Review Article

Hematological Malignancies in Adults With a Family Predisposition

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Summary

Background: Some hematological malignancies arise in persons with a hereditary predisposition. The hereditary nature of these diseases often goes unrecognized, particularly when symptoms begin in adulthood.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed.

Results: Many rare germline mutations have been identified that lead to acute leukemia and myelodysplastic syndromes. They differ from one another with respect to their penetrance, the age of onset of disease, and the clinical manifestations. In view of this heterogeneity, no uniform recommendations have yet been formulated for their diagnosis and treatment. The most common types of hematological malignancy with a hereditary predisposition are traceable to an underlying disturbance of DNA damage response and repair mechanisms and to mutations of hematological transcription factors. With regard to the selection of patients for testing, the consensus is that cytogenetic and molecular-genetic findings that are suspect for a hereditary predisposition, such as CEBPA and RUNX1 mutations, call for further investigation, as do any clinical features that are typical of tumor syndromes, or a positive family history. The knowledge that a hereditary predisposition may be present is highly stressful for patients; testing should only be carried out after the patient has received genetic counseling. The confirmation of a germline mutation always requires a comparison with healthy tissue. A fibroblast culture is recommended as the gold standard for this purpose.

Conclusion: The detection of a hereditary predisposition to hematological neoplasia is often relevant to treatment and follow-up care: for example, it may motivate early allogeneic stem-cell transplantation. Counseling, predictive testing, and follow-up care are available to the patients' relatives as well.

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The significance of hereditary cancer predisposition syndromes has been established for solid tumors, such as the Lynch syndrome or familial breast and ovarian cancer, and raised awareness of the role of hereditary predisposition in other cancer entities, including hematological malignancies. While for Lynch syndrome or familial breast and ovarian cancer diagnostic and therapeutic algorithms have been established for routine clinical use (*Box 1 and 2*) (1, 2), potential hereditary predisposition to hematological malignancies, such as acute leukemias or myelodysplastic syndromes (MDS), is frequently overlooked, especially in adults (3). The reasons why an underlying familial predisposition is often not recognized in adult patients with hematological malignancies are manifold. Since most cases of hereditary leukemia or MDS occur in children (4), hemato-oncologists treating adult patients are not very familiar with these diseases. In addition, hematological malignancies are associated with a very complex and heterogenic spectrum of various hereditary genetic changes, so-called hereditary mutations. Since usually only some of the mutation carriers develop clinical manifestations, the family history is often unrevealing. In addition, a comprehensive family history is frequently not taken in the first place (5).

Molecular genetic and cytogenetic tests, such as sequencing of individual genes or groups of genes (so-called gene panel sequencing), and testing for smaller or larger chromosomal changes have shown that numerous hematological malignancies are associated with hereditary predisposition (6). While the exact proportion of cases of acute leukemia or MDS associated with a hereditary predisposition is still unknown, it is estimated to be 5% to 10%; thus, a hereditary predisposition is not rare at all (3, 7–9). For patient populations comprising children and young adults, predisposing hereditary mutations have been reported in approximately 10% of cases (3, 8–10). Among adults, this rate appears to be lower, but, on the other hand, not all hereditary predisposing mutations have yet been identified and new predisposing genetic changes continue to be discovered (11, 12). There still are patients with a family history of cancer who test negative for all of the hereditary mutations identified so far.

It is important to identify genetic predispositions as they may be relevant to the therapeutic approach and detection of a hereditary predisposition provides

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family members with the opportunity to undergo genetic testing and benefit from improved cancer screening.

It is common that patients ask their treating physicians whether their relatives are at an increased risk of developing the disease too. In any case, the issue of hereditary predisposition triggers fears and concerns for family members in patients.

The aim of the article is to present those conditions among the numerous hematological malignancies with a hereditary background which typically do not manifest before adulthood and to discuss the diagnostic approaches and the therapeutic consequences.

Methods

This paper is based on review articles, expert opinions as well as retrospective and prospective case series. Preference was given to recent analyses of the last 5 to 10 years. The selective search of the published literature was performed using the PubMed database. No evidence from randomized trials is available for this question. Reference was made to guidelines from scientific specialist societies, where available.

Acute leukemias and myelodysplastic syndromes (MDS)

Various conditions and pathomechanisms are associated with a predisposition to acute leukemias and MDS. These include

- disorders of DNA repair
- genetic instability syndromes
- telomeropathies
- mutations in signal transduction pathways, transcription factors and tumor suppressor genes
- immune deficiency syndromes(13).

The disease spectrum extends from syndromic disorders with phenotypic abnormalities to a general cancer predisposition to germline mutations with isolated increases in the risk of acute leukemia and MDS. A selection of the most relevant gene mutations associated with a predisposition to acute leukemia and MDS is compiled in the *eTable*. Interestingly, the various gene mutations show

- variable penetrance
- differences in age at time of onset
- varying clinical characteristics.

The most important hereditary predisposition syndromes to hematological malignancies

Disturbed DNA damage response and repair

The development of acute leukemia in patients with Fanconi anemia typically occurs in childhood. The median age at the time Fanconi anemia is first diagnosed is 6.5 years and at the time of occurrence of acute myeloid leukemia (AML) 13 years (14, e1). Even though Fanconi anemia is rarely the cause of AML in adults, it should be included in the differential diagnostic work-up if corresponding clinical signs, such as short stature, café-au-lait spots, congenital heart defects or skeletal abnormalities, are present (9, 14–15).

BOX 1

Lynch syndrome (HNPCC)*

With an estimated frequency of at least 1 in every 300 affected, the Lynch syndrome is one of the most common hereditary cancer syndromes.

It is caused by heterozygous germline mutations in the DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) (e23). While the cancer predisposition is inherited in an autosomal dominant pattern, the actual manifestation of the disease on a somatic level follows a recessive pattern: Only if a somatic mutation occurs in the second allele (second hit), genetic changes can accumulate as the result of the defective repair mechanism and microsatellite instability (MSI) develop and the cell undergo malignant transformation (e24).

Apart from colorectal cancer (lifetime risk of 30–80%, depending on the underlying mutation), patients develop numerous other types of cancer, especially endometrial cancer, more frequently. The type of mutation has an effect on the incidence rates of the various types of cancers (e25). Colorectal cancer patients with Lynch syndrome develop the disease at an earlier age compared to sporadic colorectal cancer, the tumors are more frequently located proximal to the left colic flexure (e26) and of mixed-type histology with mucinous, signet ring cell or medullary components (e27).

Lynch syndrome is underdiagnosed. Lynch syndrome testing selection criteria for patients with overt tumors have been defined in recent years; for example, the Bethesda criteria, last revised in 2004, or more recent recommendations to perform microsatellite instability testing on all colorectal carcinomas. Recommendations for diagnostic work-up and screening have been issued by the German HNPCC Consortium.

In addition, detection of microsatellite instability as a predictive biomarker for the effectiveness of immune checkpoint blockade with anti-PD(L)-1 antibodies has gained increasing attention (e28).

*further reading (1, e29, e30)

Due to its early discovery, the Li-Fraumeni syndrome, which is associated with a germline mutation of the *TP53* tumor suppressor gene, became the prototype of a cancer predisposition syndrome (4, 16–18). Apart from other types of cancer, such as soft tissue sarcoma and osteosarcoma, breast cancer, central nervous system (CNS) tumors, and adrenocortical carcinoma, it is associated with an increased risk of developing leukemias and lymphomas. Typically, half of those affected have already developed the first cancer by their thirties and forties. Likewise, patients with germline mutation-linked ataxia telangiectasia (ataxia telangiectasia mutated, *ATM*) tend to develop hematological malignancies (19). Here, short stature and ataxia are the suggestive clinical features.

Acute leukemia associated with telomere disorders typically occurs in adults (3, 15, 20). An example of this type of diseases is dyskeratosis congenita which is associated with acute leukemias, head and neck squamous cell carcinomas and anogenital tumors. In the differential diagnostic work-up, the following clinical signs are suggestive of this condition:

BOX 2

Familial breast and ovarian cancer*

Up to 10% of all breast and ovarian cancer cases are caused by familial hereditary factors.

Suggestive of a hereditary predisposition are a cluster of cases in families, younger age at onset or the presence of second primary cancers of the breast and ovary.

For people seeking advice and affected individuals from families with this familial clustering of cancer cases, interdisciplinary gynecological, genetic and psychosomatic counselling with analysis of the family tree and potential genetic testing has been established through the German Consortium of Familial Breast and Ovarian Cancer at designated Consortial Centers and collaborating medical practices (www.konsortium-familiaerer-brustkrebs.de).

A dominantly inherited BRCA1 or BRCA2 gene mutation causes disease development with a lifetime risk of 55–60% for breast cancer and about 17–60% for ovarian cancer. With this, they are the most common triggers of these hereditary gynecological diseases (e31). Other breast cancer-associated genes have been identified, including *RAD51C*, *RAD51D*, *CHEK2*, *BARD1*, *CDH1*, *NBN*, *PALB2*, *ATM*, and *TP53*.

Identified high-risk individuals include patients who tested positive for a mutation or who are at an increased risk according to family tree analysis (risk in heterozygotes >20% and/or lifetime risk >30%). They are invited to participate in intensified screening and follow-up care programs which have been established nationwide in Germany. In healthy female mutation carriers, prophylactic surgery, for example mastectomy or salpingo-oophorectomy, may also be considered as a management strategy. In female mutation carriers with moderate or low risk, the type of mutation determines the screening and follow-up care strategy.

*further reading (2, e32–e34)

- short stature
- skeletal abnormalities
- pulmonary fibrosis
- cryptogenic liver cirrhosis
- abnormal pigmentation
- leukopenia
- preceding pancytopenia.

It is conspicuous that all of the hereditary predisposition syndromes from the DNA damage response and repair group are associated not only with an increased risk of hematological malignancies, but also with an increased risk of solid tumors. Interestingly, even in heterozygous carriers of Fanconi anemia or *ATM* germline mutations an up to three times higher risk of hereditary breast cancer was observed (21, 22, e2–e5).

Mutations of hematological transcription factors

Patients with *CEBPA* germline mutations typically develop acute myeloid leukemia (AML) as young adults with almost complete penetrance (3, 4, 23–26). The mean age of onset is reported to be 24 years (1.8–46 years). The prognosis is favorable—as it is for AML with sporadic biallelic *CEBPA* gene mutations.

Carriers of hereditary *RUNX1* mutations have a lifetime risk of developing acute leukemia of only about 35%. The age at which leukemia is first diagnosed in these patients varies widely. Typically, moderate thrombocytopenia is found in carriers of a hereditary *RUNX1* mutation from childhood on, a condition referred to as familial platelet disorder with propensity to myeloid malignancy (FPDMM) (27–29).

An underlying thrombocytopenia is also observed in germline *ETV6*-mutated carriers who are at an increased risk of developing acute lymphoblastic or myeloid leukemias (30).

DDX41 germline mutation carriers typically develop a myelodysplastic syndrome (MDS) or AML only at a mean age of 60 years. Characteristically, the prognosis in patients with these conditions is poor, despite unremarkable chromosome analysis (31–33).

By contrast, hereditary *GATA2* mutation carriers develop MDS or AML typically while they are young. Thus, evaluation for this germline mutation should primarily be performed in young adults with additional clinical signs such as

- immune deficiency
- hearing loss
- pulmonary disease, or
- lymphedema (4, 34).

Newly discovered hereditary predisposition syndromes include, for example, *SAMD9* and *SAMD9L* mutations which give rise to myeloid malignancies with chromosome 7 involvement in combination with neurological symptoms; in severe case, they manifest as MIRAGE syndrome (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, enteropathy) (11, 12, 35).

Clinical consequences of diagnosed germline mutation

For the following reasons, it is of clinical relevance for patients diagnosed with acute leukemia or MDS to find out about a potential hereditary predisposition:

- It provides the opportunity to involve a specialized center in patient management which should closely cooperate with the patient's family physician or community-based hematologist. Carriers of a predisposing germline mutation who have not yet developed overt acute leukemia are advised to have complete blood counts performed regularly, usually at six-month intervals. The actual intervals between the blood tests and the need for additional bone marrow biopsies should be determined based on each patient's individual risk profile (4, 6, 8, 36, 37). In this situation, early detection of a clonal development can facilitate timely planning of allogeneic stem cell transplantation. Specific consensus recommendations have only been prepared for Fanconi anemia and other hereditary anemias (8, e6).

- Some predisposition syndromes are associated with a special sensitivity to chemotherapy and radiation therapy; it is vital to take this into account when

making treatment decisions (4). For example, in patients with Fanconi anemia, standard anthracycline-containing chemotherapy for acute myeloid leukemia or full conditioning prior to allogeneic hematopoietic stem cell transplantation should be avoided because of the disease-specific chromosomal instability which may result in catastrophic adverse events if DNA-damaging substances are administered (3, 14). In patients with Li-Fraumeni syndrome, each chemotherapy or radiation therapy is associated with a high risk for a second primary malignancy (SPM); therefore, treatment decisions should only be made after careful consideration of the risks and benefits of these therapies (18, e7–e9).

- Identification of a germline mutation also helps to pay more attention to non-hematological symptoms, such as pulmonary adverse events in patients with telomere diseases, and to organize interdisciplinary co-treatment of these patients (8).

- Detection of a germline mutation can be critical for the decision to perform early allogeneic hematopoietic stem cell transplantation (e10, e11). For example, patients with acute leukemia and predisposing germline mutation who are treated with conventional chemotherapy with curative intention are exposed to an increased risk of developing acute leukemia again because of their predisposition. For AML patients with hereditary *CEBPA* mutation, clonal differences between the initial leukemia and the second leukemia were shown which indicate that these leukemias are independent of each other and the second leukemia is not a disease recurrence (26).

- With awareness of the germline mutation, potential family donors of allogeneic transplants can be tested for the mutation and transplantation of stem cells from mutation carriers can be avoided (4, 6, 8, 18, 35, 36). This strategy aims at eliminating the risk of donor leukemia after family donor allogeneic stem cell transplantation in case of a common genetic predisposition of the siblings (e12).

- In addition, for family members it offers the opportunity to receive genetic counselling, predictive genetic testing, and, if necessary, early-diagnosis and screening services. The decision when to start cancer screening should take the mutated gene, the mutation type and the typical age at onset in the family into account (32, 38). The transition from carrier status only to overt hematological disease is often gradual. The germline mutation alone can already be associated with a mild disturbance of hematopoiesis and with cytopenia; for example, the *RUNX1* mutation can lead to thrombocytopenia.

The high clinical significance of hereditary predisposition to acute myeloid leukemia is reflected in the WHO classification revised in 2016 which introduced hereditary myeloid malignancies as an independent—still provisional—entity (39).

Patient selection for testing

For hematological malignancies, no standard protocol defining which patients should be selected for testing

TABLE

Possible hereditary predisposition testing selection criteria for patients with acute leukemia or MDS*

Group 1	Cytogenetic and molecular genetic aberrations in leukemia cells typical for predisposition syndrome: gene mutations in leukemia cells, such as biallelic <i>CEBPA</i> , <i>RUNX1</i> and, in younger adults, <i>GATA2</i> mutations, which are likely sporadic in nature, may also be germline mutations. Cytogenetic features, such as loss of the long arm of chromosome 7 in children or young adults with MDS, also justify further testing.
Group 2	Clinical signs suggestive of predisposition syndrome: clinical features suggestive of predisposition syndrome, such as short stature, skeletal abnormalities, pulmonary fibrosis, abnormal skin or hair
Group 3	Bone marrow failure or MDS in younger patients: occurrence of bone marrow failure, aplastic anemia or MDS in young adults, reported in a study of DiNardo et al. with age ≤ 50 years (3)
Group 4	Occurrence of excessive toxicity after chemotherapy or radiation therapy: strong toxicity after treatment; in this case, Li-Fraumeni syndrome and Fanconi anemia should be considered in the differential diagnosis
Group 5	Suggestive personal history: multiple cancers in the individual patient or occurrence of a further malignancy in early adulthood
Group 6	Suggestive family history: Clustering of leukemia and MDS cases or cases of cytopenia of unclear origin or at least occurrence once among first-degree relatives or twice among second-degree relatives (3) or severe clustering of cases with other solid tumors

For hematological malignancies, no standard recommendations or guidelines on how patients should be selected for hereditary predisposition testing have yet been prepared (4). Thus, the table is based on published expert opinions.

CEBPA: CCAAT/enhancer-binding protein alpha; MDS, myelodysplastic syndrome;

RUNX1: runt-related transcription factor 1

*modified according to (3, 8, 36)

for potential hereditary mutations has yet been established (37). However, expert consensus has been reached that with patients of the groups listed in the Table the possibility of an underlying germline mutation should be taken into consideration (3, 8, 36). Here, it is important to thoroughly take and document a detailed family history, including the

- type of malignancy
- age at first diagnosis
- precise degree of kinship and lineage.

Myeloproliferative syndromes, lymphomas and plasma cell diseases

Myeloproliferative syndromes

For myeloproliferative syndromes (MPS), such as essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF), familial clustering has been reported too. First-degree relatives of MPS patients are three to seven times more likely to develop MPS themselves (e13, e14). The frequency of familial cases in MPS is estimated to be approximately 8% (e15). The clinical signs and symptoms of familial MPS are identical with those of sporadic MPS, with an age peak at about age 60 years. Likewise, the risks (bleeding, thrombosis, secondary bone marrow fibrosis, transition to AML, and others) and the prognosis are similar (e13, e14). Interestingly, it appears that in

FIGURE

Algorithm for evaluation of potential hereditary hematological malignancies (HM) by the Chicago Hematopoietic Malignancies Cancer Risk Team (modified according to [7], courtesy of Grune & Stratton, New York). CNV, copy number variation (testing for chromosomal changes); HMMS, hereditary myeloid malignancy syndrome; HM, hematological malignancy; susp., suspicion of

familial MPS the underlying *JAK2* mutation is not inherited directly, but only the predisposition to develop this mutation (e13).

Lymphoma and plasma cell diseases

For lymphomas, familial clustering has also been described. First-degree relatives of patients with non-Hodgkin lymphoma and Hodgkin lymphoma are slightly more likely to develop lymphoma themselves. With chronic lymphocytic leukemia, this risk is even elevated 8.5 times (e16). Likewise, plasma cell diseases, such as multiple myeloma, show weak familial clustering.

A large proportion of these familial hematological malignancies without identified monogenetic cause appear to have a multifactorial or genetically complex etiology where, besides exogenous factors, numerous genetic risk factors with low or moderate penetrance are involved. The combined genetic factors can only explain part of the risk and remain largely

unexplored; therefore, they do not play a role in routine genetic testing as yet.

Genetic counselling and testing

In Germany, the German Genetic Diagnostics Act provides the legal framework for hereditary predisposition testing. The purpose of this law is to protect the patient's right to information self-determination and to prevent discrimination because of genetic features. The diagnostic work-up to determine whether a patient actually has a predisposing germline mutation as well as predictive testing of clinically unaffected relatives must only be performed by specialists in human genetics after a detailed informed consent discussion. This discussion is highly sensitive and has to take ethical aspects into account (e17). For example, knowing about a germline mutation may cause even greater distress and uncertainty for those affected as they already experience because of the disease per se. Furthermore, it should always be critically questioned whether the

knowledge of a genetic change contributes to treatment decision-making and whether effective screening and intervention programs are available for the patients and their relatives. The decision for or against genetic testing is particularly difficult for parents as they have to make it for their children. In this group, testing should only be performed in case of known early manifestation. In some cases, genetic counselling is even made more difficult by the fact that the pathogenicity of a detected mutation is unclear. Usually, mutations are classified as pathogenic, likely pathogenic, of uncertain significance, likely benign, and benign (8, 40). The clinical significance of individual mutations may have to be re-evaluated from time to time in the light of new scientific insights.

Diagnostic techniques

Gene mutations are identified using cytogenetic and molecular genetic methods. Besides the gene mutations covered by routine testing, increasingly whole gene groups are tested for, using panel sequencing methods. In patients with suspected hereditary etiology, targeted testing of corresponding genes is performed. If, despite highly suspicious family history, no mutation can be detected with these methods, whole genome sequencing may be performed. An algorithm proposed by scientists at the University of Chicago is presented in the *Figure (7)*.

Identification of a mutation in cancer cells which is typically found in patients with hereditary cancer and fits to the condition does not allow to draw the conclusion that the patient suffers from a germline disease because the mutation per se does not reveal whether it is a germline mutation or a sporadic mutation only present in the cancer tissue. Thus, testing of healthy material is always required for cross-checking and confirmation.

In patients with hematological diseases, it can usually not be differentiated between hereditary and sporadic mutations by testing of blood samples, because malignant cells are frequently released into the peripheral blood. As an alternative, buccal swab samples can be used; however, this strategy is also associated with a risk of leukocyte contamination. For this reason, some authors regard a fibroblast culture derived from a skin biopsy as the gold standard (3). Alternatively, the use of hair or nail specimens may be considered.

Conclusion

Numerous hematological malignancies can be associated with an underlying hereditary predisposition. In view of the implications for diagnosis and treatment, this possibility should be taken into consideration in older patients, too. Predictive testing may then be offered to asymptomatic family members at risk. Due to the substantial heterogeneity of hereditary predisposition syndromes, randomized controlled trials and consensus recommendations are not available.

Key messages

- In acute leukemias and myelodysplastic syndromes (MDS), up to an estimated 10% of cases have an underlying hereditary predisposition which is often not recognized if the onset is in adulthood.
- The spectrum of hereditary predisposition to develop acute leukemias and MDS is very complex and heterogeneous—with large differences in penetrance, first-diagnosis age peak and clinical picture.
- Identifying a hereditary mutation provides the opportunity to involve a specialized center in the management of the affected individuals and to offer examinations at regular intervals and treatments tailored to the disease.
- There is substantial consensus that patients with cytogenetic and molecular genetic profiles suspicious of a hereditary predisposition should be further assessed, as well as patients with suspicious clinical features or family history.
- Genetic counselling is obligatory. Difficult points include concerns for family members and uncertainties in case of disorders with variable penetrance or detection of gene mutations with as yet undetermined clinical significance.

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► Supplementary material

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Supplementary material to:

Hematological Malignancies in Adults With a Family Predisposition

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eTABLE

Gene mutations with leukemia predisposition, modified according to Di Nardo et al. 2016 (3), Porter 2016 (4), Furutani und Shimamura 2017 (8), Godley 2017 (37), Alter 2018 (20)

Gene mutation	Leukemia type	Frequency of germline mutation	Inheritance	Penetrance of hematological disease	Median age at onset	Other cancers	Other clinical features	References
<i>FANCF</i> genes, <i>PALB2</i> and others (Fanconi anemia)	– MDS, AML – aplastic anemia	1–2% of total cases with suspected germline mutation ^{*1}	AR XR	For bone marrow failure: very high (80% by age 10 years) For AML/MDS: 10–30 % (also dependent on mutation)	For AML/MDS: about 15 years (1–57)	– Head and neck cancer (squamous cell carcinoma) – Gastrointestinal and genital tumors – CNS tumor – Breast cancer	– Short stature – Café-au-lait spots – Congenital heart defects – Renal malformations – Skeletal abnormalities	(3) (10) (14) (15) (20)
<i>TP53</i> (17p13.1) (Li-Fraumeni syndrome)	– ALL (susp. hypodiploid karyotype) – AML, MDS – Lymphoma	0.7% of pediatric ALL cases	AD	2–4%	About 12 years (ALL typically affects older children)	– Multiple cancers, susp. soft tissue and osteosarcoma – Breast cancer – CNS tumor – Adrenal cancer	–	(17) (18) (e18)
<i>ATM</i> (11q22.3) (ataxia telangiectasia)	ALL Lymphomas	Sporadic cases	AR	3% (ALL) 4% (Hodgkin) 14% (NHL)	11 years 10 years 24 years	– Breast cancer – Ovarian cancer – Stomach cancer – Other solid tumors	– Cerebellar ataxia – Telangiectasia – Immune deficiency	(19)
<i>TERT</i> (5p15.33) <i>TERC</i> (3q26.2) <i>DKC1</i> (Xq28) and other (dyskeratosis congenita)	MDS, AML, aplastic anemia	1–2% of total cases with suspected germline mutation ^{*1}	AD/AR AD XR	3% (AML) 11% (MDS)	About 35 years (4–73)	– Head and neck cancer (squamous cell carcinoma) – Anogenital tumors	– Immune deficiency – Nail dystrophy – Oral leukoplakia – Idiopathic pulmonary fibrosis – Idiopathic liver cirrhosis	(3) (15) (20)
<i>CEBPA</i> (19q13.1)	De-novo AML – AML FAB M1/2 – normal karyotype – CR1 rate 91%	5–10% of cases with biallelic <i>CEBPA</i> mut., in total about 0.5% ^{*2}	AD (typical N-terminal germline mutation + additional somatic C-terminal mutation)	high, almost 100%	About 25 years (2–46)	–	–	(23) (24) (25) (e19) (26)
<i>RUNX1</i> (21q22.12)	– MDS/AML (also T-ALL, HCL, CMML) – preceding thrombocytopenia	About 20% of cases with <i>RUNX1</i> mutation, in total about <2% ^{*3}	AD	35–40%	Median age about 33 years (5–77 years)	–	–	(27) (28) (29)
<i>GATA2</i> (3q21.3)	– MDS – CMML – MPS – AML (often monosomy 7, trisomy 8)	7–15% (children, adolescents) 0.5% (adults)	AD	75%	About 20 years	–	– Immune deficiency – Deafness – Lymphedema – Lung disease	(34) (e20)

Gene mutation	Leukemia type	Frequency of germline mutation	Inheritance	Penetrance of hematological disease	Median age at onset	Other cancers	Other clinical features	References
<i>ETV6</i> (12p13.2)	– ALL, AML/MDS – preceding thrombocytopenia	Sporadic cases	AD	about 35% (variable, depending on mutation and family)	Variable, depending on mutation and family	Potentially higher risk of solid tumors	–	(30)
<i>DDX41</i> (5q35.3)	– MDS/AML – also CMML, CMML, NHL, Hodgkin – Normal karyotype – Poor prognosis	60% of cases with <i>DDX41</i> mutation	AD (frequently second somatic <i>DDX41</i> mutation)	High	62 years (44–70)	–	–	(31) (32)
<i>SAMD9</i> 7q21.2 (MIRAGE) <i>SAMD9L</i> 7q21.2 (ataxia-pancytopenia syndrome)	– MDS/AML – frequently loss of long arm of chromosome 7	Very rare, sporadic cases	AD AD	Still unknown	1 year (0–51)	–	– Short stature – Adrenal hypoplasia – Infections – Developmental delay – Ataxia	(11) (12) (35)

The e Table shows the most relevant hereditary predisposition syndromes to acute leukemias and myelodysplastic syndromes. It reveals that these syndromes form a very heterogeneous group of rare diseases. These predisposition syndromes vary significantly with regard to clinical manifestation, penetrance and typical age at onset of the first disease manifestation. It is conspicuous that disorders of DNA damage response and repair—this includes the four above described conditions Fanconi anemia, Li-Fraumeni syndrome, ataxia telangiectasia, and dyskeratosis congenita—not only result in hematological malignancies, but also predispose to numerous solid tumors, while mutations in the transcription factors *CEBPA*, *RUNX1*, *ETV6*, and *DDX41* almost always cause hematological malignancies.

Their proportion of the total population of patients with leukemia can only be estimated for the two most common groups, the *RUNX1* and the *CEBPA* mutations. All other percentages listed in the Table are strongly biased by the preselection of the patient groups. Rarer hereditary leukemia predispositions, such as thrombocytopenia 2 (ANKRD26), myeloid neoplasms with germline predisposition (*ATG2B/GSKIP*) and familial aplastic anemia (*AA*)/MDS with *SRP72* mutation are not listed in the Table.

*1 In the study by Di Nardo et al. 2016 (3), only 1/67 studied cases each; however, this rate is unreliable because of the small group size and the strong influence of patient preselection.

*2 The frequency of biallelic *CEBPA* mutations in the total AML patient population is reported to be 5% (Wouters et al. 2009 (e21)). With a proportion of hereditary cases of 5–10%, the overall frequency of hereditary cases appears to be almost 0.5%.

*3 The frequency of *RUNX1* mutations in the total AML patient population is reported to be 10–15% (Sood et al. 2017 (28); Gaidzik et al. 2016 (e22)). In the study by Di Nardo et al. (3), 2/9 cases tested for *RUNX1* mutation had a germline mutation. The overall frequency of hereditary cases appears to be almost 2%.

Gene mutations: ATM, ataxia telangiectasia mutated; *CEBPA*, CCAAT/enhancer-binding protein alpha; *DDX41*, DEAD-Box helicase 41; *DKC1*, dyskeratosis congenita 1; *ETV6*, translocation-Ets-leukemia virus; *FANCA*, Fanconi; *PALB2*, partner and localizer of *BRCA2*; *GATA2*, *RUNX1*, runt-related transcription factor 1; *SAMD9*, sterile alpha motif domain-containing protein 9; *SAMD9L*, sterile alpha motif domain-containing protein 9 like; *TERC*, telomerase RNA component; *TERF*, telomerase reverse transcriptase; *TP53*, tumor protein P53

Diseases: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CMML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR1 rate, rate of first complete remission; De-novo AML, without preceding MDS; FAB M1/2, French American British classification; HCL, hairy cell leukemia; hypodiploid karyotype, karyotype with chromosome losses; karyotype, set of chromosomes; MDS, myelodysplastic syndrome; monosomy 7, loss of chromosome 7; MPS, myeloproliferative syndrome; NHL, non-Hodgkin lymphoma; T-ALL, T-cell acute lymphoblastic leukemia; trisomy 8, addition of chromosome 8

Frequency: Biallelic: on both alleles, also homozygote

Inheritance: AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive