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REVIEW

The genetics of familial leukemia

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Familial leukemia is rare, but, as is the case with other cancer family syndromes, its study is likely to lead to the identification of genes causative of the far more common, sporadic cases. I review the clinical and, what is known of the molecular genetic features of familial leukemia. I propose a nosology based on whether the leukemia is a component of a medical syndrome or exists as a solitary disease, the apparent mode of inheritance, and the distribution of leukemia types and subtypes in affected family members. I review the recent findings from my group that leukemia is inherited with 'anticipation', in the form of a declining age of onset with each passing generation. I consider two models of leukemia genesis that can potentially account for anticipation in familial cases and incorporate epidemiological observations made in sporadic cases. The first model is analogous to trinucleotide repeat expansion in Huntington disease, myotonic dystrophy, and other inherited neurodegenerative illness demonstrating anticipation. The second model considers evidence that anticipation may be common to multiple types of familial cancer and is based on the intergenerational inheritance of multiple downstream mutations resulting from a defect in a single DNA repair gene.
Keywords: leukemia; familial; anticipation

Introduction

A family history of leukemia in a first degree relative increases the risk for leukemia by approximately three- to five-fold.[1,2] The magnitude of this risk elevation is equivalent to or even greater than that exhibited for malignancies well known to have a substantial proportion of cases resulting from autosomal dominant inheritance of a mutant tumor suppressor gene, such as breast cancer[3] and colorectal carcinoma.[4] On the other hand, familial leukemia is exceptionally rare, and only a few pedigrees obviously transmitting leukemia have ever been recognized. This paradox and other observations suggest that the fraction of leukemia attributable to heritable factors could be markedly under appreciated. First, acute lymphocytic leukemia (ALL) is predominately a disease of childhood.[5] In other childhood malignancy, such as retinoblastoma and Wilm's tumor, a large proportion of cases are the result of germline mutations in a tumor suppressor gene.[6] Conceivably, an analogous phenomenon pertains to leukemia. Second, although epidemiological studies have failed to find consistent links between leukemia and environmental exposures (excepting radiation and chemotherapy[7]), which would influence somatic mutation rates, there is evidence that parental environmental exposures, which would influence *de novo* germline mutations, may be of significance: childhood ALL increases with maternal age.[8] Parental exposure to radiation[9] and chemical carcinogens[10] are controversial leukemia risk factors. There may be an excess of multiple congenital anomalies among children with sporadic leukemia,[11–14] and the occurrence of multiple congenital anomalies often indicates a *de novo* gonadal mutation.[15] Third, the concordance for leukemia among identical twins is high.[16–19] Fourth, my group's recent review of rare pedigrees transmitting autosomal dominant leukemia finds evidence for 'anticipation' in the form of a declining age of onset with each passing generation.[20] Anticipation may result in an age-dependent penetrance phenomenon that makes autosomal dominant inheritance more difficult to discern.

Here I review the situations in which leukemia is inherited as a single-gene disorder following Mendelian principles. Familial leukemia can occur in the context of a medical syndrome, in which it is one component of the overall disease, or it can occur as isolated, 'pure' leukemia minimally associated with co-morbid conditions. The observation of anticipation in the rare familial cases may offer a clue to mutational mechanisms operating in the common, sporadic cases. Anticipation occurs in Huntington disease, myotonic dystrophy, and other inherited neurodegenerative illness where it results from the expansion of unstable trinucleotide repeat sequences. Since this remains as the only molecularly defined instrument for anticipation, I weigh the possibility that an analogous situation holds for leukemia genes. I also review evidence that anticipation may be present in other types of familial cancer, including those in which the gene has been characterized and does not contain trinucleotide repeat tracts, but is involved in maintaining genome integrity. Here I propose a novel and alternative hypothesis for anticipation in familial cancer based on the inheritance of a cascade of *de novo* mutations in secondary tumor suppressor genes resulting from a primary defect in a gene responsible for DNA fidelity.

Leukemia as part of a syndrome

Several syndromic illnesses have leukemia as a component feature (Table 1).

Down syndrome

Down syndrome is characterized by dysmorphism, mental retardation with hypotonia, frequent congenital heart disease and gastrointestinal anomalies, and results from trisomy of at least the distal long arm of chromosome 21.[21] Individuals with Down syndrome have a 10–18-fold increased risk for leukemia.[22] The type of leukemia varies with age. There is a high frequency of a clonal leukemoid reaction in the newborn period, that usually spontaneously remits.[23] Before 3 years of age, acute myelogenous leukemia (AML) predominates, with the FAB M7 megakaryoblastic being the most common subtype.[24] Since M7 AML is relatively rare in the general population, the

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Table 1 Nosology of familial leukemia

	Inheritance	*Locus*	*Gene*
Syndromic with other illness			
Constitutional trisomy			
Down syndrome	sporadic, parental translocation carrier	21q	
Chromosome 8 trisomy mosaicism	sporadic	8	
DNA repair deficiency			
Bloom syndrome	AR	15q26.1	BLM
Ataxia telangiectasia	AR	11q22-23	ATM
Nijmegen/Berlin breakage syndrome	AR	8q21	
Fanconi anemia	AR	9q22.3	FACC
		16q24.3	FAA
Tumor suppressor gene syndromes			
Neurofibromatosis 1	AD	17q11.2	NF1
Li Fraumeni syndrome	AD	17p13.1	p53
Immunodeficiency syndromes			
Wiskott–Aldrich syndrome	XLR	Xp11.23	WASP
Bruton agammaglobulinemia	XLR	Xq21.3	BTK
Other			
Schwachman–Bodian pancreatic lipomatosis	AR	?t(6;12)	
Kostmann's infantile genetic agranulocytosis	AR	1p35	
Blackfan–Diamond syndrome	AD, AR		
Pure familial leukemia			
Childhood myelodysplasia with monosomy 7	AR	?inv1p	
Myelodysplasia and/or AML (multiple subtypes)	AD with anticipation	21q22.3	
			?AF9
			?fra16q22
			?CBL2
M5 AML	AD with anticipation		
M6 AML	AD with anticipation		
CLL	AD with anticipation, ?AR		
ALL	AR, ?AD with anticipation		
CML	AD with anticipation		
Multiple leukemia types	AD with anticipation, ?XLR		
Myeloproliferative disease	AD with ?anticipation		
Lymphoma	AD with anticipation		

AR, autosomal recessive; AD, autosomal dominant; XLR, X-linked recessive; t, translocation; inv, inversion; fra, fragile site.

specific increase in risk for M7 AML among Down syndrome individuals is estimated at up to 400-fold.[21] After the age of 3, acute lymphocytic leukemia (ALL) predominates.[24,25] Individuals mosaic for Down syndrome who develop leukemia[26] or transient leukemoid reactions[27] invariably have leukemic involvement of the trisomy 21 clones, confirming that a locus or loci on this chromosome is responsible. Attempts have been made to define the critical region for leukemia by comparing atypical Down syndrome karyotypes, such as ring chromosomes and isochromosomes,[28–30] and two leukemia genes map to this region on the long arm of chromosome 21. The AML1 locus on 21q22.3 encodes the A subunit of core binding factor (CBFA) and is the site of recurrent t(8;21)(q22;q22) translocation resulting in a chimeric fusion protein.[31] This translocation is among the most frequent chromosomal abnormalities in AML, especially the M2 subtype. The core binding factor binds to a DNA sequence motif common to many genes expressed in hematopoietic cells and is a homologue of the *Drosophila* runt segmentation gene. Knockout mouse experiments demonstrate that CBFA is required for embryonic hematopoiesis.[32] The second gene is defined by a large family inheriting autosomal dominant platelet granule defects and predisposition to AML, for which linkage to a 15 cM region of 21q22.3 has been established.[33] In addition to AML1, this region contains IFNAR, CRF2-4, GART, and SON.

Trisomy 8 syndrome

Among hematologic malignancies with a single chromosomal aberration, acquired trisomy 8 is the most common finding (reviewed in Ref. 34). Trisomy 8 is found in up to 25% of myeloid dysplasia and leukemia. As a sole chromosomal change, it is most common with M5 monocytic AML, present in about 10% of all cases. Constitutional trisomy 8 is extremely rare, and, presumably owing to the lethality of the multiple attendant congenital abnormalities, exists primarily in individuals in the mosaic state. Clinical features of constitutional trisomy 8 mosaicism include a characteristic facial and skeletal limb dysmorphism with variable degrees of mental retardation. There are several case reports of trisomy 8 mosaic individuals developing aplastic anemia, myelodysplasia, and acute and chronic myelogenous leukemia, with, in all cases, the malignant clone being derived from the trisomy 8 population of cells. Potential chromosome 8 genes responsible for this association may be suggested by the translocation breakpoints found in sporadic leukemia. The reciprocal gene fusion partner for t(8;21)(q22;q22) with CBFA is ETO on chromosome 8, a gene of uninvestigated function expressed during hematopoiesis.[31] Recurrent translocations involving 8p11 occur in some AML and are characteristically found in M4/M5 myelomonocytic subtypes.[35] The breakpoint has recently been molecularly defined[36] and found to be rooted at chromo-

some 8 in the coding sequence of MOZ, a novel zinc finger containing gene with putative acetyltransferase activity, and for the most common translocation with 16p13, in the coding sequence of the CREB binding protein.

DNA repair syndromes

Autosomal recessive syndromes of DNA repair deficiency are well known to predispose to malignancy, especially hematologic neoplasms.

Bloom syndrome: Bloom syndrome features growth retardation, characteristic facies, photosensitive telangiectatic erythema, café-au-lait skin pigmentation, and immunodeficiency with recurrent infections[37] and is most common in the Ashkenazi Jewish population.[38] AML, ALL, lymphoma, and other malignancy occur in about 25% of patients. Cells from affected individuals demonstrate an increased frequency of sister chromatid exchanges,[39] and the responsible gene on 15q26.1 has been identified as a putative DNA helicase,[40] related to *E. coli* RecQ.

Ataxia telangiectasia: Ataxia telangiectasia is characterized by progressive cerebellar ataxia, telangiectatic skin lesions, and recurrent sinopulmonary infections consequent to the combination of neurologic depression and mild immunodeficiency.[41,42] About 15–20% of patients develop malignancy, usually by age 15 years, and most are of lymphoid origin, including Hodgkin and non-Hodgkin lymphoma, and T cell ALL.[43,44] The cellular defect is characterized by a failure to inhibit DNA synthesis following radiation and disobedience to the G1-S transition checkpoint of the cell cycle.[45] The culprit gene on 11q22-q23 encodes ATM, a putative phosphatidylinositol kinase homologous to yeast proteins involved in meiotic recombination and cell cycle control.[46] Two variants of ataxia telangiectasia, Nijmegen breakage syndrome and Berlin breakage syndrome, have similar cellular, immunological, and chromosomal findings, but differ clinically by the presence of microcephaly and a characteristic birdlike facies.[47] The gene for these disorders was recently mapped to chromosome 8q21.[48]

Fanconi anemia: Fanconi anemia consists of pancytopenia with variable congenital abnormalities including short stature and skeletal dysplasia with hypoplastic thumbs, mental and sexual retardation, skin pigmentary changes, and renal anatomic anomaly.[49] The chromosomes of cultured cells from affected individuals are unusually susceptible to breaks induced by alkylating and other agents of DNA damage.[50] 52% of Fanconi anemia patients develop myelodysplasia or AML by age 40.[51] There are at least four cellular complementation groups for Fanconi anemia.[52] Mutations in a gene FACC on 9q22.3, encoding a cytoplasmic protein of unknown function, have been identified in complementation group C.[53] Linkage for complementation group A was established to 16q24.3[54] and the gene was recently cloned through a positional strategy[55] and independently by complementation of cellular phenotype.[56] The protein product is predicted to contain a leucine zipper and nuclear localization signals.

Neurofibromatosis I

Neurofibromatosis I is a common (approximately 1/3000) autosomal dominant genodermatosis comprised of neurofibromas and hyperpigmented café-au-lait skin lesions resulting from mutations in the neurofibromin tumor suppressor gene on chromosome 17q11.2.[57] The encoded protein is in the GAP family and down-regulates the p21-*ras* proto-oncogene.[58] Individuals with neurofibromatosis 1 are at markedly elevated risk for developing CNS and peripheral nerve tumors that include gliomas, schwannomas, and neurofibrosarcomas, as well as rhabdomyosarcomas of skeletal muscle.[59] Although less frequent, there is an estimated 221-fold increased risk for juvenile CML, usually with associated monosomy 7, and a five-fold increased risk for ALL and a 10-fold increased risk for non-Hodgkin lymphoma.[60] Myelodysplasia, occasionally evolving to AML, occurs disproportionately commonly among patients.[61] There seems to be an association between leukemia in neurofibromatosis I and the additional skin finding of xanthogranuloma.[62] Loss of heterozygosity with deletion of the normal allele has been demonstrated in malignant myeloid-derived clones from children with neurofibromatosis I.[63] Epidemiological evidence suggests that myeloproliferative disease occurs more commonly in boys with neurofibromatosis I and is more frequently associated with maternal inheritance.[60,64]

Li–Fraumeni syndrome

Li–Fraumeni syndrome is the consequence of autosomal dominantly inherited germline mutation of the p53 tumor suppressor gene on chromosome 17p13.1.[65] Affected individuals are predisposed to the development of multiple types of tumors, most especially sarcomas of muscle, bone, and soft tissue, as well as brain tumors, melanoma, breast cancer, bronchogenic lung cancer, melanoma, and prostate and pancreatic carcinoma. Although leukemia and lymphoma occur in the Li–Fraumeni syndrome, they are somewhat less frequent than the other tumor types.[66]

Immunodeficiency syndromes

The X-linked recessive Wiskott–Aldrich syndrome is characterized by eczema, thrombocytopenia with small platelets, immunodeficiency, and bloody diarrhea.[44] The responsible gene encodes a proline-rich protein on Xp11.23-p11.22.[67] Death usually occurs before age 10 years from a combination of infections and recurrent hemorrhage, although patients are also susceptible to malignancy, particularly B cell lymphomas.[68,69] ALL and AML have also been reported.[70]

Bruton agammaglobulinemia is an X-linked immunodeficiency disorder characterized by recurrent bacterial infection[71] resulting from failure to produce mature B lymphocytes and failure of Ig heavy chain rearrangement. The defective gene is Bruton tyrosine kinase[72] mapping to the Xq21.3-q22 boundary. There is a 6% risk for development of malignancy,[73] usually of lymphoreticular origin, with a median age of onset of 4 years.[74] There also appears to be an increased risk for colorectal carcinoma.[75]

Other inherited immunodeficiency syndromes, including common variable immunodeficiency, X-linked lymphoproliferative syndrome, and selective IgA deficiency are associated with non-Hodgkin lymphoma.[76] In considering leukemia

and malignancy associated with genetically determined immunodeficiency syndromes, two possibilities need to be distinguished, namely (1) that the leukemia is directly related to the underlying genetic defect; or (2) that the leukemia is a consequence of the immunodeficiency and that the precise nature of the genetic defect is irrelevant. Support for the latter possibility comes from the observations of increased malignancy, frequently hematopoietic, among acquired immunodeficiencies, including AIDS, autoimmune disease, chemotherapy- and radiotherapy-associated immunodeficiency, and transplant-related immunosuppression.[76]

Other syndromes

The Shwachman-Bodian syndrome of autosomal recessive pancreatic insufficiency with congenital pancreatic lipomatosis and moderate dwarfism has bone marrow abnormalities similar to Fanconi anemia in that there is early onset pancytopenia with a similar distribution of hematologic malignancy[77] but also an increased risk for pediatric myelodysplasia.[13] A differentiating feature is that there appears to be an absence of chromosomal fragility.[78] A t(6;12)(q16.2;q21.2) chromosomal translocation observed in one patient may suggest a causative locus.[79]

Autosomal recessive Kostmann's infantile genetic agranulocytosis usually terminates with death from AML by the age of 3.[80] Many of the affected individuals come from Norrbotten county in northern Sweden, where the gene was probably introduced through a founder effect.[81] In several non-Swedish patients mutations in the GCSF receptor on chromosome 1p35-p34.3 have been identified.[82]

The Blackfan–Diamond syndrome of congenital hypoplastic anemia and growth retardation with characteristic facies has also been associated with AML.[83] Both autosomal dominant and autosomal recessive forms are known.

Pure familial leukemia

Non-syndromic leukemia can be classified on the basis of its inheritance pattern and by the spectrum of the involved hematopoietic lineages (Table 1).

Autosomal recessive childhood myelodysplasia with monosomy 7

At least nine families have been reported in which multiple siblings have developed myelodysplasia, often progressing to AML.[84–91] The constant features in these families are a childhood onset and the presence of bone marrow monosomy for chromosome 7. The consistent absence of cases in other generations is compatible with autosomal recessive inheritance. Estimates for the proportion of cases of childhood myelodysplasia that are familial range from about 2%[91] to 33%.[92] In one sibship of two affected brothers, both had constitutional inversion of chromosome 1p22q23, potentially implicating a gene at these breakpoints as causative.[87]

Autosomal dominant myelodysplasia and AML

The autosomal dominant inheritance of pure myelodysplasia (with infrequent progression to AML), pure AML (without significant antecedent myelodysplastic illness), or families with combinations of myelodysplasia and AML have all been reported. There is one family with just myelodysplasia.[93] There are at least another four in which individuals developed either AML or myelodysplasia with or without progression to AML (Refs 13, 94, 95, and a family I have consulted upon). There are 16 families in which individuals developed nearly exclusively AML, without evidence of protracted myelodysplasia (Refs 96–108, pedigree Nos 18 and 21 of Ref. 109, and an additional family that I have cared for).

Many of the individuals in these families were reported before the current era of FAB classification and molecular refinement of diagnosis; it is therefore difficult to establish subtype. In those families in which modern criteria have been applied to AML subtyping, it appears that multiple, different AML subtypes occur within the same family, as for example, documented in Ref. 94. Presumably, the defective gene acts early in the course of hematopoietic differentiation, and the particular subtype is determined by the spectrum of secondary mutagenic events in genes acting later in the sequence of hematopoietic differentiation. Two exceptions to this are found in families with monocytic (FAB M5) or erythroleukemic subtypes (M6). Two families have been reported in which three individuals presented identically with monocytic AML.[100,110] (The second of these families[110] differs in that all the affected are siblings within a single generation and the onset is in infancy. Such a pattern is consistent with autosomal recessive transmission, or autosomal dominant inheritance with anticipation, see below.) Four families[105,106,108,111] and a fifth that I have cared for, have been reported with individuals presenting with a unique myelodysplasia involving erythropoietic precursors frequently culminating in acute erythroleukemia. The term 'erythremic myelosis' or DiGuglielmo syndrome has been used to describe the characteristic myelodysplasia. Presumably, the aberrant genes in these families are limited to initiating leukemia only in restricted subtypes of myeloid lineages. The proband in the erythroleukemia family that I evaluated was positive for mitomycin and diepoxybutane induced chromosome fragility, suggesting that familial DiGuglielmo syndrome could be related to, or a variant of, Fanconi anemia. Chromosome fragility testing has apparently not been performed on the other erythroleukemia families.

Autosomal dominant chronic lymphocytic leukemia (CLL)

Epidemiological evidence suggests that CLL may have the strongest hereditary component of all the leukemias. In some surveys, up to a third of patients with CLL have at least one first degree relative with hematologic malignancy.[2,112] Nevertheless, reports of familial CLL are uncommon, and few pedigrees are known. Seven families are multigenerational, consistent with autosomal dominant inheritance (Refs 113–117 and pedigree Nos 16 and 17 of Ref. 109). Four families have multiple occurrences within a sibship (Refs 118 and 119, and pedigree Nos 45 and 71 of Ref. 17), consistent with either autosomal recessive inheritance or autosomal dominant transmission with anticipation (see below). As CLL is, in general, a disease of the elderly, even in the cases of familial CLL, where the age of onset tends to be younger, there may be problems in establishing the family history because of the necessary expanse of time between senior generations. As is true for the sporadic case, a male predominance is present in the familial cases.

Familial ALL

There are five published reports of multigenerational ALL (Refs 120–122, and pedigree Nos. 23 and 33 of Ref. 109), possibly consistent with autosomal dominant inheritance. The small size and number of such pedigrees, however, makes it possible that these represent chance clusterings without a heritable component. In a large study of 382 offspring of survivors of childhood leukemia (usually ALL) and non-Hodgkin lymphoma,[123] no increased risk of malignancy was observed, suggesting that the heritable component of, at least ALL, may be small or non-existent. Reports of three families with multiple affected children within a sibship (Refs 124 and 125, and in the cosanginuous family of Refs 126 and 127) are unlikely to represent sporadic clustering and are consistent with autosomal recessive inheritance.

Familial chronic myelocytic leukemia (CML)

There are four families with multigenerational CML (Refs 128 and 129 and pedigree Nos. 28 and 59 of Ref. 109), consistent with autosomal dominant inheritance.

Autosomal dominant inheritance of multiple leukemia types

Twenty-four families have been reported with multiple individuals developing different or unspecified types of leukemia among the affected individuals (Refs 103, 104, 130–137, pedigree Nos. 20, 22, 24, 27, 28, 38, and 39 of Ref. 109 pedigree Nos. 58, 90, 91 and numerous first degree relative pairs with leukemia in Ref. 17), and two other families I have been informed of). In some families there is co-segregation of acute and chronic myeloid leukemia, while in other families there are mixtures of myeloid and lymphoid leukemias.

X-linked recessive leukemia

There is one family in which seven males were affected with differing subtypes of leukemia, and X-linked recessive inheritance has been proposed.[138] This pattern of inheritance could also be explained through autosomal dominance and anticipation (see below).

Other hematopoietic malignancy

A smattering of families with familial myeloproliferative disease (Refs 139–142 and references contained therein), generally stopping short of CML, and lymphoma[143,144] have been reported. Autosomal dominant inheritance (with anticipation, see below) appears to be the mode of genetic transmission for these illnesses, as well.

Anticipation in familial leukemia

Anticipation is the observation of increasing severity or earlier age of onset of disease occurring with each passing generation for an autosomal dominant disorder. It was first reported early in the century for Huntington disease and myotonic dystrophy (reviewed in Ref. 145) and was widely regarded as a true phenomenon until the publication in 1948[146] of an influential paper by the mathematician and geneticist Penrose. Penrose persuasively argued that anticipation is an artifact of three sampling biases: (1) the selection of parents with late disease onset due to limitation of reproductive success in those affected early in life; (2) selection of offspring with early onset due to rarity or severity increasing medical attention; and (3) selection of cases with simultaneous onset in parent and child, resulting in increased reporting. His conclusions were largely considered as authoritative on the subject until quite recently, when it was definitively shown to the contrary that anticipation is a reality in at least Huntington disease, myotonic dystrophy, and some other inherited neurological diseases, whose molecular mechanism results from the intergenerational expansion of unstable trinucleotide repeat sequences (reviewed in Ref. 147).

My group first considered the possibility that anticipation was operative in autosomal dominant leukemia after observing a drop in age from one generation to the next in the family that we first reported.[94] We were also intrigued by the possible coincidence of ataxia and leukemia in this and a second family[89] as well as the co-existence of myeloproliferative disease and Huntington disease in a third family.[142] Since CAG trinucleotide repeats encoding polyglutamine are a motif common to some transcriptional activator genes,[148] which could conceivably be attractive candidate leukemia genes, we were motivated to test this hypothesis. We reviewed all of the reports of familial leukemia that we could identify and that also met select criteria likely to exclude families with appreciable ascertainment bias.[20] The pedigrees were aligned by generation, and age-dependent penetrance curves were constructed for each generation (Figure 1). Of 49 affected individuals in nine families transmitting AML, the mean age of onset is 57 years in the grandparental generation, 32 years in the parental generation, and 13 years in the youngest generation. We also analyzed the age of onset in affected parent–child pairs in these families and found a mean intergenerational age decline of 28 years in the 21 affected parent–child pairs. Of 18 affected individuals from seven families transmitting CLL, age-dependent penetrance curve analysis is shown (Figure 2), and the mean age of onset in the parental generation is 66 years and in the youngest generation is 51 years. (Most of the pedigrees with CLL consisted of just two generations.) Of nine parent–child pairs with CLL, the mean

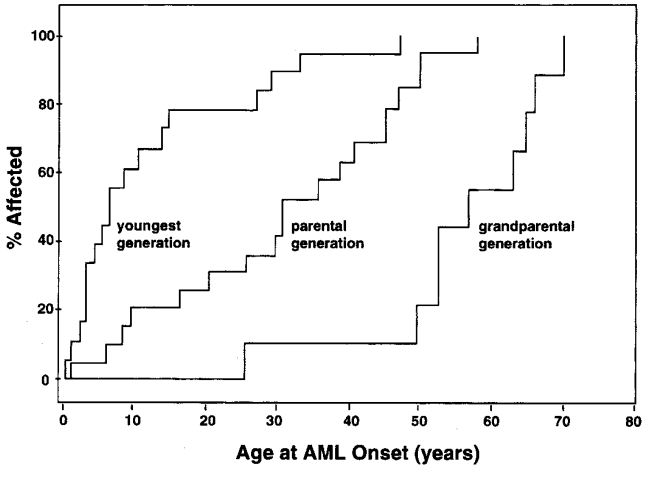

Figure 1 Age-dependent penetrance of familial AML by generation.

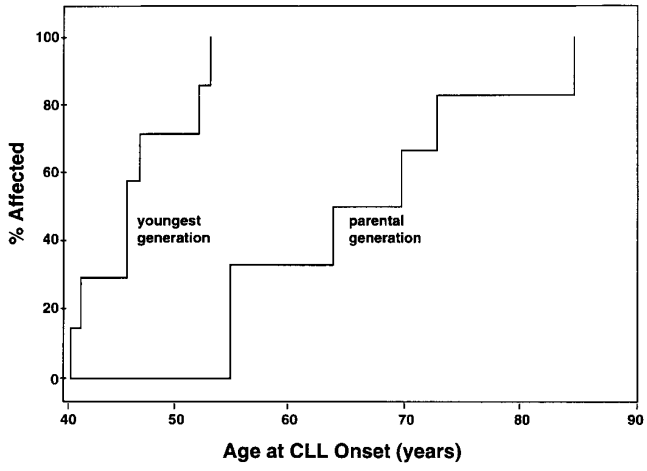

Figure 2 Age-dependent penetrance of familial CLL by generation.

age of intergenerational decline is 21 years. For both AML and CLL the results are highly statistically significant and robust in the face of rigorous tests to exclude ascertainment bias. Inspection of the rare pedigrees transmitting other types of leukemia also appear consistent with anticipation with similar intergenerational age drops in virtually every parent–child pair. While sampling biases can never be completely excluded, anticipation appears evident in each of the multigenerational leukemia families that I review here.

Remarkably confirmatory evidence for anticipation in familial leukemia can be drawn from earlier studies. Videbaek[109,149] observed anticipation in his exhaustive review of all cases of familial leukemia prior to 1947. Collectively analyzing pedigrees with all forms of familial leukemia, he found an average age of onset in parents at 57.0 years, children at 33.8 years, and grandchildren at 11.7 years.[109,150] Sampling bias again seems unlikely, because a similar intergenerational drop in age was found between affected uncle–aunt and nephew–niece pairs, but was not seen when comparing the age of onset between the oldest and youngest individuals within large sibships. In a population-based survey that considered familial relationships in all forms of hematopoietic malignancy, including leukemia, lymphoma, and myeloma, the mean difference between ages at death in affected parent–child pairs was 38 years.[130]

Further evidence for anticipation is found in a peculiar inheritance pattern seen in seven pedigrees in which parallel sibships related as first cousins are affected with leukemia (Refs 132, 151–155, and pedigree No. 31 of Ref. 109). Such a pattern is not easily explained by either autosomal recessive or autosomal dominant inheritance. The most plausible explanation is to suppose that there is autosomal dominant inheritance with anticipation and that the parental generation (where all the individuals are related as siblings) has a reduced penetrance because of a requirement for a greater age of onset in this generation.

A model for leukemia initiation based on trinucleotide repeat expansion

The molecular mechanism of anticipation in leukemia is unknown. It is possible that anticipation in leukemia results from expansion of an unstable repetitive sequence in analogy to the situation with trinucleotide repeat expansion in inherited neurodegenerative disease. Should this prove true, then there are unique implications for the genesis of leukemia in the more common, non-inherited cases. The CAG/CTG repeats of Huntington disease, myotonic dystrophy, and the spinal cerebellar ataxias, in addition to demonstrating intergenerational meiotic instability, also exhibit mitotic instability.[156] Replicative instability of repetitive DNA sequences is a phenotypic feature of many solid tumors, such as spontaneous and hereditary nonpolyposis colorectal carcinoma, and results from abnormalities in DNA repair.[157] Somatic expansion of an unstable repeat sequence in one such gene could be the initiating event in leukemia. Supportive observations come from the findings that subsets of leukemia demonstrate both microsatellite[158–160] and trinucleotide repeat instability.[161]

A speculative model for leukemia initiation incorporating pure familial leukemia, familial leukemic syndromes, and sporadic cases is advanced in Figure 3. I postulate that there are a set of leukemia genes. These genes, limited in number to the few different clinical phenotypes of familial leukemia syndromes, would have an unstable repetitive DNA sequence tract. In the germline of individuals from the rare autosomal dominant pure leukemia families, this tract has expanded in length. Expansion beyond some critical length both confers the phenotype (either through inactivation, as is the case with CGG repeat expansion in Fragile X syndrome, or through toxic gain-of-function, as is the case with CAG repeat expansion in Huntington disease[147]) and also results in vulnerability to continued expansion during meiosis (thus accounting for anticipation). Rarely, repetitive tracts of normal length in normal individuals could spontaneously expand either during meiosis or mitosis. If the *de novo* expansion occurred during meiosis in the formation of gametes, this may give rise to childhood onset leukemia, such as ALL, in the offspring of normal individuals. It is conceivable that parental exposure to DNA damaging agents could predispose to *de novo* expansions. Alternatively, the *de novo* expansion could occur mitotically in the somatic tissue of the bone marrow or lymph nodes. Since the likelihood of significant somatic expansion should be proportional to the total number of mitotic events, it would be expected that such events would become increasingly probable with advancing age, such as in CLL and AML, where the incidence increases in the elderly, or following exposure to carcinogens. In the case of DNA repair deficiency, such as with Bloom syndrome, the underlying inherited defect could predispose to repeat expansion. Alternatively, the mitotic expansion could result from the stepwise malignant progression involving other known proto-oncogenes and tumor suppressor genes.

The nature of the postulated repetitive sequences is uncertain, but trinucleotide repeats should at least be considered, because they are so far the only known sequences that have been associated with anticipation. A significant observation is that leukemia is the type of malignancy that overwhelmingly results from exposure to radiation or alkylating agents used in chemotherapy.[7] It might thus be supposed that the repetitive sequences in these postulated leukemia genes should be uniquely vulnerable to the spectrum of DNA damage induced by these events.

Candidate leukemia genes containing unstable repeats

A number of genes are known to contain repetitive sequence motifs, particularly trinucleotide repeats, and many of these

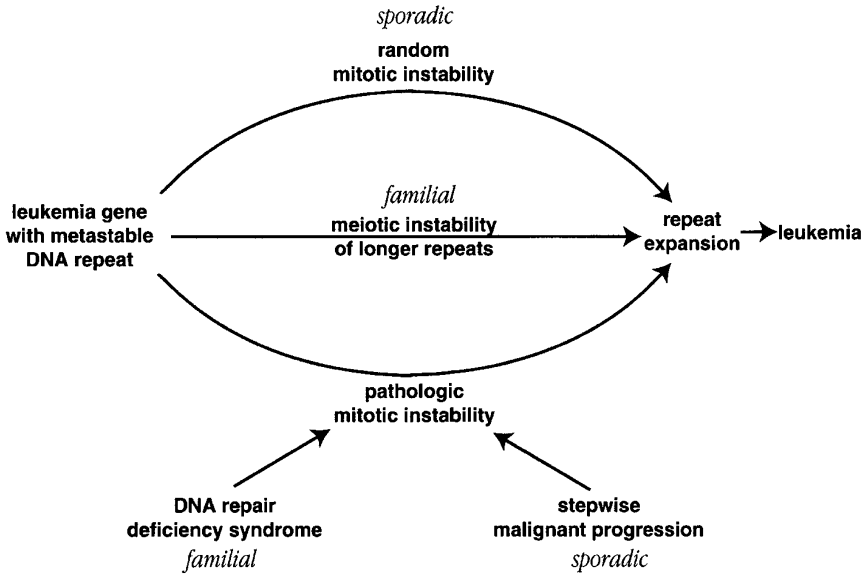

Figure 3 Model for leukemia initiation based on DNA repeat expansion.

sequences are polymorphic in the population. For some of these genes circumstantial arguments for a role in neoplasia have been advanced (reviewed in Ref. 162). There is some limited evidence potentially implicating these loci as leukemia genes.

AF9

In the AML family that my group first reported,[94] at least two affected individuals co-inherited a constitutional cytogenetically visible banding variation on the proximal region of the short arm of chromosome 9p22. This provides some weak evidence for linkage to this region. One attractive candidate gene in this region is AF9, which is the frequent site of reciprocal translocation with the HRX trithorax gene on chromosome 11 in recurrent t(9p22;11q23) associated with AML.[163] The gene is a homologue of ELL[164] which functions as an RNA polymerase processivity factor. Another RNA polymerase processivity factor is encoded by the VHL locus (reviewed in Ref. 165), which is well-established to be a tumor suppressor gene, causative of the Von Hippel–Lindau syndrome of cerebroretinal hamartomas and renal cell carcinoma. Interestingly, AF9 has a large CAG repeat encoding a polyserine tract that is polymorphic in the population.[166]

CBL2

Another of the recognized trinucleotide repeat diseases is the Jacobsen syndrome. In this disease there is expansion of a CCG repeat on chromosome 11q23.3 in the CBL2 protooncogene.[167] Individuals with expansion of this sequence are at risk for chromosome breakage with consequent terminal deletion of the distal long arm of chromosome 11 during gamete formation. Offspring inheriting this chromosomal abnormality are affected, although the phenotype is described as rather mild in comparison to other congenital chromosomal abnormalities and consists of subtle facial dysmorphism and variable mild to moderate mental retardation. There is some evidence for CBL2 mutation in sporadic leukemia,[168] and leukemia has been reported in the mother of at least one patient with the Jacobsen syndrome[169] (who, although reported some years ago and not molecularly tested, would presumably have CCG repeat expansion in CBL2). CBL2 was first cloned as the B cell lymphoma-inducing oncogene of a murine retrovirus. It contains a RING finger zinc-binding motif, multiple consensus bindings sites for SH3 domains, and may modify receptor tyrosine kinase-mediated signal transduction.[170]

Additional evidence implicating the distal long arm of chromosome 11 in the initiation of leukemia is that it is the site of frequent chromosomal abnormality in secondary, treatment-related AML,[171] as well as being the locus for the ATM and HRX trithorax genes. It is conceivable that genetic instability in the vicinity of CBL2 leads to larger abnormalities of 11q.

BCR

There is a polymorphic CGG repeat in the first exon of the BCR gene on chromosome 22q11, which when translocated with the ABL oncogene on chromosome 9q34 forms the Philadelphia chromosome characteristic of 90% of CML, 10% of ALL, and 5% of AML patients.[172] The length of the repeat has not been found to differ, however, in patients with Philadelphia chromosome positive leukemias.[173]

21q22 locus

As mentioned, in a large family inheriting platelet granule defects and a predisposition toward myeloid leukemia, linkage to chromosome 21q22.1-22.2 has been determined.[33] From the published clinical descriptions of this family there is inadequate data to comment on the presence or absence of anticipation nor on the magnitude of risk for leukemia. Two other families (Ref. 131, and one I have consulted upon) with a similar phenotype, however, do have some evidence of anticipation.

16q22 fragile site and satellite repeat instability

A distinguishing feature of anticipation in familial leukemia is an absence of parental sex effect. In contrast, in Huntington disease trinucleotide repeat expansion occurs preferentially through paternal meiosis while in myotonic dystrophy and fragile X syndrome expansion occurs preferentially in female meiosis. It is therefore possible that a different sequence repeat or even a different molecular mechanism is responsible for anticipation in leukemia. In fact, a different sort of repetitive sequence vulnerable to intergenerational instability is repetitive 'satellite' DNA.[174] Variations in satellite repeat length have been associated with cancer risk at HRAS[175] and ovarian cancer risk in BRCA1 families.[176]

Evidence that microsatellite repeat instabilities could lead to leukemia comes from a report of a family with leukemia transmitting a chromosome 16q22 folate-sensitive fragile site.[177] In this family, a 69-year-old man presented with simultaneous AML and lymphoma while his 14-year-old daughter presented with ALL. A fragile site in this region has been observed in association with sporadic hematopoietic malignancy.[178] This fragile site is likely to be the 16q22 distamycin A-sensitive FRA16B site that was recently cloned and found to result from amplification of an AT-rich minisatellite repeat.[179]

Gene duplication

The finding of linkage to chromosome 21 in some leukemia/myelodysplasia families is particularly interesting in light of the association of Down syndrome with leukemia (and also trisomy 8 mosaicism and leukemia), where it is clear that a gene dosage effect is causative. Instead of expansion of a limited sequence repeat, this raises the possibility that whole gene duplication could be the causative mutation, as has been reported with a polymorphic gene duplication in poly(ADP-ribose) polymerase associated with an increased incidence of prostate cancer and multiple myeloma.[180]

A model for leukemia initiation based on intergenerational inheritance of secondary hits

It should be additionally noted that leukemia is not the only cancer family syndrome for which anticipation occurs. Anticipation has been reported in familial breast cancer[107,181–185] and hereditary nonpolyposis colorectal carcinoma.[186–188] In comparison to leukemia, the data may be more uniquely vulnerable to so-called 'cohort' effects reflecting advancements in diagnostic technology and changes in overall disease incidence.[150,189,190] Nevertheless, the data cannot be easily ignored with respect to their implication for anticipation in familial leukemia, and because much of it comes from population registries, it may not be subject to the ascertainment bias issues discussed by Penrose. Two familial breast cancer genes[191] and four hereditary nonpolyposis colorectal carcinoma genes[192] have now been identified, and, with the exception of the satellite repeat in BRCA1 noted above, these genes do not have repetitive sequence elements. This raises the possibility of a completely unique molecular mechanism being responsible for anticipation in familial cancer.

What other potential mechanisms could conceivably account for anticipation in familial malignancy syndromes? One clue may come from the function of these genes. The hereditary nonpolyposis colorectal carcinoma genes function in DNA repair.[192] Although the role of the BRCA genes remains controversial,[191] the most recent data suggest it to be involved in maintaining chromosomal fidelity during mitosis.[193] Before the discovery of these genes, it was proposed that a mutation in a DNA repair gene could be an initiating step in carcinogenesis, as it would invoke a cascade of mutations in downstream tumor suppressor and proto-oncogenes.[194–196] The discovery of a 'mutator phenotype' in hereditary nonpolyposis colorectal carcinoma and other sporadic malignancies[197] seems to prove these predictions. A speculative hypothesis accounting for anticipation in familial malignancy is that the secondary mutations that result from such genomic infidelity may not be just somatic, but could conceivably occur in the germline and be transmitted to children (Figure 4). If it were indeed the case that the familial leukemia genes are involved in the maintenance of genomic integrity, then a child's risk of leukemia may not result only from the inheritance of a single defective gene, but could in addition require the inheritance of multiple *de novo* germline mutations in downstream genes. In this way, the multistep evolution of leukemia would actually begin in the parental germline and leukemia would be transmitted not simply through an autosomal dominant pattern but through a polygenic inheritance model with a single major ancestral gene and multiple minor genes each resulting from *de novo* mutation. The unique and variable spectrum of the *de novo* secondary mutations might account for the clinical variability of leukemia subtypes in multiple family members while the progressive accumulation of mutations across generations would account for anticipation.

A prediction of this hypothesis is that in a leukemia family, a parent with the leukemia gene would have a 1/2 probability of having a child who did not inherit the leukemia gene but who did inherit 1/2 of the cumulative *de novo* gonadal mutations. It might therefore be expected that there would be an increased incidence of congenital abnormalities in leuke-

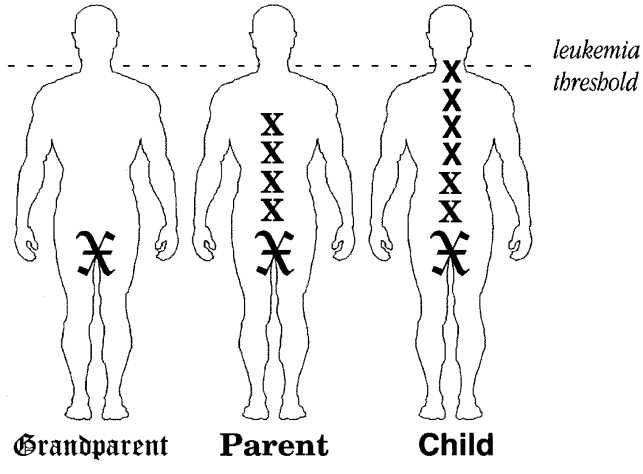

Figure 4 Model for inheritance of leukemia based on intergenerational inheritance of *de novo* gonadal mutations. The large 'X' represents an ancestral mutation in the leukemia gene responsible for maintaining genomic integrity. Each small 'X' corresponds to a *de novo* mutational event resulting from the ancestral mutation's effect on loss of genomic fidelity. The typeface of the 'X' corresponds to the generation in which the *de novo* mutation appeared. This fits a polygenic model of inheritance with a single major gene and multiple minor genes. Leukemia occurs after reaching a threshold of mutations, representing the sum of the more heavily weighted ancestral gene mutation and the cumulative *de novo* mutations.

mia families reflective of *de novo* gonadal mutational events. In fact, this may be true. Several of the leukemia families have coincidental occurrence of Down syndrome (three families in Ref. 198, and 96, 128 and 177). Also of relevance are studies documenting the coincidence of birth defects among the siblings of leukemic children.[12,198] Siblings of leukemic children have an increased incidence of Down syndrome, solid tumors, and an elevated noncancer death rate. There are reports of coincidences of leukemia with Klinefelter XXY syndrome[199] and Turner XO syndrome.[200]

Congenital anomalies as evidence that sporadic leukemia results from *de novo* germline mutation

An extension of the postulate that anticipation in familial leukemia results from genomic infidelity in the parent is that sporadic cases of leukemia also result from *de novo* gonadal events in a parent. What evidence is there for this? Major congenital anomalies, which is often evidence of a *de novo* aneuploidy,[15] such as a chromosomal microdeletion, are seen in excess in leukemia, and mothers of leukemic children report more frequent spontaneous abortions.[12,14] Also, in two surveys of sporadic childhood myelodysplasia and leukemia,[11,13] patients exhibited frequent growth and developmental delay with a characteristic range of congenital abnormalities. Often, this involves the development of the upper limb. Three families have been reported with AML and/or mixed types of leukemias with variable deformities of the digits of the upper limbs,[103,104] and the Poland anomaly of isolated absence of the pectoralis major muscle has been associated with leukemia.[201] (Interestingly, abormalities of the thumb are recurrently associated with inherited hematopoietic disorders. Hypoplastic or other thumb anomalies are features of Fanconi anemia, the 'TAR' syndrome[202] of congenital thrombocytopenia and absent radius (another hematopoietic syndrome associated with chromosomal trisomy, in this case chromosome 18[203]), Blackfan–Diamond anemia, and the Rothmund–Thomson syndrome of poikiloderma and an increased risk for malignancy that also includes leukemia)[204]. The association of these congenital anomalies with leukemia calls attention to the possibility that a *de novo* mutation has occurred, and may conceivably mean that the first significant 'hit' in the multistep evolution of leukemia is actually a germline, rather than somatic event.

Conclusion

The catalog of genes found to be mutated in leukemia – through the cloning of acquired translocation breakpoints and the screening of candidate genes encoding tumor suppressers, apoptotic pathways, cell cycle regulators, cytokines, transcription factors, proto-oncogenes, etc – is overwhelming in number.[205] While all these mutations probably contribute to the progression of malignancy, it is doubtful that more than a few, if any, are responsible for leukemia initiation. In contrast, even assuming that separate genes are responsible for each of the varied clinical presentations of pure familial leukemia, it is possible that there are no more than a few genes responsible for familial leukemia. Presumably, mutations in these genes are sufficient to either initiate a multistep pathway of leukemia or to signal a dangerous turn in a multistep pathway initiated from a different direction and lumbering along a less malignant course.

The nature of the mutations in these leukemia genes must be capable of explaining these observations of leukemia biology. Familial leukemia demonstrates anticipation. Leukemia is found in excess in constitutional chromosomal trisomy syndromes. Leukemia is among the most common malignancies in inherited disorders of DNA repair. Leukemia is the malignancy most strongly associated with exposure to DNA-damaging agents. I have proposed two different models based on genomic instability to account for these observations. The first model proposes a set of genes with unstable repetitive sequences that are vulnerable to intergenerational expansion in familial leukemia and mitotic instability in sporadic cases. The second model posits that a defect in a gene contributing to genome fidelity establishes a pattern for the intergenerational inheritance of multiple secondary mutations required for leukemia progression. Both have significant implications for the role of *de novo* germline and somatic mutational events in common, sporadic leukemia.

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References

1 Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 1994; **86**: 1600–1608.
2 Gunz FW, Gunz JP, Veale AMO, Chapman CJ, Houston IB. Familial leukemia: a study of 909 families. *Scand J Haematol* 1975; **15**: 117–131.
3 Narod SA. Genetics of breast and ovarian cancer. *Br Med Bull* 1994; **50**: 656–676.
4 Thomas G. Advances in the genetics and molecular biology of colorectal tumors. *Curr Opin Oncol* 1995; **6**: 406–412.
5 Pui C-H. Childhood leukemias. *New Engl J Med* 1995; **332**: 1618–1630.
6 Knudson AG. Hereditary cancer: two hits revisited. *J Cancer Res Clin Oncol* 1996; **122**: 135–140.
7 Vogel VG, Fisher RG. Epidemiology and etiology of leukemia. *Curr Opin Oncol* 1993; **5**: 26–34.
8 Kaye SA, Robison LL, Smithson WA, Gunderson P, King FL, Neglia JP. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic leukemia. *Cancer* 1991; **68**: 1351–1355.
9 Wakeford R. The risk of childhood cancer from intrauterine and preconceptional exposure to ionizing radiation. *Enrion Health Perspect* 1995; **103**: 1018–1025.
10 Bhatia S, Neglia JP. Epidemiology of childhood acute myelogenous leukemia. *J Pediatr Hematol Oncol* 1995; **17**: 91–93.
11 Kobrinsky NL, Nesbit ME, Ramsay NKC, Arthur DC, Krivit W, Brunning RD. Hematopoietic dysplasia and marrow hypocellularity in children: a preleukemic condition. *J Ped* 1982; **100**: 907–913.
12 Miller RW. Down's syndrome (mongolism), other congenital malformations and cancers among the sibs of leukemic children. *New Engl J Med* 1963; **268**: 393–401.
13 Passmore SJ, Hann IM, Stiller CA *et al*. Pediatric myelodysplasia: a study of 68 children and a new prognostic scoring system. *Blood* 1995; **85**: 1742–1750.
14 Narod SA, Hawkins MM, Robertson CM, Stiller CA. Congenital anomalies and childhood cancer in Great Britain. *Am J Hum Genet* 1997; **60**: 474–485.

15 Epstein CJ. Mechanisms of the effects of aneuploidy in mammals. *Ann Rev Genet* 1988; **22**: 51–75.
16 Pearson HA, Grello FW, Cone TE. Leukemia in identical twins. *New Engl J Med* 1963; **268**: 1151–1156.
17 Guasch J. Heredité des leucemies. *Sang* 1954; **25**: 384–421.
18 Anderson RC, Hermann HW. Leukemia in twin children. *JAMA* 1955; **158**: 652–654.
19 Cooke JV. Acute leukemia in twins. *JAMA* 1953; **152**: 1028–1029.
20 Horwitz M, Goode EL, Jarvik GP. Anticipation in familial leukemia. *Am J Hum Genet* 1996; **59**: 990–998.
21 Epstein CJ. Down syndrome (trisomy 21). In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). *The Metabolic and Molecular Bases of Inherited Disease*, seventh edn, vol 1. New York: McGraw-Hill, 1995, pp 749–794.
22 Evans DIK, Steward JK. Down's syndrome and leukaemia. *Lancet* 1972; **2**: 1322.
23 Seibel NL, Sommer A, Miser J. Transient neonatal leukemoid reactions in mosaic trisomy 21. *J Pediatr* 1984; **104**: 251–254.
24 Rosner F, Lee SL. Down's syndrome and acute leukemia: myeloblastic or lymphoblastic. *Am J Med* 1972; **53**: 203–218.
25 Stiller CA, Kinnier Wilson LM. Down syndrome and leukaemia. *Lancet* 1981; **2**: 1343.
26 Rowley JD. Down syndrome and acute leukaemia: increased risk may be due to trisomy 21. *Lancet* 1981; **ii**: 1020–1022.
27 Homans A, Verissimo AM, Vlacha V. Transient abnormal myelopoiesis of infancy associated with trisomy 21. *Am J Pediatr Hematol Oncol* 1993; **15**: 392–399.
28 Shen JJ, Williams BJ, Zipursky A *et al*. Cytogenetic and molecular studies of Down syndrome individuals with leukemia. *Am J Hum Genet* 1995; **56**: 915–925.
29 Korenberg JR, Chen X-N, Schipper R *et al*. Down syndrome phenotypes: the consequences of chromosomal imbalance. *Proc Natl Acad Sci USA* 1994; **91**: 4997–5001.
30 Iselius L, Jacobs P, Morton N. Leukaemia and transient leukaemia in Down syndrome. *Hum Genet* 1990; **85**: 477–485.
31 Nucifora G, Rowley JD. AML1 and the 8;21 and 3;21 translocations in acute and chronic myeloid leukemia. *Blood* 1995; **86**: 1–14.
32 Wang Q, Stacy T, Binder M, Marin-Padilla M, Sharpe AH, Speck NA. Disruption of the Cbfa2 gene causes necrosis and hemorrhaging in the central nervous system and blocks definitive hematopoiesis. *Proc Natl Acad Sci USA* 1996; **93**: 3444–3449.
33 Ho CY, Otterud B, Legare RD *et al*. Linkage of a familial platelet disorder with a propensity to develop myeloid malignancies to human chromosome 21q22.1-22.2. *Blood* 1996; **87**: 5218–5224.
34 Secker-Walker LM, Fitchett M. Constitutional and acquired trisomy 8. *Leukemia Res* 1995; **19**: 737–740.
35 Hanslip JI, Swansbury GJ, Pinkerton R, Catovsky D. The translocation t(8;16)(p11;p13) defines an AML subtype with distinct cytology and clinical features. *Leuk Lymphoma* 1992; **6**: 479–486.
36 Borrow J, Stanton VP. Andresen JM *et al*. The translocation t(8;16)(p11;p13) of acute myeloid leukaemia fuses a putative acetyltransferase to the CREB-binding protein. *Nat Genet* 1996; **14**: 33–41.
37 German J. Bloom's syndrome: incidence, age of onset, and types of leukemia in the Bloom's syndrome registry. In: Bartsocas CS, Loukopoulos D (eds). *Genetics of Hematological Disorders*. Hemisphere: Washington DC, 1992, pp 241–258.
38 German J, Bloom D, Passarge E *et al*. Bloom's syndrome. VI. The disorder in Israel and an estimation of the gene frequency in the Ashkenazim. *Am J Hum Genet* 1977; **29**: 553–562.
39 German J, Schonberg S, Louie E, Chaganti RSK. Bloom's syndrome. IV. Sister chromatid exchanges in lymphocytes. *Am J Hum Genet* 1977; **29**: 248–255.
40 Ellis NA, Groden J, Ye T-Z *et al*. The Bloom's syndrome gene product is homologous to RecQ helicases. *Cell* 1995; **83**: 655–666.
41 Gatti RA, Boder E, Vinters HV, Sparkes RS, Norman A, Lange K. Ataxia-telagiectasia: an interdisciplinary approach to pathogenesis. *Medicine* 1991; **70**: 99–117.
42 Taylor AMR, Metcalfe JA, Thick J, Mak Y-F. Leukemia and lymphoma in ataxia telangiectasia. *Blood* 1996; **87**: 423–438.
43 Morrell D, Cromarties E, Swift M. Mortality and cancer incidence in 263 patients with ataxia-telangiectasia. *JNCI* 1986; **77**: 89–92.
44 Deiss A. Non-neoplastic diseases, chemical agents, and hematologic disorders that may precede hematologic neoplasms. In: Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN (eds). *Wintrobe's Clinical Hematology*, ninth edn. Lea and Febiger: Philadelphia, 1993, pp 1946–1968.
45 Hartwell L. Defects in a cell cycle checkpoint may be responsible for the genomic instability of cancer cells. *Cell* 1992; **71**: 543–546.
46 Savitsky K, Bar-Shira A, Gilad S *et al*. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science* 1995; **268**: 1749–1753.
47 van der Burgt I, Chrzanowska KH, Smeets D, Weemaes C. Nijmegen breakage syndrome. *J Med Genet* 1996; **33**: 153–156.
48 Saar K, Chrzanowska K, Stumm M *et al*. The gene for the ataxia-telangiectasia variant, Nijmegen breakage syndrome, maps to a 1-cM interval on chromosome 8q21. *Am J Hum Genet* 1997; **60**: 605–610.
49 Auerbach AD. Fanconi anemia. In: Cohen PR, Kurzrock R (eds). *Dermatologic Clinics*. WB Saunders: Philadelphia, 1995, pp 41–49.
50 Auerbach AD. Fanconi anemia, diagnosis and the diepoxybutane (DEB) test. *Exp Hematol* 1993; **21**: 731–733.
51 Butturini A, Gale RP, Verlander PC *et al*. Hematologic abnormalities in Fanconi anemia: an international Fanconi anemia registry study. *Blood* 1994; **84**: 1650–1655.
52 Strathdee CA, Duncan AMV, Buchwald M. Evidence for at least four Fanconi anaemia genes including FACC on chromosome 9. *Nat Genet* 1992; **1**: 196–198.
53 Strathdee CV, Gavish H, Shannon WR, Buchwald M. Cloning of cDNAs for Fanconi's anaemia by functional complementation. *Nature* 1992; **356**: 763–767.
54 Pronk JC, Gibson RA, Savoia A *et al*. Localisation of the Fanconi anaemia complementation group A gene to chromosome 16q24.3. *Nat Genet* 1995; **11**: 338–340.
55 Consortium FABC. Positional cloning of the Fanconi anaemia group A gene. *Nat Genet* 1996; **14**: 324–328.
56 Lo Ten Foe JR, Rooimans MA, Bosnoyan-Collins L *et al*. Expression cloning of a cDNA for the major Fanconi anaemia gene, FAA. *Nat Genet* 1996; **14**: 320–323.
57 Gutmann DH, Collins FS. von Recklinghausen neurofibromatosis. In: Scriber CR, Beaudet AL, Sly WS, Valle D (eds). *The Metabolic and Molecular Bases of Inherited Disease*, seventh edn. McGraw-Hill: New York, 1995, pp 677–696.
58 McCormick F. Ras signaling and NF1. *Curr Opin Genet Dev* 1995; **5**: 51–55.
59 Huson SM, Clark D, Compston DAS, Harper PS. A genetic study of von Reclinkghausen's neurofibromatosis in south-east Wales. I: Prevalance, fitness, mutation rate and effect of parental transmission on severity. *J Med Genet* 1989; **26**: 704–711.
60 Stiller CA, Chessels JM, Fitchett M. Neurofibromatosis and childhood leukaemia/lymphoma: a population-based UKCCSG study. *Br J Cancer* 1994; **70**: 969–972.
61 Largaespada DA, Brannan CI, Shaughnessy JD, Jenkins NA, Copeland NG. The neurofibromatosis type 1 (NF1) tumor suppressor gene and myeloid leukemia. *Curr Top Microbiol Immunol* 1996; **211**: 233–239.
62 Zvulunov A, Barak Y, Metzker A. Juvenile xanthogranuloma, neurofibromatosis, and juvenile chronic myelogenous. World statistical analysis. *Arch Dermatol* 1995; **131**: 904–908.
63 Shannon KM, O'Connell P, Martin GA *et al*. Loss of the normal NF1 allele from the bone marrow of children with type 1 neurofibromatosis and malignant myeloid disorders. *New Engl J Med* 1994; **330**: 637–639.
64 Shannon KM, Watterson J, Johnson P *et al*. Monosomy 7 myeloproliferative disease in children with neurofibromatosis, type 1: epidemiology and molecular analysis. *Blood* 1992; **79**: 1311–1318.
65 Malkin D. Germline p53 mutations and heritable cancer. *Annu Rev Genet* 1994; **28**: 443–465.
66 Imamura J, Miyoshi I, Koeffler HP. p53 in hematologic malignancies. *Blood* 1994; **84**: 2412–2421.
67 Derry JMJ, Ochs HD, Francke U. Isolation of a novel gene mutated in Wiskott–Aldrich syndrome. *Cell* 1994; **78**: 635–644.

68 Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott–Aldrich syndrome. *J Pediatr* 1994; **125**: 876–885.
69 Cotelingam JD, Witebsky FG, Hsu SM, Blaese RM, Jaffe ES. Malignant lymphoma in patients with the Wiskott–Alrich syndrome. *Cancer Invest* 1985; **3**: 515–522.
70 Filipovich AH, Heinitz KJ, Robison LL, Frizzera G. The immunodeficiency cancer registry. A research resource. *Am J Pediatr Hematol Oncol* 1987; **9**: 183–184.
71 Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. *Medicine* 1985; **64**: 145–156.
72 Vetrie D, Vorechovsky I, Sideras P *et al*. The gene involved in X-linked agammaglobulinaemia is a member of the src family or protein-tyrosine kinases. *Nature* 1993; **361**: 226–233.
73 Groopman JE, Broder S. Cancers in AIDS and other immunodeficiency states. In: DeVita VT, Hellman S, Rosenberg SA (eds). *Cancer: Principles and Practice of Oncology*, third edn. JB Lippincott: Philadelphia, 1989, pp 1953–1970.
74 Frizzera G, Rosai J, Dehner LP, Spector BD, Kersey JH. Lymphoreticular disorders in primary immunodeficiencies: new findings based on an up-to-date histologic classification of 35 cases. *Cancer* 1980; **46**: 692–699.
75 van der Meer JWM, Weening RS, Schellekens PTA, van Munster IP, Nagengast FM. Colorectal cancer in patients with X-linked agammaglobulinaemia. *Lancet* 1993; **341**: 1439–1440.
76 Mueller BU, Pizzo PA. Cancer in children with primary or secondary immunodeficiencies. *J Pediatr* 1995; **126**: 1–10.
77 Woods WG, Roloff JS, Lukens JN, Krivit W. The occurrence of leukemia in patients with the Shwachman syndrome. *J Pediatr* 1981; **99**: 425–428.
78 Fraccaro M, Scappaticci S, Arico M. Shwachman syndrome and chromosome breakage. *Hum Genet* 1988; **79**: 194.
79 Masuno I, Imaizumi K, Nishimura G *et al*. Shwachman syndrome associated with *de novo* reciprocal translocation t(6;12)(q16.2;q21.1). *J Med Genet* 1995; **32**: 894–895.
80 Gilman PA, Jackson DP, Guild HG. Congenital agranulocytosis: prolonged survival and terminal acute leukemia. *Blood* 1970; **36**: 576–585.
81 Iselius L, Gustavson KH. Spatial distribution of the gene for infantile genetic agranulocytosis. *Hum Hered* 1984; **34**: 358–363.
82 Dong F, Brynes RK, Tidow N, Welte K, Lowenberg B, Touw IP. Mutations in the gene for the granulocyte colony-stimulating factor receptor in patients with acute myeloid leukemia preceded by severe congenital neutropenia. *New Engl J Med* 1995; **333**: 487–493.
83 Halperin DS, Freedman MH. Diamond–Blackfan anemia: etiology, pathophysiology, and treatment. *Am J Pediat Hemat Oncol* 1989; **11**: 380–394.
84 Carroll WL, Morgan R, Glader BE. Childhood bone marrow monosomy 7 sydrome: a familial disorder? *J Pediatr* 1985; **107**: 578–580.
85 Gilchrist DM, Friedman JM, Rogers PCJ, Creighton SP. Myelodysplasia and leukemia syndrome with monosomy 7: a genetic perspective. *Am J Med Gen* 1990; **35**: 437–441.
86 Shannon KM, Turhan AG, Rogers PCJ, Kan YW. Evidence implicating heterozygous deletion of chromosome 7 in the pathogenesis of familial leukemia associated with monosomy 7. *Genomics* 1995; **14**: 121–125.
87 Paul B, Reid MM, Davison EV, Abela M, Hamilton PJ. Familial myelodysplasia: progressive disease associated with emergence of monosmy 7. *Br J Haematol* 1987; **65**: 321–323.
88 Kamiyanma R, Shibata T, Mori W. Two autopsy cases of atypical myeloproliferative disorder with group C monosomy occurring in siblings. *Acta Pathol Japan* 1973; **23**: 815–835.
89 Li F, Hecht F, Kaiser-McCaw B, Baranko PV, Upp Potter N. Ataxia-pancytopenia: syndrome of cerebellar ataxia, hypoplastic anemia, monosomy 7, and acute myelogenous leukemia. *Cancer Genet Cytogenet* 1981; **4**: 189–196.
90 Kaur J, Catovsky D, Valdimarsson H, Jensson O, Sjpiers ASD. Familial acute myeloid leukaemia with acquired Pelger–Heut anomaly and aneuploidy of C group. *Br Med J* 1972; **4**: 327–333.
91 Hasle H, Kerndrup G, Jacobsen BB. Childhood myelodysplastic syndrome in Denmark: incidence and predisposing conditions. *Leukemia* 1995; **9**: 1569–1572.
92 Fenaux P. Les syndromes myelodysplasiques ou anemies refractaires. *Rev Prat* 1993; **43**: 1379–1385.
93 Marsden K, Challis D, Kimber R. Familial myelodysplastic syndrome with onset late in life. *Am J Hematol* 1995; **49**: 153–156.
94 Horwitz M, Sabath DE, Smithson WA, Radick J. A family inheriting different subtypes of acute myelogenous leukemia. *Am J Hematol* 1996; **52**: 295–304.
95 Olopade OI, Roulston D, Baker T *et al*. Familial myeloid leukemia associated with loss of the long arm of chromosome 5. *Leukemia* 1996; **10**: 669–674.
96 Heath CW, Moloney WC. Familial leukemia: five cases of acute leukemia in three generations. *New Engl J Med* 1965; **272**: 882–886.
97 Gordon RD. Hereditary factors in human leukaemia: a report of four cases of leukaemia in a family. *Australasian Ann Med* 1963; **12**: 202–207.
98 Li-zhen H, Lu L-H, Chen Z-Z. Genetic mechanism of leukemia predisposition in a family with 7 cases of acute myeloid leukemia. *Cancer Genet Cytogenet* 1994; **76**: 65–69.
99 Gunz FW, Gunz JP, Vincent PC *et al*. Thirteen cases of leukemia in a family. *J Natl Cancer Inst* 1978; **60**: 1243–1250.
100 Kjellstrom T, Barkenius G, Malmquist J, Rausing A. Familial monocytic leukaemia. *Scand J Haematol* 1979; **23**: 272–276.
101 Snyder AL, Li FP, Henderson ES, Todaro GH. Possible inherited leukaemogenic factors in familial acute myelogenous leukaemia. *Lancet* 1970; **1**: 586–589.
102 Fischer P, Karpas A, Nacheva E, Haas O, Winterleitner H, Krepler P. Characteristics of a cell line established from a child with familial acute myeloid leukaemia. *Br J Haematol* 1980; **46**: 23–31.
103 Smith ACM, Hays T, Harvey LA, Dowman C. WT syndrome: a third family. *Am J Hum Genet* 1987; **41**: A84.
104 Gonzalez CH, Durkin-Stamm MV, Geimer NK *et al*. The WT syndrome – a 'new autosomal dominant pleiotropic trait of radial-ulnar hypoplasia with high risk of bone marrow failure and/or leukemia. *Birth Defects Orig Art Ser* 1977; **XIII(3B)**: 31–38.
105 Davidson RJL, Walker W, Watt JL, Page BM. Familial erythroleukemia: a cytogenetic and haematological study. *Scand J Haematol* 1978; **20**: 351–359.
106 Nissenblatt MJ, Bias W, Borgaonkar D, Dixon S, Cody RP. Familial erythroleukemia: four cases of the Diguglielmo syndrome in close relatives. *John Hopkins Med J* 1982; **150**: 1–9.
107 Paterson AD, Kennedy JL, Petronis A. Evidence for genetic anticipation in non-Mendelian diseases. *Am J Hum Genet* 1996; **59**: 264–268.
108 Siebert R, Jhanwar S, Brown K, Berman E, Offit K. Familial acute myeloid leukemia and DiGuglielmo syndrome. *Leukemia* 1995; **9**: 1091–1094.
109 Videbaek A. Heredity in human leukemia and its relation to cancer. *Opera ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis*, vol 13. Munksgaard: Copenhagen, 1947.
110 Campbell WAB, MacAfee AL, Wade WG. Familial neonatal leukaemia. *Arch Dis Child* 1961; 93–98.
111 Peterson HR, Bowlds CF, Yam LT. Familial DiGuglielmo syndrome. *Cancer* 1984; **54**: 932–938.
112 Cuttner J. Increased incidence of hematologic malignancies in first-degree relatives of patients with chronic lymphocytic leukemia. *Cancer Invest* 1992; **10**: 103–109.
113 Neuland CY, Blattner WA, Mann DL, Fraser MC, Tsai S, Strong DM. Familial chronic lymphocytic leukemia. *J Natl Cancer Inst* 1983; **6**: 1143–1150.
114 Branda RF, Ackerman SF, Handwerger BS, Howe RB, Douglas SD. Lymphocyte studies in familial chronic lymphatic leukemia. *Am J Med* 1978; **64**: 508–514.
115 Gunz G, Dameshek W. Chronic lymphocytic leukemia in a family, including twin brothers and a son. *JAMA* 1957; **164**: 1323–1325.
116 Wisniewski J, Weinreich J. Lymphatische Leukamie bei Vater und Sohn. *Blut* 1966; **12**: 241–244.
117 Furbetta D, Solinas P. Hereditary chronic lymphatic leukemia? Proc 2nd Int Cong Hum Genet. Rome, September 6–12, 1961, pp 1078–1079.
118 Reilly E, Rapaport SI, Karr NW, Mills H, Carpenter GE. Familial chronic lymphatic leukemia. *AMA Archives Int Med* 1952; **90**: 87–89.
119 Shah AR, Maeda K, Deegan MJ, Roth MS, Schnitzer B. A clinico-

pathologic study of familial chronic lymphocytic leukemia. *Am J Clin Pathol* 1992; **97**: 184–188.
120 Felix CA, D'Amico D, Mitsudomi T *et al*. Absence of hereditary p53 mutations in 10 familial leukemia pedigrees. *J Clin Invest* 1992; **90**: 653–658.
121 Bridges JM, Nelson MG. Familial Leukaemia. *Acta Haematol* 1961; **26**: 246–251.
122 Cramblett HG, Friedman JL, Najjar S. Leukemia in an infant born of a mother with leukemia. *New Engl J Med* 1958; **259**: 727–729.
123 Hawkins MM, Draper GJ, Winter DL. Cancer in the offspring of survivors of childhood leukaemia and non-Hodgkin lymphomas. *Br J Cancer* 1995; **71**: 1335–1339.
124 Anderson RC. Familial leukemia. *AMA Am J Dis Child* 1951; **81**: 313–322.
125 Gunz FW, Fitzgerald PH, Crossen PE, Mackenzie IS, Powles CP, Jensen GR. Multiple cases of leukemia in a sibship. *Blood* 1966; **27**: 482–489.
126 Johnson MJE, Peters CH. Lymphomas in four siblings. *JAMA* 1957; **163**: 20–25.
127 Anonymous. Four cases of leukemia reported in one South Dakota family. *J Ind St Med Assoc* 1957; **50**: 206.
128 van den Berghe H, Creemers J. Mosaic trisomy in phenotypically normal mother of mongol. *Lancet* 1964; **i**: 526–527.
129 Lillicrap DA, Sterndale H. Familial chronic myeloid leukaemia. *Lancet* 1984; **ii**: 699.
130 Rigby PG, Pratt PT, Rosenlof RC, Lemon HM. Genetic relationships in familial leukemia and lymphoma. *Arch Int Med* 1968; **121**: 67–71.
131 Gerrard JM, Israels ED, Bishop AJ *et al*. Inherited platelet-storage pool deficiency associated with a high incidence of acute myeloid leukaemia. *Br J Haematol* 1991; **79**: 246–255.
132 McPhedran P, Clar WH, Lee J. Patterns of familial leukemia: ten cases of leukemia in two interrelated families. *Cancer* 1969; **24**: 403–407.
133 Barbier J, Guilleret J, Morel P. Deux leucemies aigues successives dan une même famille. *Lyon Med* 1949; **182**: 379–381.
134 Debre BJ, Buhot S. Leucose aigue familiale. Evolution rapprochée d'une leucose aigue du même type chez une enfant et chez son père. *Bull Mem Soc Med Hop de Paris* 1951; **67**: 183–194.
135 Kolmeier KH, Bayrd ED. Familial leukemia: report of instance and review of the literature. *Proc Mayo Clin* 1963; **38**: 523–531.
136 Bowie W. Report of leukaemia occurring in father and daughter. *Canad MAJ* 1958; **78**: 259–262.
137 Steinberg AG. A genetic and statistical study of acute leukemia in children. Proc Third Natl Cancer Conf, 1956. JB Lippincott: Philadelphia, 1957, pp 353–356.
138 Li FP, Marchetto DJ, Vawter GF. Acute leukemia and preleukemia in eight males in a family: an X-linked disorder. *Am J Hematol* 1979; **6**: 61–69.
139 Gilbert HS. Familial myeloproliferative disease. In: Wasserman BB (ed). *Polycythemia Vera and the Myeloproliferative Disorders*. WB Saunders: New York, 1995, pp 222–225.
140 Kaufman PS, Bernard J. Syndromes myeloproliferatifs familiaux. Etude á propos de six familles et revue de la litterature. *Nouv Rev Franc d'Hematol* 1978; **20**: 1–16.
141 Lawrence JH, Goetsch AT. Familial occurrence of polycythemia and leukemia. *Calif Med* 1950; **73**: 361–364.
142 Doll H, Rothschild K. Familiares aufreten von Polycythaemia Rubra in Verbendung mit Chorea Progressiva Hereditaria Huntington. *Klin Wchnschr* 1922; **1**: 2580.
143 Fraumeni JF, Wertelecki W, Blattner WA, Jensen RD, Leventhal BG. Varied manifestations of a familial lymphoproliferative disorder. *Am J Med* 1975; **59**: 145–151.
144 Razis DV, Diamond HD, Craver LF. Familial Hodgkin's disease: its significance and implications. *Ann Int Med* 1959; **51**: 933–967.
145 Howeler CJ, Busch HFM, Geraedts JPM, Niermeijer MF, Staal A. Anticipation in myotonic dystrophy: fact or fiction? *Brain* 1989; **112**: 779–797.
146 Penrose LS. The problem of anticipation in pedigrees of dystrophia myotonica. *Ann Eugenics* 1948; **14**: 124–132.
147 La Spada AR, Paulson HL, Fischbeck KH. Trinucleotide repeat expansion in neurological disease. *Ann Neurol* 1994; **36**: 814–822.
148 Seipel K, Georgiev O, Gerber HP, Schaffner W. Basal components of the transcription apparatus (RNA polymerase II, TATA-binding protein) contain activation domains: is the repetitive C-terminal domain (CTD) of RNA polymerase II a 'portable enhancer domain'? *Mol Reprod Dev* 1994; **39**: 215–225.
149 Videbaek A. Familial leukemia: a preliminary report. *Acta Medica Scand* 1947; **CXXVII**: 26–52.
150 Busk T. Some observations on heredity in breast cancer and leukemia. *Ann Eugenics* 1949; **14**: 213–229.
151 Chitambar CR, Robinson WA, Glode LM. Familial leukemia and aplastic anemia associated with monosomy 7. *Am J Med* 1983; **75**: 756–762.
152 Randall DL, Reiquam CW, Githen JH, Robinson A. Familial myeloproliferative disease. *Am J Dis Child* 1965; **110**: 479–500.
153 Jelicka VL, Hermanska Z, Smida I, Kouba A. Paramyeloblastic leukaemia appearing simultaneously in two blood cousins after simultaneous contact with gammexane (hexachlorcylohexane). *Acta Medica Scand* 1958; **CLXI**: 447–451.
154 Ward JE, Galinsky I, Newton BL. Familial leukemia: a report of three cases of leukemia and one leukemoid reaction in one family. *Am J Hum Genet* 1952; **4**: 90–93.
155 Larsen WE, Schimke RN. Familial acute myelogenous leukemia with associated C-monosomy in two affected members. *Cancer* 1976; **38**: 841–845.
156 Sutherland GR, Richards RI. Simple tandem DNA repeats and human genetic disease. *Proc Natl Acad Sci USA* 1995; **92**: 3636–3641.
157 Loeb LA, Christian FC. Multiple mutations in human cancers. *Mutat Res* 1996; **350**: 279–286.
158 Indraccolo S, Simon M, Hehlmann R, Erfle V, Chieco-Bianchi L, Lieb-Moesch C. Genetic instability of a dinucleotide repeat-rich region in three hematologic malignancies. *Leukemia* 1995; **9**: 1517–1522.
159 Robledo M, Martinez B, Arranz E *et al*. Genetic instability of microsatellites in hematological neoplasms. *Leukemia* 1995; **9**: 960–964.
160 Gartenhaus R, Johns MM, Wang P, Rai K, Sidransky D. Mutator phenotype in a subset of chronic lymphocytic leukemia. *Blood* 1996; **87**: 38–41.
161 Shen Q, Townes PL, Padden C, Newburger PE. An in-frame trinucleotide repeat in the coding region of the human cellular glutathione peroxidase (GPX1) gene: *in vivo* polymorphism and *in vitro* stability. *Genomics* 1994; **23**: 292–294.
162 Panzer S, Kuhl DPA, Caskey CT. Unstable triplet repeat sequences: a source of cancer mutations? *Stem Cells* 1995; **13**: 146–157.
163 Nakamura T, Alder H, Gu Y *et al*. Genes on chromosome 4, 9, and 19 involved in 11q23 abnormalities in acute leukemia share sequence homology and/or common motifs. *Proc Natl Acad Sci USA* 1993; **90**: 4631–4635.
164 Shilatifard A, Lane WS, Jackson KW, Conaway RC, Conaway JW. An RNA polymerase II elongation factor encoded by the human ELL gene. *Science* 1996; **271**: 1873–1876.
165 Krumm A, Groudine M. Tumor suppression and transcription elongation: the dire consequences of changing partners. *Science* 1995; **269**: 1400–1401.
166 Walker GJ, Walters MK, Palmer JM, Hayward NK. The MLLT3 gene maps between D9S156 and D9S171 and contains an unstable polymorphic trinucleotide repeat. *Genomics* 1994; **20**: 490–491.
167 Jones C, Penny L, Mattina T *et al*. Association of a chromosome deletion syndrome with a fragile site within the proto-oncogene CBL2. *Nature* 1995; **376**: 145–149.
168 Young BD. Cytogenetic and molecular analysis of chromosome 11q23 abnormalities in leukaemia. *Ballières Clin Haematol* 1992; **5**: 881–895.
169 Jacobsen P, Hauge M, Henningsen K, Hobolth N, Mikkelsen M, Philip. An (11;21) translocation in four generations with chromosome 11 abnormalities in the offspring. *Hum Hered* 1973; **23**: 568–585.
170 Yoon CH, Lee J, Jongeward GD, Sternberg PW. Similarity of sli-1, a regulator of vuvlval development in *C. elegans*, to the mammalian proto-oncogene c-cbl. *Science* 1995; **269**: 1102–1105.
171 Pui C-H, Behm FG, Raimondi SC *et al*. Secondary acute myeloid

leukemia in children treated for acute lymphoid leukemia. *New Engl J Med* 1989; **321**: 136–142.
172 Kurzrock R, Gutterman JU, Talpaz M. The molecular genetics of Philadelphia chromosome-positive leukemias. *New Engl J Med* 1988; **319**: 990–998.
173 Riggins GJ, Sherman SL, Philips CN, Stock W, Westbrook CA, Warren ST. CGG-repeat polymorphism of the BCR gene rules out predisposing alleles leading to the Philadelphia chromosome. *Genes Chromos Cancer* 1994; **9**: 141–144.
174 Richards RI, Sutherland GR. Repeat offenders: simple repeat sequences and complex genetic problems. *Hum Mutat* 1996; **8**: 1–7.
175 Krontiris TG, Devlin B, Karp D, Robert NJ, Risch N. An association between the risk of cancer and mutations in the HRAS1 minisatellite locus. *New Engl J Med* 1993; **329**: 517–523.
176 Phelan CM, Rebbeck TR, Weber BL *et al*. Ovarian cancer risk in BRCA1 carriers is modified by the HRAS1 variable number of tandem repeat (VNTR) locus. *Nat Genet* 1996; **12**: 309–311.
177 Ferro MT, Garcia-Sagredo JM, Resino M *et al*. Chromosomal disorder and neoplastic diseases in a family with inherited fragile 16. *Cancer Genet Cytogenet* 1994; **78**: 160–164.
178 Chary-Reddy S, Prasa VS, Ahuja YR. Expression of common fragile sites in untreated non Hodkin's lymphoma with aphidicolin and folate deficiency. *Cancer Lett* 1994; **86**: 111–117.
179 Yu S, Mangelsdorf, Hewett D *et al*. Human chromosomal fragile site FRA16B is an amplified jAT-rich minisatellite repeat. *Cell* 1997; **88**: 367–374.
180 Lyn D, Cherney BW, Lalande M *et al*. A duplicated region is responsible for the poly(ADP-ribose) polymerase polymorphism, on chromosome 13, associated with a predisposition to cancer. *Am J Hum Genet* 1993; **52**: 124–134.
181 Vioque J, Francisco Navarro Garcia J, Millas Ros J, Mateo de las Heras E. Evolucion y prediccion de la incidencia de cancer de mam en Zaragoza, 1961–2000. *Med Clin (Barc)* 1993; **101**: 12–17.
182 Phelps Morse D. The hereditary aspect of breast cancer in mother and daughter. *Cancer* 1951; **4**: 745–748.
183 Bucalossi P, Veronesi U. Some observations on cancer of the breast in mothers and daughters. *Br J Cancer* 1957; **11**: 337–347.
184 Narod S, Lynch H, Conway T, Watson P, Feunteun J, Lenoir G. Increasing incidence of breast cancer in family with BRCA1 mutation. *Lancet* 1993; **341**: 1101–1102.
185 Jacobsen O. *Heredity in Breast Cancer*. HK Lewis: London, 1946.
186 Warthin AS. The further study of a cancer family. *J Cancer Res* 1925; **9**: 279–286.
187 Vasen HFA, Taal BG, Griffioen G *et al*. Clinical heterogeneity of familial colorectal cancer and its influence on screening protocols. *Gut* 1994; **35**: 1262–1266.
188 Rodriguez-Bigas MA, Lee PHU, O'Malley L *et al*. Establishment of a hereditary nonpolyposis colorectal cancer registry. *Dis Colon Rectum* 1996; **39**: 649–653.
189 Ostermeyer EA, Friedman LS, Lynch ED *et al*. Green pigs, red herrings, and a golden hoe: a retrospective on the identification of BRCA1 and the beginning of its characterization. *Cold Spring Harb Symp Quant Biol* 1994; **59**: 523–530.
190 Hernandez Avila M, Walker AM. Age dependence of cohort phenomena in breast cancer mortality in the United States. *Am J Epidemiol* 1987; **126**: 377–384.
191 Cannon-Albright LA, Skolnick MH. The genetics of familial breast cancer. *Semin Oncol* 1996; **23**: 1–5.
192 Lynch HT, Smyrk T. Hereditary nonpolyposis colorectal cancer (Lynch syndrome). An updated review. *Cancer* 1996; **78**: 1149–1167.
193 Scully R, Chen J, Plug A *et al*. Association of BRCA1 with Rad51 in mitotic and meiotic cells. *Cell* 1997; **88**: 265–275.
194 Strauss BS. The origin of point mutations in human tumor cells. *Cancer Res* 1992; **52**: 249–253.
195 Nowell PC. The clonal evolution of tumor cell populations. *Science* 1976; **194**: 23–28.
196 Loeb LA. Mutator phenotype may be required for multistage carcinogenesis. *Cancer Res* 1991; **51**: 3075–3079.
197 Kunkel TA, Resnick MA, Gordenin DA. Mutator specificity and disease: looking over the FENce. *Cell* 1997; **88**: 155–158.
198 Holland WW, Doll R, Carter CO. The mortality from leukaemia and other cancers among patients with Down's symdrome (mongols) and among their parents. *Br J Cancer* 1962; **XVI**: 9–186.
199 Geraedts JP, Ford CE, Briet E, Hartgrink-Groeneveld CA, den Ottolander GJ. Klinefelter syndrome: a predisposition to acute non-lymphocytic leukaemia? *Lancet* 1980; **1**: 1092.
200 Wertelecki W, Shapiro JR. 45,XO Turner's syndrome and leukaemia. *Lancet* 1970; **1**: 789–790.
201 Hicsonmez G, Ozsoylus S. Poland's syndrome and leukemia. *Am J Dis Child* 1982; **136**: 1098–1099.
202 Hall JG. Thrombocytopenia and absent radius (TAR) syndrome. *J Med Genet* 1987; **24**: 79–83.
203 Rabinowitz JG, Moseley JE, Mitty HA, Hirschorn K. Trisomy 18, esophageal atresia, anomalies of the radius, and congenital hypoplastic thrombocytopenia. *Radiology* 1967; **89**: 488–491.
204 Vennos EM, James WD. Rothmund–Thomson syndrome. In: Cohen PR, Kurzrock R (eds). *Dermatologic Clinics*, vol 13. WB Saunders: Philadelphia, 1995, pp 143–150.
205 Sachs L. The control of hematopoiesis and leukemia: from basic biology to the clinic. *Proc Natl Acad Sci USA* 1996; **93**: 4742–4749.