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## Familial Aspects of Chronic Lymphocytic Leukemia, Monoclonal B-Cell Lymphocytosis (MBL), and Related Lymphomas

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### Abstract

Families with multiple individuals affected with chronic lymphocytic leukemia (CLL) and other related B-cell tumors have been described in the literature. Familial CLL does not appear to differ from sporadic CLL in terms of prognostic markers and clinical outcome. While some environmental factors (such as farming related exposures and occupational chemicals) may increase risk of CLL, results of epidemiological studies have been generally inconsistent. Large, population-based case-control and cohort studies have also shown significant familial aggregation of CLL and related conditions including non-Hodgkin lymphomas, especially other indolent lymphomas. The precursor condition, monoclonal B-cell lymphocytosis (MBL) also aggregates in CLL families. However because the baseline population risks for CLL and other indolent lymphomas are low, the absolute risk to a first-degree relative for developing CLL or a related disease is also low. Linkage studies have been conducted in high-risk CLL families to screen the whole genome for loci that contribute to susceptibility but no gene mutations have yet been identified by this method. Association studies of candidate genes have implicated several genes as being important in CLL but more studies are needed to verify these findings. Results from whole genome association are promising. The ability to conduct large scale genomic studies will play an important role in detecting susceptibility genes for CLL over the next few years and thereby help to delineate etiologic pathways.

### Keywords

chronic lymphocytic leukemia; monoclonal b-cell lymphocytosis; familial risk; germ line susceptibility; environmental risk factors

### Introduction

Chronic lymphocytic leukemia (CLL) is a malignancy characterized by the accumulation of small, mature-appearing lymphocytes in the bone marrow, blood, and lymphoid tissues. It is estimated that in 2009, CLL will account for 34% of all adult leukemias in the United States.

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1 The latest WHO classification scheme considers CLL as a mature B-cell neoplasm and does not distinguish it from small lymphocytic lymphoma (SLL).<sup>2</sup> Data from the United States Surveillance, Epidemiology, and End Results (SEER) Registry estimate the U.S. incidence in the period 2002-2006 to be 4.1 per 100,000 with a median age at diagnosis of 72 years.<sup>3</sup> Incidence rates in men are nearly twice as high as in women. Although advanced age, white ancestry, and family history of hematologic malignancies are risk factors, the etiology of CLL is unknown.<sup>4</sup> This report will review what is known about the familial aggregation of CLL and other lymphoid malignancies, possible environmental risk factors, the association of CLL with a precursor condition, monoclonal B-cell lymphocytosis (MBL), and the evidence for specific genes associated with CLL.

## Familial Aggregation

### High risk families

Since CLL is an uncommon cancer, a CLL patient with at least one affected relative is considered “familial”. In population-based samples, approximately 5% of patients with CLL reported a family history of leukemia (reviewed in Houlston et al.<sup>5</sup>). Clinical descriptions of CLL families have appeared in the literature over a number of years,<sup>6</sup> and some studies have compared the clinical features between sporadic and familial CLL cases. Generally, familial cases have an earlier age of onset than sporadic cases.<sup>7</sup> Some investigators have noted that there is anticipation in age of onset in multigenerational pedigrees, where younger generations have an earlier age of onset than older generations.<sup>8</sup> However, it is hard to eliminate ascertainment bias in these studies. There have been some attempts to look for other features that distinguish familial CLL from sporadic CLL. Both subtypes appear with mutated and non-mutated *IgVH* status.<sup>9</sup> Further, studies have reported shorter telomeres or CD38 positivity in a proportion of familial cases, similar to findings in sporadic CLL cases.<sup>10</sup> Ng et al found that 12/14 familial cases studied by FISH had a chromosome 13q deletion,<sup>11</sup> which contrasts with a rate of 50-60% in large case series.<sup>12</sup> However, families had to have two or more living cases of CLL in order to participate in their studies and this may have preferentially selected more indolent patients (and therefore those more likely to carry the 13q deletion). A recent study found that levels of B-lymphocyte stimulator were higher in familial CLL cases than in sporadic cases or controls.<sup>13</sup> Another recent study of 1449 CLL patients found that female patients were more likely to have a family history of a hematologic malignancy but family history was not associated with an adverse prognosis.<sup>14</sup> The literature to date is limited but striking or consistent differences between familial and sporadic CLL have not been identified.

We have conducted clinical and genetic studies in a series of CLL pedigrees collected at the National Cancer Institute.<sup>7</sup> Figures 1 and 2 show examples of some of the more striking pedigrees in our study in terms of aggregation of lymphoproliferative (LP) tumors. These pedigrees show CLL and other LPD (including the precursor condition, MBL) segregating in relatives. Figure 2 shows a family segregating CLL and Waldenström’s macroglobulinemia (WM). These families illustrate that there is no consistent pattern of illness that can be explained by a simple mode of genetic transmission but it is likely that there are shared genes explaining the variant B-cell tumors in these families.

### Case-Control Studies of familial risk

There are data from case-control and cohort studies addressing the familiarity of CLL. Early population-based case-control studies of CLL reported family history of lymphoproliferative (LP) tumors to be a significant risk factor.<sup>15</sup> More recently, a family history analysis of case-control samples pooled from the InterLymph consortium examined family history of LP by histological subtype of lymphoma in the cases.<sup>16</sup> Because of the large number of

studies that were pooled, they were able to consider CLL/SLL cases separately and found that family history of “any LP” or family history of “leukemia only” were both significant predictors of risk for CLL/SLL.

### Registry studies of Familial Risk

We have published a series of studies based on linked registry data from Sweden and Denmark to quantify familial aggregation of CLL and other lymphomas.<sup>17-23</sup> These studies were conducted by linking population-based registries that contain parent-offspring links to the cancer registries. These are the largest studies to date that are population-based and these studies have the advantage that they are able to quantify risks to relatives of LP tumors in a comprehensive manner. In Sweden, the multigenerational register (contains individuals born in 1932 and later linked to parents) was linked with the Swedish cancer registry. In Denmark, the Danish Central Population Register which contains parent-offspring links starting in 1968, was linked with the Danish Cancer Register. Controls and their relatives were also chosen from each population registry. We applied a survival analysis method that accounted for correlations among family members.<sup>24</sup> In our most recent study of CLL using Swedish registry data, we evaluated outcomes in 26,947 first-degree relatives of 9,717 CLL patients (diagnosed 1958-2004) compared with 107,223 first-degree relatives of 38,159 matched controls. The results for CLL and other LPDs are shown in Table 1. We show that compared to relatives of controls, relatives of CLL patients had an increased risk for CLL (RR=8.5, 6.1-11.7) and other non-Hodgkin lymphomas (RR=1.9, 1.5-2.3). In Table 2, we evaluated a more detailed panel of lymphoma subtypes among relatives of CLL patients and found a striking excess of indolent B-cell NHL, specifically lymphoplasmacytic lymphoma (LPL)/WM and hairy cell leukemia (HCL). No excesses of aggressive B-cell or T-cell lymphomas were found. There was no statistical excess of Hodgkin lymphoma (HL), multiple myeloma (MM), or the precursor condition, monoclonal gammopathy of undetermined significance (MGUS), among CLL relatives. In a recent study, we found first-degree relatives of LPL/WM patients to have a 20-fold (4.1-98.4), 3.0-fold (2.0-4.4), 3.4-fold (1.7-6.6), and 5.0-fold (1.3-18.9) increased risk of developing LPL/WM, NHL, CLL, and MGUS, respectively.<sup>22</sup> In another study, we reported that relatives of patients with MGUS had an increased risk of MGUS, MM, LPL/WM, and CLL.<sup>25</sup> In an analysis of the major lymphoma subtypes, we evaluated risk of lymphoma subtypes among first-degree relatives of 2668 follicular lymphoma (FL) patients, 2517 diffuse large B-cell lymphoma (DLBCL) patients, and 6963 Hodgkin lymphoma (HL) patients compared to first-degree relatives of controls.<sup>17</sup> DLBCL was 10-fold increased among relatives of DLBCL patients, FL was 4-fold increased among relatives of FL patients and HL was 4-fold increased among relatives of HL patients. There was no co-aggregation of DLBCL and FL in families. However, DLBCL and HL did significantly co-aggregate. These series of studies all indicate that relatives of lymphoma patients have the highest risk for developing the same lymphoma as the proband but are also at risk for other related lymphoma subtypes. It appears that the indolent subtypes (CLL, LPL/WM, HCL) aggregate together and may share a component of common etiology.

### Monoclonal B-cell Lymphocytosis (MBL) and CLL

As described above, CLL aggregates in families with other indolent lymphomas. MBL is an asymptomatic hematologic condition characterized by small B-cell clones with a surface phenotype similar to that of CLL.<sup>26,27</sup> These clones are detectable at low cell numbers in otherwise healthy individuals using sensitive 6 or 8 color flow cytometry analysis. This technology was used to evaluate clonal B-cell expansion in adults (as a potential early marker of CLL) in a series of environmental health studies.<sup>26</sup> In flow cytometry studies, we and others have reported MBL in 13-18% of first degree relatives of CLL patients in high risk families.<sup>28,29</sup> This can be compared to 3-5% in the general population using

comparable laboratory detection methods suggesting that MBL is a marker of inherited predisposition to CLL.<sup>30-32</sup> Several studies have addressed factors that influence the prognosis of MBL.<sup>33-35</sup> For this type of analysis, one must make a distinction between MBL diagnosed in the clinic after referral for lymphocytosis ("clinical" MBL) and MBL detected in asymptomatic individuals from investigational screening studies. In follow-up studies, individuals with clinical MBL progress to need CLL-specific treatment at a rate of about 1.1% per year.<sup>34</sup> However, individuals with "low count" MBL (i.e. MBL detected in an individual with a normal B-absolute lymphocyte count) have not been observed to progress over the course of several years consistent with findings that progression is associated with higher B-cell counts.

A scientifically important question related to the recognition of MBL is whether all CLL cases truly are preceded by MBL, or if CLL cases commonly develop *de novo*. For example, if MBL consistently precedes CLL, that would imply that researchers could develop prospective natural history studies including (high-risk) MBL cases, with the aim to uncover mechanisms of CLL progression. Ultimately, such efforts could facilitate the development of early intervention strategies. To address the question whether all CLL cases are preceded by MBL, we recently conducted a prospective cohort study based on 77,469 healthy adults who were enrolled in the nationwide, population-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.<sup>36</sup> We identified 45 subjects with peripheral whole-blood collection and a diagnosis of CLL up to 6.4 years after blood collection draws. Using six-color flow cytometry (see Figure 3 for an example) and immunoglobulin heavy-chain gene rearrangement (*IGHV*) by reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay. We found evidence of prediagnostic monoclonality among B-cells (by either of the two methods) in 44 patients (98%; 95% CI 88-100%), up to 6.4 years before the initial diagnosis. In 41 patients (91%; 95% CI 79-98%), the clone was confirmed by both methods. The presence of *IGHV* genes was determined in 35 of 45 prediagnostic clones (78%). Of these clones, 16 (46%) were *IGHV3* subgroup genes (including 6 [17%] *IGHV3-23* genes) and 9 (26%) were *IGHV4* subgroup genes (including 4 [11%] *IGHV4-34* genes). Furthermore, the distribution of mutated clones, as compared with unmutated clones, was very similar regardless of the time at which the blood samples was obtained and the subsequent CLL diagnosis. In addition, although based on small numbers, among the eight unmutated prediagnostic clones, three were present more than 3 years before the CLL diagnosis, with two being detectable 5 years before. Thus, this study suggests that virtually all cases of CLL (both with mutated and unmutated *IGHV* genes) are preceded by MBL.

In another recent study (unpublished data), we conducted flow cytometry on 430 relatives from 132 CLL families from the Genetic Epidemiology of CLL Consortium. The overall rate of MBL was substantially higher among first-degree relatives compared to the general population and also increased with age. If MBL is an early step in the process of development of CLL, then germ line genes are likely to be acting early in leukemogenesis with more oncogenic events required before CLL develops.

## Environmental risk factors

One can argue that the strong familial aggregation of CLL and related lymphomas is a result of relatives sharing environmental risk factors. CLL shows substantial geographic variation worldwide. Rates show as much as a 40-fold difference being the highest among Caucasians in North America and Europe and very low in Asians.<sup>37</sup> Within the U.S., CLL is more frequent in the north central part of the country and lower in the southern states. Based on U.S. SEER rates per 100,000 for 2000-2004, Whites have the highest rates (4.14), followed by Blacks (3.03), Hispanics (1.94), Native Americans (1.44) and Asians (0.84). The rates of CLL in the United States have been relatively stable over time.<sup>3</sup> Studies of Asian

populations in the U.S. have reported rates similar to their counterparts in Asia.<sup>38</sup> Thus, unlike other cancers, risk of CLL does not seem to increase in individuals who migrate to the United States from low risk countries. This supports a stronger role for genetic factors than environmental factors in disease etiology.

Case-control and cohort studies have examined the effects of environmental risk factors in CLL. Some studies have found that farming exposures (pesticides, herbicides, exposure to animals) are significant.<sup>37</sup> Studies of occupational cohorts and case-control studies have found increased risk of CLL due to exposure of rubber industry chemicals and benzene<sup>39</sup> although results are not consistent.<sup>37</sup> In studies of atomic bomb survivors, CLL was not found to be elevated and thus has been thought to be a non-radiogenic cancer. However, CLL is very rare in Asia and thus its lack of association with A-bomb survivors may be in part due to insufficient power. Larger studies would be required to rule out a small or modest effect. Studies of other occupational radiation exposed cohorts have not found an increased risk but there are several methodological difficulties relevant to CLL that plague these studies, including the long latency of this tumor, the varying classifications of leukemias among studies, and the difficulty in obtaining accurate outcome data for cohort studies relying on death certificates.<sup>40</sup> There is some evidence that radiation due to magnetic fields is associated with risk of CLL.<sup>37</sup> Overall, the evidence for association with specific environmental factors is weak and inconsistent, and the relative rarity of CLL and other methodological difficulties in evaluating the risk for CLL have limited the conclusions of these studies. However, these exposures are unlikely to account for the familial aggregation of CLL.

## Approaches to Finding Genes

### Linkage Studies

Linkage studies localize genes using the co-inheritance of genetic markers and disease (e.g., CLL) in families. They are based on the idea that the occurrence of multiple individuals with CLL from the same family share genetic risks or a shared “genetic” exposure. Using the knowledge of the family relationship and known CLL status, one searches the genome for shared genes that are shared more often than what is expected by chance given the familial relationship. The most complete data assessing linkage in high risk CLL families was based on collaboration including several groups where 206 CLL pedigrees were studied.<sup>41</sup> The strongest evidence for linkage was found on chromosome 2q21.2 ( $p=0.001$ ) under a common recessive model of disease susceptibility. Two other chromosomal regions were suggestive including 6p22.1 (HLA region) and 18q21.1. None of these regions coincided with areas of chromosomal abnormalities observed in CLL. These results suggest that multiple disease loci cause susceptibility in high risk families.

### Association Studies

Candidate-gene studies are epidemiological studies that focus on a gene or a set of genes that have biological plausibility in the pathophysiology of the disease. They are powerful study designs for detecting common genetic variants of low to modest risk. The basic study design consists of comparing the frequency of alleles (or genotypes) in cases to that of unrelated controls. Recently, several promising genes have been identified, particularly for immunoregulatory genes<sup>42</sup>, toll like receptor genes,<sup>43</sup> and inflammation and immune genes.<sup>44</sup> One study took a large scale candidate gene approach. Rudd et al.<sup>45</sup> evaluated 1,467 nonsynonymous SNPs from 865 genes in a large case-control study. They found genes in the *ATM-BRCA2-CHEK2* pathway to be associated with CLL. An alternative to candidate genes studies is to conduct genome wide association studies (GWAS). These studies are agnostic in that one looks for association across the entire genome without any biological

assumptions. A recent GWAS study of 517 CLL patients and 1438 controls followed by a validation of the strongest findings in 1529 cases and 3115 controls reported 6 novel genes associated with CLL and reached genome wide significance including at 6p25.3 (*IRF4*), 19q13.32 (*PRKD2*), 2q37.1 (*SP140*), 2q13, 11q24.1, and 15q23.<sup>46</sup> There was supporting evidence for SNPs in *IRF4* in a small study.<sup>47</sup> As more GWAS studies are carried out, it seems promising that several new susceptibility genes for CLL will be identified.

### Other genetic approaches

There are other possible germ line changes that could lead to carcinogenesis and CLL. For example, differences in gene regulation have been studied in relation to familial CLL. Calin et al.<sup>48</sup> have described germ line mutations in a microRNA gene (*miR-16-1*) located in the commonly deleted region on 13q14 in 2/75 CLL cases tested (1/2 had a family history of CLL). Raval et al.<sup>49</sup> have recently described a germ line change near the *DAPK1* gene on chromosome 9 that was associated with increased methylation of the gene and decreased allelic expression in CLL cases from one family. Copy number changes in genes could play a role in expression that leads to disease susceptibility. If several rare variants account for familial aggregation of CLL, then these will be hard to detect by linkage or association studies. Large scale gene sequencing studies may be able to identify these changes and then test for associations of rare variants with diseases.

### Clinical Applications

It is important to consider the clinical implications of our findings. Compared to relatives of controls, first degree relatives of CLL patients have an 8.5- fold relative risk for developing CLL and also at an increased risk for developing other indolent forms of NHL.<sup>18</sup> Relatives are at 2.6-fold relative risk for developing any lymphoproliferative tumor. However, because the baseline risk of these conditions in the population is low, the absolute risk of a relative of a CLL patient developing CLL or a related malignancy is still very low. The National Cancer Institute SEER program estimates the lifetime risk of CLL to be 0.50% and that of other NHLs as a group to be 2.09%.<sup>3</sup>

One can still question whether there is an advantage for prevention or early detection for a relative knowing that they are at increased risk for CLL. Currently, early detection of CLL is not likely to affect outcome since stage 0 CLL is usually not treated (studies have shown that treatment at an early stage is not associated with a better outcome<sup>50</sup>). As discussed above, relatives of CLL cases from high risk families are at increased risk for having MBL. However, the transformation rate from MBL to CLL requiring therapy is only about 1% per year and has been shown to increase proportionally with the degree of lymphocytosis seen at diagnosis.<sup>34,35</sup> In our high risk CLL families, most of the MBL cases had low cell counts and are not at high risk for progression. These characteristics of CLL make it quite different from other common solid tumors where early detection of the tumor or precursor can affect survival. For example, relatives of patients with colon cancer are at increased risk for developing colon cancer. Consequently, they are advised to be screened for colon cancer at an earlier age and more frequently than individuals at average risk in order to detect tumors or precancerous lesions at a treatable stage.<sup>51</sup> In contrast, while relatives of patients with CLL can be informed that they are at higher relative risk for CLL and related lymphomas (compared to family members of unaffected individuals), it should be emphasized that the absolute risk for developing CLL and other hematologic malignancies is low, there is no treatment for early lesions, and thus no increased medical surveillance is necessary at this time. One exception to this conclusion may be the need to screen for MBL/CLL in a first-degree relative of a CLL patient who is a potential stem cell donor.<sup>52</sup>

Currently, there is no consensus on whether or not matched relatives with MBL should be disqualified as donors. For many patients, no alternative donor may be available and, even if available; the use of a matched unrelated donor could expose the patients to greater risk than transplant using a matched relative with MBL. Future studies are needed to clarify these issues.

## Conclusions and Future Directions

It is clear that there is significant familial aggregation of CLL, with the evidence pointing to a greater importance of genes rather than shared environments. There are likely to be specific genes associated with CLL but also genes common to CLL and other related LP tumors. However, the failure to identify any specific mutation with a large effect suggests that multiple genes with smaller effects cause much of the familial aggregation. These genes may be harder to identify but the advances in large scale genomics methods that can be applied to large population samples or high risk families offer promise that specific genes causing susceptibility to CLL and other LP will be identified in the near future. As our knowledge of germ line changes that lead to susceptibility for CLL expands, we will obtain a better understanding of the etiologic pathways relevant to both familial and sporadic CLL. This will therefore lead to better treatment approaches to this still incurable tumor.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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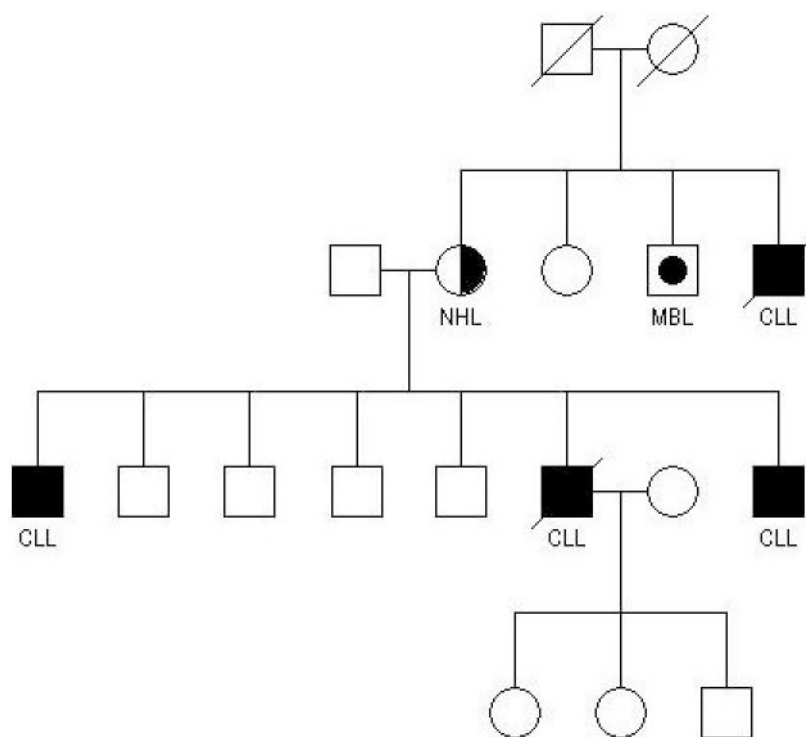
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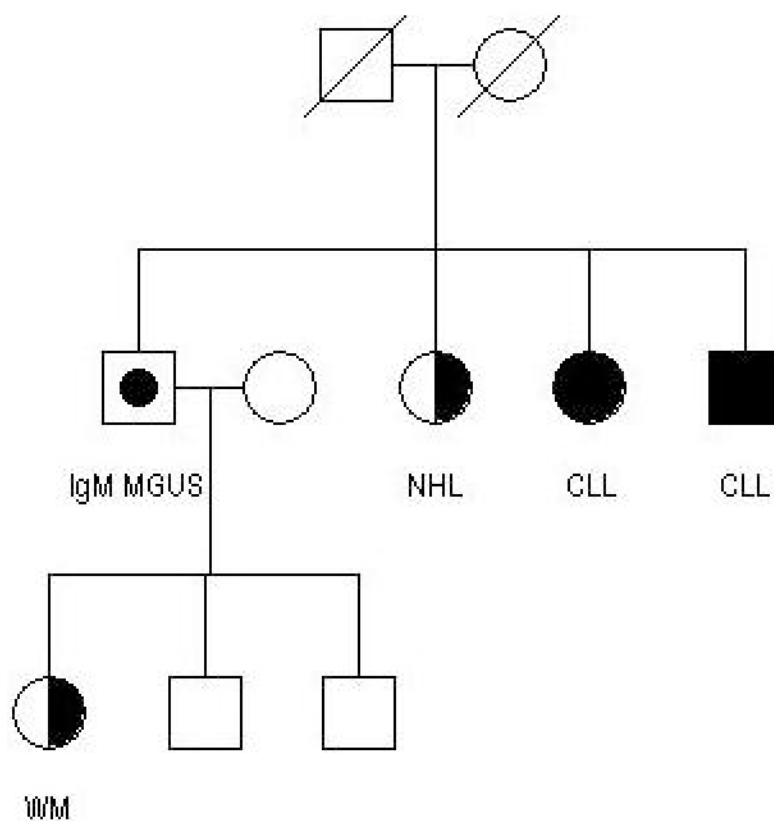
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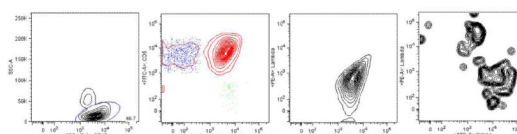
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**Figure 1.**  
Pedigree with multiple cases of CLL and other LPD



**Figure 2.**  
Pedigree with both CLL and WM cases, as well as the precursor MGUS.



**Figure 3.**

Six-Color Flow-Cytometric Analysis, Showing Representative Kappa Light-Chain Restriction in Prediagnostic Blood Samples from the Patients. (Reprinted from Landgren et al,<sup>36</sup>)

Panel A shows a bivariate plot of CD45 against side scatter, showing the isolation of lymphocytes incubated with anti-CD45 allophycocyanin H7 (APC-H7). Panel B shows a plot of CD19 against CD5. The monoclonal B-cell lymphocytosis (MBL) clone (red), positive for anti-CD19 peridinin–chlorophyll–protein cyanine 5.5 (PerCP-Cy5.5), shows coexpression of CD19 and CD5. The green population represents the remaining CD5-positive T cells, and the blue population represents the remaining polyclonal B cells. Panel C shows that the red population, positive for anti-kappa allophycocyanin (APC), has a kappa light-chain restriction. Panel D shows that the remaining B cells (blue) are polyclonal. FITC denotes fluorescein isothiocyanate, and PE phycoerythrin.

**Table 1**

Relative risks of LP tumors in first-degree relatives of LP probands compared to first-degree relatives of controls<sup>\*\*</sup>

|         | LP Tumor in Relative |      |        |      |      |      |  |
|---------|----------------------|------|--------|------|------|------|--|
|         | CLL                  | NHL  | LPL/WM | MGUS | HL   | MM   |  |
| Proband |                      |      |        |      |      |      |  |
| CLL     | 8.5*                 | 1.9* | 4.0*   | 1.4  | 1.5  | 1.2  |  |
| NHL     | 1.6*                 | 1.5* | 3.1*   | 1.2  | 1.6  | 1.0  |  |
| LPL/WM  | 4.0*                 | 3.0* | 20.0*  | 5.0* | 0.7  | 1.6  |  |
| MGUS    | 2.0*                 | 1.1  | 4.0*   | 2.8* | 0.8  | 2.9* |  |
| HL      | 1.4                  | 1.6* | 0.3    | 0.8  | 3.9* | 1.0  |  |
| MM      | 1.2                  | 1.1  | 0.9    | 2.3* | 0.9  | 2.1* |  |

\* p < 0.05

\*\* see references 17-20,22,23,25

**Table 2**

Relative risks of LP tumor in first-degree relatives of CLL cases compared to first-degree relatives of controls

| Outcome               | RR (95% CI)    |
|-----------------------|----------------|
| B-cell NHL            | 1.8 (1.3-2.5)  |
| Indolent B-cell NHL   | 2.2 (1.5-3.2)  |
| Follicular lymphoma   | 1.6 (0.87-2.8) |
| Mantle cell lymphoma  | 1.1 (0.24-5.5) |
| Hairy cell leukemia   | 3.3 (1.0-10.9) |
| LPL/WM                | 4.0 (2.0-8.2)  |
| Aggressive B-cell NHL | 1.0 (0.41-2.5) |
| T-cell NHL            | 1.3 (0.36-4.9) |