

Differential characteristics of Waldenström macroglobulinemia according to patterns of familial aggregation

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Familial aggregation of Waldenström macroglobulinemia (WM) and related B-cell disorders (BCDs) suggests a role for genetic factors, but few data address environmental influences. We designed a questionnaire-based study to examine clinical and environmental factors in a cohort of WM families with various patterns of case aggregation. We analyzed data on 103 WM patients and 272 unaffected relatives from 35 multiple-case WM and 46 mixed WM/BCD kindred and 28 nonfamilial (sporadic) WM patients,

using logistic regression models with generalized estimating equations to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for association. In this study population, the WM disease process appeared similar among patients regardless of family history. Familial WM patients were more likely than unaffected relatives to report a history of autoimmune disease (OR, 2.27; 95% CI = 1.21-4.28) and infections (OR, 2.13; 95% CI = 1.25-3.64). Familial WM patients were also more likely to report exposure to

farming (OR, 2.70; 95% CI = 1.34-5.42), pesticides (OR, 2.83; 95% CI = 1.56-5.11), wood dust (OR, 2.86; 95% CI = 1.54-5.33), and organic solvents (multiple-case WM OR, 4.21; 95% CI = 1.69-10.51) compared with unaffected family members. These data provide clues to both genetic and environmental factors that may influence development of WM. Well-designed case-control studies are needed to confirm these findings. (*Blood*. 2010;115(22):4464-4471)

Introduction

Waldenström macroglobulinemia (WM) is classified as a type of non-Hodgkin lymphoma (NHL) characterized primarily by lymphoplasmacytic infiltrate in the bone marrow accompanied by hypersecretion of monoclonal immunoglobulin M (IgM).^{1,2} Clinical features of WM are variable, with many patients having asymptomatic or indolent disease, although others present with symptoms attributable to direct tumor infiltration and/or monoclonal serum IgM protein.³ The incidence of WM is unknown because of changes in diagnostic criteria over time; however, WM is predicted to be rare.⁴ IgM monoclonal gammopathy of undetermined significance (MGUS) may precede development of WM.⁵ Although the true incidence of IgM MGUS is also unknown, prevalence data suggest that it is more common than WM.⁶

Although age, race, sex, and pre-existing IgM MGUS are recognized risk factors,^{7,8} the etiology of WM is largely unknown. Environmental and occupational exposures, such as exposure to leather, rubber, dyes, and paints, have been implicated in case reports.⁹⁻¹¹ In a small, hospital-based case-control study of environmental and occupational exposures, WM patients were found to be slightly better educated, but no significant differences were found for other socioeconomic characteristics, occupational exposures, alcohol or tobacco use, medication history, or history of previous medical conditions.¹²

The study of familial disease clusters is a useful approach for defining the clinical phenotype of specific disorders, identifying new susceptibility genes, and facilitating the understanding of the pathogenesis of hereditary and nonhereditary cancers at both the individual and population levels.¹³ Although familial cluster-

ing of WM has been previously documented and a role for genetic predisposition has been suggested,^{14,15} until recently there were very limited data regarding the risks for relatives of WM patients. Early descriptions of familial aggregation of WM focused on families presenting multiple cases of WM exclusively.^{14,16-18} Emerging data at the population^{19,20} and clinical²¹ levels have confirmed that a diagnosis of WM confers significantly elevated risk for relatives of WM patients to be diagnosed with WM or a related B-cell disorder. In addition, the spectrum of familial WM may include relatives with IgM monoclonal gammopathy and/or immunologic disorders.^{18,22,23}

To begin to address the gaps in our understanding of familial WM and its etiology, we designed a questionnaire-based study in a large cohort of WM families that have been recruited by the National Cancer Institute to examine demographic, clinical, environmental, and occupational differences among WM families with various degrees of case aggregation.

Methods

The National Cancer Institute WM Family Registry

The National Cancer Institute of the National Institutes of Health has maintained a registry of WM-prone families for more than 30 years.²⁴ Families are eligible for inclusion in the registry if they have a member diagnosed with WM accompanied by at least 1 other bloodline relative diagnosed with WM or another disease of interest, such as other B-cell

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disorders (BCDs; including chronic lymphocytic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, or multiple myeloma), MGUS, or autoimmune disease. Because young age at onset may be associated with increased genetic risk, families having a single patient diagnosed with WM before age 40 years are also eligible. In addition, a limited number of WM patients who do not fulfill any of these criteria have been recruited to serve as a nonfamilial comparison group. Patients with the disorders of interest, together with their first- and second-degree bloodline relatives, are eligible for inclusion. More distantly related relatives may be included if they connect 2 cases or are otherwise informative. Families are ascertained through self-, physician, or genetic counselor referral. A variety of organized Institutional Review Board–approved recruitment methods have been undertaken; for example, an informational brochure that describes the registry and related studies has been available for distribution at national hematology and oncology meetings, a letter soliciting referrals was sent to practicing hematologists in the United States in 2003, and information about the study has been made available on the National Cancer Institute's clinical trials Web site. Increasingly, patients are self-referred after learning about the registry through an Internet search or through WM patient advocacy organizations. After verification of eligibility, families are initially classified based on the pattern of case aggregation before further data collection. Because most families are followed indefinitely, categorization of persons and families may change as new cases are diagnosed or new information emerges.

Study population

Patients with WM, together with any of their living unaffected bloodline relatives 18 years or older, were eligible for this study and evaluated during the 5-year period from January 1, 2001, through December 31, 2006. Children 10 years or older were also eligible, contingent on their assent and parental consent, but were not routinely recruited. Family history of WM or related BCD was obtained systematically using a standardized family history questionnaire. For this study, patients were classified as familial or nonfamilial (ie, sporadic) based on the presence or absence, respectively, of a history of WM or related BCD in blood relatives. Familial patients were further stratified according to the pattern of cancer presenting within a given pedigree. Multiple-case WM families presented with at least 2 members diagnosed with WM and are thus enriched for the presence of WM; these families may or may not have members diagnosed with other BCDs. Mixed WM/B-cell disorder (BCD) families were defined as having 1 patient with a diagnosis of WM and at least 1 patient with a diagnosis of another B-cell or plasma cell disorder or MGUS.

We attempted to verify the diagnosis of WM, using the 2003 consensus panel criteria for the clinicopathologic definition of WM,¹ or other BCD for all patients. Among 131 patients who were initially referred with WM, 6 patients were reclassified as MGUS of IgM type (IgM MGUS) and 1 patient was found to have IgG MGUS based on review of their medical records and/or direct bone marrow examination; these 7 patients were excluded from the WM-specific analyses. During study evaluation, all participants were screened using serum immunofixation electrophoresis. Seven persons discovered to have IgM monoclonal gammopathy during screening were subsequently diagnosed with WM and reclassified for inclusion in the WM-specific analyses. Among the 131 WM patients identified for analysis, the diagnosis was validated in 126 cases (96.2%) by review of the original pathology report (n = 122, 93.1%) or by referring physician report (n = 4, 3.0%).

A variety of B-cell and/or plasma cell disorders were reported in family members by WM patients from mixed WM/BCD families, including chronic lymphocytic leukemia (12 families, 25.0%), non-Hodgkin lymphoma (12 families, 25.0%), Hodgkin lymphoma (4 families, 8.3%), multiple myeloma (10 families, 20.8%), and MGUS (8 families, 16.7%). In addition, 2 of these families (4.2%) reported at least 2 different B-cell or plasma cell disorders (chronic lymphocytic leukemia and non-Hodgkin lymphoma, 1 family; multiple myeloma and non-Hodgkin lymphoma, 1 family). Among persons reported to have related BCDs, the specific diagnosis was validated in 34 (70.8%) of 48 cases by medical record and/or pathology review (n = 23, 47.9%), direct clinical and/or laboratory evaluation (n = 10, 20.8%), or referring physician

report (n = 1, 2.1%). We were unable to obtain confirmatory records for 19 persons.

At the time of this analysis, there were 36 multiple-case WM families, 48 mixed WM/BCD families, and 28 sporadic WM patients in the registry. We analyzed available data on all eligible consenting subjects from these families. Mounting evidence suggests that WM coaggregates and may share risk factors with other B-cell disorders²⁰ and that IgM-MGUS is a precursor condition for WM.^{5,24-26} In our analysis, we included 28 relatives who had a history of a non-WM B-cell disorder or MGUS and who completed questionnaires (see "Data collection") with the unaffected group. However, a sensitivity analysis based on excluding these 28 persons from the control group did not change the results (data not shown).

Data collection

The study was conducted under the approval of the National Cancer Institute Clinical Center Institutional Review Board, and all participants gave written informed consent for data collection and analysis in accordance with the Declaration of Helsinki. All participants completed a standardized self-administered questionnaire that included questions regarding demographic information, selected personal medical history, occupational history, and history of certain environmental exposures. Medical conditions of interest included selected autoimmune and/or rheumatologic diseases, chronic inflammatory and/or infectious conditions including asthma, chronic cholecystitis, chronic hepatitis, chronic sinusitis, or chronic bronchitis, and a limited number of other infections including pneumonia requiring hospitalization, tuberculosis, hepatitis, pyelonephritis, or osteomyelitis. Autoimmune diseases were categorized as systemic, organ specific, or suspected, as previously described.²⁷ Participants were queried regarding allergies, which were classified as drug, diet, or environment related. Persons who reported a history of allergy were further asked to identify the specific allergen(s) associated with their allergic history. History of hyposensitization therapy was not obtained. Because there was limited a priori evidence implicating specific environmental exposures,⁹⁻¹² nonoccupational environmental exposures of interest were addressed broadly in an exploratory fashion and included tobacco and alcohol use, as well as prolonged exposure to livestock and/or domestic animals, paints, glues, solvents, leather/metal cleaning compounds, wood dust, asbestos, and hair dye. We used these broad groupings and did not query persons regarding exposure to specific chemical compounds because we lacked power to analyze more discrete categories. We used a history of at least 6 consecutive months of exposure as the threshold for classifying a person as exposed to any given class of agent.

Patients known to have WM at ascertainment also completed questions pertaining to the diagnosis and treatment of their disease. The 7 patients who were diagnosed with WM after ascertainment and completion of the study questionnaire contributed information regarding demographics, symptoms, and medical and exposure history but did not complete questions addressing the diagnosis and treatment of WM.

Statistical analysis

Means and frequencies for continuous and categorical variables were determined. We used unconditional logistic regression with generalized estimating equations (GEEs)²⁸ to account for correlations within the families in the variance computation. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) from multivariable models adjusted for sex, continuous age, and family type. We assessed heterogeneity of the ORs from each of the family types (mixed vs multiple-case WM families) using the likelihood ratio test (LRT). If the effects were not significantly different, we combined the different family types to compute a combined OR. We present 95% CIs and *P* values based on the independent working correlation matrix. Other working correlations yielded similar results (SAS 9.1; PROC GENMOD).

Table 1. Demographic characteristics of WM patients and their unaffected relatives according to family type and affection status

Characteristic	Familial WM patients			Nonfamilial WM patients, n = 28, no. (%)	Unaffected relatives, n = 272, no. (%)
	Multiple-case WM, n = 57, no. (%)*	Mixed WM/BCD, n = 46, no. (%)	All familial WM patients, n = 103, no. (%)		
Age, y					
Mean	62.3	60.6	61.6	64.6	48.6
Median	64.0	61.0	62.0	66.5	47.0
Range	35-90	37-86	35-90	39-79	17-94
Sex					
Male	34 (59.6)	25 (54.3)	59 (57.3)	13 (46.4)	125 (46.0)
Female	23 (40.4)	21 (45.6)	44 (42.7)	15 (53.6)	147 (54.0)
Race					
White	54 (94.7)	46 (100.0)	100 (97.1)	29 (100.0)	263 (96.7)
Black	—	—	—	—	—
Asian	3 (5.3)	—	3 (2.9)	—	9 (3.3)

WM indicates Waldenström macroglobulinemia; BCD, B-cell disorder; and —, no relevant data.

*Numbers and percentages may not sum to total because of missing data and rounding, respectively. Percentages are based on nonmissing values.

Results

We identified 131 WM patients (57 multiple-case, 46 mixed WM/BCD, 28 nonfamilial) and 272 unaffected family members (167 from multiple-case and 105 from mixed WM/BCD families) for whom questionnaire data were available.

Demographic information for participants according to family type is presented in Table 1. Because of the relatively late age of onset of WM, more family members were available from generations younger than the cases ($n = 129, 47.4\%$) than from the same ($n = 108, 39.7\%$) or older ($n = 35, 12.9\%$) generations. All but one family in this study were white, with most families reporting Northern European descent. Interestingly, some members of the single Asian family also reported remote French ancestry. Twelve (14.8%) familial WM patients (4 multiple-case WM, 8 mixed WM/BCD), and 4 nonfamilial WM patients (14.3%) reported having at least one Jewish-born parent.

Overall, WM patients were predominantly male, although the excess was more apparent among familial than nonfamilial WM patients (57.3% male vs 46.4% male, respectively; $P = .37$). The median age at diagnosis of WM was 59.0 years (95% CI: 56.7-61.3) for familial WM patients and 62.2 years (95% CI: 57.9-66.5) for nonfamilial patients (Table 2). Subsets of both familial and nonfamilial patients reported a prior diagnosis of MGUS (34.3% vs 35.7%, respectively; $P = .94$). Most patients, familial and nonfamilial, reported eventually experiencing symptoms from their WM at some point during their illness. Nonfamilial WM patients were more likely than familial WM patients overall to have ever reported symptoms (OR, 1.45; 95% CI 0.46-4.55), but the difference was not significant ($P = .51$). When we explored this issue further, we found that compared with WM patients from multiple-case WM families, WM patients from both nonfamilial WM (OR, 2.48; 95% CI 0.75-8.21) and mixed WM/BCD WM (OR, 4.82; 95% CI 1.44-16.13) families were more likely to report having ever experienced symptoms. However, we did not observe significant differences between groups stratified by family type for any other disease-related variable aside from symptoms (data not shown). Reported symptoms were similar among familial and nonfamilial patients. The most commonly reported symptoms included fatigue and malaise, followed by neurologic symptoms and dyspnea.

After diagnosis of WM, mean time to treatment was similar for familial and nonfamilial patients, but there was substantial variability among patients. Among those receiving any form of treatment,

most patients (76 familial and 22 nonfamilial; 73.8% vs 78.6%, respectively; $P = .90$) reported having received chemotherapy. Thirty-five patients (28 familial and 7 nonfamilial, 29.2% vs 25.0%, respectively; $P = .97$) reported having received plasmapheresis or supportive treatment (ie, blood component transfusion) in addition to chemotherapy.

Table 3 shows the distribution of selected medical conditions for all participants. No family members reported a history of amyloidosis. A single family member from a multiple-case WM family reported a history of hypogammaglobulinemia. We found no significant differences between familial and nonfamilial WM patients for any of the conditions of interest. We then stratified familial WM patients by family type and found no significant differences between familial WM patients based on the pattern of WM and other BCD aggregation. Because unaffected family members tended to be younger than familial WM cases, we examined the risk of familial WM stratified by age younger than 60 years and 60 years or older to further evaluate the potential effect of age. Formal assessment using the likelihood ratio test (LRT) revealed no differences between groups, with certain exceptions. The risk of WM associated with tonsillectomy and/or adenoidectomy, organic solvents, and therapeutic radiation was higher in patients younger than 60 years compared with those 60 years or older ($P_{LRT} = .02, .01, \text{ and } .02$, respectively).

We then estimated ORs and 95% CIs for the association of exposure histories with WM using all family data. We found that familial WM patients were significantly more likely than unaffected persons to report a history of autoimmune disorders (OR, 2.27; 95% CI = 1.21-4.28; $P = .01$), specified infections (OR, 2.13; 95% CI = 1.25-3.64; $P = .005$), and allergies (OR, 1.94; 95% CI = 1.09-3.46; $P = .02$). Among autoimmune diseases, risk was significantly increased for organ-specific autoimmune diseases (OR, 3.07; 95% CI = 1.29-7.28; $P = .01$). We also observed a similar nonsignificant elevation in risk for systemic and/or suspected autoimmune diseases (OR, 1.86; 95% CI = 0.82-4.23; $P = .14$), which we combined into a single category because of small numbers. Although the association with allergies was not entirely consistent, we saw some evidence of increased risk of WM associated with allergies, which seemed strongest for drug allergies (OR, 1.75; 95% CI = 0.94-3.24; $P = .08$). For most conditions, the observed elevations in risks were similar for all familial WM patients, irrespective of familial aggregation pattern. The risk associated with a history of organ-specific autoimmune disease appeared to be higher for patients from mixed WM/BCD families (OR, 5.42; 95% CI 1.67-17.53) compared with patients from

Table 2. Distribution of clinical features of WM diagnosis and treatment with adjusted ORs and 95% CIs for reporting specific symptoms or signs according to family type

Characteristic	Familial WM patients				OR† (95% CI) for nonfamilial vs all familial
	Multiple-case WM, n = 57*	Mixed WM/BCD, n = 46	All familial WM, n = 103	Nonfamilial WM patients, n = 28	
Age at WM diagnosis, y					
Mean (95% CI)	58.7 (55.3-62.1)	58.3 (54.4-60.9)	58.3 (55.9-60.6)	60.4 (56.5-64.3)	—
Median (95% CI)	58.7 (54.6-62.7)	59.8 (57.0-62.5)	59.0 (56.7-61.3)	62.2 (57.9-66.5)	—
Range	33.5-85.1	34.8-84.1	33.5-85.1	37.3-76.2	—
Prior history of MGUS, no. (%)	23 (40.4)	12 (26.1)	35 (34.0)	10 (35.7)	0.98 (0.42-2.30)
Occurrence of symptoms and/or signs of disease					
Ever had symptoms, no. (%)	44 (77.2)	43 (97.7)	87 (86.1)	25 (89.3)	1.45 (0.46-4.55)
Had symptoms before diagnosis, no. (%)	29 (51.8)	29 (64.4)	58 (57.4)	18 (66.7)	—
Yes: time, symptoms to diagnosis; mean y (range)‡	2.2 (0.1-16.8)	1.4 (0.7-16.0)	1.6 (0.1-16.8)	1.4 (0.2-20.2)	—
No: time, diagnosis to symptoms; mean y (range)§	0.8 (0.0-21.6)	0.4 (0.0-6.3)	0.8 (0.0-21.6)	0.2 (0.0-0.4)	—
Ever had signs of WM, no. (%)¶	29 (50.9)	32 (69.6)	61 (59.2)	19 (67.8)	0.70 (0.29-1.67)
Reported symptoms, n (%)					
Fatigue	29 (50.9)	36 (80.0)	65 (63.1)	16 (57.1)	0.81 (0.34-1.93)
Malaise	25 (43.9)	24 (53.3)	49 (47.6)	15 (53.6)	1.27 (0.54-2.97)
Paresthesia	12 (21.1)	15 (33.3)	27 (26.2)	9 (32.1)	1.42 (0.57-3.54)
Dyspnea	8 (14.0)	15 (33.3)	23 (22.3)	9 (32.1)	1.61 (0.62-4.20)
Visual problems	5 (8.8)	4 (8.9)	9 (8.7)	6 (21.4)	2.76 (0.94-8.06)
Bruising	7 (12.3)	9 (20.0)	16 (15.5)	5 (17.8)	0.96 (0.32-2.91)
Joint pain	5 (14.3)	11 (24.4)	16 (19.8)	4 (14.3)	0.49 (0.13-1.87)
Bleeding	4 (7.1)	10 (22.2)	14 (13.6)	3 (10.7)	0.85 (0.22-3.39)
Other , no. (%)	28 (49.1)	23 (50.0)	51 (49.5)	11 (39.3)	—
Reported signs (%)					
Anemia or low blood count	26 (45.6)	27 (58.7)	53 (51.5)	12 (42.8)	0.71 (0.29-1.71)
Enlarged lymph nodes	7 (12.3)	7 (15.2)	14 (13.6)	2 (7.1)	0.58 (0.12-2.86)
Hepatosplenomegaly	3 (5.3)	3 (6.5)	6 (5.8)	4 (14.3)	2.10 (0.37-11.99)
Treatment characteristics**					
Never treated, no. (%)	16 (32.0)	4 (8.7)	20 (20.8)	6 (21.4)	—
Time from diagnosis, mean y (range)	2.4 (0.0-10.4)	1.2 (0.6-5.9)	2.0 (0.0-10.4)	3.3 (2.2-13.9)	—
Treated, no. (%)	34 (68.0)	42 (91.3)	76 (79.2)	22 (78.6)	—
Time, diagnosis to first treatment; mean y (range)	0.2 (0.0-22.0)	0.2 (0.0-9.8)	0.2 (0.0-22.0)	0.2 (0.0-13.3)	—
Cytotoxic, no. (%)					
Chemotherapy and/or immunotherapy††	34 (68.0)	42 (91.3)	76 (79.2)	22 (78.6)	—
Plasmapheresis	7 (14.3)	11 (23.9)	18 (18.9)	4 (14.3)	—
Supportive‡‡	10 (18.9)	6 (14.0)	16 (16.7)	3 (11.5)	—

WM indicates Waldenström macroglobulinemia; OR, odds ratio; CI, confidence interval; BCD, B-cell disorder; and —, no relevant data.

*Numbers and percentages may not sum to total because of missing data and rounding. Percentages are based on nonmissing values.

†Adjusted for age and sex.

‡Includes participants who reported experiencing symptoms before a WM diagnosis.

§Includes participants who reported experiencing symptoms only after a WM diagnosis.

¶Signs include anemia or cytopenia, lymphadenopathy, or hepatosplenomegaly.

||Other reported symptoms were defined as symptoms reported by fewer than 20% of participants in each category. Other symptoms included fever, night sweats, weight loss, headaches, Raynaud phenomenon, gastrointestinal symptoms, confusion, inability to concentrate, memory changes, myalgia, rash, lightheadedness/syncope, edema, and palpitations.

**Treatment data for multiple-case WM patients exclude 7 patients who were diagnosed during the study after questionnaire completion.

††Includes one patient from a multiple-case family who had a bone marrow transplantation and one patient from a mixed WM/BCD family who had a stem cell transplantation.

‡‡Supportive treatment includes red blood cell and/or platelet transfusion.

multiple-case families (OR, 1.74; 95% CI 0.52-5.84). However, there was no evidence of multiplicative interaction between organ-specific autoimmune disease and family type ($P_{LRT} = .2$).

We also collected information for potential environmental and occupational exposures for affected WM patients and unaffected family members (Table 4). Comparing cases only, we found no significant differences between familial and nonfamilial WM patients or between familial WM patients stratified by family type (data not shown). Comparing WM patients and unaffected relatives, we observed that familial WM patients were more likely to report exposure to farming (OR, 2.70; 95% CI = 1.34-5.43;

$P = .005$), pesticides (OR, 2.83; 95% CI = 1.56-5.11; $P < .001$), and wood dust (OR, 2.86; 95% CI = 1.54-5.33; $P < .001$) compared with unaffected family members. Organic solvent exposure was also notable because the relative risk for organic solvents was significantly greater for members of multiple-case WM families compared with mixed WM/BCD families (ORs 4.21 vs 1.14, respectively; $P_{LRT} = .05$), whereas the association with farming was borderline significantly greater for members of mixed WM/BCD families compared with multiple-case families (ORs 5.52 vs 1.52, respectively; $P_{LRT} = .06$). Although familial WM patients were overall less likely than their relatives to report a history of

Table 3. Distribution, ORs, and 95% CIs for personal medical history of selected conditions reported by WM patients and their unaffected relatives according to family type and affection status

Characteristic	Frequency of reported condition, no. (%)										OR (95% CI)*				
	Cases only					Cases vs controls					Cases vs controls: all familial WM vs all unaffected		LRT‡		
	Multiple-case WM, n = 57†	Mixed WM/BCD, n = 46	All familial WM, n = 103	Unaffected relatives, n = 272	Multiple-case WM vs mixed WM/BCD	Nonfamilial WM vs all familial WM	Multiple-case WM families	Mixed WM/BCD families							
Medical condition															
Autoimmune disorders	9 (15.8)	17 (37.0)	26 (25.2)	26 (9.6)	0.49 (0.18-1.30)	1.54 (0.60-3.96)	1.71 (0.62-4.71)	2.94 (1.41-6.16)‡	2.27 (1.21-4.28)‡	0.4					
Organ-specific¶	5 (8.8)	12 (26.1)	17 (16.5)	12 (4.4)	0.48 (0.15-1.54)	0.87 (0.23-3.31)	1.74 (0.52-5.84)	5.42 (1.67-17.53)‡	3.07 (1.29-7.28)‡	0.2					
Systemic and/or suspected	4 (7.0)	7 (15.2)	11 (10.7)	16 (5.9)	0.44 (0.11-1.74)	1.53 (0.49-4.82)	1.91 (0.44-8.24)	2.02 (0.75-5.47)	1.86 (0.82-4.23)	1.0					
Specific infections**	19 (33.3)	18 (39.1)	37 (35.9)	59 (21.7)	0.97 (0.42-2.24)	1.00 (0.41-2.44)	2.79 (1.25-6.22)‡	1.85 (0.88-3.89)	2.13 (1.25-3.64)‡	0.5					
Chronic inflammation††	17 (29.8)	18 (39.1)	35 (34.0)	61 (22.4)	0.74 (0.31-1.77)	1.46 (0.62-3.46)	1.19 (0.76-3.61)	1.65 (0.76-3.60)	1.58 (0.90-2.80)	0.5					
Allergy	36 (65.5)	29 (67.4)	65 (67.0)	153 (56.5)	0.99 (0.38-2.60)	3.14 (0.72-13.57)	2.04 (0.84-4.92)	1.98 (0.96-4.09)	1.94 (1.09-3.46)‡	0.9					
Drug	25 (47.2)	19 (46.3)	44 (46.8)	89 (32.8)	1.25 (0.50-3.15)	1.12 (0.42-2.98)	2.49 (0.89-6.93)	1.29 (0.61-2.72)	1.75 (0.94-3.24)	0.2					
Environmental	20 (36.4)	15 (35.7)	35 (36.1)	98 (36.2)	0.96 (0.42-2.16)	1.53 (0.64-3.64)	1.30 (0.63-2.69)	1.60 (0.76-3.34)	1.36 (0.82-2.27)	0.5					
Dietary	6 (11.1)	4 (9.5)	10 (10.4)	30 (11.0)	1.22 (0.30-4.90)	2.02 (0.65-6.24)	1.11 (0.38-3.21)	0.94 (0.36-2.45)	1.02 (0.50-2.11)	0.9					
Surgical procedure	35 (61.4)	34 (73.6)	69 (67.0)	114 (41.9)	0.57 (0.23-1.39)	0.80 (0.32-2.01)	1.47 (0.65-3.29)	1.67 (0.79-3.63)	1.55 (0.88-2.73)	0.6					
Tonsillectomy/adenoidectomy	25 (43.9)	27 (58.7)	52 (50.5)	95 (34.9)	0.49 (0.21-1.14)	1.54 (0.62-3.78)	1.16 (0.55-2.43)	0.98 (0.49-1.95)	1.05 (0.62-1.76)	0.3					
Appendectomy	17 (29.8)	12 (26.1)	29 (28.2)	45 (16.5)	1.21 (0.50-2.92)	0.35 (0.12-1.03)	1.87 (0.85-4.12)	0.99 (0.45-2.17)	1.29 (0.75-2.21)	0.1					

OR indicates odds ratio; CI, confidence interval; WM, Waldenström macroglobulinemia; BCD, B-cell disorder; and LRT, likelihood ratio test.

*Accounting for familial clustering among relatives and adjusted for age, sex, and family type (in all familial WM models).

†Numbers and percentages may not sum to total because of missing data and rounding, respectively. Percentages are based on nonmissing values.

‡P parameters that differed significantly ($P < .05$) between groups. See "Results."

§Likelihood ratio test (LRT) performed for case-versus-control analyses.

¶Includes report of thyroiditis, Grave disease, hemolytic anemia, pernicious anemia, thrombocytopenic purpura, and multiple sclerosis.

||Includes report of Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, psoriasis, celiac disease, polymyalgia rheumatica, and rheumatic fever.

**Includes report of hepatitis, mononucleosis, osteomyelitis, pneumonia requiring hospitalization, pyelonephritis, and tuberculosis.

††Includes report of asthma, chronic cholecystitis, chronic hepatitis, chronic sinusitis, and chronic bronchitis.

Table 4. Distribution, ORs, and 95% CIs for selected exposures in familial WM patients and their unaffected blood relatives

Exposure	Frequency of reported exposure, no. (%)				OR (95% CI)*			LRT
	Multiple-case WM, n = 57†	Mixed WM/BCD, n = 46	All familial WM, n = 103	Unaffected relatives, n = 272	Cases vs controls: multiple-case families	Cases vs unaffected: mixed WM/BCD families	All familial WM vs all controls	
Smoking, ever	30 (53.6)	26 (57.8)	56 (55.4)	122 (45.2)	1.41 (0.68-2.91)	1.38 (0.70-2.73)	1.36 (0.83-2.20)	0.9
Alcohol, ever	46 (80.7)	38 (82.6)	84 (81.6)	206 (76.0)	2.21 (0.83-5.90)	1.30 (0.49-3.48)	1.74 (0.84-3.59)	0.9
Farming	11 (19.6)	10 (22.2)	21 (20.8)	24 (8.8)	1.52 (0.70-3.31)	5.52 (1.92-15.88)‡	2.70 (1.34-5.43)‡	0.06
Pesticides	9 (16.1)	9 (19.6)	18 (17.6)	26 (9.6)	2.22 (0.98-5.04)	3.10 (1.31-7.35)‡	2.83 (1.56-5.11)‡	0.4
Livestock	10 (17.8)	6 (13.3)	16 (15.8)	34 (12.6)	1.06 (0.44-2.55)	0.99 (0.35-2.83)	1.07 (0.55-2.10)	0.8
Organic solvents	14 (27.4)	9 (20.4)	23 (24.2)	30 (12.2)	4.21 (1.69-10.51)‡	1.14 (0.49-2.63)	—	0.05
Wood dust	11 (23.4)	7 (17.1)	18 (20.4)	28 (11.7)	2.57 (1.09-6.06)‡	3.21 (1.16-8.85)‡	2.86 (1.54-5.33)‡	0.6
Asbestos	5 (11.1)	5 (12.8)	10 (11.9)	9 (3.9)	1.97 (0.41-9.56)	4.88 (1.07-22.20)‡	2.64 (0.85-8.19)	0.5
Hair dye	10 (21.3)	8 (18.6)	18 (20.0)	38 (15.8)	2.11 (0.96-4.66)	1.16 (0.48-2.81)	1.53 (0.83-2.82)	0.5
Radiation-related occupation	2 (3.6)	4 (8.9)	6 (5.9)	18 (6.8)	0.58 (0.06-5.13)	0.86 (0.26-2.82)	0.74 (0.25-2.21)	0.8
Therapeutic radiation	2 (3.5)	2 (4.3)	4 (3.9)	21 (7.8)	0.41 (0.08-1.99)	0.16 (0.02-1.07)	0.21 (0.05-0.81)‡	0.3

OR indicates odds ratio; CI, confidence interval; WM, Waldenström macroglobulinemia; BCD, B-cell disorder; LRT, likelihood ratio test; and —, no relevant data.

*Accounting for familial clustering among relatives and adjusted for age, sex, and family type (in all familial WM models).

†Numbers and percentages may not sum to total because of missing data and rounding, respectively. Percentages are based on nonmissing values.

‡Parameters that differed significantly ($P < .05$) between groups. See "Results."

therapeutic radiation exposure, the OR was not significant when stratified by family type, and numbers were small.

Discussion

Although it is now well-established that family members of WM patients face an increased risk for developing WM and related B-cell malignancies,²⁰ the etiologic basis of enhanced susceptibility in these families remains undefined. We have conducted, to our knowledge, the first large systematic assessment of patterns of familial aggregation of WM and other BCDs to explore disease-specific characteristics of familial WM and to identify potential associations with a broad range of host and environmental factors.

Several features of WM emerged in this study in relation to disease characteristics and familial patterns of WM aggregation. First, in this study population, the nature and course of the WM disease process appeared to be similar in many respects in patients with and without a family history of WM or other BCD. We were unable to identify significant differences in features of clinical presentation, diagnosis, time to treatment, or requirement for supportive treatment between groups. Overall, WM patients were more likely to be male, which has been noted in other studies of WM specifically^{20,21} and NHL overall.²⁹⁻³¹ This association with male sex suggests that environmental and genetic factors that are shared among male relatives should be investigated in the future. Patients with WM from multiple-case families tended to be more likely than nonfamilial WM patients to be asymptomatic. Although we validated the histopathologic diagnosis of WM in most patients, this observation could be due to diagnosis earlier in the disease course because of heightened surveillance in persons with a family history of WM. Disease course in this group of patients may be better assessed by evaluating survival after onset of symptomatic disease. We do not yet have sufficient events in this cohort to determine whether there are survival differences associated with family history of WM.

Of particular interest are our findings that WM, particularly among familial WM patients, was associated with a personal history of autoimmune disease and selected infections. In contrast to an early report,¹² emerging data from several studies now

support a role for chronic immune stimulation in the etiology of WM. Analysis of immunoglobulin (Ig) gene mutations implicates antigenic drive as an important element in WM development.^{32,33} Recently, 2 large hospital record studies in US veterans have demonstrated significantly increased risk for WM after infections, including hepatitis C virus,³⁴ hepatitis B virus, human immunodeficiency virus, and rickettsiosis.³⁵ Additional studies have linked bacterial or viral infection and excess risk of other subtypes of lymphoma^{36,37} and plasma cell disorders including MGUS³⁸ and multiple myeloma.³⁹ Likewise, other conditions associated with immune deficiency and/or chronic antigenic stimulation, such as hereditary immunodeficiency syndromes⁴⁰ and autoimmune disorders,^{27,41} have been found to be associated with increased risk of NHL. Increased risk for WM specifically has been associated with both systemic and organ-specific autoimmune diseases overall and particularly with Sjögren syndrome, immune thrombocytopenic purpura, and Crohn disease.³⁵ Alternative explanations for our results include surveillance bias, which is an inherent limitation of surveys of this type. In addition, immune deficiency and disordered immune response, including autoimmune phenomena, might be a consequence of WM (ie, "reverse causation"), as has been observed for autoimmune thrombocytopenia and non-Hodgkin lymphoma.⁴² If this were the case, it might then be reasonable to expect cases to report other symptoms, especially nonspecific symptoms such as fatigue or malaise, as well. In this cohort, however, more than 40% of familial WM patients reported no symptoms before diagnosis. Koshiol et al³⁵ examined latency patterns associated with various conditions and found that increased risk of WM persisted for more than 5 years after a diagnosis of autoimmune disease, suggesting that not all autoimmune diseases can be attributed to undiagnosed WM. Nonetheless, it will be important in future studies to obtain information regarding disease chronology and to incorporate specific latency thresholds to minimize potential surveillance bias. Our results agree with prior studies and suggest that host factors relating to immune regulation and response to chronic antigenic stimulation may influence development of WM in families. Nonetheless, they need to be interpreted with caution, given the large number of exposures and analyses.

In this exploratory study, we found that familial WM patients were significantly more likely than their unaffected relatives to report a history of exposure to farming, pesticides, solvents, and

wood dust, suggesting a possible role for environmental factors in the development of familial WM. Apart from conditions related to immune response, data for other risk factors for WM are sparse. The only study addressing environmental exposures, to our knowledge, was a case-control analysis based on 65 WM cases that found no significant association between WM and specific occupational exposures or employment in particular industries or occupations.¹² That study was limited by small numbers and geographic constraints. In contrast, a wide variety of potential environmental exposures have been evaluated in relation to overall NHL risk. Although the epidemiologic data have been mixed,⁴³ some data suggest more consistent small increases in risk for farming and pesticide and herbicide exposure, but not for solvents, hair dye, and asbestos.⁴⁴ Thus, our findings are consistent with the literature for NHL overall. Again, caution is warranted, given the number of exposures evaluated. However, when we applied a formal Bonferroni correction for 103 tests, pesticide ($P < .001$) and wood dust ($P < .001$) exposure remained highly suggestive. In addition, the associations of farming and pesticide exposure with WM were not substantively changed by taking geographic location into account. An alternative explanation for our observations is the potential effect of recall bias, which is an unavoidable problem in any retrospective exposure assessment. Although WM patients were more likely to report certain exposures, this tendency was not uniform across all variables, suggesting that selective recall likely does not entirely account for our results. Future studies using precise exposure metrics are needed to confirm these findings.

Our study has several strengths, including a high level of validation of the underlying malignancy, consistent definition of WM, comprehensive demographic, medical, and exposure data, and inclusion of nonfamilial patients and unaffected family members. Limitations include relatively small numbers, which are an inevitable constraint in studies of rare diseases, and lack of systematic population-based ascertainment that may limit the generalizability of our findings. Thus, power to detect biologic differences between familial and nonfamilial WM was limited. Because the study was designed to be exploratory, we did not have in-depth data (eg, date of diagnosis or treatment) on nonmalignant

conditions of interest. As we assessed a wide range of exposures, multiple comparisons may result in chance findings. Nonetheless, this study represents the largest and best-characterized cohort of familial WM patients reported to date.

In summary, we found that features of familial and nonfamilial WM appear to be similar in most respects, regardless of family history. Our observations provide additional evidence implicating chronic immune stimulation in the development of WM. Based on our results, we hypothesize that both genetic and environmental factors may modulate susceptibility to WM and that familial WM may contain distinct subsets based on the pattern of B-cell disorders aggregating within families. These hypotheses may be tested once a gene or genes predisposing to WM is identified. Meanwhile, additional studies are needed to confirm our findings and to expand our understanding of WM.

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Authorship

Contribution: M.L.M. designed the study; T.R.G., L.G.V., and M.L.M. obtained and managed the data; R.H.R., J.K., and R.M.P. designed and conducted the statistical analyses; R.H.R., J.K., and M.L.M. analyzed the data, interpreted the results, and wrote the paper; and all authors had access to the primary data and read, provided comments, and approved the final version of the paper.

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