

REVIEW

Genetic susceptibility to chronic lymphocytic leukemia

RS Houlston¹, D Catovsky² and MR Yuille²

¹Section of Cancer Genetics, Institute of Cancer Research, Sutton, UK; and ²Academic Department of Haematology and Cytogenetics, Institute of Cancer Research, Sutton, UK

There is increasing evidence that a subset of chronic lymphocytic leukemia is caused by an inherited predisposition. Here we review the evidence for an inherited predisposition, the characteristics of familial cases and evidence for the involvement of specific genes.

Leukemia (2002) 16, 1008–1014. DOI: 10.1038/sj/leu/2402538

Keywords: inherited susceptibility; chronic lymphocytic leukemia

Introduction

In Western countries, leukemia affects 1–2% of the population.¹ B cell chronic lymphocytic leukemia (CLL) is the most common form of leukemia accounting for around 30% of all cases.² The incidence rate of CLL increases logarithmically from age 35 with a median age of diagnosis at 65 years.³

A very small number of acute leukemia cases are well documented to occur at a higher frequency in individuals with constitutional chromosome anomalies or are a feature of some Mendelian cancer syndromes. While there is general awareness of these associations, by contrast, CLL and associated B cell lymphoproliferative disorders (LPDs) have not been thought of until recently as having an inherited genetic component. However, evidence from epidemiological studies and family studies suggests that a subset of CLL may also be caused by an inherited predisposition which gives rise to familial forms of the disease. Identification of the gene or genes underlying familial forms of CLL may be useful for diagnosis and treatment of those at high risk, as well as serving as a model for CLL tumorigenesis in general.

Evidence for a genetic predisposition to chronic lymphocytic leukemia

Epidemiological studies

Seven epidemiological studies have systematically examined the risk of CLL and other LPDs in relatives of patients (Table 1). Four of the studies were case–control and three were cohort in design. All of the case–control studies examined the risk of leukemia in relatives of CLL patients. All found risks of leukemia or lymphocytic leukemia in relatives. The three cohort studies were all retrospective in design. The study reported by Gunz *et al.*⁴ was based on a survey of 909 families ascertained through leukemia cases. The study reported by Giles *et al.*⁵ made no distinction between type of LPD in their analysis of the family histories of cases diagnosed between 1972 and

1980 in Tasmania. The study reported by Goldgar *et al.*⁶ was a systematic analysis of clustering of malignancy at 28 distinct sites using the Utah population database. Relatives of lymphocytic leukemia cases were at a 5.7-fold increased risk of the same hematological malignancy. The risk of LPD in relatives reported in the three studies was comparable to that observed in the case–control studies.

Although none of these studies has systematically examined the familial risk of leukemia by specific subtype, it is likely that the familial risk of leukemia in relatives of lymphocytic leukemia patients reflects an increased risk of CLL since acute lymphoblastic leukemia is the primary potential confounding diagnosis, but does not display an increased sibling risk.⁷

A number of inherited susceptibility genes cause cancer at several sites. Therefore any excess of cancer at sites other than CLL in relatives may reflect in part the pleiotropic effects of an inherited predisposition gene. In addition to a possible relationship between CLL and other B cell LPDs, a relationship between lymphocytic leukemia and granulocytic leukemia and rectal cancer was observed in the study reported by Goldgar *et al.*⁶

Survey of published familial cases

Over 50 pedigrees have been reported which show clustering of CLL (Table 2). It has often been suggested that even very striking familial clusters of common malignancies can be ascribed to ascertainment bias. This is, however, a statistical fallacy. For example, Table 2 identifies reports of 24 families with three or more affected individuals, nine of which were ascertained by the authors yet a family with three affected siblings would be expected to occur by chance about every 1000 years.

A few reports of relatively large kindreds clearly show vertical transmission of CLL and other LPDs, suggesting that predisposition to CLL and other LPD is caused by the inheritance of a dominantly acting gene (or genes) with incomplete penetrance and pleiotropic effects. Although most of the families reported are nuclear rather than multigenerational, it is conceivable that many family members may have subclinical disease as CLL generally has an indolent course. Such a notion is supported by the observation that in some of the families reported apparently unaffected family members had a persistent lymphocytosis.⁸

It is relatively difficult to determine the proportion of CLL cases that have a family history of the disease because much disease goes undetected. However, in a recent systematic survey of CLL, 6% of patients reported a family history of CLL and another 5% a family history of a LPD.⁹

Published CLL pedigrees appear to be characterized by an earlier onset than sporadic forms of the disease, suggesting a more aggressive clonal expansion. One intriguing feature seen

Correspondence: RS Houlston, Section of Cancer Genetics, Institute of Cancer Research, 15 Cotswold Road, Sutton Surrey SM2 5NG UK; Fax: +44 208 722 4362

Received 4 April 2001; accepted 20 September 2001

Table 1 Familial risks of CLL and other LPDs

Study	Diagnosis in index case	Relative	Observed	Expected	Risk (95% CI)
Cohort studies					
Giles <i>et al</i> ⁵	LPD	LPD in first-degree relatives	35	10.3	3.4 (2.4–4.7)
Gunz <i>et al</i> ⁴	Leukemia	Leukemia in first-degree relatives	16	6.61	2.4 (1.9–3.9)
Goldgar <i>et al</i> ⁶	Lymphocytic leukemia	Lymphocytic leukemia in first-degree relatives	18	3.6	5.7 (2.6–10.0)
Case-control studies					
Cartwright <i>et al</i> ⁶⁶	CLL	Lymphocytic leukemia in blood relatives	5/330	2/559	4.3 (0.9–19.5)
Linet <i>et al</i> ⁴⁷	CLL	Leukemia in parents and siblings	25/342	10/342	2.6 (1.2–5.5)
Pottern <i>et al</i> ⁴⁸	CLL	Leukemia in parents and siblings	13/237	30/1207	2.3 (1.2–4.4)
Radovanovic <i>et al</i> ⁴⁹	CLL	Leukemia in first- and second-degree relatives	7/130	0/130	—

in the expression of CLL in many of the families reported is anticipation, the phenomenon of earlier onset and more severe phenotype in successive generations.^{10–14} This phenomenon is observed in other Mendelian diseases, where it is known to have a specific molecular basis. Anticipation in familial CLL may have a similar basis, although other possibilities exist, such as a cohort effect in relation to viral or other environmental exposures, which act as risk factors.

Molecular genetics of familial chronic lymphocytic leukemia

Molecular studies of neoplastic disease have shown that multiple genetic alterations are an essential feature of the tumorigenic process. These alterations involve two broad classes of genes: tumor suppressor genes, whose products normally directly inhibit neoplastic development by negatively regulating growth and differentiation; and oncogenes which positively contribute to the neoplastic transformation when activated. Inactivation of tumor suppressor genes coupled with activation of oncogenes leads to malignancy. Genetic alterations involved in the transformation of normal cells to the malignant state can be both inherited in the germline and arise somatically in the tissue in which the cancer arises.

The genetics of CLL are conceivably similar to the genetics of breast and colon cancers, in which a subset of the disease occurs in individuals who possess in their germline one or more of the causal genetic alterations required for the neoplastic transformation. In the majority of cases, these genes are altered at the tissue level by random errors in cellular processes. According to the multistep model of carcinogenesis, the development of the full neoplastic phenotype in both inherited and non-inherited forms of CLL depends upon multiple genetic alterations.

The genetic basis of CLL is largely unknown. Cytogenetic abnormalities appear, probably for technical reasons, to be less frequent in CLL than in many other hematological malignancies.¹⁵ A number of chromosome breakage syndromes have been known for many years to be associated with an increased risk of leukemia,¹⁶ including the recessive disease, ataxia telangiectasia (A-T). A-T maps to chromosome 11q23.¹⁷ A-T patients have an increased risk of lymphomas and leukemias, while A-T heterozygotes may have a significantly

increased risk of breast cancer.^{18,19} CLL has also been reported in A-T families²⁰ suggesting that A-T heterozygotes may be at an increased risk. In a retrospective study of the cancer incidence in 110 A-T families the risk of hematological and lymphoid malignancies was increased in blood relatives of A-T patients and CLL accounted for all but one of the leukemias seen in adult blood relatives. However, these observations did not attain statistical significance. It has been demonstrated that the *ATM* gene is mutant in approximately 20% of samples from CLL patients and that some patients have heterozygous germline mutations.^{21–24} The *ATM* gene specifies a 12 kb mRNA encoding an approximate 350 kDa.²⁵ The 3' end of the gene has some homology to phosphoinositide 3-kinases and to *S. cerevisiae* TEL1 that controls telomere length and maintenance of genome integrity.²⁶ Homozygous germline mutations in *ATM* are associated with radiosensitivity and genomic instability: the mutation rate is increased; double strand breaks are misrepaired; there is a high frequency of cytogenetic rearrangements; homologous recombination is increased and error-prone. A-T cells also show defects in cell cycle checkpoints. These defects underlie a model,²⁷ in which the *Atm* protein functions to survey the genome for radiation damage. This and the prevalence of leukemia in relatives of patients with A-T led a number of researchers to question whether germline *ATM* mutations are involved in familial cases of CLL. Stankovic *et al*²¹ observed two germline *ATM* mutations in 32 cases (6.3%) of CLL ($P = 0.04$; 95% CI: 1–21%). We recently assessed the role of *ATM* in familial CLL through a linkage analysis of 28 families.²⁸ The observed distribution of sharing of *ATM* haplotypes between affected individuals did not lend support to the notion that *ATM* is involved in familial CLL. However, the study was not sufficiently large to preclude that *ATM* might account for up to a two-fold sibling relative risk. Multigenerational families are characteristic of highly penetrant susceptibility genes, it is therefore conceivable that genes conferring susceptibility to CLL are associated with more modest risks. Assuming that approximately 6% of CLL is caused by *ATM*,²¹ mutations in this gene should only confer a sibling relative risk of 1.1. *ATM* therefore represents a credible candidate predisposition locus for CLL. While *ATM* is an attractive CLL predisposition gene candidate, there is currently insufficient evidence to show unambiguously that *ATM* acts as a susceptibility locus.

The established relationship between HLA and Hodgkin's

Table 2 Published familial CLL cases

Reference	Affected family members*	Additional information
Guasch 1954 ⁵⁰	Sibs M, M Parent F, offspring M Sibs M, M Sibs M, M, M, F Sibs M, M, M Sibs M, M Sibs M, M Sibs M, M Sibs M, M, F Parent F, offspring F MZ twins M, M Parent M, offspring M Parent M, offspring M Sibs M, M	
Brem <i>et al</i> 1955 ⁵¹	Sibs M, M	Sib M LK
Videbaek 1958 ⁵²	Uncle, nephew	
Hudson <i>et al</i> 1960 ⁵³	Sibs M, M; Sibs M, M Sibs F, M, M	
Gunz <i>et al</i> 1962 ⁵⁴		
Fitzgerald <i>et al</i> ⁵⁵		
Furbetta <i>et al</i> 1963 ⁵⁶	Grandparent M, parent F, offspring F	
Wisniewski 1966 ⁵⁷	Parent M, offspring M	
Rigby 1966 ⁵⁸	2 half-sibs	
Ardizzone <i>et al</i> 1968 ⁵⁹	Sibs M, M	
Magaraggia <i>et al</i> 1968 ⁶⁰	Sibs M, M	
McPhedran <i>et al</i> 1969 ⁶¹	Sibs F, M, F, cousins F, M, M	
Fraumeni <i>et al</i> , ⁶² Blattner <i>et al</i> 1969 ⁶³	Sibs F, M, M	Sib CGL
Gunz <i>et al</i> 1969 ⁶⁴	Sibs M, F Sibs M, M	
Undritz <i>et al</i> 1971 ⁶⁵	Sibs M, M, M, F	Sib LY, sib LY, sib acute LK
Potolovsky <i>et al</i> 1971 ⁶⁶	Sibs F, F	
Schweitzer <i>et al</i> 1973 ⁶⁷	Sibs F, M, M, F, F	
Blattner <i>et al</i> , ⁶⁸ Neuland <i>et al</i> , ⁶⁹ Shen <i>et al</i> , ⁷⁰	Parent M, offspring M, M, F, F	
Caporaso <i>et al</i> 1991 ⁷¹		
Gunz 1975 ⁷²	3 first degree; 3 others	
Petzholdt 1976 ⁷³	Sibs M, M, M	
Fazekas <i>et al</i> 1978 ⁷⁴	Sibs M, M, M	
Branda <i>et al</i> 1978 ⁷⁵	Parent F; offspring M	
Conley <i>et al</i> 1980 ⁷⁶	Sibs F, F Sibs M, M Nephew, maternal aunt; Nephew M; great-aunt	
Alfinito <i>et al</i> 1982 ⁷⁷	Sibs F, F	
Vanni <i>et al</i> 1983 ⁷⁸	Sibs F, F	
Brok-Simoni <i>et al</i> ⁷⁹	MZ twins F, F, sib F	
Hakim <i>et al</i> 1987 ⁸⁰		
Eriksson <i>et al</i> 1987 ⁸¹	Sibs M, M; Sibs M, F; Sibs M, F; MZ twins M; Parent M, offspring M; Parent M, offspring M	
Shah <i>et al</i> 1992 ⁸²	Sibs F, M, F	Sib M NHL
Cuttner 1993 ⁸³	Sibs M, M; Parent M, offspring M; MZ twins M, M	
Fernhout <i>et al</i> 1997 ⁸⁴	Sibs F, F, F, F	
Yuille <i>et al</i> 2000 ⁹	Parent M, offspring M, pat cousin F; Parent F, offspring M; Parent F, offspring M; Parent F, offspring F; Parent M, offspring M; Parent F, offspring M; Sibs M, F; Sibs M, M; Parent M, offspring M; Parent F, offspring M; Parent F, offspring F; Sibs M, M	Nephew NHL Sib F LK Offspring F LK Offspring M HL

CGL, chronic granulocytic leukemia; HL, Hodgkin's lymphoma; LK, leukemia; LY, lymphoma; NHL, non-Hodgkin's leukemia.

lymphoma, another B cell disorder and the association between autoimmune disease and CLL raises the possibility that genes within the MHC region may be determinants of CLL susceptibility. Hodgkin's lymphoma shows strong linkage to HLA.^{29,30} The underlying basis of linkage is not through a common haplotype, but it appears that certain HLA-DPB1 alleles may affect susceptibility and resistance to specific subtypes of Hodgkin's lymphoma.^{31,32} Patients with CLL frequently share common HLA haplotypes with relatives with autoimmune disease. The majority of B cell CLL is CD5⁺ and B cells are implicated in autoimmunity. Hence genetic determinants of CD5⁺ B cell proliferation or differentiation are likely to be involved in both B-CLL and autoimmune disease. The notion of a relationship between CLL and autoimmune disease is supported by animal studies using congenic New Zealand mouse strains.^{33,34} In Hodgkin's disease, the allele sharing probabilities between affected siblings suggest that the HLA locus is likely to explain a two-fold sibling relative risk with more than half of all cases arising in susceptible individuals. There is no evidence that such a situation exists with respect to familial CLL. In the linkage study reported by Bevan *et al*³⁵ there was no evidence for linkage in an analysis of 27 families. However, the 95% confidence limit for the estimate of the sibling relative risk ascribable to the HLA did not preclude that variation within HLA or the MHC is a determinant of CLL susceptibility in some instances.

The B cell antigen receptor (BCR) comprises membrane Igs (mIgs) and a heterodimer of Ig (CD79a) and Ig (CD79b) transmembrane proteins, encoded by the mb-1 and B29 genes, respectively. These accessory proteins are necessary for surface expression of mIg and BCR signaling.³⁶ CLL B cells frequently express low to undetectable surface Ig, as well as CD79b protein and show abnormal B29 expression and/or function. The possibility that these abnormalities might be caused by B29 gene mutations has been assessed recently in a study of 10 CLL families.³⁶ While a few silent or replacement mutations were observed, none led to a truncated CD79b protein, furthermore there was no evidence of co-segregation of mutation with disease strongly implying that germline mutations in B29 are not implicated in familial CLL.

Linkage of Hodgkin's disease to the pseudo-autosomal region of the genome has recently been proposed Horwitz and Wiernik³⁷ on the basis of an excess of sex concordance among affected siblings. The common lineage of Hodgkin's and CLL prompted us to examine whether familial CLL also shows pseudo-autosomal linkage. An analysis of published CLL and families shows that the frequency of sex-concordant sibling pairs is skewed beyond random expectation, however it is impossible to preclude publication bias and so the implicated pseudo-autosomal linkage in CLL is questionable.³⁸

In a number of Mendelian diseases, anticipation has been shown to be indicative of a dynamic mutation mechanism involving expansion of a triplet repeat motifs.³⁹ If the genetic basis of familial CLL involves a similar mechanism this offers a novel method of identifying a predisposition locus for the disease, since specialized methods exist specifically for cloning genes associated with such expansions.⁴⁰

Somatic changes in familial CLL

Investigation of somatic genetic changes in familial cancer tumor samples can, in principle, provide information on the etiology of the disease. Two types of investigation on familial CLL samples have been conducted that have used this approach.

One type of investigation is to look for a region of recurrent genomic loss in tumor cells from familial cases. Such a region may harbor a CLL tumor suppressor gene. The technique of comparative genomic hybridization (CGH) permits this type of investigation by examining the whole genome for regions of chromosomal loss or gain. We have applied CGH to 24 familial cases of CLL (unpublished data). The data indicated that three regions of the genome may harbor predisposition genes: Xp11.2-p21, Xq21-qter, 2p12-p14 and 4q11-q21. Considerable caution is called for in extrapolating from CGH data and only detailed investigation of these regions of the genome by linkage analysis or by closer delineation of regions of shared loss between affected family members may permit candidate familial CLL gene identification.

A second line of investigation has characterized immunoglobulin variable regions in familial CLL. This type of study may characterize familial CLL as genetically homogeneous or genetically heterogenous. During the B cell response to T cell-dependent antigens, B cells undergo a rapid proliferative phase in the germinal center. This is accompanied by the introduction of mutations into the immunoglobulin (Ig) variable region (V) genes. The B cells are then selected according to the affinity of the encoded immunoglobulin for antigen, resulting in affinity maturation of the response. It is now apparent that there are two subsets of CLL, one with a low load of mutations and poor prognosis and one with a heavy load of mutations with a much more favorable prognosis. Between 20% and 50% of all CLL cases have IgV mutations.^{41,42} Two investigations have assessed IgV status in familial CLL.^{43,44} In 23 CLL families, 66% of 48 affected family members had IgV mutations. This frequency is significantly higher for familial CLL than sporadic CLL (assuming a mutation frequency of approximately 50%, significance levels are <0.001 in Pritsch *et al*⁴³ and 0.04 in Sakai *et al*⁴⁴).

Using the data from these studies it is also possible to assess whether there is intra-familial concordance for IgV status. Table 3 shows the number of concordant and discordant pairs in each of these studies. To formally assess the significance, the observed distribution is compared with the random distribution predicted on the basis of the observed prevalence of the mutated phenotype. Whilst the distribution of phenotypes in the families reported study by Pritsch *et al*⁴³ is not significantly different from that expected, the distribution in the families reported by Sakai *et al*⁴⁴ shows a clear deviation. Combining data from the two studies, the concordance is significant within families ($\chi^2 = 11.2$, 1 df, $P < 0.001$). This strongly suggests that determining IgV status will be helpful in subgroup analyses of linkage data and future meta-analyses.

Conclusions

Chronic lymphocytic leukemia has not generally been considered to have an inherited genetic basis. However, there is

Table 3 Frequency of IgV concordancy

IgV mutation status familial phenotype	Pritsch <i>et al</i> ⁴³	Sakai <i>et al</i> ⁴⁴	Combined
N/N	1	5	6
N/Mut	2	2	4
Mut/Mut	11	6	17

Mut, IgV mutation present; N, no IgV mutation present.

indirect evidence that a subset of CLL cases may be ascribed to the inheritance of an autosomal dominant gene. It is therefore desirable not to restrict the collection of family histories to hematology patients with the rare inherited cancer syndromes. Furthermore, there is some evidence that familial forms of CLL may warrant more attentive clinical management, owing to a more aggressive phenotype.

Identification of the genes involved in inherited forms of CLL should provide insights into the pathogenesis of CLL in general. At present there is no convincing evidence that any specific gene acts as a susceptibility locus and identification of these genes for CLL awaits future linkage studies. Genetic heterogeneity severely reduces the power of any linkage analysis to detect disease genes. Since subcategorization of a disease provides a strategy to mitigate the impact of heterogeneity on linkage, IgV^{43,44} and BCL-6⁴⁵ status may achieve this for familial CLL.

The identification of a CLL predisposition gene through genetic linkage is clearly contingent on the acquisition of a large series of informative families. Experience in other fields of cancer research has shown that such family collections are only readily achievable through the establishment on large pan-country collaborations. Therefore to expedite the ascertainment and collection of families we have established an International CLL Linkage consortium. We invite interested parties who identify families segregating CLL with or without an associated LPDs to contribute to the initiative we have established.

Acknowledgements

The authors' work is supported by the Leukaemia Research Fund. We thank all the families and their clinicians that have contributed to our research.

Editor's note

We are very indebted to Dr Peter Daniel who recruited and evaluated all the Reviews published in this Spotlight. Authors who are interested in contributing a Review for this Spotlight are invited to contact the Editor-in-Chief, Dr Muller Bérat.

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