Monoclonal chronic lymphocytic leukemia (CLL)—phenotype cells are detectable in 3.5% of otherwise healthy persons using flow cytometric analysis of CD5/CD20/CD79b expression on CD19-gated B cells. To determine whether detection of such CLL-phenotype cells is indicative of an inherited predisposition, we examined 59 healthy, first-degree relatives of patients from 21 families with CLL. CLL-phenotype cells were detected in 8 of 59 (13.5%) relatives, representing a highly significant increase in risk (P = .00002). CLL-phenotype cell levels were stable with time and had the characteristics of indolent CLL. Indolent and aggressive clinical forms were found in family members, suggesting that initiation and proliferation involves distinct factors. The detection of CLL-phenotype cells provides a surrogate marker of carrier status, potentially facilitating gene identification through mapping in families and direct analysis of isolated CLL-phenotype cells. 

From the Academic Unit of Haematology and Oncology, University of Leeds, HMDS, West Yorkshire, Academic Department of Haematology and Cytogenetics, Institute of Cancer Research, Surrey; Section of Cancer Genetics, Institute of Cancer Research, Surrey, United Kingdom.


Supported by grants from the Leukaemia Research Fund and Yorkshire Cancer Research.

Reprints: Richard S. Houlston, Section of Cancer Genetics, Institute of Cancer Research, Surrey, United Kingdom; e-mail: r.houlston@icr.ac.uk.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 U.S.C. section 1734.

© 2002 by The American Society of Hematology
of CLL (median, 5 cells/μL; range, 3-127 cells/μL) and were similar to the levels detected in the outpatient survey (median, 13 cells/μL; range, 2-1458 cells/μL; \(P = .07\)). The observation that 13.5% of relatives harbor CLL-phenotype cells translates to a 7-fold increase in risk for subclinical disease (odds ratio [OR], 6.6; 95% confidence interval [CI], 2.7-16.0; \(P = .00002\), Figure 1). CLL-phenotype cells were only detected in 1 of 23 unrelated family members, a prevalence not significantly different from that in the outpatient group (\(P > .1\)). This patient came from a different family than the affected relatives. The highly significant increase in risk for family members indicates that CLL-phenotype cells represent a surrogate marker of carrier status in CLL families.

Repeat analysis of most of the relatives was performed in a masked fashion to examine whether aberrant cells were persistently detectable. Median time between sampling was 18 weeks (range, 13-25 weeks). Six of the 8 relatives with detectable CLL-phenotype cells were reassessed, and all were positive at second assessment. The levels of CLL-phenotype cells were not different between the 2 time points (\(P = .1\), with the second assessment level representing a median 85% of the initial level (range, 30%-112%). Long-term follow-up is required to determine whether the relationship between the CLL-phenotype cells and clinical disease follows a pattern similar to that seen in MGUS and myeloma.13,14 However, the fact that the levels are stable with time suggests that the generation of CLL-phenotype B cells is governed by genetic mechanisms different from their proliferative potential.

CLL-phenotype cells were not detectable in 38 of the relatives assessed at both time points. However, in 2 relatives, CLL-phenotype cells were detectable at either first or second assessment only. Levels were low in each (1.4/μL and 1.9/μL, respectively), below the range found in the outpatient study. As these relatives were not categorized as having CLL-phenotype cells, our estimate of the prevalence of this phenotype in relatives is likely to represent an underestimate of the true risk.

Indolent forms of clinical CLL are characterized by a high degree of immunoglobulin H (IgH) hypermutation and a low level of CD38 expression.15-18 CLL-phenotype cells present in otherwise healthy persons show these characteristics.19 CD38 expression was also undetectable on the CLL-phenotype cells from the affected relatives. CD38\(^{+}\) CLL-phenotype cells are presumably not seen in subclinical form because such clones would expand rapidly and present as clinical disease. However, aggressive CD38\(^{-}\) and indolent CD38\(^{-}\) forms of clinical disease were present in the familial patients with clinical disease. This also indicates that proliferative potential is regulated separately from the oncogenic process and may have to do with the stage of differentiation in the B cell undergoing neoplastic transformation. Recent data have shown that CLL cells are most similar to memory B cells.19 As in clinical disease, the CLL-phenotype cells in healthy persons and familial CLL relatives all express CD27, which is normally restricted to postgerminal–center B cells.20 In addition, the level of bel-2 expression in the CLL-phenotype cells is equivalent to that of normal circulating memory B cells, a level approximately twice that of naive B cells (median, 1.9-fold higher; \(P = .018\)). This supports the hypothesis that all CLL-phenotype cells are derived from memory B cells. Additional studies are warranted to determine whether clinical features relate to particular memory B-cell subsets from which the neoplastic cells are derived.

In addition to detecting a CLL-phenotype in 8 relatives, a non–CLL-phenotype monoclonal B-cell population was detected in a relative from another family, with an extended phenotype suggestive of marginal zone lymphoma. Non–CLL-phenotype monoclonal B-cell expansions were also detected in 9 of 910 outpatients. The detection of subclinical disease in myeloma, follicular lymphoma, and now CLL, as well as other B-cell disorders, suggests that all common chronic lymphoproliferative disorders have a premalignant counterpart. Furthermore, the finding that all these lymphoproliferative disorders appear within certain families at the clinical and the subclinical levels raises the possibility of a common genetic predisposition to the development of B-cell malignancies. As in MGUS and myeloma, comparison of cells from patients with subclinical, indolent, and progressive disease should allow identification of some of the genetic factors responsible for oncogenesis and disease progression.21-23 Application of our observation should facilitate identification of CLL genes through mapping in families and direct analysis of isolated CLL-phenotype populations.

---

**Table 1. Age, sex, and hematologic parameters of relatives with detectable B-cell expansions**

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex</th>
<th>Phenotype</th>
<th>Age, y</th>
<th>Monoclonal B-cell count (cells/μL)</th>
<th>Leukocyte count (10^9/L)</th>
<th>Hemoglobin (g/dL)</th>
<th>Platelet count (10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110205</td>
<td>F</td>
<td>CLL</td>
<td>62</td>
<td>2.5</td>
<td>10.8</td>
<td>13.1</td>
<td>267</td>
</tr>
<tr>
<td>267204</td>
<td>M</td>
<td>CLL</td>
<td>53</td>
<td>2.7</td>
<td>6.1</td>
<td>15.1</td>
<td>223</td>
</tr>
<tr>
<td>267207</td>
<td>M</td>
<td>CLL</td>
<td>49</td>
<td>2.7</td>
<td>9.1</td>
<td>15.3</td>
<td>269</td>
</tr>
<tr>
<td>001202</td>
<td>M</td>
<td>CLL</td>
<td>87</td>
<td>4.5</td>
<td>8.2</td>
<td>12.8</td>
<td>749</td>
</tr>
<tr>
<td>096203</td>
<td>F</td>
<td>CLL</td>
<td>57</td>
<td>6.3</td>
<td>8.8</td>
<td>12.5</td>
<td>244</td>
</tr>
<tr>
<td>227302</td>
<td>F</td>
<td>CLL</td>
<td>35</td>
<td>6.6</td>
<td>8.5</td>
<td>13.0</td>
<td>208</td>
</tr>
<tr>
<td>019303</td>
<td>M</td>
<td>CLL</td>
<td>29</td>
<td>9.2</td>
<td>7.3</td>
<td>16.4</td>
<td>281</td>
</tr>
<tr>
<td>060205</td>
<td>F</td>
<td>CLL</td>
<td>68</td>
<td>126.9</td>
<td>7.7</td>
<td>12.3</td>
<td>446</td>
</tr>
<tr>
<td>18203</td>
<td>M</td>
<td>Non-CLL</td>
<td>81</td>
<td>54.0</td>
<td>5.4</td>
<td>12.7</td>
<td>163</td>
</tr>
<tr>
<td>Spouse</td>
<td>M</td>
<td>CLL</td>
<td>65</td>
<td>20.8</td>
<td>6.6</td>
<td>15.0</td>
<td>244</td>
</tr>
</tbody>
</table>

**Figure 1. Prevalence of monoclonal CLL-phenotype cells in relatives of familial CLL index cases compared with the general population.** (A) Highly significant overall difference (\(P = \text{age-adjusted}\)). (B) Increase in prevalence in the familial relatives is seen at all age groups, but it is not significant because of the numbers of relatives available for assessment.
References


Erratum

In the article by Lin et al entitled “Relationship between p53 dysfunction, CD38 expression, and IgVH mutation in chronic lymphocytic leukemia,” which appeared in the August 15, 2002, issue of Blood (Volume 100:1404-1409), the seventh sentence of the abstract should read, “Intriguingly, all p53- dysfunctional patients and all but one of the CD38+ patients had less than 5% IgVH mutation.”
Inherited predisposition to CLL is detectable as subclinical monoclonal B-lymphocyte expansion

Andy C. Rawstron, Martin R. Yuille, Julie Fuller, Matthew Cullen, Ben Kennedy, Stephen J. Richards, Andrew S. Jack, Estella Matutes, Daniel Catovsky, Peter Hillmen and Richard S. Houlston