloid neoplasm with germline CEBPA mutation. CEBPA is a single exon gene in the chromosomal region of 19q13.1 encoding for a granulocyte differentiation factor.[11] Biallelic mutations are often recognized in acute myeloid leukemias (AMLs), defining a unique subtype with good outcome.[12,13] It has been shown that nearly 10% of these cases also carry a germline CEBPA mutation, typically a frameshift or nonsense mutation near the amino terminus of the encoded protein.[14] Progression to AML occurs with a near complete penetrance, often in the second or third decade of life, and may develop without a previous myelodysplastic syndrome (MDS). It is commonly associated with an acquired mutation in the remaining wild-type CEBPA allele.[14,15] One of the peculiar features of this entity is that when these patients have disease recurrence after chemotherapy, they present new clones with a different spectrum of acquired mutations, including new somatic CEBPA mutations, demonstrating that these second leukemias are not true relapses.[15]

Table 2. The ICC of hematologic neoplasms with germline predisposition.

Hematologic neoplasms with germline predisposition without a constitutional disorder affecting multiple organ systems	Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder	Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems	ALL with germline predisposition
Myeloid neoplasms with germline CEBPA mutation	Myeloid or lymphoid neoplasms with germline RUNX1 mutation	Myeloid neoplasms with germline GATA2 mutation	Acute lymphoblastic leukemia with germline PAX5 mutation
Myeloid or lymphoid neoplasms with germline DDX41 mutation	Myeloid neoplasms with germline ANKRD26 mutation	Myeloid neoplasms with germline SAMD9/SAMD9L mutation	Acute lymphoblastic leukemia with germline IKZF1 mutation
Myeloid or lymphoid neoplasms with germline TP53 mutation	Myeloid or lymphoid neoplasms with germline ETV6 mutation	Myeloid neoplasms associated with BMF syndromes	
		JMML associated with neurofibromatosis	
		JMML associated with Noonan-syndrome-like disorder (CBL-syndrome) Myeloid or lymphoid neoplasms associated with DS	

ALL = acute lymphoblastic leukemia; **BMF** = bone marrow failure; **DS** = Down syndrome; **ICC** = International Consensus Classification.

Myeloid or lymphoid neoplasms with germline TP53 mutation. TP53 is commonly considered the guardian of the genome, as it plays a pivotal role in the cell cycle, DNA repair, and apoptosis.[16] Germline mutations are the defining feature of Li-Fraumeni syndrome (LFS) and predispose to a diverse range of tumors in adults and children, particularly breast cancer, sarcomas, and brain tumors. In contrast, hematological malignancies are relatively uncommon.[17–19] Leukemias occur with an estimated incidence of 4% and are predominantly hypodiploid ALL and therapy-related myeloid disorders, including AML and MDS.[20–22] In particular, germline TP53 alterations are a hallmark of low hypodiploid ALL, as found in more than half of the children affected.[23] Leukemic transformation is associated with somatic alterations of IKZF2, CDKN2A, and CDKN2B.[23]

Due to the very increased susceptibility to second cancers, patients with LFS and a hematological malignancy should avoid exposure to radiation therapy when possible.

Myeloid or lymphoid neoplasms with germline DDX41 mutation. Unlike the other genes cited in this review, germline DDX41 mutations predispose to neoplasm arising during adulthood, typically in the 6th decade.[24–26] These alterations probably underlie more than 5% of AMLs, making them the most common predisposing events reported in AML.[27] Patients carrying DDX41 germline mutations represent a unique AML subset with male sex skewing, older age, low leukocyte count, few somatic genetic events, and high response rates to intensive chemotherapy leading to prolonged survival.[28] A second somatic DDX41 mutation represents the main driver for AML progression.[28] Lymphoid neoplasms have also been described but are less common.[25]

Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder.

Myeloid or lymphoid neoplasms with germline RUNX1 mutation. RUNX1 is a transcription factor that plays a critical role in regulating blood cell development and differentiation, especially involved in megakaryocyte maturation, differentiation, ploidization, and proplatelet formation.[29] Whereas somatic alterations in RUNX1 are among the most common mutations in both adults and children with ALL, AML and MDS, germline mutations define familial platelet disorder with predisposition to myeloid malignancy (FDP-MM), initially described in 1999.[30] Several mutations have been identified to date, including larger gene deletions, nonsense or frameshift mutations, and point mutations acting by haploinsufficiency with dominant negative effects.[31] All these alterations result in an autosomal dominant disorder with a variable penetrance, characterized by quantitative and/or qualitative platelet defects with a predisposition to developing hematological malignancies. The symptomatic patients typically present with mild-to-moderate thrombocytopenia.

Platelet morphology is normal but is associated with a severe decrease in platelet aggregation due to decreased dense granules.[31] The risk of malignant transformation into MDS and AML usually occurs in adulthood and is estimated to be 30%–40%;[32] patients carrying RUNX1 mutations with a dominant-negative effect appear to have a higher risk than patients carrying loss-of-function alleles.[31,33] The progression is associated with the acquisition of somatic mutations in the remaining wild-type RUNX1 allele, as well as GATA2 mutations, and less commonly, other genes recurrently mutated in AML and MDS. More rarely, a malignant transformation in other hematological malignancies may occur, T-ALL being the most frequent.[31,34–37]

Myeloid neoplasms with germline ANKRD26 mutation. Gain-of-function single nucleotide substitutions in the ANKRD26 gene, typically in the promoter region, lead to increased gene transcription and signaling through the MPL pathway and impaired proplatelet formation by megakaryocytes.[38] Carriers present with moderate thrombocytopenia, a normal mean platelet volume, and an absent or mild bleeding tendency.[39] The risk of progression to malignancies is estimated at 5% for AML, 2.2% for MDS, and 1.3% for chronic myeloid leukemia (CML).[40]

Myeloid or lymphoid neoplasms with germline ETV6 mutation. ETV6 is a tumor suppressor gene frequently mutated by somatic alterations, such as the ETV6-RUNX1 fusion commonly seen in childhood ALL.[41] Germline mutations are associated with mild to moderate thrombocytopenia with normal-sized platelets and mild to moderate bleeding tendency.[42,43] They can be found in approximately 1% of pediatric ALL cases[44] and are predominantly missense variants. Other than ALLs, ETV6 germline mutations are also associated with MDS/AML, mixed-phenotype acute leukemia, chronic myelomonocytic leukemia (CMML), plasma cell myeloma and polycythemia vera, as well as with solid tumors including colorectal, breast, kidney, and skin cancers, and meningioma.[42,43]

Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems.

Myeloid neoplasms with germline GATA2 mutation. GATA2 is a transcription factor that plays a leading role in hematopoiesis but can also be expressed in endothelial cells, central nervous system, placenta, fetal liver, and fetal heart.[45,46] This ubiquitous expression is reflected in the wide range of clinical features that patients carrying germline mutations may present, like pulmonary alveolar proteinosis, lymphedema and sensorineural deafness, and miscarriages. However, bone marrow dysfunction represents the hallmark of the disease, leading to recurrent infections (mainly atypical mycobacterial infections and recurrent HPV-related warts) and hematological malignancies.[47–49] Patients carry loss-of-functions mutations, involving mostly the second zinc finger domain and resulting in GATA2 haploinsufficiency.[50] GATA2 deficiency underlies 15% of advanced forms and 7% of all primary MDS in childhood.[51,52] Clinical onset can occur over a highly variable time frame, at a median age of 18 years, whereas some carriers may remain asymptomatic for life though the penetrance at age 60 is 90%.[53] Therefore, intrafamily donor genetic testing, even if asymptomatic, must be warranted before proceeding to SCT. At birth, carriers typically have normal cell counts; however, a progressive reduction of CD34+ cells in bone marrow occurs over time, resulting in monocytopenia, dendritic cell deficiency, NK cell deficiency, B cell deficiency, and, less commonly, neutropenia.[54,55] The progression into MDS is associated with monosomy 7 or trisomy 8,[46,56] whereas progression to AML is frequently driven by ASXL1 alterations.[51] Currently, clear guidelines for managing patients with GATA2 mutations are lacking. A possible algorithm for patient monitoring is proposed in.[57]

Myeloid neoplasms with germline SAMD9 or SAMD9L mutation. Together with GATA2, SAMD9/SAMD9L mutations, two interferon-inducible genes located on chromosome 7, are the most frequent germline mutations in pediatric MDS.[52] They were initially recognized to underlie MIRAGE (Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes, and Enteropathy) syndrome and ataxia-pancytopenia syndrome, respectively.[58,59] The penetrance is incomplete, and MDS can also arise in patients without syndromic features.[60] SAMD9/SAMD9L mutations are typically gain-of-function mutations and enhance the effects of the wild-type genes leading to growth arrest when exogenously expressed in cells.[58] The strong selective pressure to not express the mutant allele is responsible for losing the copy of chromosome 7 carrying the altered gene. Together with the SAMD9/SAMD9L gene, several genes on chromosome 7 (e.g., EZH2, SAMD9, SAMD9L, CUX1, and KMT2C) resulted lost, perturbing hematopoiesis and ultimately leading to progression into MDS and AML.[52,58] Importantly, somatic revertant mosaicism that can restore correct hematopoiesis represents another unique feature of SAMD9/9L syndromes. Two main mechanisms have been observed so far: the acquisition of loss-of-function SAMD9/9L mutations neutralizing the gain-of-function germline mutation or an independent uniparental disomy of 7q (UPD7q).[52,56] The timing for performing SCT must be decided on a case-by-case basis, taking into account that children with high expression of the MIRAGE

Table 3. Inherited bone marrow failure syndromes predisposing to hematological malignancies.

	FA	SCN	SDS	DC	DBA
Inheritance pattern	AR, XLR, AD	AD, AR	AR, AD	XLR, AR, AD	AR, XLR
Somatic abnormalities	Yes	Rare	Yes	Yes	Yes
Genes identified	FANCA, FANCB, FANCC, FANCG/XRCC9, FANCJ/BRIP1, FANCE, FANCF, FANCP/SLX4, FANCD1/BRCA2, FANCD2, FANCI, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C, FANCQ/ERCC4, FANCR/RAD51, FANCS/BRCA1, FANCT/UBE2T, FANCU/XRCC2, FANCV/REV7, FANCW/RFWD3	ELANE, GFI1, HAX1, G6PC3, VPS45, CSF3R, JAGN1	SBDS, DNAJC21 EFL1, SRP54	TIN2, TERC, TERT, NAF1, ZCCHC8, NPM1, MDM4, USB1, RTEL1, PARN, NOP10, TERT, NHP2, WRAP5313, CTC1, ACD/TPP1	RPS19, RPL5, RPS26, RPL11, RPL35A, RPS10, RPS24, RPS17, RPL15, RPS7, RPS28, RPS29, RPL26, RPS15, RPS27, RPL9, RPL18, RPL27, RPL31, GATA1, TSR2

AR = autosomal recessive; **AD** = autosomal dominant; **DBA** = Diamond-Blackfan Anemia; **DC** = Dyskeratosis congenita; **SCN** =Severe congenital neutropenia; **SDS** = Shwachman-Diamond syndrome; **XLR** = X-linked recessive.

phenotype experience a high rate of transplant-related comorbidities.[61]

Myeloid neoplasms associated with bone marrow failure syndromes. Inherited bone marrow failure syndromes (IBMFS) are a group of various disorders characterized by failure in the production of one or more blood lineages, usually associated with extra hematopoietic abnormalities, that present during childhood in most cases.[62] Different genes involved in diverse cellular functions, including DNA repair, telomere maintenance, and ribosome biogenesis, underlie these disorders (**Table 3**).

Fanconi Anemia. Fanconi anemia (FA) is a heterogeneous disorder characterized by BMF with a predisposition to AML, increased risk of other solid tumors, growth retardation, and congenital abnormalities, including kidney and urinary tract malformations, thumb and radial ray abnormalities and café au-lait spots.[63–65] It is mostly inherited as an AR trait but can rarely be an X-linked or an AD disorder.[62] Overall, germline mutations affecting 23 genes, all encoding proteins involved in DNA repair, underlie the disease.[62] The cumulative incidence of AML at 40 years is estimated at 15–20%, and the cumulative incidence of MDS at 50 years is 40%.[66] The FANCD1/BRCA2 mutation carriers have a higher risk of developing AML, with a cumulative incidence of 80% at age 10 years.[66] Due to the high toxicity, FA patients suffer when exposed to irradiation and alkylating agents, fludarabine-based conditioning regimens are currently preferred.[62]

Severe congenital neutropenia. Severe peripheral neutropenia (< 0.2 x 10^9/L) is the hallmark of severe congenital neutropenia (SCN), causing an increased risk for recurrent and often life-threatening infections.[67] Several germline mutations can underlie SCN, but it is most commonly caused by AD mutations in ELANE, which encodes neutrophil elastase, and AR mutations in HAX1, involved in the granulocyte-colony stimulating factor signaling pathway.[68,69] SCN patients have a high risk of developing MDS or AML, with a median incidence of 21%.[70,71] Malignant transformation is often driven by acquired mutations in CSF3R (encoding G-CSF receptor) and subsequently in other leukemia-associated genes (such as RUNX1).[72]

Shwachman-Diamond syndrome. Shwachman-Diamond syndrome (SDS) is usually an AR disorder caused mostly by biallelic mutations in the SBDS gene, encoding a protein involved in ribosome biogenesis.[73] The disease is characterized by exocrine pancreatic insufficiency, BMF, and extra hematopoietic abnormalities such as metaphyseal dysostosis.[62] Patients have a cumulative risk of developing MDS/AML reaching 36% by 30 years of age.[74]

Dyskeratosis congenita and telomere biology disorders. Dyskeratosis congenita (DC) belongs to a spectrum of

disorders caused by pathogenic germline variants in telomere biology genes that share a high risk of hematologic and solid malignancies. Only a minority of patients present with the classical triad of mucosal leukoplakia, abnormal skin pigmentation, and nail dystrophy.[75] Most patients carry X-linked pathogenic variants in dyskerin, encoded by DKC1.[76] Other genes were found to underlie these disorders, both AD and AR, while in a significant percentage of cases, the gene responsible is not identified.[77] A cumulative incidence of 2% by age 50 years for leukemia has been reported.[78] When they underwent HSCT, patients with DC suffer from increased transplant-related mortality due to predisposition to both pulmonary and endothelial disease as well as increased susceptibility to alkylating agents and irradiation; therefore, low-intensity fludarabine-based conditioning regimens are currently preferred.[79,80]

Diamond-Blackfan anemia. Diamond-Blackfan anemia (DBA) is characterized by pure red blood cell aplasia, often associated with congenital anomalies, including thumb abnormalities and short stature.[81,82] Pathogenic AD variants in ribosomal proteins underlie the disease, while X-linked pathogenic mutations in GATA1 can be found in a minority of patients.[62,82] Patients with DBA have an estimated 5-fold increased risk of cancer, including osteogenic sarcoma, colon cancer, and AML.[83]

JMML and related disorders. The ICC separates JMML from adult MDS/MPN. JMML is now considered a genetic entity defined by the presence of molecular alteration of RAS pathway genes,[8] including NRAS, KRAS, PTPN11, NF1, CBL, or rarely RRAS. As might be expected, genetic syndromes associated with germline mutations in these genes, known collectively as Rasopathies, have a significantly increased risk of developing this disease.[84–90] In particular, two JMML subtypes are now defined by germline events in either NF1 or CBL, with malignant progression driven by acquired biallelic inactivation of the respective genes in hematopoietic cells. Importantly, patients harboring germline CBL mutations often experience spontaneous disease resolution, unlike patients with germline NF1 mutations.[87,91–95]

In addition, the ICC distinguishes another entity defined as Noonan syndrome–associated myeloproliferative disorder, associated with germline mutations in PTPN11, KRAS, NRAS, or RIT1. This disorder is characterized by a myeloproliferative disorder occurring in the first year of life and lacking acquired somatic mutations. Although it resembles the typical clinical and hematological parameters of JMML, the disorder generally has a self-limiting course.[90,96–98]

Myeloid or lymphoid neoplasms associated with Down syndrome. Children with Down Syndrome (DS) have an increased risk of developing hematological neoplasms, particularly AML, with nearly a 150-fold increased risk in the first 5 years of life.[99] Morphologically it is commonly a megakaryoblastic AML, with a favorable outcome compared to the counterpart arising in non-DS patients.[100–102] Furthermore, a transient myeloproliferative disorder (TMD) occurs in the neonatal period in 10% of infants with DS, characterized by an accumulation of immature megakaryoblasts in the fetal liver and peripheral blood.[103,104] Despite TMD regressing, 20–30% of children that experienced TMD will develop DS-AML within the first 4 years of life.[103] A somatic GATA1 mutation is usually found in both TMD and DS-AML.[104–106]

Patients with DS also have an increased incidence of B-ALL, often characterized by alterations in cytokine receptors or kinase signaling pathways (e.g., Philadelphia chromosome-like ALL), notably with CRLF2 dysregulation.[107,108] DS patients are particularly susceptible to treatment-related toxicity, especially with high-dose methotrexate.[109] Consequently, they require tailored therapy with reduced doses of chemotherapy and reduced intensity conditioning regimens when SCT is needed.[110,111]

Acute lymphoblastic leukemia with germline predisposition.

Acute lymphoblastic leukemia with a germline PAX5 mutation. PAX5 encodes a transcription factor involved in B-lymphoid lineage maturation, commonly found as a target of somatic alterations in B-ALL.[41,112–114] Germline mutations were recognized in families with increased incidence of B-ALL, inherited as an autosomal dominant trait with variable penetrance.[115,116] B-ALL develops as a result of the loss of 9p containing the wild-type copy.[114]

Acute lymphoblastic leukemia with germline IKZF1 mutation. IKZF1 encodes for IKAROS, a zinc-finger transcription factor that acts as a master transcription regulator in lymphoid development.[117,118] Somatic IKZF1 alterations often occur as secondary events in kinase-driven B-ALL (Ph+ or Ph-like ALL) and DUX4-rearranged ALL.[119,120] Importantly, in kinase-driven ALL, IKZF1 alterations are associated with poor outcome, unlike in DUX4-rearranged.[121–124] Germline mutations have been found in several families affected by immunodeficiency with B-cell lymphopenia and increased incidence of B-ALL.[125–127] Similarly, germline mutations in other members of IKAROS transcription factor, namely IKZF2 and IKZF3, have been recognized as related to immunodeficiency syndromes with immune dysregulation.[128]

Additional germline mutations associated with hematologic neoplasm predispositions. In the context of hereditary syndromes, several germline mutations

predispose to the development of hematologic malignancies: Bloom's syndrome (BLM), constitutional mismatch repair deficiency (MLH1, MSH2, MSH6, EPCAM, PMS2), DNMT3A, ERCC6L2, MBD4, Ataxia-Telangiectasia, Nijmegen breakage syndrome, and xeroderma pigmentosum (XPC).[129–138] In addition, hematological malignancies can frequently arise in patients affected by immunodeficiency or immune dysregulation.[139]

Conclusions. The increasingly widespread availability of next-generation sequencing techniques expands the knowledge of the genetic mechanisms underlying cancer development. It enables the identification of a growing number of germline variants associated with hematologic neoplasms. Early identification of these variants at the time of diagnosis allows for personalized treatment and optimized donor selection if SCT is needed. On the other hand, this relatively easy access to genetic information raises some ethical considerations. For example, related donors could not want to know if they carry a pathogenetic germline mutation; however, they may feel forced to do so unwillingly because of pressure from other family members, although they might not be ready to handle the results should they test positive. This situation is even more challenging in the pediatric setting, where consent is expressed by proxy from parents or guardians, and the child, once he or she becomes an adult, may suffer the consequences of decisions not made by himself or herself.[10]

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