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Genetic predisposition to leukemia and other hematologic malignancies

Simone Feurstein[a,b], Michael W. Drazer[a], Lucy A. Godley[a,*]

[a]Section of Hematology/Oncology, Department of Medicine, The Center for Clinical Cancer Genetics, and The University of Chicago Comprehensive Cancer Center, The University of Chicago, Chicago, IL, USA
[b]Klinik für Innere Medizin III, Abteilung Hämatologie und Onkologie, Universitätsklinikum Ulm, Germany

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ABSTRACT

In this review, we provide an overview of familial myelodysplastic syndromes (MDS)/acute leukemia (AL) and bone marrow failure syndromes, as well as insights into familial myeloproliferative neoplasms (MPNs), familial multiple myeloma (MM), familial Waldenström macroglobulinemia (WM), familial lymphoma, and cancer predisposition syndromes with increased risk of MDS/AL. This field will continue to accelerate as next-generation sequencing (NGS) techniques identify novel predisposition alleles in families with a genetic predisposition to hematologic malignancies. Newly identified predisposition genes continue to inform the field of inherited leukemia and other hematologic malignancies. Current developments in clinical translation include techniques detailing the acquisition of appropriate germline material for patient work-ups, methods for genetic testing, and nuances essential for the treatment and clinical management of patients with a genetic predisposition to hematologic malignancies.

1. Introduction

The first step in identifying individuals at risk for inherited cancer predisposition syndromes is to obtain a detailed family history from any individual who has been diagnosed with cancer. This history should span at least three generations and include all first-degree relatives and children. Age at diagnosis should be included for any family members diagnosed with cancer or other relevant diseases. The history should include information pertaining to non-cancer symptoms that may be suggestive of an underlying inherited syndrome, such as cytopenias, immune deficiencies, autoimmune disorders, lymphedema, pulmonary disorders, unexplained hepatic cirrhosis, dermatologic abnormalities, deafness, and congenital limb abnormalities. A rigorous family history should be obtained from any individuals who are being considered as potential donors for an allogeneic hematopoietic stem cell transplant. Likewise, further assessment is needed for any blood abnormalities detected in the donor or if the donor fails to mobilize stem cells well [1]. Any individual with a concerning family history or the above symptoms should be referred to a genetic counselor.

To date, more than 50 hereditary cancer syndromes have been described. The majority of these are caused by highly penetrant mutations that are inherited in a dominant fashion. Cancer predisposition syndromes associated with an increased risk of hematologic malignancies are well characterized and are summarized in Tables 1 and 2. In this review, we will focus specifically on familial syndromes associated with a predisposition to myeloid or lymphoid malignancies.

2. Inherited myeloid malignancies

2.1. Familial myelodysplastic syndromes/acute leukemia

Familial myelodysplastic syndromes (MDS) and acute leukemia (AL) syndromes were once considered rare, but are more common than previously appreciated. The first genes involved in inherited MDS/AL, *RUNX1* and *CEBPA*, were identified a decade ago [2,3], but the number of genes involved in inherited MDS/AL has grown dramatically in recent years with the advent of more affordable next-generation sequencing (NGS). This is exemplified by multiple autosomal dominant, highly penetrant inherited cancer syndromes resulting from germline mutations in *GATA2, ANKRD26*, *SRP72*, *ETV6*, and *DDX41* that have been identified in the past 4 years alone [4–8]. Most of these syndromes are inherited in an autosomal dominant manner and may be grouped by their clinical presentations. Table 2 shows all known classes of inherited hematologic malignancies, involved genes and hematologic phenotypes. An overview of all classes of inherited MDS/AL syndromes, their lifetime risk of malignancy and median age of onset is provided in Table 3.

* Corresponding author. Lucy A. Godley 5841 S Maryland Ave., Chicago, IL 60637. Tel.: +773-702-4140; fax: +773-702-9268.
E-mail address: lgodley@medicine.bsd.uchicago.edu (L.A. Godley).

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Table 1
Overview of hereditary cancer and/or hematologic malignancy predisposition syndromes.

Syndrome	OMIM	Genes	Prevalence	Mode of inheritance	Cancer risk
Ataxia teleangiectasia	208900	*ATM*	1/100,000	AR	AL, lymphoma, other solid tumors
Autoimmune lymphoproliferative syndrome	601859	*FAS, FASL, CASP10*	Very rare	AD/AR	Lymphoma
Bloom syndrome	210900	*BLM*	Very rare	AR	MDS/AL, lymphoma, colon and skin cancer, other solid tumors
Common variable immunodeficiency	146830	variety of genes	1/25,000	AD/AR	NHL, AL
Diamond-Blackfan anemia	105650	*RPS19, RPL5, RPL11, RPL35A, RPS24, RPS17, RPS7, RPS10, RPS26, RPL26, RPL15, RPS29, GATA1*	Very rare	AD/X-linked	MDS/AML, osteogenic sarcoma, other solid tumors
Down syndrome	190685	trisomy 21	1/1,000	na	Transient myeloproliferative disorder, AL
Hereditary breast and ovarian cancer	604370, 612555	*BRCA1, BCRA2*	1/400	AD	AL, early onset breast and ovarian cancer, prostate cancer, pancreatic cancer
Neurofibromatosis type I	162200	*NF1*	1/3,000	AD	JMML, MDS, malignant peripheral nerve sheath tumor, breast cancer
Nijmegen breakage syndrome	251260	*NBN*	1/100,000	AR	lymphoma, medulloblastoma, glioma, rhabdomyosarcoma
Noonan syndrome	163950	*PTPN11, SOS1, RAF1, KRAS, NRAS, BRAF, MAP2K1*	1/1,000-1/2,500	AD	JMML, myeloproliferative disorder, rhabdomyosarcoma, neuroblastoma, other solid tumors
Severe combined immunodeficiency		variety of genes	1/100,000	AR/X-linked	Lymphoma, AL
Severe congenital neutropenia		*ELANE, HAX1, G6PC3, GFI1, TCIRG1*	< 1/1,000,000	AD/AR/X-linked	MDS/AML
Shwachman Diamond syndrome	260400	*SBDS*	1/77,000	AR	MDS/AML
Wiskott Aldrich syndrome	277970	*WAS*	1/100,000-1/1,000,000	X-linked	Lymphoma
X-linked lymphoproliferative disorder	300635	*SH2D1A, XIAP*	1/1,000,000	X-linked	Lymphoma

The most frequent syndromes and the syndromes with the highest risk of developing hematologic malignancies are listed here.
AD = autosomal dominant; AL = acute leukemia; AML = acute myeloid leukemia; AR = autosomal recessive; JMML = juvenile myelomonocytic leukemia; na = not applicable; MDS = myelodysplastic syndrome; NHL = non-Hodgkin lymphoma.

The first group of inherited MDS/AL syndromes stems from germline mutations in *RUNX1*, *ANKRD26*, or *ETV6* and is characterized by thrombocytopenia, functional platelet defects, and an increased risk of MDS/AL.

RUNX1 mutations are associated with a predisposition to bleeding, mild to moderate thrombocytopenia, and an increased risk of hematologic malignancies, including MDS/acute myeloid leukemia (AML) and, less frequently, T-ALL and hairy cell leukemia [9]. Notably, a significant number of families with inherited germline genomic rearrangements of *RUNX1* have been described, which emphasizes the need for array analyses of mutation-negative cases who possess classic *RUNX1*-mutated phenotypes [10].

Patients with *ANKRD26* mutations experience moderate thrombocytopenia and dysmegakaryopoiesis with small megakaryocytes and hypolobulated nuclei [7]. Mutations are clustered in the 5′ UTR of the gene, with only one reported family possessing a point mutation within the coding region [11]. Germline mutations in *ANKRD26* are associated with an increased risk of MDS/AML, and less frequently, chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML) [12].

Germline mutations in *ETV6*, encoding a master hematopoietic transcription factor like *RUNX1*, were first described in 2015 [13–15]. Affected families display mild to moderate thrombocytopenia and a predisposition to a broad spectrum of hematologic and solid malignancies, including MDS/AML, pre–B-cell ALL, multiple myeloma (MM), skin cancer, and colorectal cancer. A higher risk for colorectal cancer and slightly earlier age at onset has also recently been reported for the G allele of a SNP in intron 4 of *ETV6*, rs2238126, probably by altering the binding affinity of transcriptional enhancer MAX [16]. There exist relatively few pedigrees with germline *ETV6* mutations, but some display predisposition toward non-malignant pathologies, such as myopathy, developmental delay, dysmorphic features, an increased risk of autoimmune diseases, esophageal stricture, and gastroesophageal reflux disease. However, more cases will need to be studied to determine whether these features are part of the phenotype. An overview of organ manifestations associated with familial MDS/AL syndromes is given in Table 4.

The second group of inherited MDS/AL syndromes consists of syndromes with an increased risk of MDS/AML, but no thrombocytopenia or other organ manifestations. Germline mutations in *CEBPA*, *SRP72*, and *DDX41* constitute this group.

The familial form of AML with germline *CEBPA* mutations is associated with biallelic mutations, with the germline mutation in the 5′ end of the gene being most commonly observed. Germline-mutated *CEBPA* is present in approximately 1% of all AML cases and in 11% of individuals with biallelic *CEBPA* mutations at the time of diagnosis [17]. Patients with germline *CEBPA* mutations have near-complete penetrance for AML, which classically involves a normal karyotype, the presence of Auer rods, and aberrant CD7 expression. The overall prognosis is favorable with 5-year overall survival rates approaching 70% [18]. Interestingly, this prognosis is somewhat better than in AML with acquired mutations in both *CEPBA* alleles [19]. Despite the relatively favorable prognosis, AML patients with germline *CEBPA* mutations are prone to development of future leukemias, which have been shown to be second primaries with a different acquired 3′ mutation as the second hit [20].

There is ongoing discussion about considering patients with germline *CEBPA* mutations for allogeneic hematopoietic stem cell