Risk of lymphoproliferative disorders among first-degree relatives of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia patients: a population-based study in Sweden

Sigurður Y. Kristinsson,1 Magnus Björkholm,1 Lynn R. Goldin,2 Mary L. McMaster,2 Ingemar Turesson,3 and Ola Landgren1,2

1Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden; 2National Cancer Institute, National Institutes of Health, Bethesda, MD; and 3Department of Medicine, Section of Hematology, Malmö University Hospital, Malmö, Sweden

A role for genetic factors in the etiology of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) is implicated based on prior findings from multiply affected families and small case-control and cohort studies. We identified 2144 LPL/WM patients (1539 WM [72%] and 605 LPL [28%]) diagnosed in Sweden, 8279 population-based matched controls, and linkable first-degree relatives of patients (n = 6177) and controls (n = 24 609). Using a marginal survival model, we calculated relative risks and 95% confidence intervals as measures of familial aggregation. We found first-degree relatives of LPL/WM patients to have 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 risks of developing LPL/WM, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and monoclonal gammopathy of undetermined significance (MGUS), respectively. However, there was no evidence of an increased risk of developing multiple myeloma or Hodgkin lymphoma. In analyses stratified by type of first-degree relative (parent, sibling, offspring), age at diagnosis of the probands (greater or less than 70 years), and sex of the first-degree relative, we did not observe the risk estimates to be significantly different compared with the overall analyses. Our findings of highly increased risks of developing LPL/WM, NHL, CLL, and MGUS support the operation of shared susceptibility genes that predispose to LPL/WM and other lymphoproliferative disorders. (Blood. 2008;112:3052-3056)

Introduction

Based on the current WHO classification of hematologic malignancies, lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (WM) is a non-Hodgkin lymphoma (NHL) subtype characterized by small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow, lymph nodes, and spleen.1 Clinically, WM can be distinguished from LPL on the basis of a detectable monoclonal immunoglobulin (IgM) spike in serum.1 However, biologically it remains controversial whether LPL and WM are different manifestations of a single disease or 2 unique entities.1,3

LPL/WM is a rare malignancy, accounting for only 1% to 2% of all hematologic tumors, reflected in an incidence rate of 3 to 4 cases per million people per year.4,5 The median age at diagnosis is around 70 years.6 Males and white people are known to be predominantly affected.4,6 A personal history of the precursor condition, monoclonal gammopathy of undetermined significance (MGUS) of IgM class has been associated with an increased risk of developing WM.7

The etiology of LPL/WM is unknown. A few studies have reported evidence of somatic Ig gene mutations, suggesting that chronic antigen stimulation might play an etiologic role.8,9 In further support of this, population-based studies from the United States have found autoimmunity and hepatitis C viral infection to be associated with an increased risk of developing WM.10,11 In addition, a role for genetic factors in the etiology of WM is implicated based on prior observations showing evidence of familial aggregation. The first report on familiarity in WM was published in 1962,12 and since then several families with multiple cases, as well as small case-control and cohort studies, have been published showing familial clustering of LPL and WM.11,13-23 However, due to the restricted sample sizes in prior studies, the extent of familial aggregation in LPL/WM is not well defined.

We have conducted the first large population-based study, including 6177 first-degree relatives of 2144 LPL/WM patients diagnosed in Sweden. The aim of our study was to quantify the risk for LPL/WM and other lymphoproliferative disorders among first-degree relatives of patients compared with 24 609 first-degree relatives of 8279 matched controls.

Methods

Central registries, patients, controls, and first-degree relatives

All residents of Sweden are, upon birth or immigration, assigned a unique national registration number that is used in government-maintained nationwide health care and population registers, whereby record linkage is possible with a high degree of accuracy. Each individual’s date of death is centrally registered in the Swedish Cause of Death Registry.

Since the mid-1950s Sweden has provided universal medical health care for the entire population, currently approximately 9 million people. In contrast to many other countries, for example the United States (where the majority of hematologic patients are seen and treated primarily by physicians in private practice, outside hospitals), the Swedish health care system has a geographically defined referral structure for specialist assessments. Patients with hematologic disorders are typically diagnosed, treated, and followed clinically by physicians at hospital-based hematology or oncology centers. These centers are affiliated with a few regional...
university hospitals, which offer inpatient hospital care to a defined primary catchment area in addition to being the hematology and oncology referral center for a larger health care region.

Since 1958, all physicians and pathologists/cytologists in Sweden have been obliged by law to report each incident case of cancer that they diagnose and/or treat to the centralized nationwide Swedish Cancer Registry. The Registry contains information on diagnosis, sex, date of birth, date of diagnosis, and region/hospital where the diagnosis was made.24 In a recent validation study focusing on lymphoproliferative malignancies diagnosed 1964-2003, we found the completeness and the overall diagnostic accuracy of the Registry to be higher than 90% to 95%.25 For NHL, Hodgkin lymphoma (HL), and multiple myeloma (MM) the accuracy and completeness of the Cancer Registry was very high (> 93%). For WM, the diagnostic accuracy was 93%; however, we found the completeness for WM to be 68%.25

Based on these findings, in our present study we used multiple parallel approaches to establish a nationwide LPL/WM cohort. First, we identified all LPL/WM patients diagnosed from 1958 through 2005 from the nationwide Swedish Cancer Registry. Second, we retrieved information on all incident cases through our national network, which included all major hematology or oncology centers in Sweden. Third, we identified all patients who were reported in the Swedish Inpatient Registry, which captures information on individual patient-based discharge diagnoses and discharge listings from all inpatient care, with a very high coverage.26 Data on all LPL/WM patients from these 3 sources were merged into one master database, and duplicate cases were removed. Thus, by using these 3 sources, we were able to create a unique nationwide LPL/WM cohort.

For each LPL/WM patient, 4 population-based controls (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish population database. All controls had to be alive at the time of LPL/WM diagnosis for the corresponding case and with no previous cancer diagnosis at the date of the corresponding case’s diagnosis.

From the Swedish Multigenerational Registry,26 which includes information on parent-sibling-offspring relations for all Swedish citizens who were born in or since the year 1932, we obtained information on all first-degree relatives (parents, siblings, and offspring) of cases and controls. LPL/WM patients and controls with no relatives identified from the linkage, as well as duplicate controls, were removed from the study. As a final step, we conducted record linkages with the Swedish Cancer Registry, the nationwide LPL/WM cohort, and a nationwide MGUS cohort (established from a national network and from the Swedish Inpatient Registry, as described for the nationwide LPL/WM cohort above) to obtain information on lymphoproliferative malignancies and MGUS among all LPL/WM patients, controls, and first-degree relatives.

Approval was obtained from the Karolinska Institutional Review Board (IRB) for this study. Informed consent was waived because we had no contact with study subjects. An exemption from IRB review was obtained from the National Institutes of Health Office of Human Subjects Research because we used existing data without personal identifiers.

Statistical analysis

The statistical approach is based on a model proposed by Liang27 and described in detail elsewhere.24 We classified relatives as “affected” if they had a primary cancer registration with the tumor of interest (examining up to 5 cancer registrations). Here, the age or age at onset of disease in a relative of a proband is modeled by a proportional hazards model. Familial aggregation for each condition is evaluated by testing the hazard ratio of being a relative of a case compared with being a relative to a control. The model was fitted to the data using the PHREG procedure in SAS version 8.02 (SAS Institute, Cary, NC). We use RR to denote the hazard ratio defined above, with 95% confidence intervals (CIs). Because we have complete ascertainment of cases, every case is a “proband” and thus families with more than one case appear twice in the dataset. The robust sandwich covariance matrix accounts for dependencies among family members, including dependence due to the overlapping family clusters.28 We tested separately for increased risk for LPL/WM, NHL (ie, NHL excluding LPL/WM), chronic lymphocytic leukemia (CLL), HL, MM, and MGUS in relatives. Because chronic lymphocytic leukemia and MGUS were very rare in relatives, we combined the data from all 3 disorders.

Results

A total of 2144 LPL/WM patients (605 LPL [28%] and 1539 [72%] WM), 8279 population-based matched controls and corresponding first-degree relatives of patients (n = 6177) and controls (n = 24 609) were included in the study. The characteristics of LPL/WM patients and controls are shown in Table 1. There was a male predominance, and the mean age at diagnosis was 72.4 years (range, 18-97). The patients were diagnosed over a long period of time; however the majority (93%) of patients was diagnosed during the past 2 decades. Table 1 shows the numbers and types of first-degree relatives that were linkable to LPL/WM cases. As expected, the offspring group is the largest given the late onset of LPL/WM diagnoses and inherent characteristics of the applied database.

Risks among first-degree relatives of LPL/WM patients

As shown in Table 2, first-degree relatives of LPL/WM cases had a 20-fold (95% CI 4.1-98.4), 3.0-fold (95% CI 2.0-4.4), 3.4-fold (95% CI 1.7-6.6), and 5.0-fold (95% CI 1.3-18.9) increased risks of developing LPL/WM, NHL, CLL, and MGUS, respectively. However, there was no evidence of a significantly increased risk of developing MM or HL.

When assessing the risk in relation to type of first-degree relative (parent, sibling, offspring), age at diagnosis for the probands (above/below 70 years), and sex of the first-degree relative, the estimates were very similar (Table 3). To assess whether there are differences in familial aggregation patterns among relatives of LPL and WM patients, respectively (supporting the theory that they are 2 unique entities, rather than different manifestations of a single disease1-3), we conducted stratified analyses restricted to first-degree relatives of LPL and WM patients only. Among first-degree relatives of LPL patients, we found increased risk of LPL/WM (RR = 16.6, 95% CI 1.7-162.2), NHL (RR = 2.3, 95% CI 1.2-4.3), and CLL (RR = 4.8, 95% CI 1.6-14.1; Table 2). In analyses based on first-degree relatives of WM patients only, we observed similar excess risks (LPL/WM: RR = 24.0, 95% CI 2.9-201.1; NHL: RR = 3.5, 95% CI 2.1-5.8; CLL: RR = 2.7, 95% CI 1.1-6.5). When we conducted subanalyses restricted to LPL/WM patients diagnosed after 1986, we found the risk estimates to be virtually the same (data not shown).

In exploratory analyses, we assessed familial risks for other cancers (including nonhematologic) and found no evidence of statistically increased risks.
Discussion

In this first large population-based case-control study including more than 2000 LPL/WM patients, more than 8000 matched controls, and more than 30 000 linkable first-degree relatives, we found first-degree relatives of LPL/WM patients (compared with first-degree relatives of controls) to have a prominent 20-fold increased risk of developing LPL/WM and a 3-fold increased risk of NHL and CLL. Based on small numbers, we found a 5-fold elevated risk of MGUS; however, there was no excess risk of HL or MM. Our findings are important in that they support the theory that there are shared common susceptibility genes in LPL/WM and various types of lymphomas.29,30

Our finding of a highly increased risk of LPL/WM among first-degree relatives of LPL/WM patients substantially adds to the restricted literature on this topic. When considering LPL and WM as separate entities, the estimates were similar to the combined analyses, suggesting shared biologic features. In contrast, Schop et al found LPL tumor cells to have frequent t(9;14)(p13;q32) translocations, while WM tumor cells appear to be diploid or near diploid and often have deletions of 6q21.7 When we assessed the familial risk of LPL/WM by type of first-degree relative, we observed similar risk estimates among parents, siblings, and offspring. Thus, our findings favor the operation of dominant or codominant gene effects, rather than recessive genes, which typically manifest by showing higher risk among siblings. We also quantified risk by sex of first-degree relatives and found familial cases to be nonsignificantly more likely to be male (70% vs 59% for nonfamilial LPL/WM patients in our sample; \( P = .08 \)), as has been observed in a previous study.22

We also observed 3-fold increased risks of NHL and CLL among first-degree relatives of LPL/WM patients. These findings are consistent with prior population-based studies showing evidence of familial coaggregation for various types of lymphomas.29,30 Furthermore, we found relatives of LPL/WM to have a 5-fold increased risk of MGUS. It is unclear whether this finding represents IgM isotype MGUS only or other isotypes as well. Unfortunately, we did not have access to MGUS isotype data, so we were unable to answer this question. Future studies are needed to confirm this finding. Finally, we did not find an increased risk of HL or MM among first degree relatives suggesting that MM and HL are independent of LPL/WM in families.

Based on available literature, there are several genes that could be causing susceptibility to LPL/WM and related conditions. Prior studies have assessed the role of gene polymorphisms in lymphoma genesis. For example, immune function and DNA repair genes have been found to be associated with elevated risk of CLL,31,32 HL,33 and NHL.11,34-36 Furthermore, in support of the theory that there are shared underlying mechanisms across various lymphoma

Table 1. Characteristics of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) patients and matched controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LPL pts</th>
<th>WM pts</th>
<th>LPL/WM pts combined</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>605</td>
<td>1539</td>
<td>2144</td>
<td>8279</td>
</tr>
<tr>
<td>Sex, M/F, %</td>
<td>59/41</td>
<td>60/40</td>
<td>60/40</td>
<td>59/41</td>
</tr>
<tr>
<td>Mean age at diagnosis, y (range)</td>
<td>68.7 (18-95)</td>
<td>72.0 (31-95)</td>
<td>71.0 (18-95)</td>
<td></td>
</tr>
</tbody>
</table>

### Age group, n (%)

| Younger than 40 y | 10 (1.7) | 9 (0.6) | 19 (0.9) |
| 40-49 y           | 40 (6.6) | 47 (3.1) | 87 (4.1) |
| 50-59 y           | 89 (14.7) | 170 (11.1) | 259 (12.1) |
| 60-69 y           | 146 (24.1) | 323 (20.1) | 469 (21.9) |
| 70-79 y           | 181 (29.9) | 579 (37.6) | 760 (35.5) |
| 80 y and older    | 139 (23.0) | 411 (26.7) | 550 (25.7) |

### Calendar period, n (%)

| 1966-1975 | 0 (–) | 20 (1.3) | 20 (0.9) |
| 1976-1985 | 30 (5.0) | 64 (4.2) | 94 (4.4) |
| 1986-1995 | 218 (36.0) | 690 (44.8) | 908 (42.4) |
| 1996-2005 | 357 (59.0) | 765 (49.7) | 1122 (52.3) |

### Relatives, n (%)

| Any relative | 1924 (100) | 4253 (100) | 6177 (100) | 24,609 (100) |
| Parents      | 334 (17.4) | 538 (12.6) | 872 (14.1) | 3440 (14.0) |
| Siblings     | 267 (13.9) | 367 (9.1)  | 654 (10.6) | 2775 (11.3) |
| Offspring    | 1323 (68.8) | 3328 (78.3) | 4651 (75.3) | 18,394 (74.7) |

Table 2. Relative risk of lymphoproliferative malignancies and MGUS among first-degree relatives of LPL/WM patients

<table>
<thead>
<tr>
<th>Risk among first-degree relatives</th>
<th>Relatives of LPL/WM patients</th>
<th>Relatives of WM patients</th>
<th>Relatives of LPL/WM patients combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts</td>
<td>Co</td>
<td>RR (95% CI)*</td>
</tr>
<tr>
<td>LPL/WM</td>
<td>4</td>
<td>1</td>
<td>16.6 (1.7-162.2)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>15</td>
<td>26</td>
<td>2.3 (1.2-4.3)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>7</td>
<td>6</td>
<td>4.8 (1.6-14.1)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>3</td>
<td>2</td>
<td>5.9 (1.0-36.0)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>6</td>
<td>11</td>
<td>2.2 (0.8-5.9)</td>
</tr>
<tr>
<td>MGUS</td>
<td>2</td>
<td>1</td>
<td>8.1 (0.7-90.6)</td>
</tr>
</tbody>
</table>

RR indicates relative risk; CI, confidence interval; LPL, lymphoplasmacytic lymphoma; WM, Waldenström macroglobulinemia; MGUS, monoclonal gammopathy of undetermined significance; Pts, patients; and Co, controls.

*All estimates were adjusted for sex of first-degree relative.
Table 3. Relative risk of lymphoproliferative malignancies and MGUS among first-degree relatives of LPL/WM patients by sex of relative, type of relative, and age of probands at diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>LPL/WM</th>
<th>NHL</th>
<th>CLL</th>
<th>HL</th>
<th>MM</th>
<th>MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex of relative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 1</td>
<td>24.4 (2.8-212.1)</td>
<td>23 35 2.7 (1.6-4.5)</td>
<td>7 13 2.2 (0.9-5.4)</td>
<td>4 9 1.7 (0.5-5.7)</td>
<td>5 12 1.7 (0.6-4.9)</td>
</tr>
<tr>
<td>Female</td>
<td>4 1</td>
<td>15.7 (1.8-139.3)</td>
<td>20 23 3.4 (1.8-6.4)</td>
<td>9 6 5.9 (2.1-16.4)</td>
<td>0 12 0</td>
<td>6 15 1.6 (0.6-4.0)</td>
</tr>
<tr>
<td>Type of relative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>4 1</td>
<td>15.9 (1.8-140.1)</td>
<td>16 17 3.7 (1.7-7.3)</td>
<td>11 9 4.8 (2.0-11.6)</td>
<td>0 6 0</td>
<td>7 15 1.8 (0.7-4.4)</td>
</tr>
<tr>
<td>Sibling</td>
<td>0 0</td>
<td>NA</td>
<td>11 10 4.7 (2.0-11.0)</td>
<td>3 2 6.3 (1.1-37.2)</td>
<td>0 3 0</td>
<td>3 4 3.1 (0.7-13.8)</td>
</tr>
<tr>
<td>Offspring</td>
<td>6 1</td>
<td>24.4 (2.7-216.8)</td>
<td>16 31 2.1 (1.1-3.8)</td>
<td>2 8 1.0 (0.2-4.9)</td>
<td>4 12 1.3 (0.4-4.0)</td>
<td>1 8 0.5 (0.1-4.0)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70 y</td>
<td>4 2</td>
<td>8.0 (1.5-43.1)</td>
<td>29 33 3.5 (2.2-5.8)</td>
<td>14 11 5.1 (2.3-11.1)</td>
<td>2 13 0.6 (0.1-2.8)</td>
<td>10 19 2.1 (1.0-4.5)</td>
</tr>
<tr>
<td>&gt; 70 y</td>
<td>6 0</td>
<td>inf*</td>
<td>14 25 2.2 (1.1-4.4)</td>
<td>2 8 1.0 (0.2-4.9)</td>
<td>2 8 1.0 (0.2-4.6)</td>
<td>1 8 0.5 (0.1-3.9)</td>
</tr>
</tbody>
</table>

RR indicates relative risk; CI, confidence interval; LPL, lymphoplasmacytic lymphoma; WM, Waldenström macroglobulinemia; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; Pts, patients; Co, controls; NA, not applicable; and inf*, infinity.

*All estimates were adjusted for sex of first-degree relative.
†Age at diagnosis for corresponding proband.

subtypes, prior population-based studies from Scandinavia have found HL, NHL, and CLL to aggregate in families. In addition, gene expression studies have found similar expression profiles for patients affected with WM, CLL, and NHL. There are also data with regard to the role of extrinsic factors in the etiology of LPL/WM. Prior investigations have found patients with viral hepatitis, human immunodeficiency virus, and autoimmune diseases to be associated with an increased risk of developing LPL/WM. Taken together, these studies support the notion that chronic immune stimulation has a role in the causation of LPL/WM, likely in interaction with genes. Future work is needed to assess the roles of environmental factors among probands and relatives in multiplex families and the complex role of gene-environment interactions.

Our study has several strengths, including its large size as well as the application of high-quality data from Sweden in a stable population with access to standardized universal medical health care during the entire study period. Furthermore, the use of the nationwide register-based case-control design ruled out recall bias and ensured both a population-based setting and generalizability of our findings.

Limitations include incomplete numbers of first-degree relatives, few numbers of the outcome of interest among first-degree relatives of cases and controls, lack of information on potential confounders (although the matched design and analyses ensured adjustment for sex, age, and geography), and lack of clinical data. Another potential limitation is the absence of a systematic blinded validation of all LPL/WM diagnoses. Due to the size of the study, we were not able to validate individual medical records. An inherent limitation of our study, which includes LPL/WM patients diagnosed during a 40-year study period, is the fact that diagnostic criteria have evolved over time. However, in our large nationwide study on the ascertainment and diagnostic accuracy of lymphoproliferative malignancies diagnosed in Sweden we found the diagnostic accuracy for LPL/WM cases to be 93%. As expected, due to its generally more indolent natural course, we found approximately 30% underreporting of LPL/WM patients from the hospitals to the central Swedish Cancer Registry. Therefore, in the present study, we identified LPL/WM patients from 3 parallel sources: the Swedish Cancer Registry, the Swedish Inpatient Registry, and a nationwide hospital network that included all major hematology and oncology units in the country. We believe that we have identified the vast majority of LPL/WM patients diagnosed in Sweden during the study period for the current investigation. Because we assessed familial aggregation using relatives of LPL/WM cases and matched controls obtained from the same registries, the validity of the diagnosis should be nondifferential and the relative risks should not be biased. Finally, the fact that our study population comprises primarily whites might limit the generalizability of our results. Future investigations are needed to assess whether familial risk of LPL/WM varies across different ethnic and racial groups.

In summary, we found highly increased risks of developing LPL/WM, NHL, CLL, and MGUS among first-degree relatives of LPL/WM patients. These results support the theory that there are shared susceptibility genes that predispose to LPL/WM and other lymphoproliferative disorders. Our study provides novel information supporting the application of gene mapping and candidate gene approaches in high risk families and case-control studies. Because immune-gene polymorphisms have and a personal history of immune-related medical conditions have been associated with an increased risk of developing LPL/WM, the operation of some gene-environment interactions is likely.

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Authorship

Contribution: S.Y.K., M.B., I.T., and O.L. initiated this work. S.Y.K., M.B., L.R.G., and O.L. designed the study. S.Y.K., M.B., I.T., and O.L. obtained data. All authors were involved in analyses and the interpretation of the results. S.Y.K. and O.L. wrote the report. All authors read, commented on, and approved the final version of the manuscript. All
authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

References


Correspondence: Sigurur Yngvi Kristinsson, MD, Department of Medicine Division of Hematology, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden; e-mail: sigdurur. kristinsson@karolinska.se.
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