EUROPEAN HEMATOLOGY ASSOCIATION

Syndromes predisposing to hematological malignancies

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Take-home messages

- Disruption of several biologic pathways leads to an increased leukemia risk.
- The underlying germline defects overlap with genes/pathways disrupted in sporadic leukemia.
- Patients with various leukemia predisposition syndromes differ substantially regarding cancer risk, spectrum, age of leukemia onset and other clinical or biological features.

Introduction

Genetic conditions predisposing to myeloid and lymphoblastic neoplasms can be grouped based on the underlying defect into seven distinct groups: (1) Li-Fraumeni syndrome; (2) transcription factor defects; (3) inherited bone marrow failure syndromes (IBMFS) / DNA repair defects / immunodeficiency disorders; (4) chromosomal anomalies; (5) Rasopathies; (6) defects of epigenetic regulation; and (7) other (new) entities. As illustrated in Figure 1, syndromes vary in terms of (*i*) hematologic cancer risk; (*ii*) age of onset of hematologic cancer; (*iii*) hematologic cancer spectrum (AML, ALL, MDS, MPN, HL/NHL); (*vi*) risk of developing non-hematologic cancers; (*v*) presence and severity of physical anomalies; (*vi*) benign hematologic anomalies; (*vii*) immunodeficiency; and (*viii*) somatic mutation signature. All syndromes have in common that affected individuals require special attention in the care for their malignant and non-malignant health related problems and psychosocial needs.

Current state of the art

Li-Fraumeni syndrome (LFS)

LFS is an aggressive cancer predisposition syndrome with a broad cancer spectrum caused by germline mutations of the tumor suppressor gene *TP53*. In children with low-hypodiploid ALL, ~40% of patients harbor a *TP53* germline mutation and *TP53* germline defects are associated with relapsed ALL. LFS patients are at increased risk of therapy related-MDS/AML, especially after being treated with alkylating drugs.[1,2]

Transcription factor defects

The same hematopoitic transtriction factors that are somatically altered in multiple hematopoietic neoplasms can be mutated in the germline resulting in leukemia predisposition. The domintantly inherited *PAX5*^{G183S} mutation has been described in familial precursor B-cell ALL. *IKZF1* germline defects occur in patients with immunodeficiency and ALL. Germline mutations of *ETV6* lead to an autosomal dominant syndrome with thrombocytopenia, red cell macrocytosis and cancer predisposition (precursor B-cell ALL, but also other leukemia and tumor types). *RUNX1* mutations cause a familial platelet disorder with associated myeloid malignancy. T-cell ALL and other cancers occur less frequently. *GATA2*-associated predisposition to MDS/AML is an autosomal dominant condition that can be associated with immune deficiency (MonoMAC syndrome) or lymphedema (Emberger syndrome). *GATA2* mutations are common in primary pediatric MDS, especially in adolescents with MDS and -7. ~50% of patients with *CEBPA*-associated predisposition to AML develop leukemia.[3-8]

IBMFS / DNA-repair defects / immunodeficiency

Constitutional mismatch repair deficiency (CMMRD) is caused by bi-allelic germline mutations of *MLH1*, *MSH2*, *MSH6*, or *PMS2* and leads to a highly penetrant, early onset predisposition to brain, gastrointestinal, and hematopoietic cancers (T-NHL most common). Fanconi anemia (FA) is a mainly recessive disorder with at least 21 associated DNA-repair genes (*FANCA-V*). The gene products repair DNA interstrand cross-links and interact with DNA damage response pathways. Dyskeratosis congenita (DC) is classically characterized by nail dystrophy, abnormal skin pigmentation, and oral leukoplakia and caused by mutations in telomere biology genes (X-linked: *DKC1*; autosomal dominant: *TERC*, *TINF2*;

Hereditary hematological disorders - Section 1

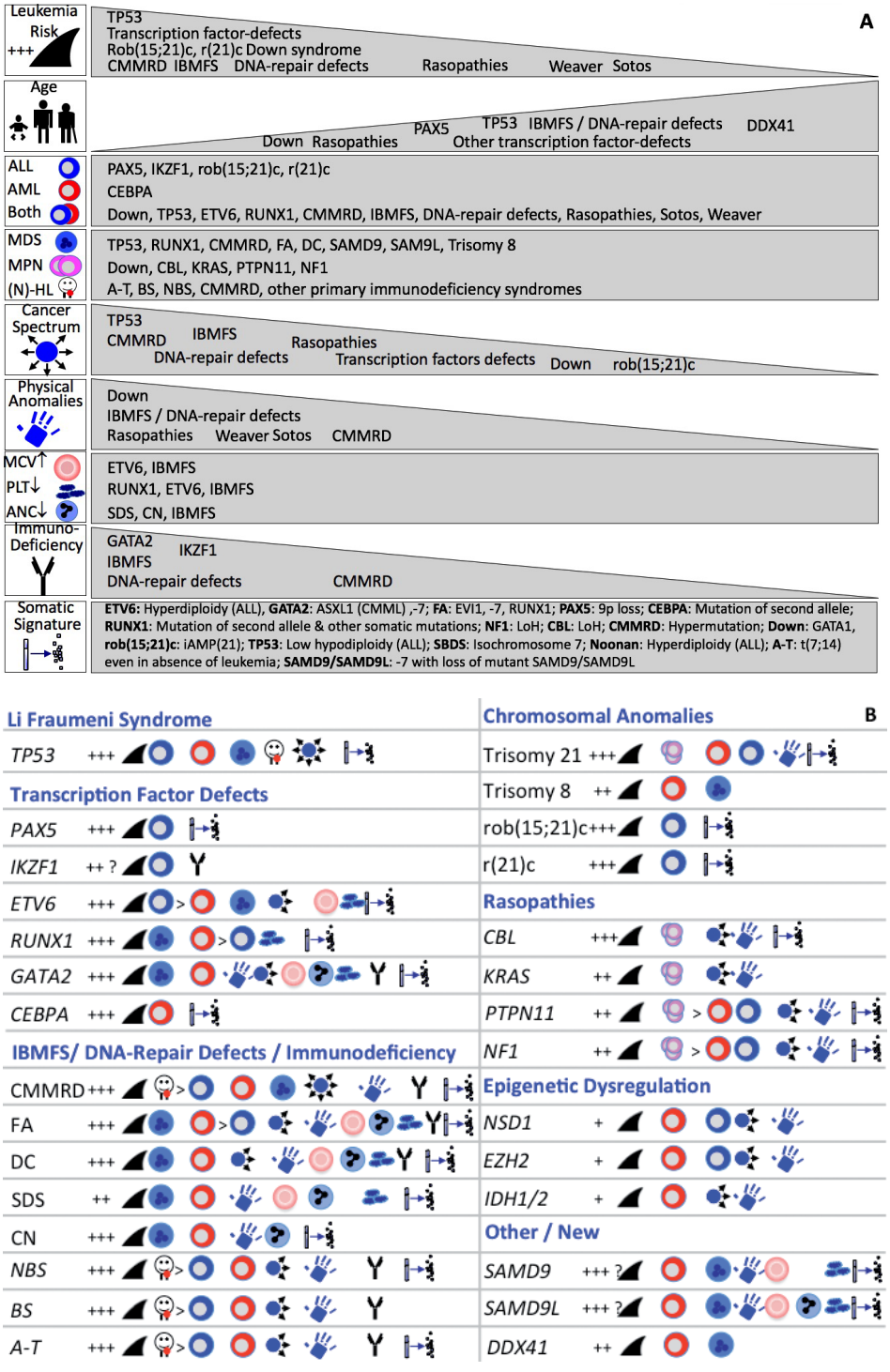

Figure 1. Syndromes predisposing to hematologic malignancies differ regarding different clinical and biological features. A, Overview, and B, more detailed information given for different syndromes.

autosomal recessive: *CTC1, NHP2, NOP10, PARN*, *WRAP53*; dominant or recessive: *ACD, RTEL1*, *TERT*). Patients with FA and DC physical occasionally lack obvious physical anomalies. Both conditions are associated with bone marrow failure, predisposition to MDS/AML and solid tumors (mainly squamous cell carcinoma). An increased MDS/AML risk is also observed in patients with Shwachman-Diamond syndrome (autosomal recessive, *SBDS*) and congenital neutropenia (autosomal dominant: *ELANE*, *GFI1*, autosomal recessive: *HAX1*, *G6PC3*, *VPS45A*, *CSF3R*).[9-12]

Nijmegen breakage syndrome (NBS) is an autosomal recessive disorder caused by *NBN* (nibrin) mutations. Nibrin belongs to the MRE11/RAD50 double stranded break repair complex. Patients show immunodeficiency and a 'bird-like' face. T- and B-NHL are the most common cancer types. Bloom's syndrome (BS) is an autosomal recessive disorder caused by *BLM* mutations (BLM is a RECQ family member DNA helicase). BS patients have severe anomalies and develop a range of neoplasms, including lymphoma and leukemia. Ataxia telangiectasia (A-T) is an autosomal recessive condition caused by *ATM* mutations (ataxia-telangiectasia mutated, cell cycle checkpoint kinase and regulator of TP53, BRCA1, CHEK2, and NBN, important in response to DNA damage). Patients show progressive cerebellar ataxia, conjunctival telangiectasias, immunodeficiency, and high lymphoma and leukemia risk.[13-15]

Chromosomal anomalies

An increased leukemia risk is observed in individuals with Down syndrome (DS) and the rare constitutional trisomy 8 mosaicism (CT8M). Individuals with the constitutional Robertsonian translocation rob(15;21)(q10;q10)c, have a 2,700-fold increased risk of developing ALL. Individuals with constitutional ring chromosomes involving chromosome 21, r(21)c, are also predisposed ALL.[16]

Rasopathies

Patients with *CBL*-syndrome (*CBL*), Noonan syndrome (*PTPN11*, *KRAS*) and Neurofibromatosis 1 (*NF1*) are at increased risk of leukemia, especially juvenile myelomonocytic leukemia. In patients with *CBL*-syndrome the clonal disease may take a benign course. In patients with Noonan syndrome due to a germline mutation of *PTPN11* or *KRAS* a JMML-like picture can be caused by a transient polyclonal proliferative disorder.[17]

Epigenetic dysregulation

Rare cases of leukemia have been described in patients with Weaver (*EZH2*), Sotos (*NSD1*) and Ollier disease/Maffuci syndrome (*IDH1/2* mosaic mutations), suggesting that mutations of these genes represent moderate leukemia risk alleles.[18]

Recently discovered leukemia predisposition syndromes

Ataxia-pancytopenia syndrome (APS) and myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes and enteropathy (MIRAGE) syndrome are caused by activating mutations of *SAMD9L* and *SAMD9* (involved in endosome fusion), respectively. Interestingly, -7 occuring in these rare patients leads to loss of the mutant allele on 7q21. Germline mutations in the DEAD/H-box helicase gene *DDX41* have been recenty identified in adult familial AML.[19,20]

Future perspectives

As new leukemia and lymphoma predisposing genes are continuously being discovered it is important to precisely study the natural history and phenotypic spectrum of each syndrome as well as the implications for cancer prevention and therapy. This is particularly important because some of the conditions discussed in this overview may be associated with significant side effects such as therapy related cancers in patients with LFS. Increasing awareness for these conditions, early diagnosis and - where appropriate - enrolment in surveillance programs and clinical therapeutic trials may improve the lives of affected individuals in the future. Studying these rare conditions has broad implications for cancer biology in general.

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Hereditary hematological disorders - Section 1

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