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Anticipation in Familial Leukemia

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Summary

Anticipation refers to worsening severity or earlier age at onset with each generation for an inherited disease and primarily has been described for neurodegenerative illnesses resulting from expansion of trinucleotide repeats. We have tested for evidence of anticipation in familial leukemia. Of 49 affected individuals in nine families transmitting autosomal dominant acute myelogenous leukemia (AML), the mean age at onset is 57 years in the grandparental generation, 32 years in the parental generation, and 13 years in the youngest generation ($P < .001$). Of 21 parent-child pairs with AML, 19 show younger ages at onset in the child and demonstrate a mean decline in age at onset of 28 years ($P < .001$). Of 18 affected individuals from seven pedigrees with autosomal dominant chronic lymphocytic leukemia (CLL), the mean age at onset in the parental generation is 66 years versus 51 years in the youngest generation ($P = .008$). Of nine parent-child pairs with CLL, eight show younger ages at onset in the child and reveal a mean decline in age at onset of 21 years ($P = .001$). Inspection of rare pedigrees transmitting acute lymphocytic leukemia, chronic myelogenous leukemia, multiple types of leukemia, and lymphoma is also compatible with anticipation. Sampling bias is unlikely to explain these findings. This suggests that dynamic mutation of unstable DNA sequence repeats could be a common mechanism of inherited hematopoietic malignancy with implications for the role of somatic mutation in the more frequent sporadic cases. We speculate on three possible candidate genes for familial leukemia with anticipation: a locus on 21q22.1-22.2, *CBL2* on 11q23.3, and *CBFB* or a nearby gene on 16q22.

Introduction

Anticipation is the observation that an inherited disease demonstrates intensified clinical severity and/or earlier age at onset with each succeeding generation. It has been observed primarily with myotonic dystrophy (Harper et al. 1992), Huntington disease (Ranen et al. 1995), and the spinal cerebellar ataxias (Banfi and Zoghbi 1994). Prior to the identification of the genes responsible for these illnesses, several explanations were hypothesized, including epigenetic effects, gene conversion, crossing-over defects, and statistical artifact resulting from sampling bias (reviewed in Höweler et al. 1989). It is now clear that the genetic basis of these disorders results from, respectively, CTG and CAG trinucleotide repeat expansions (reviewed in La Spada et al. [1994] and Sutherland and Richards [1995]). Beyond a characteristic number of repetitions, these sequence tracts tend to increase in length when transmitted to affected offspring. Age at onset and clinical severity correlate with the length of the trinucleotide repeat. The molecular explanation of anticipation in these illnesses is attributable to the meiotic instability of these repetitive sequences. The finding of anticipation for an inherited disease might therefore suggest that the responsible molecular mechanism involves expansion of repetitive DNA sequences or some other novel mutational event. Although the molecular mechanism has yet to be determined, anticipation has also been reported in schizophrenia (Sasaki et al. 1996), familial Parkinsonism (Carero-Valenzuela et al. 1995), and truncal heart defects (Bleyl et al. 1995), among other diseases.

In our earlier study (Horwitz et al. 1996) of a large family apparently transmitting autosomal dominant acute myelogenous leukemia (AML), we observed that the age at onset decreased with each generation. (The pedigree is shown in the lower right corner of fig. 1*A*.) We also were intrigued by the coincidence of leukemia and ataxia in this family and a second family (Li et al. 1981). We note that CAG repeats encoding polyglutamine or polyserine are a motif common to some transcriptional activators and helicases (Muchardt and Yaniv 1993; Seipel et al. 1994), which are conceivably attractive candidate genes for familial leukemia. To therefore investigate whether anticipation is a regular occurrence in familial leukemia, we have reviewed all of the rare reports of familial AML and chronic lymphocytic leukemia (CLL) that we could identify. We find that anticipation is a generalized phenomenon in famil-

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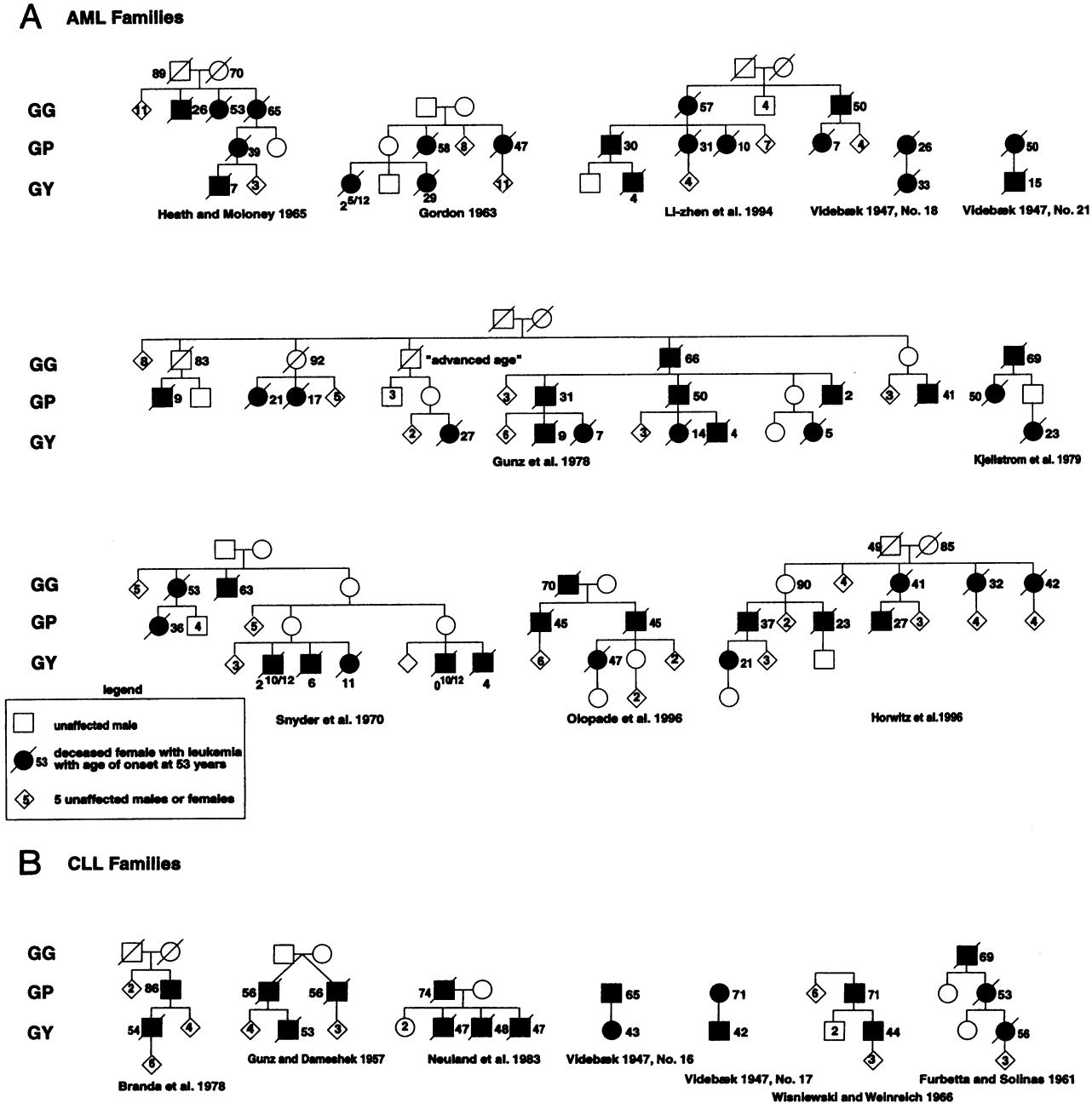

Figure 1 (*A*) AML and (*B*) CLL pedigrees. All pedigrees except for the AML family (Horwitz et al. 1996), from which the hypothesis of anticipation was generated, are used in the statistical analysis. Only affecteds and their first-degree relatives are shown. The ages listed for affecteds are at the time of diagnosis. Individuals with a possible diagnosis (as suspected by the authors of the original report) or a related hematologic diagnosis are not shown as affected. The ages of obligate carriers are indicated, when available. The pedigrees have been aligned to show generational assignments: generation-youngest (GY), generation-parental (GP), generation-grandparental (GG).

ial leukemia. This observation may provide a clue helpful in the search for leukemia genes. The prospect that DNA sequence instability may underlie the cause of rare instances of familial leukemia may illuminate the role of somatic mutation in the common, sporadic occurrences of leukemia.

Subjects and Methods

Sample

The medical literature after 1947 was reviewed. For cases of familial leukemia prior to 1947, we relied on the critical review by Videbæk (1947). Only pedigrees

in which there were two or more affected individuals, each with the same type of leukemia, from at least two generations and with at least one affected parent-child pair were included in the statistical analyses. Ten AML pedigrees and nine CLL pedigrees meeting these criteria were identified (fig. 1). Twenty familial leukemia pedigrees not meeting these criteria are listed in figure 4 (see Discussion); additional examples of excluded pedigrees are found in Videæk's review. Also excluded were familial myeloproliferative disease (reviewed by Gilbert 1995), apparent autosomal recessive myelodysplasia associated with monosomy 7 (reviewed by Horwitz et al. 1996), and a large family with a platelet disorder and tendency toward AML (Dowton et al. 1985) for which age-at-onset data are unavailable (about this family, see Discussion). Only individuals with a diagnosis of AML or CLL from these pedigrees were included in the analysis. Individuals with other hematological diagnosis were considered unaffected. There are two exceptions to the latter. Two individuals with "malignant reticuloendotheliosis" in a large AML pedigree (Snyder et al. 1970) were included in the analysis. This term is not in current usage; the finding of monocytic involvement is consistent with AML. In some of the pedigrees taken from the study by Videbæk (1947) (numbers 23, 25, and 33) and referred to only in the discussion section of this manuscript (but not included in the statistical analysis), individuals with a diagnosis of "stem-cell leukemia" were assumed to have the same type of leukemia as other affected family members given a more specific diagnosis; the unavailability of lineage markers in the era in which these cases were reported leaves a more differentiated diagnosis open to conjecture. "Obligate carriers" were considered unaffected. Because obligate carriers are defined by the presence of disease in the child, who must be younger than they, including them as affected at their present age or later would bias the analysis toward anticipation. While it is possible that some of these individuals will later develop AML, they may, alternatively, be nonpenetrant carriers. Sporadic cases in these families cannot be ruled out.

Statistical Methods

Individuals were assigned to one of three generations (fig. 1), regardless of age at onset, on the basis of their position within the pedigree: GY (youngest generation), GP (parental generation), or GG (grandparental generation). Youngest was defined by the most recently born generation containing an affected individual, regardless of age at onset.

Four analysis methods were used to evaluate possible anticipation separately in familial AML and CML. First, difference in survival to onset of cancer between generations was evaluated using survival analysis. The log rank test was used to test for significance in the difference in the disease-free survival curves between generations. Second, ANOVA was used to test for a significant difference in mean ages at onset between generations. Third, for each affected parent-child pair, the difference between age at onset was tested against the null hypothesis that there was no difference in the age at onset, by using a one sample t-test. Fourth, ANOVA was used to test whether the distribution of the difference between ages at onset in parent-child pairs was the same for male and female parents. As a conservative measure, analysis of parent-child onset differences was repeated after removal of all individuals ≤ 25 years of age, because reproductive success might be restricted. In the CLL families, all onset ages were >25 years. To avoid biasing the result toward anticipation, the pedigree from which the observation of possible anticipation was generated (fig. 1 and Horwitz et al. 1996) was not used in these analysis. Anticipation analysis on diseases where the onset age is difficult to define because symptoms are minimal may result in bias toward diagnosis at a younger age in subsequent family members because of increased surveillance. This is not an issue in the case of AML, where the interval from onset to serious illness or death is short.

It is important to note that these statistical methods assume that unrelated individuals are considered. Their use here relies on their robustness to the violation of this assumption. To test this, one parent-child pair was selected from each pedigree (the oldest-generation parent, left-most pair on the pedigree). The older generation was chosen for this analysis to minimize possible sources of bias associated with the younger generation. The t-test for difference in parent-child age at onset was repeated in these pairs, which will be termed the "unrelated pairs." All analyses were done using SPSS for Windows (SPSS 1991).

Results

The cumulative survival-to-diagnosis curve for AML is shown in figure 2. There are 19 affected individuals in GY, 20 in GP, and 10 in GG. The log rank test rejects equality of the age-at-onset distributions between generations ($P < .0001$). The mean ages at onset ($\pm$ SD) for GY, GP, and GG are 13 $\pm$ 13, 32 $\pm$ 17, and 57 $\pm$ 13 years, respectively, and are significantly different ($P < .001$). Of 21 parent-child pairs, in only two cases was the child's onset at a later age than that of the parent. The mean decline in age at onset in parent-child pairs was 28 years (standard error = 3.4 years). Using a one-sample t-test, the hypothesis that there is no difference between the age at onset for the 21 parent-child pairs is rejected ($P < .001$). This hypothesis is rejected even when only the eight unrelated pairs are considered

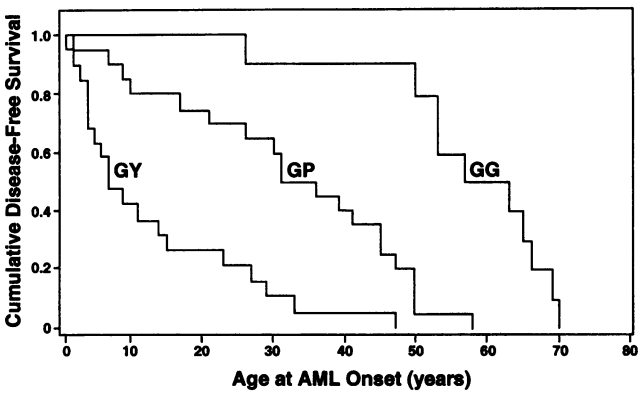

Figure 2 Age at onset, stratified by generation, for AML

(P = .003). The parent-child onset-age difference was 26 years for the 10 male parents and 29 years for the 11 female parents (not significantly different, P = .13). Removal of the 21 affected individuals at or under the age of 25 years, who might a have a limited ability to reproduce, did not change the conclusions.

The cumulative survival-to-diagnosis curve for CLL is shown in figure 3. For CLL there are 10 GY, 7 GP, and 1 GG individuals. The one GG individual was excluded from the curve, because of limited sample size. The log rank test rejects equality of the GY and GP distributions ($P < .01$). The mean ages at onset (± SD) of 51 ± 9 and 66 ± 12 years for GY and GP, respectively, are significantly different (P = .008). The mean decline in age at onset for the nine parent-child pairs is 21 years (standard error = 4.1 years) and is significantly different than zero (P = .001), and remained statistically significant in the six unrelated pairs (P = .003). In only one case was the child's onset at a later age than that of the parent. Because only two affected parents were female, a test of whether parental sex influenced the age-at-onset difference was not possible.

Discussion

Studies of anticipation are vulnerable to ascertainment bias (Penrose 1948; Hodge and Wickramaratne 1995), primarily because the identification of an affected individual may lead to heightened reporting of other affected family members, and, when soliciting the family history, individuals from the preceding generations are necessarily older than those in the proband's generation. Penrose (1948) enumerated three potential ascertainment biases that can suggest anticipation: (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 physician attention; and (3) selection of cases with simultaneous onset in parent and child, resulting in increased physician awareness of both individuals being affected and increased reporting by physicians. The optimal design for a study of anticipation would be to consider only prospectively obtained cases. Because of the rarity of leukemia in general (a total incidence of ~1/13,000 (Champlin and Gold 1991)) and the extreme rarity of familial occurrences, such a study would require a population of impractically large size as well as time for multiple generations to become affected. We have therefore relied on published leukemia pedigrees. We have taken the following measures to mitigate potential ascertainment bias: (1) We have excluded the pedigree (Horwitz et al. 1996) from which our hypothesis of anticipation was formulated. (2) For AML, we have included only pedigrees with uniform diagnoses, excluding those with multiple individuals with myelodysplasia. Since myelodysplasia can be a "preleukemic" illness of protracted duration, an early age at diagnosis might result from the medical attention that the family history would attract. Nevertheless, in two families with myelodysplasia, but that otherwise meet our sampling criteria, there is suggestive evidence for anticipation (Marsden et al. 1995; W. Raskind and M. Horwitz, unpublished data). Likewise for CLL, we have excluded those pedigrees with related hematologic syndromes. (3) We have excluded nonpenetrant obligate carriers. Since these individuals are found only when they have affected children, they are in the older generations; assuming them to be affected at an age equal to or greater than their attained age would bias the result toward anticipation. (4) Generational assignments are made in reverse order, beginning with the most recently affected generation, so that assignment to generation was independent of age at onset. (5) We have repeated the analysis for AML, excluding younger individuals, whose reproductive success may be limited. This is an unlikely source for bias in CLL, since the youngest onset

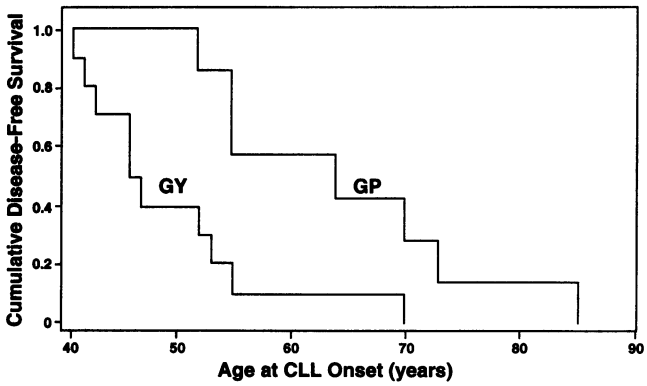

Figure 3 Age at onset, stratified by generation, for CLL

is at age 42 years. Although we cannot eliminate all sources of ascertainment bias, the results presented here are unlikely to be due to ascertainment bias alone.

Additional arguments against ascertainment bias being the primary cause of the observed anticipation include the following: (1) In at least some families (Gunz and Dameshek 1957; Gunz et al. 1978; Horwitz et al. 1996), additional affected individuals presented after the proband and family history were ascertained; in a sense, these individuals were prospectively ascertained. These cases are not subject to the same ascertainment problems of retrospectively ascertained cases and are also consistent with anticipation. (2) It might be expected that ascertainment bias would apply not just between generations, but within a generation; where birth order within a sibship is available, the age at onset does not decline among the younger children. (3) We emphasize that the clinical features of leukemia, particularly AML, are generally severe and obvious, so that most cases result in prompt medical attention and death, regardless of cognition of family history. (4) In the general population, the overall incidence of AML and CLL increases steeply with age, with pronounced breakpoints in the age-distribution curves commencing at ~50 years of age (Champlin and Golde 1991); the abundance of juvenile cases in the younger generations reviewed here sharply contrasts with the expected distribution of onset ages if anticipation were not occurring. (5) While future cases of leukemia may increase the mean age at onset for the younger generations, it is clear that the older generations simply do not have pediatric cases.

Corroborating evidence for anticipation can be extracted from an earlier, population-based survey (Rigby et al. 1968) in which parent-child pairs of individuals affected with all types of leukemia, lymphoma, and myeloma were considered. The mean difference between ages at death in parent-child pairs was 38 years. However, analysis of parent-child pairs may suggest anticipation due to a bias in reporting of pairs who are both diagnosed in a short time span. This is much less of an issue in the AML families reported here, because of the large number of affected members in most families and the necessary gap in diagnosis of the parent-child pair. The smaller families are more susceptible to this bias. Anticipation may also explain additional AML (pedigree 31 of Videbæk 1947; Chitambar et al. 1983) and CLL (HS family of McPhedran et al. 1969) pedigrees in which multiple cousins have been affected. For these families the inheritance is consistent with either autosomal dominant transmission with incomplete penetrance in the preceding generation or autosomal recessive inheritance with unusual clustering of carrier spouses. The most plausible explanation is that the age at onset is greater for the parental generation. Similarly, in the pedigrees used in our analysis there are several cases of an affected individual with an unaffected parent but several affected aunts or uncles. In addition, some of the pedigrees used in our analysis can be traced to an unaffected founder couple where both members of the couple have survived to advanced ages without developing leukemia. It thus seems that incomplete penetrance is most apparent in the earliest generations of the leukemia pedigrees, as expected under anticipation.

Anticipation is apparent for both AML and CLL. Analyses for other types of leukemia has not been performed, because of the rarity of such pedigrees. Inspection (fig. 4) of the few available pedigrees transmitting autosomal dominant acute ALL (pedigrees 23 and 33 of Videbæk 1947; Bridges and Nelson 1961; pedigree I of Felix et al. 1992), CML (pedigrees 25 and 34 of Videbæk 1947), multiple types of leukemias (pedigrees 20, 22, 24, 27, 28, 38, and 39 of Videbæk 1947; Rigby et al. 1968; HD family of McPhedran et al. 1969; Li et al. 1979; Gerrard et al. 1991), or lymphomas (families 31 and 33 of Razis et al. 1959; Fraumeni et al. 1975), however, reveals findings consistent with anticipation. (Note that seven families with mixed lineage leukemias meet the selection criteria for the analysis that we applied to AML and CLL. Anticipation is evident in these families, but we are hesitant to include these as statistical results, because different leukemia types may have characteristically different ages at onset.) Anticipation may be a general feature of all inherited hematologic malignancy.

One explanation for anticipation occurring with different types of hematologic malignancy may be that all are vulnerable to the same unknown statistical biases. A possible nongenetic explanation is that, since the observed anticipation (21–28 years) is about the same as the generational age difference, parent and child could have been simultaneously exposed to an environmental agent. In fact, this was entertained by Rigby et al. (1968) in their population-based survey, which was confined to a specific geographical region. However, this fails to explain the data from the larger families in which cases were distributed geographically and across time. In addition, few environmental factors, short of atomic blasts, have been affirmatively linked with leukemia (Champlin and Golde 1991). A nontrivial possibility is that a related genetic mechanism underlies different types of hematologic malignancy. Support for this conclusion comes from the observations that a few families (Videbæk 1947; Rigby et al. 1968; McPhedran et al. 1969; Li et al. 1979) transmit different types of leukemias, in which it is possible that they are deficient in a gene fundamental to the appropriate maturation of multiple hematopoietic lineages. It should also be pointed out that in some syndromes associated with aberrant DNA

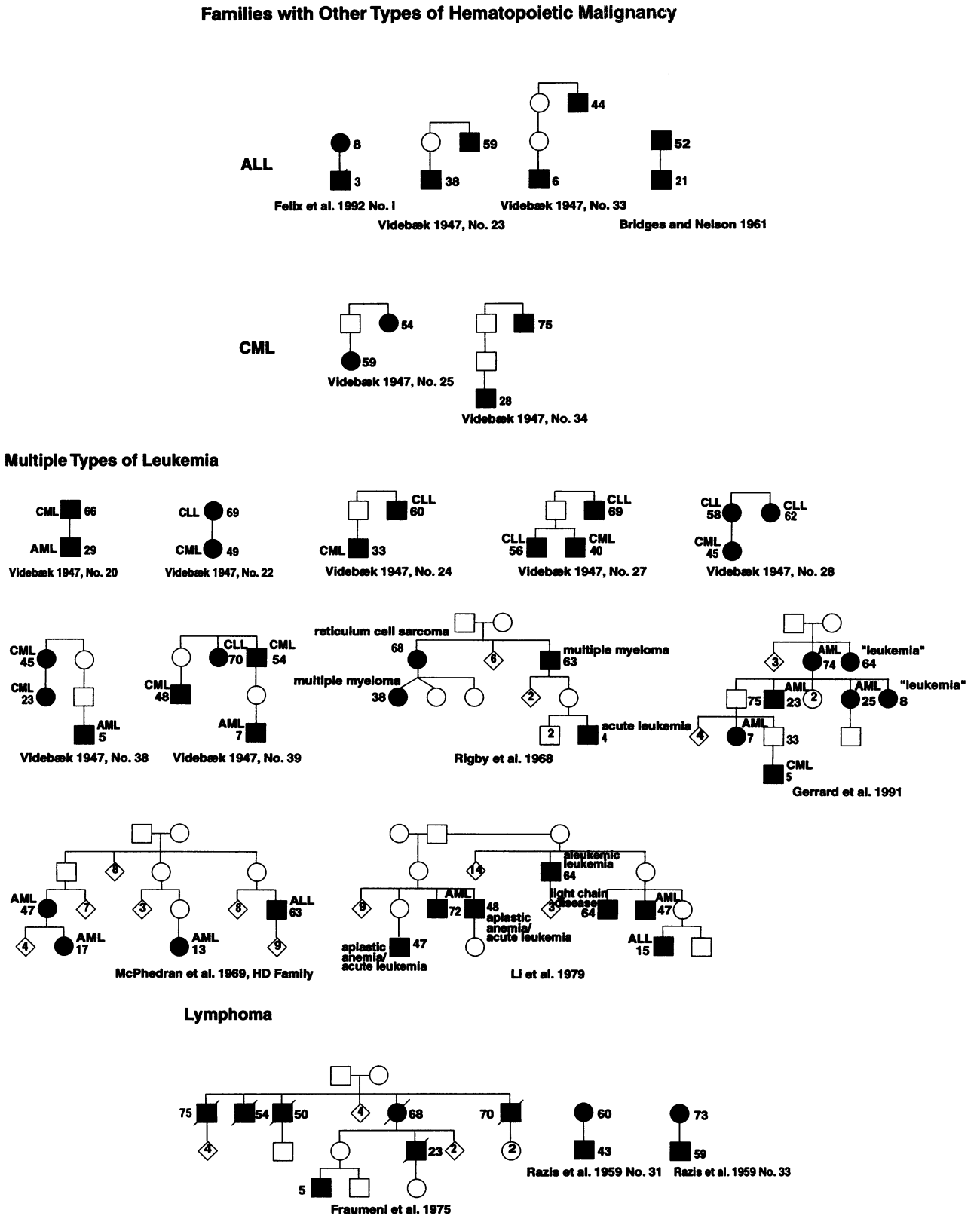

Figure 4 Pedigrees transmitting other types of hematopoietic malignancy. Shown are all the multigenerational pedigrees that we could find in a review of the literature. They have not been selected with respect to the criteria used for the AML and CLL families.

repair, such as Bloom syndrome, patients are disposed toward hematological malignancy, and the spectrum spans the maturation of the different hematopoietic lineages (German 1983), lending support to the possibility that a related mutational mechanism may be operative in different types of hematopoietic malignancy.

The extent of anticipation, 28 years for AML and 24 years for CLL, is, in general, of a greater magnitude than has been found for diseases associated with trinucleotide repeats (as reviewed by La Spada et al. 1994). The absence of a parental sex effect in promoting anticipation also distinguishes familial AML from myotonic dystrophy and the fragile X syndrome, where there is maternal disposition toward trinucleotide repeat expansion and anticipation, and Huntington disease, where anticipation is associated with paternal inheritance (as reviewed by La Spada et al. 1994). Anticipation in familial leukemia could therefore derive from a different mechanism that has not been previously described. Nevertheless, the possibility that mutation by trinucleotide repeat instability is responsible for familial leukemia should be considered, because it is, so far, the only known mechanism for anticipation.

Should unstable repetitive DNA sequences be the explanation for anticipation in familial leukemia, this hypothesis would have some bearing on the far more common sporadic occurrences of leukemia in individuals without familial disposition. The trinucleotide repeats of fragile X syndrome, Huntington disease, and myotonic dystrophy demonstrate somatic variation in repeat length (as reviewed by Sutherland and Richards 1995), presumably resulting from incomplete mitotic fidelity. Somatic expansion of an unstable repeat in a critical gene could be the rare, yet signal step in the genesis of sporadic cases of leukemia. A supportive observation is that of microsatellite (Indraccolo et al. 1995; Robledo et al. 1995; Gartenhaus et al. 1996) and trinucleotide repeat (Shen et al. 1994) DNA sequence instability in some leukemias.

Several genes are known to contain trinucleotide repeats, and many of these genes could conceivably be involved in malignancy (reviewed by Panzer et al. 1995). We speculate on three possible candidate loci. First, linkage to a locus on chromosome 21q22.1-22.2 (Ho et al. 1996) has been established for a family (Dowton et al. 1985) inheriting a platelet defect and predisposition to myeloid leukemia. Age-at-onset data are not available for this pedigree, but a family with an indistinguishable phenotype (Gerrard et al. 1991, as shown in fig. 4) does demonstrate anticipation. A third family inheriting a similar phenotype in a pattern consistent with anticipation appears by preliminary analysis to be linked to this locus (W. Raskind and M. Horwitz, unpublished data). Second, expansion of a CCG repeat on chromosome 11q23.3 in the proto-oncogene *CBL2* has been shown to predispose to terminal deletion of 11q and consequently the Jacobsen syndrome (Jones et al. 1995). Evidence for *CBL2* mutation has been found in some sporadic leukemia (Young 1992), and leukemia has been reported in the Jacobsen syndrome (Jacobsen et al. 1973). Third, in a family transmitting a chromosome 16q22 fragile site (Ferro et al. 1994) there is occurrence of AML in a man at age 69 years and ALL in his daughter at age 14 years. The *CBFB* gene, mutation of which has been associated with AML subtypes (Liu et al. 1995), maps to this region and contains a CGG repeat (Hajra and Collins 1995). It is possible that expansion of this CGG repeat or of a nearby repeat (Liu et al. 1995) may account for the fragile site in this family.

Note added in proof.—We have subsequently learned that, in a 20-year prospective follow-up of the AML family reported by Gunz et al. (1978), there have been three new cases, in a pattern still consistent with anticipation. Two of the cases occurred in individuals with unaffected parents and grandparents. The third was to a child of one of the two new cases, with age at onset of AML at 3 mo.

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