



Germ line mutations associated with leukemias

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Several genetic syndromes have long been associated with a predisposition to the development of leukemia, including bone marrow failure syndromes, Down syndrome, and Li Fraumeni syndrome. Recent work has better defined the leukemia risk and outcomes in these syndromes. Also, in the last several years, a number of other germ line mutations have been discovered to define new leukemia predisposition syndromes, including *ANKRD26*, *GATA2*, *PAX5*, *ETV6*, and *DDX41*. In addition, data suggest that a substantial proportion of patients with therapy related leukemias harbor germ line mutations in DNA damage response genes such as *BRCA1/2* and *TP53*. Recognition of clinical associations, acquisition of a thorough family history, and high index-of-suspicion are critical in the diagnosis of these leukemia predisposition syndromes. Accurate identification of patients with germ line mutations associated with leukemia can have important clinical implications as it relates to management of the leukemia, as well as genetic counseling of family members.

Learning Objectives

- Understand the leukemia risk and therapeutic implications in syndromes with phenotypic abnormalities
- Recognize that some familial disorders of hematopoiesis may have increased risk of hematologic malignancy
- Recognize that certain molecular findings in leukemia may indicate an underlying leukemia predisposition

Introduction

Cancer predispositions due to germ line mutations have long been recognized to contribute to the development of many solid tumors. Until recently, with the exception of Li Fraumeni syndrome (LFS), leukemia susceptibility has been primarily associated with clinical syndromes such as Fanconi anemia (FA), dyskeratosis congenita, and trisomy 21 (Down syndrome). However, in the last several years, population and family studies have identified a number of germ line genetic mutations that increase the risk of leukemia in carriers. Many of these mutations are in genes already implicated in leukemogenesis, shedding further light on their importance, and in some cases the function of these genes in the pathogenesis of leukemia. The development of massively parallel sequencing platforms has facilitated many of these findings. The increasing use of targeted and unbiased sequencing in both research and clinical settings necessitates familiarity with these genetic syndromes in the evaluation and management of patients with hematologic malignancies.

Herein, this review highlights new scientific and clinical insights in well-known syndromes associated with leukemia, as well as new leukemia predisposition disorders caused by germ line mutations. These disorders are loosely categorized as syndromic, with associated phenotypic anomalies; disorders of abnormal hematopoiesis; and isolated cancer/leukemia predispositions (Table 1). A few emerging leukemia predisposition syndromes are also briefly discussed. Due to space limitations, important findings from genome-

wide association studies identifying variants with strong association with the development of leukemia are not discussed, as these have been recently, thoroughly reviewed.¹

Syndromic predispositions to leukemia

Several syndromes have been recognized to be associated with the development of leukemia for decades. For example, FA is primarily an autosomal recessive syndrome that includes bone marrow failure (BMF), short stature, and abnormal thumbs among other anomalies, and a predisposition to leukemia, primarily AML. Studies from the National Cancer Institute's Inherited Bone Marrow Failure Syndrome Cohort have estimated observed to estimated ratios of AML incidence at over 300 in patients with FA. FA is caused by mutation in one of at least 19 different genes that contribute to a DNA repair mechanism.² Importantly, many patients with FA do not have overt clinical syndromic features. However, those with bi-allelic mutation in *FANCD1/BRCA2* have more phenotypic anomalies, including imperforate anus, renal anomalies, and cardiac defects, and are at the highest risk of AML, with a reported cumulative incidence of ~80% by age 10 years.³ *BRCA2* and *BRCA1* are both FA genes (*FANCD1* and *FANCS*, respectively); and although most notably associated with Hereditary Ovarian-Breast Cancer syndrome, germ line mutations in DNA damage response genes, including *BRCA1* and *BRCA2*, are found in ~20% of patients with therapy-related leukemias.^{4,5} Similarly, patients with dyskeratosis congenita, due to mutations in telomere maintenance genes (*DKC1*, *TERC*, and *TINF2* among others), have BMF and much higher than expected rates of AML.⁶ Patients with other inherited BMF syndromes such as Diamond-Blackfan anemia, Shwachman-Diamond syndrome, severe congenital neutropenia and thrombocytopenia, and absent radius syndrome may also have an increased risk of AML, although the relative risk in these diseases has not been determined, in part due to the later age of leukemia onset, in addition to the rarity of diagnosis of these diseases.⁷

Patients with Down syndrome, due to trisomy of chromosome 21 (T21), also share characteristic phenotypic anomalies, congenital defects, and

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Table 1. Germ line mutations associated with leukemia

Predisposition	Inheritance	Genes	Altered pathway/function	Hematologic malignancies
Syndromic predispositions to leukemia				
FA	AR, XLR	<i>FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, FANCM, and FANCT; FANCI and FANCD2; BRCA2/FANCD1, BRCA1/FANCS, FANCR/RAD51, FANCI, FANCN, FANCO, FANCP, and FANCO</i>	DNA damage/repair	MDS, AML
Dyskeratosis congenita	AD, AR, XLR	<i>DKC1, TERC, and TINF2; TERT, NHP2, NOP10, WRAP53, RTEL1, CTC1, PARN</i>	Telomere maintenance	MDS, AML
Down syndrome	Sporadic	Unknown	Multifactorial	AMKL, ALL
RASopathies	AD	<i>NF1, PTPN11, KRAS, NRAS, SOS1, RAF1, CBL, SHOC2, HRAS, BRAF, MEK1, MEK2, and SPRED1</i>	RAS signaling	NS-MPD, JMML
GATA2 deficiency	AD	<i>GATA2</i>	TF network	MDS, AML, CMML
Disorders of abnormal hematopoiesis				
FPDMM	AD	<i>RUNX1</i>	TF network	MDS, AML, T-ALL
THC2	AD	<i>ANKRD26</i>	MAPK signaling	MDS, AML, CML
THC5	AD	<i>ETV6</i>	TF network	MDS, B-ALL, MP-ALL
Isolated cancer/leukemia predisposition				
LFS	AD	<i>TP53</i>	DNA damage/repair	AML, ALL, sAML
CMMRD	AR	<i>MLH1, MSH2, MSH6, and PMS2</i>	DNA damage/repair	T-NHL, B-NHL, T-ALL, B-ALL, MDS, AML
<i>CEBPA</i> mutation	AD	<i>CEBPA</i>	TF network	AML
<i>DDX41</i> mutation	AD	<i>DDX41</i>	RNA splicing and/or telomere maintenance?	MDS, AML, CML, HL, NHL
<i>PAX5</i> mutation	AD	<i>PAX5</i>	TF network	B-ALL
Emerging leukemia predisposition syndromes				
<i>ATG2B/GSKIP</i> duplication	AD	<i>ATG2B/GSKIP</i>	Unknown	MPN, AML
<i>ACD</i> mutation	AD	<i>ACD</i>	Telomere maintenance?	BMF
<i>SRP72</i> mutation	AD	<i>SRP72</i>	Unknown	MDS
<i>SH2B3</i> mutation	AR	<i>SH2B3</i>	JAK/STAT signaling	B-ALL
<i>RBBP6</i> mutation	AD	<i>RBBP6</i>	DNA damage/repair?	MPN
<i>LAPTM5</i> and <i>HCLS1</i> mutations	AD	<i>LAPTM5</i> and <i>HCLS1</i>	Unknown	WM

AD, autosomal dominant; ALL, acute lymphoblastic leukemia; AMKL, acute megakaryocytic leukemia; AML, acute myeloid leukemia; AR, autosomal recessive; B-ALL, B-cell acute lymphoblastic leukemia; B-NHL, B-cell NHL; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CMMRD, constitutional mismatch repair deficiency; FPDMM, familial platelet disorder with associated myeloid malignancy; HL, Hodgkin lymphoma; JMML, juvenile myelomonocytic leukemia; MAPK, mitogen-activated protein kinase; MDS, myelodysplastic syndrome; MP-ALL, mixed phenotype acute lymphoblastic leukemia; MPN, myeloproliferative neoplasm; NF1, neurofibromatosis type 1; NHL, non-Hodgkin lymphoma; NS-MPD, Noonan syndrome-associated myeloproliferative disease; sAML, secondary AML; T-ALL, T-cell acute lymphoblastic leukemia; TF, transcription factor; THC, thrombocytopenia; T-NHL, T-cell NHL; WM, Waldenström macroglobulinemia; XLR, X-linked recessive.

a risk for leukemia, both AML and ALL. The incidences of ALL and AML in children with T21 are 33 and 150× that of age-matched disomic individuals. The myeloid leukemias of Down syndrome, as classified by the World Health Organization, are unique in harboring somatic mutations in *GATA1*, are more likely to be of M7 phenotype (acute megakaryoblastic leukemia), and are often preceded by transient abnormal myelopoiesis in neonates.⁸ Although patients with Down syndrome are at high risk of toxicity from conventional chemotherapy, cooperative groups report high cure rates of myeloid leukemias of Down syndrome with event-free survival rates of ~80%.⁹ Similarly, ALL in those with Down syndrome is biologically distinct

from ALL in those without T21. For example, the *ETV6-RUNX1* translocation, which typically confers a good prognosis, is found about three- to 10-fold less in those with T21,¹⁰ whereas aberrant expression of *CRLF2* occurs ~10-fold more.¹¹ Importantly, outcomes in those with ALL and T21 are not as good as in disomic individuals, in part because of toxicity during remission induction, and perhaps due to differences in the molecular underpinnings of the disease.⁹ However, the molecular drivers in ALL in those with T21 may ultimately serve as biomarkers indicating targeted therapy, such as JAK inhibition in cases with *CRLF2* overexpression. Interestingly, in stark contrast to FA and dyskeratosis congenita, in which the risk of solid tumors is also quite

high, patients with T21 rarely develop solid tumors, a pattern that may help in understanding carcinogenesis in the general population.

ALL in disomic individuals often demonstrates somatic trisomy of chromosome 21, suggesting unique contributions from this chromosome in leukemogenesis. More infrequently (~2% of childhood ALL), there is intrachromosomal amplification of chromosome 21 (iAMP21), which defines a unique subgroup of ALL. Recently, it was found that those with constitutional Robertsonian translocation of chromosomes 15 and 21 are at over 2000-fold risk of developing leukemia with iAMP21.¹² Robertsonian translocations are those that involve the short arms of acrocentric chromosomes, and are found in ~1 in 1000 newborns, although the t(15;21) is quite rare. Importantly, patients with iAMP21 ALL have inferior outcomes when treated as standard risk, but fare relatively well when treated as high risk.¹³ Current cooperative group protocols stratify iAMP21 ALL as high risk, necessitating intensified therapy and highlighting the importance of identifying these patients up front. The *RUNX1* gene is within the region most commonly amplified; therefore, iAMP21 ALL can be diagnosed by fluorescence in situ hybridization using the same probes for identifying *ETV6-RUNX1* fusions, when there are 5 or more copies of the *RUNX1* gene per cell.¹⁴

A number of syndromes with overlapping phenotypes caused by germ line mutations in the RAS/mitogen-activated protein kinase pathway are also associated with a high risk of leukemia. These “RASopathies” include NF1, and the NS, Costello, Noonan-like CBL, Legius, and cardio-facial-cutaneous syndromes.¹⁵ Approximately 10% of patients with NS have a transient NS-MPD during infancy.¹⁵ Analogous to transient abnormal myelopoiesis in those with T21, NS-MPD usually resolves, but can cause significant morbidity and even mortality. NS-MPD infrequently progresses to JMML. Indeed, the identification of mutations in *PTPN11* being responsible for NS, led to the identification of somatic mutations in the same gene in ~35% of cases of nonsyndromic JMML.¹⁶ Subsequent studies of RASopathies and JMML have solidified the genetic link between RAS activation via mutation in the *NF1*, *NRAS*, *KRAS*, and *CBL* genes, and JMML.¹⁶ This link has clinical implications, because targeted inhibition of MEK and/or the phosphatidylinositol 3-kinase/AKT pathway have demonstrated promising results in preclinical models of JMML,^{17,18} and planning of clinical trials of MEK inhibition in children with RAS activated cancer is underway.¹⁶

More recently, another group of overlapping syndromes has been defined by germ line mutations in *GATA2*. In addition to MDS and/or AML, patients may have immunodeficiency, sensorineural hearing loss, lymphedema, and dermatologic or pulmonary manifestations, among others (Figure 1).¹⁹ The immunodeficiency is associated with particular susceptibility to human papillomavirus and nontuberculous mycobacteria, leading some to advocate for early human papillomavirus vaccination and antibiotic prophylaxis.¹⁹ Germ line mutation in *GATA2* is also found in 7% of all children with MDS and about two-thirds of adolescents with monosomy 7 MDS, making it the most common germ line defect predisposing to pediatric MDS.²⁰ Evaluation of *GATA2* in children with MDS is important, even in the absence of a family history, because it may inform supportive care strategies and/or accelerate planning for hematopoietic stem cell transplantation.

Disorders of abnormal hematopoiesis

In the last decade or so, more subtle disorders associated with leukemia have been genetically defined. These disorders have been identified by astute clinical observations of unique familial diseases, followed by

thorough laboratory investigation, initially through linkage analysis and more recently with high throughput genome sequencing methods. Several of these leukemia predisposition syndromes are associated with abnormal hematopoiesis, particularly thrombopoiesis. Affected family members harbor germ line mutations in one of several genes, most of which are recurrently somatically mutated in sporadic cancers. In addition to shedding light on the mechanisms of leukemogenesis, identification of familial germ line mutations has clinical implications, particularly as it relates to genetic counseling of family members and donor identification in those for whom hematopoietic stem cell transplantation is indicated.

The first of these to be defined at the gene level was Familial Platelet Disorder with Associated Myeloid Malignancy, caused by a mutation in the *RUNX1* gene. Affected family members generally have moderate thrombocytopenia, mild bleeding tendency, and some develop leukemia.²¹ Most cases of leukemia are myeloid, but a few cases of lymphoid malignancies have been observed.²¹ Most mutations in *RUNX1* have been classified as being dominant negative or haplo-insufficient, leading to different levels of *RUNX1* inactivation. Although both types of mutations are associated with platelet disorders, clinical and experimental data suggest that dominant negative *RUNX1* mutations have distinct effects on hematopoiesis and may confer a higher risk of leukemia.^{21,22}

Another disorder of abnormal thrombopoiesis (Online Mendelian Inheritance in Man THC2) is caused by germ line mutation in *ANKRD26*.²³ In ANKRD26-related thrombocytopenia (ANKRD26-RT), the bleeding risk is fairly low and the thrombocytopenia tends to be moderate with normal platelet size, and with no consistent defect in *in vitro* aggregation studies. Careful examination of case and family histories indicate that patients with ANKRD-RT are at increased risk of MDS and leukemia.^{24,25} Although not fully penetrant, the observed/expected rates for AML, MDS, and CML are 23, 12, and 34, whereas the risks of lymphoid malignancy and nonhematologic cancers do not appear to be increased.²⁵

Recent examinations of families with autosomal dominant thrombocytopenia and leukemia predisposition have defined a new syndrome of thrombocytopenia, and susceptibility to malignancy (Online Mendelian Inheritance in Man THC5) caused by germ line mutation in *ETV6*.²⁶⁻²⁹ Although there is some concentration of mutations in the DNA binding domain of *ETV6*, mutations in *ETV6* are distributed throughout the gene (Figure 2). Most that have been examined cause a loss of normal transcriptional repression by *ETV6*, probably in a dominant negative manner. Although variable in presentation, patients had mild to moderate thrombocytopenia and bleeding tendency, red cell macrocytosis, and multilineage dysplasia with hypolobulated megakaryocytes, and about one-third of reported cases had hematologic malignancy. Although germ line *ETV6* mutations are most closely associated with B-cell ALL, other hematologic malignancies have been observed in carriers, including MDS, multiple myeloma, and AML. Examination of samples from the Pediatric Cancer Genome Project did not reveal germ line mutation in children with cancers other than leukemia,²⁸ but some affected family members had solid tumors in adulthood,²⁶ and *ETV6* variants were recently reported to be associated with colorectal cancer susceptibility,³⁰ raising the possibility that germ line mutations in *ETV6* contribute to a more general cancer predisposition syndrome. Importantly, in a population-based study, ~1% of children with apparently sporadic ALL harbor germ line mutations in *ETV6*,²⁹ suggesting that germ line predispositions to leukemia may be more common than previously believed.

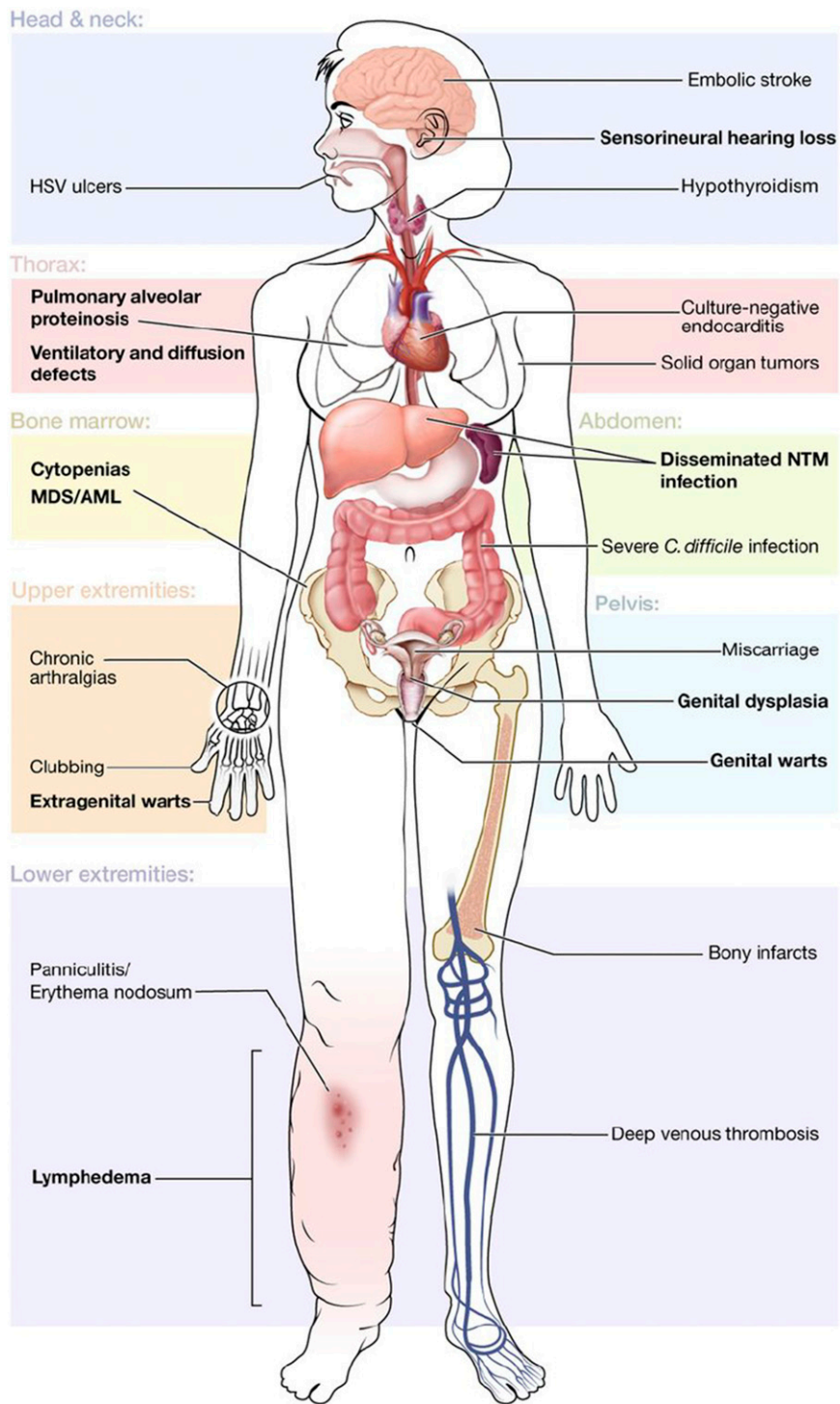


Figure 1. Clinical features of GATA2 deficiency. Common manifestations are shown by organ system, with primary features in bold. Reprinted from Spinner et al.¹⁹ *C difficile*, *Clostridium difficile*; HSV, herpes simplex virus; NTM, nontuberculous mycobacteria.

Nonsyndromic cancer/leukemia predisposition

Some inherited predispositions to cancer do not have associated syndromic findings or signs of abnormal hematopoiesis. LFS is caused by mutations in *TP53* and confers a lifetime risk of cancer, including leukemia, of ~70% for men and ~100% for women. Leukemia is among the core cancers associated with LFS, accounting for 3% to 6% of LFS tumors.³¹ Virtually all hematologic malignancies are represented in the International Agency for Research on Cancer *TP53*

database, including therapy related MDS and AML.³² Whether patients with LFS have lower remission rates with therapy remains to be determined; however, somatic mutations in *TP53* in leukemia are associated with poor outcomes in childhood and adult leukemias.³³⁻³⁵ Making a diagnosis of LFS or other cancer predisposition syndromes is critical, not only as it relates to genetic counseling and donor selection but also in considering tumor surveillance studies after successful treatment of a primary tumor. Importantly, as much as 40% of children

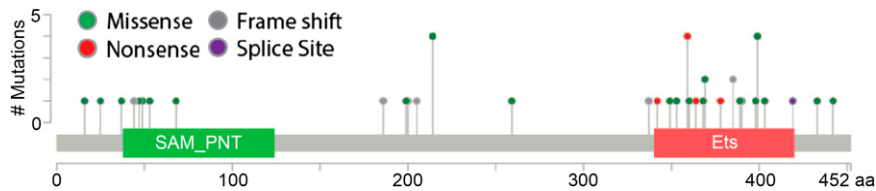


Figure 2. Distribution and frequency of reported germ line mutations in ETV6. The ETV6 protein is diagrammed with its pointed (SAM_PNT) and canonical ETS family DNA binding (Ets) domains. Germ line mutations associated with leukemia are clustered in the Ets domain, but spread throughout the protein.

with low hypodiploid ALL harbor germ line mutation in *TP53*,^{36,37} suggesting that low hypodiploid ALL is a manifestation of LFS. Thus, one should consider genetic counseling and testing for germ line *TP53* mutation in children with hypodiploid ALL.

Like LFS, Lynch syndrome is another general cancer predisposition syndrome, primarily associated with colorectal and endometrial cancer. It is caused by mutations in mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Although those with heterozygous mutations in these genes do not carry a high risk of leukemia, hematologic malignancies are among the most common cancers in those with CMMRD, an autosomal recessive disorder caused by bi-allelic mutation in one of these genes.³⁸ Over half of hematologic malignancies are of T-cell origin, although B-cell lymphoma and leukemia, and myeloid leukemias also occur at high rates.³⁹ Patients with CMMRD may have features associated with NF1, including cafe-au-lait spots and neurofibromas, a family history of gastrointestinal or gynecologic cancer, and/or parental consanguinity, and diagnostic criteria have been suggested.³⁸ As with other cancer predisposition syndromes, accurate diagnosis has implications not only for immediate family members, but may influence treatment decisions because mismatch repair-deficient cells may have altered the sensitivity to certain chemotherapeutics.³⁸

Other disorders are associated more specifically with the development of leukemia, in the absence of other tumor types. One gene that is recurrently somatically mutated in AML that is also involved in familial AML is *CEBPA*.⁴⁰ Germ line mutations in *CEBPA* cause a highly penetrant predisposition to AML in the absence of other clinical features like thrombocytopenia or preceding MDS. In contrast to *ETV6*, germ line mutations in *CEBPA* cluster at the N-terminus (Figure 3).⁴¹ Additional somatic mutations in the C-terminus were detected in all

AML samples.⁴¹ Although remission was achieved in >90% of patients and overall survival at 10 years was 67%, recurrent disease was frequent in those with *CEBPA* germ line mutation. Interestingly, the somatic mutations in AML at recurrence were usually distinct, suggesting the development of new leukemia, rather than the relapse of chemotherapy resistant clones.⁴¹ Interestingly, those with AML that harbor a double-somatic mutation in *CEBPA* and those with a germ line mutation, have a similar, better prognosis, than those with a single-somatic mutation,^{41,42} suggesting a clinically significant difference in the biology of these diseases.

Germ line mutations in *DDX41* were more recently described to define another disorder in which cancer predisposition seems to be limited to the hematopoietic system.⁴³⁻⁴⁶ Patients with a germ line mutation in *DDX41* tend to be older at the time of presentation of hematologic malignancy, as compared with other leukemia predisposition disorders, with an average age of 62 years, and have poor prognosis compared with those with wild-type (WT) *DDX41*.⁴⁵ Malignancies include MDS, AML, CML, Hodgkin lymphoma, and non-Hodgkin lymphoma. Most patients have normal complete blood counts prior to the diagnosis of hematologic malignancy.⁴⁴ Although the role of *DDX41* in hematopoietic progenitor cells is not fully understood, an intriguing observation is that those with a *DDX41* mutation have significantly shorter telomeres in peripheral blood cells.⁴³ Importantly, somatic mutations in *DDX41* are found in AML, even in some patients without germ line *DDX41* mutation, highlighting its role in leukemogenesis.⁴⁵ Nonetheless, predicted loss-of-function *DDX41* variants are found in public databases at rates higher than other leukemia predisposition variants (eg, *CEBPA*, *ETV6*), leading some to argue that these variants are risk factors for hematologic malignancies, rather than a causal Mendelian link.⁴³ Regardless of its contribution to leukemia predisposition, patients

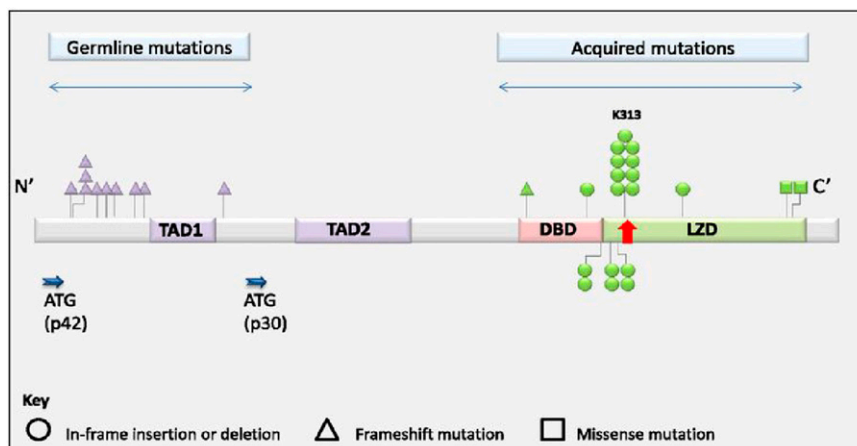


Figure 3. Distribution and frequency of germ line and acquired mutations in *CEBPA*. Reprinted from Tawana et al.⁴¹

with *DDX41* mutations responded better to lenalidomide treatment as compared with those with WT *DDX41*, which if replicated prospectively, could provide a therapeutic option for those with this high-risk disease.⁴⁵

Unique among leukemia predisposition syndromes is that caused by germ line mutation in *PAX5*, in that to date, the leukemia risk appears to be highly specific to pre-B-cell ALL.^{47,48} Outside of the nervous system, *PAX5* expression is restricted to B cells, in which it plays a critical role in normal B-cell development. It is somatically mutated in one-third of pre-B-ALL cases, highlighting a major role in leukemogenesis. In all familial cases, the WT allele was deleted in leukemia samples, whereas the mutant allele was retained. Notably, only 1 germ line *PAX5* mutation has been described (c.547G>A) from all 3 kindreds reported, resulting in lower but not absent *PAX5* transcriptional activity, whereas somatic alterations in *PAX5* have more profound dysfunction. These data and preclinical experimental models indicate that *PAX5* and other B-cell development transcription factors have complex roles in leukemogenesis that remain to be elucidated.

Emerging leukemia predisposition syndromes

There have been other reports of germ line mutations of genes causing a predisposition to leukemia that have not been replicated or reported in additional kindreds. These include the duplication of *ATG2B* and *GSKIP*, which seems to predispose to MPNs⁴⁹; mutations in *RBB6* associated with MPNs⁵⁰; mutations in *ACD* that cause a BMF syndrome⁵¹; mutations in *SRP72* that lead to MDS⁵²; mutations in *LAPTM5* and *HCLSI1* that are associated with familial Waldenström macroglobulinemia⁵³; and mutations in *SH2B3* that appear to predispose to ALL.⁵⁴ Subsequent work will determine the extent to which germ line mutations in these genes have implications outside of the reported families.

Conclusion

The ready availability of high-throughput sequencing technology has helped to define several new leukemia predisposition syndromes over the last few years, and more are expected. In some cases, these findings have helped to better understand the mechanisms of leukemogenesis that should eventually impact clinical care. With increasing use of sequencing in clinical practice, more patients will be identified with mutations in these genes in leukemia samples. A challenge for physicians will be to recognize when these mutations may represent germ line, rather than somatic mutations. It is imperative to be cognizant of the possibility of identifying these mutations with currently available targeted and unbiased sequencing platforms, and to consider plans for genetic counseling and germ line testing in the event that they are identified.

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