# Risk of plasma cell and lymphoproliferative disorders among 14 621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance in Sweden

Ola Landgren,[1-3] Sigurdur Y. Kristinsson,[3] Lynn R. Goldin,[1] Neil E. Caporaso,[1] Cecilie Blimark,[4] Ulf-Henrik Mellqvist,[4] Anders Wahlin,[5] Magnus Bjorkholm,[3] and Ingemar Turesson[6]

[1]Division of Cancer Epidemiology and Genetics, and [2]Center for Cancer Research, Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; [3]Department of Medicine, Division of Hematology, Karolinska University Hospital and Institutet, Stockholm, Sweden; [4]Department of Medicine, Section of Hematology and Coagulation, Sahlgrenska University Hospital, Gothenburg, Sweden; [5]Section of Hematology, Umeå University Hospital, Umea, Sweden; and [6]Department of Medicine, Section of Hematology, Malmö University Hospital, Malmö, Sweden

**Familial clustering of the precursor condition, monoclonal gammopathy of undetermined significance (MGUS) has been observed in case reports and in smaller studies. Using population-based data from Sweden, we identified 4458 MGUS patients, 17 505 population-based controls, and first-degree relatives of patients (n = 14 621) and controls (n = 58 387) with the aim to assess risk of MGUS and lymphoproliferative malignancies among first-degree relatives of MGUS patients. Compared with relatives of controls, relatives of MGUS patients had increased risk of MGUS (relative risk [RR] = 2.8; 1.4-5.6), multiple myeloma (MM; RR = 2.9; 1.9-4.3), lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM; RR = 4.0; 1.5-11), and chronic lymphocytic leukemia (CLL; RR = 2.0; 1.2-2.3). Relatives of patients with IgG/IgA MGUS had a 4.0-fold (1.7-9.2), 2.9-fold (1.7-4.9), and 20-fold (2.3-170) elevated risk of developing MGUS, MM, and LPL/WM, respectively. Relatives of IgM MGUS patients had 5.0-fold (1.1-23) increased CLL risk and nonsignificant excess MM and LPL/WM risks. The results were very similar when we assessed risk by type of first-degree relative, age at MGUS (above/below 65 years), or sex. Risk of non-Hodgkin lymphoma or Hodgkin lymphoma was not increased among MGUS relatives. Among first-degree relatives of a nationwide MGUS cohort, we found elevated risks of MGUS, MM, LPL/WM, and CLL, supporting a role for germline susceptibility genes, shared environmental influences, or an interaction between both. (Blood. 2009;114:791-795)**

## Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is one of the most common premalignant disorders in western countries with a prevalence of 3.2% in the white general population 50 years of age or older.[1] It is characterized by the presence of a monoclonal immunoglobulin (M-protein) in subjects lacking evidence of multiple myeloma or other lymphoproliferative malignancies such as Waldenström macroglobulinemia (WM), primary amyloidosis, chronic lymphocytic leukemia (CLL), or B-cell lymphoma.[2,3] Long-term follow-up of MGUS patients reveals an average 1% annual risk of developing lymphoproliferative malignancies.[4,5] Typically, people affected with MGUS of the immunoglobulin G (IgG) or IgA classes, progress to multiple myeloma (MM) or a related plasma cell disorder; whereas IgM MGUS progresses to WM or other lymphoproliferative disorders.[4,5]

Although the cause of MGUS remains unclear, case reports have shown familial clusters of MGUS and MM[6-9] and other rare syndromes involving MGUS.[10] Recent population-based studies have found excess risk for MGUS among first-degree relatives of MM or lymphoplasmacytic lymphoma (LPL)/WM patients.[11-13] To our knowledge, no large study has been conducted to quantify risks for MGUS and related malignancies among first-degree relatives of subjects affected by MGUS.

Using high-quality population-based and hospital-based registries in Sweden, we identified a nationwide cohort of 4458 MGUS cases and their 14 621 linkable first-degree relatives. Aims of our study were to estimate the risk of plasma cell and lymphoproliferative disorders among first-degree relatives of MGUS patients and to characterize patterns of familial disease.

## Methods

### Patients, controls, and first-degree relatives

Because MGUS is generally asymptomatic, it is usually an unexpected finding during a medical work-up for another cause. In Sweden, when a clinician detects an MGUS patient, he/she will typically consult with a hematology specialist at a regional hospital-based center, and, if needed, refer the patient for further work-up, especially to rule out an underlying malignancy. These centers are affiliated with a hospital-based hematology/oncology centers.

The first population-based MGUS screening studies were initiated by Dr Waldenström's group in Sweden in the early 1960s.[14] Indisputably, these early efforts have played an important role and facilitated to an increasing awareness regarding MGUS among Swedish clinicians. In the present nationwide study, MGUS patients diagnosed between the late 1960s and the late 1970s were primarily diagnosed by Dr Waldenström's group at Malmö University Hospital. During these years, diagnostic criteria were defined by

Submitted December 1, 2008; accepted January 23, 2009. Prepublished online as *Blood* First Edition paper, January 30, 2009; DOI 10.1182/blood-2008-12-191676.

An Inside *Blood* analysis of this article appears at the front of this issue.

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 USC section 1734.

the presence of an M-protein in serum in the absence of an underlying lymphoproliferative malignancy.[14] From the early 1980s, efforts have been made, mainly influenced by Dr Kyle's group at the Mayo Clinic, to establish stringent criteria to distinguish MGUS from asymptomatic forms of myeloma and related disorders.[3] MGUS is now defined by the presence of a monoclonal Ig of less than 3 g/dL in serum; if bone marrow examination was performed, a plasma cell content of less than 10%; no evidence of other lymphoproliferative disorders; and the absence of clinical manifestations related to the monoclonal gammopathy.[15] These criteria are essentially the same as have been used at Swedish hospitals during the study period.

The following approaches were applied to establish a nationwide MGUS cohort: first, we retrieved information on all incident patients through our national network, which included all outpatient units including all major regional hospital-based hematology/oncology centers in Sweden. For all MGUS patients, we obtained information on sex, date of birth, date of diagnosis, and region/unit where the diagnosis was made. When available, we also collected information on MGUS isotype and concentration of the monoclonal spike at diagnosis. Second, we identified all MGUS 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.[15] Information on all MGUS patients from these 2 sources were merged into one master database. Using the nationwide Swedish Cancer Registry, which includes information on all incident cancers diagnosed since 1958 (including date of diagnosis and region/hospital where the diagnosis was made),[16,17] we obtained data on all cancer diagnoses for all MGUS patients. To minimize the influence of misdiagnosis (eg, smoldering myeloma), MGUS patients with a lymphoproliferative malignancy diagnosed up to 6 months after MGUS were removed from the MGUS cohort. As an additional quality control measure, we removed any MGUS patient with a recorded preceding lymphoproliferative malignancy.[15]

For each MGUS 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 MGUS diagnosis for the corresponding case and with no previous hematological cancer at the date of the corresponding case's diagnosis.

From the Swedish Multigenerational Registry,[18] which includes information on parent-offspring relations for all Swedish citizens who were born in 1932 and later, we obtained information on all first-degree relatives (parents, siblings, and offspring) of MGUS patients and controls. MGUS patients and controls with no relatives identified from the linkage, as well as duplicate controls, were removed from the study.

As a final step, through record-linkage with the nationwide MGUS cohort, the Swedish Cancer Registry, and a nationwide LPL/WM cohort (the latter has been described in detail elsewhere[11]), we obtained information on incident MGUS and lymphoproliferative diseases among first-degree relatives of MGUS patients and controls.

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 (NIH) 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 Liang[19] and described in detail elsewhere.[20] For analyses of cancer outcomes, we classified relatives as "affected" if they had a primary cancer registration with the tumor of interest. For analyses of MGUS outcomes, we classified relatives as "affected" if they had a MGUS diagnosis in our cohort. 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. We use relative risk (RR) to denote the hazard ratio defined above, with 95% confidence intervals (CI). In our database, every case is a "proband," and thus families with more than one case appear twice in the data set. The robust sandwich covariance matrix accounts for dependencies among family members, including dependence due to the overlapping family clusters.[20] We tested separately for increased risk for MGUS, MM, LPL/WM, non-Hodgkin lymphoma (NHL; excluding LPL/WM), CLL, and Hodgkin lymphoma (HL) in relatives. Because case and control probands were matched (see "Patients, controls, and first-degree relatives"), the relatives should be generally well matched. However, because they cannot be individually matched, we adjusted for sex in all analyses.

The main effect of interest in this analysis is the risk associated with being a relative of a case compared with being a relative of a control. However, we were also interested in testing whether other factors (eg, sex, type of relative, and age of disease onset in the case probands) affected case-control comparisons. Thus, we analyzed the data both by stratifying for these factors and by testing them as interaction effects in one model. Age at diagnosis was stratified at less than 65 versus greater than 65 years.

**Table 1. Characteristics of MGUS patients and matched controls**

| | MGUS patients | Controls |
|---|---|---|
| Total, n | 4458 | 17 505 |
| Sex male/female, % | 49.9/50.1 | 50.0/50.0 |
| Median age at diagnosis, y (range) | 69 (22-97) | NA |
| **Age group, n (%)** | | |
| Less than 40 | 118 (2.7) | 471 (2.7) |
| 40-49 | 328 (7.4) | 1321 (7.5) |
| 50-59 | 749 (16.8) | 3008 (17.2) |
| 60-69 | 1091 (24.5) | 4236 (24.2) |
| 70-79 | 1389 (31.2) | 5389 (30.8) |
| 80 and above | 783 (17.6) | 3080 (17.6) |
| **Calendar period, n (%)** | | |
| 1966-1975 | 33 (0.7) | 138 (0.8) |
| 1976-1985 | 260 (5.8) | 1048 (6.0) |
| 1986-1995 | 1866 (41.9) | 7309 (41.7) |
| 1996-2005 | 2299 (51.6) | 9010 (51.5) |
| **MGUS isotype, n (%)** | | |
| IgG | 1789 (40.1) | NA |
| IgA | 482 (10.8) | NA |
| IgM | 447 (10.0) | NA |
| IgD | 1 (0.02) | NA |
| Unknown/missing | 1739 (39.0) | NA |
| First-degree relatives, n (%) | | |
| **Any relative** | 14 621 (100) | 58 387 (100) |
| Parents | 2811 (19.2) | 11 006 (18.9) |
| Siblings | 2290 (16.7) | 8962 (15.3) |
| Offspring | 9520 (65.1) | 38 419 (65.8) |

NA indicates not applicable.

## Results

A total of 4458 MGUS patients, 17 505 population-based matched controls, and corresponding first-degree relatives of patients (n = 14 621) and controls (n = 58 387) were included in the study. The characteristics of MGUS patients and controls are shown in Table 1. The median age at diagnosis was 69 years (range, 22-97). The study period was 1967-2005; the majority (93%) of patients were diagnosed after 1986. Table 1 shows the numbers and types of first-degree relatives that were linkable to MGUS patients and matched controls. With regard to the distribution of MGUS cases by isotype, there were 1789 (40.1%) IgG, 482 (10.8%) IgA, 447 (10.0%) IgM, and 1 (0.02%) IgD MGUS cases. Information on Ig isotype was missing for 1739 (39.0%) patients. M-protein concentration data were available for 2879 (64.6%) patients; the median concentration was 0.8 g/dL (interquartile range, 0.5-1.5 g/dL). Given the mean age at MGUS diagnosis and inherent

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

| | First-degree relatives of MGUS patients (n = 14 621) | First-degree relatives of controls (n = 58 387) | RR (95% CI)* |
|---|---|---|---|
| MGUS | 22 | 31 | 2.8 (1.4-5.6)† |
| Multiple myeloma | 41 | 57 | 2.9 (1.9-4.3)† |
| Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia | 8 | 8 | 4.0 (1.5-11)† |
| Chronic lymphocytic leukemia | 23 | 46 | 2.0 (1.2-2.3)† |
| Non-Hodgkin lymphoma | 44 | 161 | 1.1 (0.8-1.5) |
| Hodgkin lymphoma (< 45 y) | 8 | 24 | 1.3 (0.6-2.9) |
| Hodgkin lymphoma (> 45 y) | 1 | 18 | 0.2 (0.0-1.7) |

*All estimates were adjusted for sex of first-degree relative.
†Statistically significant (2-sided *P* value < .05).

characteristics of the applied database, as expected, the majority of linkable first-degree relatives were offspring (Table 1).

As shown in Table 2, compared with first-degree relatives of controls, first-degree relatives of MGUS patients had a 2.8-fold (95% CI 1.4-5.6), 2.9-fold (95% CI 1.9-4.3), 4.0-fold (95% CI 1.5-11), and 2.0-fold (95% CI 1.2-2.3) increased risks of developing MGUS, MM, LPL/WM, and CLL, respectively. However, we found no significantly increased risk of developing NHL or HL.

When we assessed familial aggregation patterns among relatives of MGUS patients by Ig isotype, compared with first-degree relatives of controls, we found first-degree relatives of IgG/IgA MGUS patients to have a 4.0-fold (95% CI 1.7-9.2), 2.9-fold (95% CI 1.7-4.9), and 20-fold (95% CI 2.3-170) elevated risk of developing MGUS, MM, and LPL/WM, respectively (Table 3). In first-degree relatives of IgM MGUS patients, based on small numbers, we found a 5.0-fold (95% CI 1.1-23) risk of developing CLL (Table 3). We found nonsignificant excess risk of MM (RR = 1.9, 95% CI 0.3-10) and LPL/WM (RR = 3.5, 95% CI 0.2-63) among first-degree relatives of IgM MGUS patients.

We also assessed familial aggregation patterns in relation to type of first-degree relative (parent, sibling, offspring), age at diagnosis for the probands (above/below 65 years), and sex of the first-degree relative. As shown in Table 4, the estimates were very similar (nonsignificant).

In subanalyses, we assessed whether the size of the M-protein was different or predictive of risk among first-degree relatives, and we found no difference (data not shown). We also quantified familial risks among MGUS patients diagnosed before/after 1995, and the risk estimates were virtually the same (data not shown). Finally, we explored if the risk of progression from MGUS to MM was different among familial (vs sporadic) MGUS cases; and, again, there was no difference (data not shown).

## Discussion

In this large nationwide case-control study including almost 4500 MGUS patients, more than 17 500 matched controls, and their more than 73 000 linkable first-degree relatives, we found first-degree relatives of MGUS patients (compared with first-degree relatives to controls) to have a 3-fold increased risk of developing MGUS and MM and 4- and 2-fold excess risks of LPL/WM, and CLL, respectively. Our findings are important in that they support a role for common susceptibility genes, shared environmental influences, or an interaction between both in MGUS and related lymphoproliferative malignancies.

Our observation of a 3-fold increased risk of MGUS among first-degree relatives of MGUS patients substantially adds to the literature supporting a role for susceptibility genes in the etiology of MGUS and certain lymphoproliferative malignancies.[7-9] Previously, relatives of MM patients have been found to be at a higher risk of developing MM, and, based on small numbers, there has been an excess of MGUS.[12] In addition, differences in the prevalence of MGUS between ethnic groups have been observed. Recently, we found 2- to 3-fold excess risk of MGUS and MM in African Americans (compared with whites), while the risk of progression from MGUS to myeloma was very similar for the 2 races.[21] Similarly, we found the prevalence of MGUS among Ghanaian men to be 2-fold increased compared with white men in Olmsted County, MN.[22] These differences are consistent with genetic effects, but environmental factors cannot be ruled out. Interestingly, there is emerging evidence to support a role for autoimmunity, infections, and inflammation in the etiology of MM and MGUS.[23] Potentially, immune-mediated conditions might act as triggers for MM and MGUS development.[24,25] Taken together, we believe that the observed increases of MGUS among blacks in

**Table 3. Relative risk of MGUS and lymphoproliferative malignancies among first-degree relatives of MGUS patients, by MGUS isotype in probands**

| | First-degree relatives of IgG/IgA MGUS patients (n = 7490) | First-degree relatives of controls (n = 30 076) | RR (95% CI)* | First-degree relatives of IgM MGUS patients (n = 1696) | First-degree relatives of controls (n = 6 722) | RR (95% CI)* |
|---|---|---|---|---|---|---|
| MGUS | 15 | 15 | 4.0 (1.7-9.2)† | 0 | 5 | 0 |
| Multiple myeloma | 22 | 30 | 2.9 (1.7-4.9)† | 2 | 4 | 1.9 (0.3-10) |
| Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia | 5 | 1 | 20 (2.3-170)† | 1 | 1 | 3.5 (0.2-63) |
| Chronic lymphocytic leukemia | 11 | 28 | 1.5 (0.7-3.2) | 4 | 3 | 5.0 (1.1-23)† |

The number of relatives for IgG/IgA MGUS and IgM MGUS patients, respectively, does not add up to the total number of relatives for all MGUS patients in the study because 1739 MGUS patients had no available information on MGUS isotype and 1 patient had IgD MGUS (see Table 1).
*All estimates were adjusted for sex of first-degree relative.
†Statistically significant (2-sided *P* value < .05).

**Table 4. MGUS among first-degree relatives of MGUS patients by sex of relative, type of relative, and age of probands at diagnosis**

| | First-degree relatives of MGUS patients (n = 14 621) | First-degree relatives of controls (n = 58 387) | RR (95% CI)* |
|---|---|---|---|
| **Sex of relative** | | | |
| Male | 13 | 15 | 3.5 (1.5-8.5)† |
| Female | 9 | 16 | 2.2 (0.8-5.9) |
| **Type of first-degree relative** | | | |
| Parent | 9 | 13 | 2.7 (1.2-6.3)† |
| Sibling | 6 | 5 | 4.9 (1.2-20)† |
| Offspring | 7 | 13 | 2.2 (0.9-5.6) |
| **Age at MGUS diagnosis for proband, y** | | | |
| Less than 65 | 15 | 18 | 3.2 (1.5-6.9)† |
| 65 or older | 7 | 13 | 2.2 (0.9-5.5) |

*All estimates were adjusted for sex of first-degree relative.
†Statistically significant (2-sided $P$ value $< .05$).

previous studies, as well as the excess among first-degree relatives in the present study, are likely due to unknown environmental influences, such as immune-related or infectious conditions, interacting with genetic factors.

We found risk of LPL/WM to be 4-fold increased among relatives of MGUS patients. When we assessed familial aggregation patterns by Ig isotype, based on small numbers, we found an increased risk among relatives of IgG/IgA MGUS patients, while relatives of IgM MGUS had a nonsignificant 3.5-fold increased risk. Because IgM is more closely associated with the development of WM,[4,5] we would have expected an excess among relatives of IgM MGUS patients. However, this particular analysis was limited by sample size. Similar to MM, there is recent evidence to support a role for immune-related conditions in the etiology of LPL/WM.[26-28] Future studies are needed to define the roles of immune-related conditions, genes, and other environmental factors among patients with MGUS and related malignancies.

To our knowledge, Noel and Kyle published the first and only large (n = 100) series on the co-occurrence of M-proteins in persons diagnosed with CLL.[29] Previously, we assessed familial aggregation among 14 336 first-degree relatives of 5918 CLL patients and, compared with relatives of matched controls, we found a 7.5-fold excess risk.[30] We recently expanded the database and included information on MGUS among 26 947 first-degree relatives of 9717 CLL patients. We were able to confirm the excess risk of CLL among relatives; however, we found no statistical increase in risk of MGUS.[31] In the present study, we found first-degree relatives of MGUS patients to have a 2-fold increased risk of developing CLL. Based on small numbers, a prominent 5-fold increased risk was found among relatives to IgM MGUS patients. More research is needed to clarify the association between MGUS and CLL.

We observed similar risk estimates among parents, siblings, and offspring, and our findings thus 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 that men have a higher familial risks than women, although the CIs overlapped.

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, ensured a population-based setting, and aids the generalizability of our findings. The MGUS patients are expected to have a high level of diagnostic accuracy because they were diagnosed (and worked-up if necessary) at specialized regional hospital-based hematology centers (see "Patients, controls, and first-degree relatives"). In addition, we recently assessed ascertainment and diagnostic accuracy for 997 patients with a lymphoproliferative malignancy diagnosed in Sweden between 1964 and 2003.[31] We found 98% of the patients to fulfill current diagnostic criteria for having a lymphoproliferative malignancy. Limitations include incomplete numbers of first-degree relatives, few numbers of the outcome of interest among first-degree relatives, lack of information on potential confounders (although the matched design and analyses ensured adjustment for sex, age, and geography), and lack of detailed clinical data. Another potential limitation of our study is the fact that diagnostic criteria for MGUS have evolved over time, but this should not bias our study substantially, because most of our cases were diagnosed in 1986 or later. Furthermore, because we did not actually screen for MGUS in serum samples from first-degree relatives, we would expect that MGUS cases were underascertained. Because we compared familial risks between relatives of MGUS patients and matched controls using data obtained from the same registries, the ascertainment among relatives should be nondifferential and the RRs should not be biased. Because of the retrospective study design, one might argue that there could be some bias with regard to testing for MGUS among family members. However, when we eliminated relatives of probands that developed any lymphoproliferative malignancy, the results were very similar (data not shown). Furthermore, when we eliminated MGUS cases that had a MM relative diagnosed before they were diagnosed with MGUS (n = 29), the number of MGUS cases in relatives was unchanged. These measures are consistent with our clinical knowledge, that in the absence of published data to support genetic factors in the causation of MGUS, Swedish physicians have not screened for MGUS among family members of MGUS cases or patients with lymphoproliferative malignancies. In addition, because we did not conduct screening by electrophoresis to rule out MGUS among control subjects, we would expect that MGUS was present in a fraction of the controls.[1] This might have led to some conservative bias (toward the null) in our study. Finally, the fact that our study population primarily comprises whites might limit the generalizability of our results. Future investigations are needed to assess whether familial risk of MGUS varies across different ethnic and racial groups.

It is important to consider the clinical implications of our findings. Because we found excess risks for developing MGUS among first-degree relatives of MGUS cases, one might speculate whether there is an advantage for early detection of MGUS among relatives. However, until there are available intervention strategies for MGUS, it seems reasonable to propose that such efforts should be part of research protocols. Also, our observation that first-degree relatives of MGUS cases have an elevated relative risks for developing MM, CLL, and LPL/WM has to be interpreted with caution given the low lifetime risk for these neoplasms (0.62% for MM and 0.46% for CLL) in the general population.[32] Future research is needed to better define underlying mechanisms and predictive markers for lymphoproliferative tumor transformation among MGUS cases. Ultimately, such efforts will lead to early intervention strategies.

In summary, we found increased risks of developing MGUS, MM, LPL/WM, and CLL among first-degree relatives of MGUS

patients. These results support a role for susceptibility genes, shared environmental influences, or an interaction between both, which predispose to MGUS and certain lymphoproliferative malignancies. Our study provides novel information supporting the application of gene mapping and candidate gene approaches in high-risk families and case-control studies. From a clinical perspective, given the low absolute risk for MGUS and related malignancies together with the lack of available intervention and early disease therapies, we conclude that currently familial screening for MGUS has no role outside research studies.

## Acknowledgments

The authors thank all clinicians who contributed their MGUS patients to our nationwide MGUS cohort; Ms Shiva Ayobi, The National Board of Health and Welfare, Stockholm, Sweden; Ms Susanne Dahllöf, Statistics Sweden, Örebro, Sweden; Ms Charlotta Ekstrand, Ms Molly Collin, and Ms Lisa Camner, Karolinska Institutet, Stockholm, Sweden, for invaluable ascertainment of MGUS data; and Ms Emily Steplowski, Information Management Services, Silver Spring, MD, for important efforts in the development of this database.

This research was supported by the Intramural Research Program of the NIH (Bethesda, MD) and the National Cancer Institute (Bethesda, MD), and by grants from the Swedish Cancer Society, Stockholm County Council, and the Karolinska Institutet Foundations.

## Authorship

Contribution: O.L., S.Y.K., L.R.G., M.B., and I.T. designed the study; O.L., S.Y.K., M.B., and I.T. obtained data; O.L., S.Y.K., M.B., and I.T. initiated this work; O.L., S.Y.K., M.B., L.R.G., and I.T. wrote the report; and all authors were involved in analyses and interpretation of the results, and read, gave comments, 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.

Correspondence: Ola Landgren, National Cancer Institute, National Institutes of Health, Center for Cancer Research, Medical Oncology Branch, Building 10, Room 13N240, 10 Center Drive, Bethesda, MD 20892; e-mail: landgreo@mail.nih.gov.

## References

1. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2006;354:1362-1369.
2. Anonymous. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol.* 2003;121:749-757.
3. Kyle RA. Monoclonal gammopathy of undetermined significance. Natural history in 241 cases. *Am J Med.* 1978;64:814-826.
4. Schop RF, Kuehl WM, Van Wier SA, et al. Waldenstrom macroglobulinemia neoplastic cells lack immunoglobulin heavy chain locus translocations but have frequent 6q deletions. *Blood.* 2002;100:2996-3001.
5. Kyle RA, Therneau TM, Rajkumar SV, et al. Long-term follow-up of IgM monoclonal gammopathy of undetermined significance. *Blood.* 2003;102:3759-3764.
6. Bizzaro N, Pasini P. Familial occurrence of multiple myeloma and monoclonal gammopathy of undetermined significance in 5 siblings. *Haematologica.* 1990;75:58-63.
7. Lynch HT, Ferrara K, Barlogie B, et al. Familial myeloma. *N Engl J Med.* 2008;359:152-157.
8. Lynch HT, Sanger WG, Pirruccello S, Quinn-Laquer B, Weisenburger DD. Familial multiple myeloma: a family study and review of the literature. *J Natl Cancer Inst.* 2001;93:1479-1483.
9. Lynch HT, Watson P, Tarantolo S, et al. Phenotypic heterogeneity in multiple myeloma families. *J Clin Oncol.* 2005;23:685-693.
10. Sandstrom H, Wahlin A, Eriksson M, Bergstrom I, Wickramasinghe SN. Intravascular haemolysis and increased prevalence of myeloma and monoclonal gammopathy in congenital dyserythropoietic anaemia, type III. *Eur J Haematol.* 1994;52:42-46.
11. Kristinsson SY, Bjorkholm M, Goldin LR, McMaster ML, Turesson I, Landgren O. Risk of lymphoproliferative disorders among first-degree relatives of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia patients: a population-based study in Sweden. *Blood.* 2008;112:3052-3056.
12. Landgren O, Linet MS, McMaster ML, Gridley G, Hemminki K, Goldin LR. Familial characteristics of autoimmune and hematologic disorders in 8,406 multiple myeloma patients: a population-based case-control study. *Int J Cancer.* 2006;118:3095-3098.
13. Ogmundsdottir HM, Haraldsdottirm V, Johannesson GM, et al. Familiality of benign and malignant paraproteinemias. A population-based cancer-registry study of multiple myeloma families. *Haematologica.* 2005;90:66-71.
14. Axelsson U, Bachmann R, Hallen J. Frequency of pathological proteins (M-components) om 6,995 sera from an adult population. *Acta Med Scand.* 1966;179:235-247.
15. Anonymous. *Patientregistret 1987-1996: Kvalitet och innehåll* (Swedish). Stockholm, Sweden: EpC, National Board of Health and Welfare; 1998.
16. Socialstyrelsen. *Cancer Incidence in Sweden 2006.* Stockholm, Sweden: Centre for Epidemiology; 2007.
17. Turesson I, Linet MS, Bjorkholm M, et al. Ascertainment and diagnostic accuracy for hematopoietic lymphoproliferative malignancies in Sweden 1964-2003. *Int J Cancer.* 2007;121:2260-2266.
18. Skarle A. *Flergenerationsregistret.* Stockholm, Sweden: Statistics Sweden, Population Statistics; 2001.
19. Liang KY. Estimating effects of probands' characteristics on familial risk: I. Adjustment for censoring and correlated ages at onset. *Genet Epidemiol.* 1991;8:329-338.
20. Pfeiffer RM, Goldin LR, Chatterjee N, et al. Methods for testing familial aggregation of diseases in population-basedsamples: application to Hodgkin lymphoma in Swedish registry data. *Ann Hum Genet.* 2004;68:498-508.
21. Landgren O, Gridley G, Turesson I, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. *Blood.* 2006;107:904-906.
22. Landgren O, Katzmann JA, Hsing AW, et al. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. *Mayo Clin Proc.* 2007;82:1468-1473.
23. Brown LM, Gridley G, Check D, Landgren O. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. *Blood.* 2008;111:3388-3394.
24. Landgren O, Kyle RA. Multiple myeloma, chronic lymphocytic leukaemia and associated precursor diseases. *Br J Haematol.* 2007;139:717-723.
25. Rajkumar SV. MGUS and smoldering multiple myeloma: update on pathogenesis, natural history, and management. *Hematology Am Soc Hematol Educ Program.* 2005:340-345.
26. Giordano TP, Henderson L, Landgren O, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. *JAMA.* 2007;297:2010-2017.
27. Smedby KE, Hjalgrim H, Askling J, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. *J Natl Cancer Inst.* 2006;98:51-60.
28. Koshiol J, Gridley G, Engels EA, McMaster ML, Landgren O. Chronic immune stimulation and subsequent Waldenstrom macroglobulinemia. *Arch Intern Med.* 2008;168:1903-1909.
29. Noel P, Kyle RA. Monoclonal proteins in chronic lymphocytic leukemia. *Am J Clin Pathol.* 1987;87:385-388.
30. Goldin LR, Pfeiffer RM, Gridley G, et al. Familial aggregation of Hodgkin lymphoma and related tumors. *Cancer.* 2004;100:1902-1908.
31. Goldin LR, Bjorkholm M, Kristinsson SY, Turesson I, Landgren O. Elevated risk of chronic lymphocytic leukemia (CLL) and other indolent non-Hodgkin lymphomas among relatives of CLL patients. *Haematologica.* (In press).
32. Ries LAG, Eisner MP, Kosary CL, et al, eds. *SEER Cancer Statistics Review, 1975-2000.* Bethesda, MD: National Cancer Institute; 2003.