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Characterization of familial Waldenström's macroglobulinemia

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Background: Familial clustering of B-cell disorders among Waldenström's macroglobulinemia (WM) patients has been reported, though the frequency and any differences in disease manifestation for familial patients remain to be defined.

Patients and methods: We therefore analyzed clinicopathological data from 257 consecutive and unrelated WM patients. Forty-eight (18.7%) patients had at least one first-degree relative with either WM (*n* = 13, 5.1%), or another B-cell disorder including non-Hodgkin's lymphoma (*n* = 9, 3.5%), myeloma (*n* = 8, 3.1%), chronic lymphocytic leukemia (*n* = 7, 2.7%), monoclonal gammopathy of unknown significance (*n* = 5, 1.9%), acute lymphocytic leukemia (*n* = 3, 1.2%) and Hodgkin's disease (*n* = 3, 1.2%). Patients with a familial history of WM or a plasma cell disorder (PCD) were diagnosed at a younger age and with greater bone marrow involvement.

Results: Deletions in 6q represented the only recurrent structural chromosomal abnormality and were found in 13% of patients, all non-familial cases. Interphase FISH analysis demonstrated deletions in 6q21-22.1 in nearly half of patients, irrespective of familial background.

Conclusions: The above results suggest a high degree of clustering for B-cell disorders among first-degree relatives of patients with WM, along with distinct clinical features at presentation based on familial disease cluster patterns. Genomic studies to delineate genetic predisposition to WM are underway.

Key words: Waldenström's macroglobulinemia, B-cell, familial clustering

introduction

Waldenström's macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy [1]. This condition is considered to be lymphoplasmacytic lymphoma as defined by the REAL and WHO classification systems [2, 3]. Since the report by Massari et al. in 1962 of two brothers with WM and their mother with asymptomatic IgM monoclonal gammopathy, numerous familial cases of WM have been reported, including involvement among siblings (up to four siblings), and offspring over several generations who demonstrated WM or manifested another B-cell disorder [4–17]. Hypergammaglobulinemia involving IgM, IgG, and IgA but without a monoclonal component has also been observed in relatives of patients with WM and may reflect hyper-attenuated antigen signaling [7, 8, 10, 12, 14–16, 18].

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The occurrence of various B-cell disorders, as well as the finding of different light chain pairings and idiotypic determinants for the IgM monoclonal protein among related patients with WM has suggested that for some patients a generalized predisposition for a B-cell disorder may exist, whereas for others inheritance of a specific genetic defect may predispose to WM, but occur though a different pathway of clonal evolution [13]. While the genetic basis for familial predisposition to WM remains to be clarified, impaired differentiation of peripheral blood (PB) B-cells following mitogenic stimulation has been observed among relatives of WM patients with IgM hypergammaglobulinemia suggesting that in some familial clusters predisposition to WM may involve a defect in the ability of B-cells to differentiate into plasma cells [7]. Moreover, enhanced *ex vivo* survival of PB B-cells along with overexpression of the anti-apoptotic Bcl-2 protein has also been demonstrated among kindred of WM patients [19].

While the existence of familial WM has been known for the past 40 years, the incidence as well its presenting features in comparison to non-familial WM is not known. Moreover, cytogenetic studies in patients with familial WM are very limited and may hold important clues to the pathogenesis of WM. As

such, we investigated the incidence, presenting features and cytogenetics of familial WM among 257 patients with the consensus panel definition of WM who were evaluated in the WM clinic at our Institution over a 5-year period (1999–2004). The findings of this study are presented in this report.

patients and methods

Patients with the consensus panel definition for WM and who presented to the WM clinic at the Dana Farber Cancer Institute over a 5-year period (1999–2004) were evaluated in these studies. A standardized family history intake was used in all patient interviews to identify diagnoses of B-lymphoid disorders amongst first-degree relatives (defined as a biological parent, sibling or offspring) of patients. Confirmation of the diagnosis for the first degree was available in most cases. Clinical and laboratory features at diagnosis including age, gender, presenting complaint, bone marrow involvement, presence of adenopathy or splenomegaly were stratified based on the presence or absence of any B-cell disorder, plasma cell disorder (monoclonal gammopathy of unknown significance, Waldenström's macroglobulinemia or multiple myeloma), or WM among at least one first degree relative. All bone marrow biopsies were reviewed by hematopathologists at the Brigham and Women's Hospital, Boston, MA, and bone marrow involvement was enumerated by estimating intertrabecular space involvement with lymphoplasmacytic cells. Serum immunoglobulin (IgM, IgA, IgG), hematocrit and platelet counts, and β-2-microglobulin (β_2M) levels at time of initial presentation to the WM clinic were obtained and stratified based on prior treatment status and whether or not a familial history of a B-cell disorder, plasma cell disorder (PCD) or WM in a first degree relative was present.

cytogenetic analysis

Cytogenetic studies of bone marrow specimens including conventional GTG and both metaphase and interphase fluorescence *in situ* hybridization (FISH) were performed for patients with and without a familial history of a B-cell malignancy. For conventional GTG karyotypes, unselected bone marrow cells were placed in 10% Chang Medium BMC (Irvine Scientific). The culture was incubated for 24 h and 72 h without and with pokeweed respectively. Standard harvesting procedures were used. FISH analyses were performed on cultured unsorted bone marrow specimens using bacterial artificial chromosome (BAC) probes for chromosome 6q including RP11-79L7, RP11-91C23, RP11-171J20 which hybridize to 6q21, 6q21–22, and 6q22.1 respectively and the CEP6 which hybridizes to the centromere of chromosome 6 (Children's Hospital Oakland Research Institute). Cutoffs for detection of 6q21–22 deletions using these probes were established by use of discarded pellets from bone marrow specimens submitted for analysis that were determined to be karyotypically and histopathologically normal. One hundred cells were counted, and detection of the 6q21–22 deletion was deemed to be positive when ≥5%, and ≥6% of the cells showed loss of hybridization to RP11-91C23 and RP11-71J20, and RP11-79L7, respectively. All patients provided written consent for these studies, which were approved by the Institutional Review Board of the Dana Farber Cancer Institute. Eighty-six patients with WM were enrolled in this study, 22 of whom had a family history of a related B-cell disorder in a first degree relative (9 WM, 5 Multiple Myeloma, 5 Non-Hodgkin's Lymphoma, 1 Hodgkin's disease, 1 Chronic lymphocytic leukemia, 1 Bence Jones monoclonal gammopathy). Fifteen of 22 (68%) and 18 of 54 (33%) patients with and without a familial background, respectively, had no prior therapy ($P = 0.01$ by Fisher's exact probability test).

statistical analysis

Comparison of clinical and laboratory features between familial and non-familial patients was performed using a two-tailed students t-test on Microsoft Excel™ software. A two-tailed Fisher's exact probability test (VassarStats) was used to evaluate frequency of 6q21–22 deletions and familial involvement of patients. The chi square test (Vassar Stats) was used to analyze presenting complaints among patients with and without a family history and for presence of adenopathy or splenomegaly. A P-value ≤0.05 was deemed to be significant in all analyses.

results

incidence of familial B-cell disorders among WM patients

To exclude the possibility that patient referral of a familial member with WM would skew incidence and presentation data, we excluded five patients who were referred by a family member. The remaining patients therefore represented unique family encounters. Consequently, 257 WM patients were available for this analysis of whom 48 (18.7%) had at least one first degree relative with either WM ($n = 13$; 5.1%), or a related B-cell disorder such as non-Hodgkin's lymphoma ($n = 9$; 3.5%), multiple myeloma ($n = 8$; 3.1%), chronic lymphocytic leukemia ($n = 7$; 2.7%), monoclonal gammopathy of unknown significance ($n = 5$; 1.9%) which included IgM ($n = 2$), light chain ($n = 2$) and IgG ($n = 1$) cases; acute lymphocytic leukemia ($n = 3$; 1.2%) and Hodgkin's disease ($n = 3$; 1.2%) (Figure 1).

presentation of familial and non-familial WM patients

We next sought to determine if there were any distinguishing clinical and laboratory features between patients with and without a familial history of a B-cell disorder. We further stratified those patients who had a first-degree relative with any plasma cell disorder (PCD): monoclonal gammopathy of unknown significance (MGUS), multiple myeloma (MM), and Waldenström's macroglobulinemia (WM), as well as WM alone. The median time from diagnosis to data analysis was 1492 days for patients without a familial background, and 1243, 1428, and 1188 days for patients with a familial history of any B-cell disorder, any PCD, or WM, respectively (P = NS). One hundred and thirty-six of the 209 (65.1%) patients without a family history, 26 of the 48 (54.2%), 15 of 26 (57.7%), and six of 13 (46.1%) of patients with a family history of any B-cell disorder, any PCD, and WM, respectively were untreated at time of presentation to the WM clinic (P = NS).

The median age at diagnosis for patients without any familial history of WM was 59 (range 34–84) years versus 58 (range 34–79) years for those patients who had a family history of any B-cell malignancy ($P = 0.18$). Among patients with a family history for any PCD or for WM alone the median age of diagnosis was 57 (34–73) and 53 (34–64), respectively ($P = 0.05$, and $P = 0.04$, respectively versus median age at diagnosis for patients without a family history). Females constituted 42.1% of the patients who had no family history of a B-cell disorder, while 35.4%, 30.8%, and 38.5% of patients were females among patients who had a family history of any B-cell disorder, any PCD, or WM, respectively (P = NS in

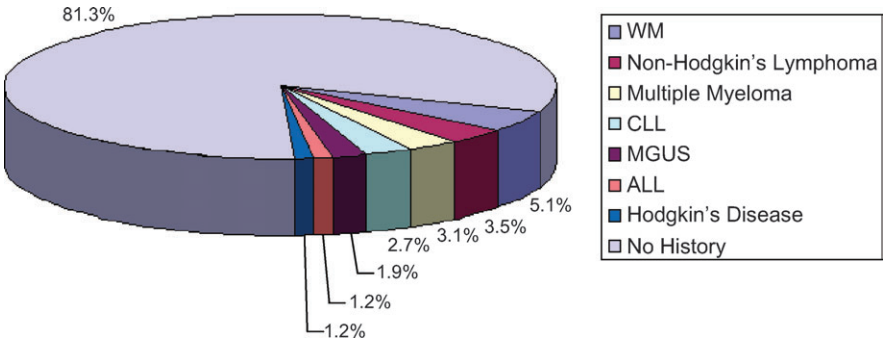

Figure 1. Reported history of B-cell disorders among first degree relatives of 257 patients with the consensus panel diagnosis of WM.

comparison to percent of females among patients without a family history).

Presenting complaints at time of diagnosis for patients with and without a family history of a B-cell disorder are presented in Table 1. By chi square testing, no significant differences were found in presenting complaints and findings leading to the diagnosis of WM between patients with and without a family history of any B-cell disorder, any PCD or WM.

We next analyzed differences in disease burden at time of diagnosis among patients with and without a family history of a B-cell disorder, PCD, and WM. As shown in Table 2, the median bone marrow involvement at time of diagnosis was 30% (range 5–95%) for patients without any familial history. Similarly, for patients with a family history of any B-cell disorder, the median bone marrow involvement was also 30% (range 5–80%); $P = 0.65$ versus patients without any familial history of a B-cell disorder. However, a higher median bone marrow involvement was observed at time of diagnosis among patients who had a family history of any PCD or WM. The median bone marrow involvement was 50% (range 5–80%) and 60% (range 10–80%), respectively for patients with a familial history of any PCD or WM ($P = 0.25$ and $P = 0.12$, respectively versus patients without any familial history).

The presence of adenopathy and splenomegaly at time of diagnosis for patients with and without a familial history of any B-cell disorder, any PCD, or WM was also evaluated (Table 2). Among all 257 patients, adenopathy and splenomegaly were present in 38 (14.7%) and 23 (8.9%) patients at time of diagnosis. When stratified for familial history, no significant differences were identified between patients with or without a familial history of any B-cell disorder, any PCD or WM for presence of adenopathy or splenomegaly at time of diagnosis using chi square analysis.

In view of inter-laboratory differences and incomplete data sets for many referred patients, we examined serum immunoglobulin (IgM, IgA, and IgG) levels, hematocrit and platelet counts, and the prognostic factor β_2-microglobulin (β_2M) obtained at initial presentation to the WM clinic, and stratified these values based on prior treatment status and whether or not a familial history of a B-cell disorder, PCD or WM in a first degree relative was present (Table 3). As noted above, no significant differences were observed in days to analysis and prior treatment status among patients with or without any relevant family history. The median number of prior therapies for all previously treated patients was 1, and was the same for all patient subsets stratified on the basis of a family history of any B-cell disorder, PCD, or WM.

Analysis of untreated patients presenting with high serum IgM levels, i.e. above 3,000 mg/dl, revealed that a significantly higher number of patients with a family history of WM (5/6; 83.3%) had such findings when compared to patients without a family history (52/136; 38.2%) using chi square analysis ($P = 0.03$). Similar trends were also observed among untreated patients with a family history of any B-cell disorder (15/26; 57.7%) or PCD (9/15; 60.0%); $P = 0.06$, and $P = 0.11$, when compared to untreated patients without any positive family history. No differences among untreated patients were observed using χ^2 analyses for presence of IgA and IgG hypogammaglobulinemia, anemia (Hct ≤30%), thrombocytopenia (Plt <100 000/ul), and for elevation in the serum prognostic factor β_2M (≥3 mg/dl) when patients were stratified for family history status. We observed no differences among all analyzed parameters among previously treated patients when stratified for family history.

cytogenetic analysis

Conventional GTG karyotyping and FISH studies were performed for 77 of the 257 patients, and included 22 patients with a family history of B-cell disorders (9 WM; 5 MM; 1 Bence-Jones proteinuria; 1 CLL; 1HD; 5 NHL). Deletions in the long arm of chromosome 6 in the region q21–q22 were observed by G-bands and constituted the only recurring structural abnormality detected (data not shown). 6q deletions were found in four of 30 (13.3%) patients without a family history, and none of the 12 patients with a family history of a B-cell disorder ($P = 0.31$). To further clarify potential differences in 6q deletions between patients, we next performed FISH analyses on bone marrow specimens using probes to 6q: RP11-91C23 and RP11-171J20 (Children 's Hospital Oakland Research Institute), which hybridize to 6q21–22.1 and 6q22.1, respectively (Figure 2A). Seventy-seven WM patients were evaluated for the loss of RP11-171J20 and RP11-91C23 probes, which included 22 patients with a family history of a B-cell disorder (9 WM, 5 MM, 5 NHL, 1 CLL, 1 Bence-Jones proteinuria, and 1 Hodgkin's disease). We observed loss of hybridization for RP11-91C23 and RP11-171J20 in 37/77 (48%) and 31/77 (40%) of all WM patients, respectively with a total of 53/77 (69%) showing loss of at least one of the probes (Figure 2; Table 4). When patients were

Table 1. Symptoms or findings leading to diagnosis of WM in 257 patients stratified for familial history of B-cell disorders

	All patients	(−) Family history for any B-cell disorder	(+) Family history for any B-cell disorder	(+) Family history for any PCD	(+) Family history for WM
Number of patients	257	209	48	26	13
Adenopathy/splenomegaly	12 (4.7%)	9 (4.3%)	3 (6.3%)	2 (7.7%)	1 (7.7%)
Anemia	71 (27.6%)	58 (27.8%)	13 (27.1%)	9 (34.6%)	2 (15.4%)
Arthropathy/bone pain	11 (4.3%)	8 (3.8%)	3 (6.3%)	3 (11.5%)	2 (15.4%)
Bleeding	14 (5.5%)	9 (4.3%)	5 (10.4%)	3 (11.5%)	2 (15.4%)
Elevated total protein	32 (12.5%)	25 (12.0%)	7 (25.0%)	3 (11.5%)	3 (23.1%)
Fatigue	44 (17.1%)	37 (17.7%)	7 (25.0%)	2 (7.7%)	1 (7.7%)
Herpes zoster	4 (1.6%)	3 (1.4%)	1 (2.1%)	1 (3.8%)	0 (0.0%)
Leg cramps	2 (0.8%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neuropathy	27 (10.5%)	24 (11.5%)	3 (6.3%)	0 (0.0%)	0 (0.0%)
Raynaud symptoms	2 (0.8%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recurrent infection	16 (6.2%)	12 (5.7%)	4 (14.3%)	2 (7.7%)	1 (7.7%)
Renal failure	3 (1.2%)	2 (1.0%)	1 (2.1%)	1 (3.8%)	1 (7.7%)
Skin manifestations	4 (1.6%)	4 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Weight loss (unexplained)	4 (1.6%)	4 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	8 (3.1%)	7 (3.4%)	1 (2.1%)	0 (0.0%)	0 (0.0%)

Table 2. Bone marrow involvement and presence of adenopathy and splenomegaly at time of diagnosis for 257 WM patients stratified for familial history of B-cell disorders

	n =	Bone marrow (%)	(+) Adenopathy	(+) Splenomegaly
All patients	257	30 (range 5–95)	38 (14.7%)	23 (8.9%)
No family history	209	30 (range 5–95)	28 (13.4%)	20 (9.6%)
Family history of any B-cell disorder	48	30 (range 5–80)	10 (20.4%)	3 (6.3%)
Family history of any PCD	26	50 (range 5–80)	7 (26.9%)	1 (3.8%)
Family history of WM	13	60 (range 10–80)	2 (15.4%)	0 (0.0%)

Table 3. Blood laboratory values at time of initial clinic presentation for 257 WM patients stratified on the basis of previous treatment status and familial history of B-cell disorders

	IgM ≥3000 mg/dl	IgA ≤70 mg/dl	IgG ≤700 mg/dl	Hct ≤30%	Plt ≤100 000/ul	β_2M ≥3.0 mg/dl
Untreated patients (*n* = 162)						
No family history (*n* = 136)	52 (38.2%)	89 (65.4%)	86 (63.2%)	22 (16.2%)	8 (5.1%)	49 (36.0%)
Family history of any B-cell disorder (*n* = 26)	15 (57.7%)	16 (61.5%)	15 (57.7%)	4 (15.4%)	0 (0.0%)	6 (23.1%)
Family history of any PCD (*n* = 15)	9 (60.0%)	8 (53.3%)	9 (60.0%)	3 (20.0%)	0 (0.0%)	4 (26.6%)
Family history of WM (*n* = 6)	5 (83.3%)	3 (50.0%)	4 (66.6%)	2 (33.3%)	0 (0.0%)	3 (50.0%)
Previously treated patients (*n* = 95)						
No family history (*n* = 73)	26 (35.6%)	47 (64.4%)	56 (76.7%)	16 (21.9%)	10 (13.7%)	2 (27.4%)
Family history of any B-cell disorder (*n* = 22)	11 (50.0%)	21 (95.5%)	17 (77.3%)	4 (18.2%)	3 (13.6%)	6 (27.2%)
Family history of any PCD (*n* = 11)	6 (54.5%)	10 (90.9%)	8 (72.7%)	1 (18.2%)	2 (18.1%)	2 (18.1%)
Family history of WM (*n* = 7)	2 (28.6%)	6 (85.7%)	5 (71.4%)	1 (14.3%)	2 (28.6%)	1 (14.3%)

stratified for presence or absence of a family history for any B-cell disorder, any PCD or WM, no significant differences in loss of hybridization to RP11-91C23 and RP11-171J20 were observed (Table 4). To further define the centromeric border for the 6q deletions, we next performed FISH analysis for 20 additional WM patients using the RP11-79L7 and CEP6 which hybridizes to 6q21 and to the centromere of chromosome 6, respectively (Figure 2). Six (30%) of these patients reported a familial history of B-cell disorders (2 WM, 1, MM, 1 MGUS, Hodgkin's disease, and one Bence-Jones). Of these 20 patients, 9 (45%) showed loss of hybridization (Figure 2; Table 4). Loss in hybridization to the chromosome 6 centromeric probe (CEP6) was observed in only one patient (data not shown), and no significant differences in loss of hybridization for either RP11-79L7 or CEP6 (Table 4) was observed when patients were stratified based on presence and type of family history.

discussion

Previous reports as well as our own clinical experience prompted us to examine familial predisposition in WM, and to examine as part of these efforts the incidence of familial disease, along with differences in disease presentation amongst patients with or without a family history for B-cell disorders. The central finding in this study was a high incidence of B-cell disorders among first degree relatives of patients with WM. Nearly one in five patients with WM had a first degree relative with a B-cell disorder which included in rank order of incidence: WM (5.1%), NHL (3.5%), MM (3.1%), CLL (2.7%), MGUS (1.9%), ALL (1.2%) and HD (1.2%). It remains possible, as we have observed in our own clinical practice, that the family members of the WM patients in this study may have been inadvertently classified with another B-cell abnormality versus WM due to ambivalent diagnostic criteria that existed prior to the consensus panel efforts of the Second International Workshop on WM. As such, the associated familial incidence of WM among first-degree relatives may in fact be proportionately higher. Due to the late onset in age for diagnosis and the indolent nature of WM for many patients, it remains possible that undiagnosed cases of WM may have existed among first-degree relatives, particularly among parents of patients who lived in the era before WM was recognized and life spans were considerably shorter. As such, we speculate that the true familial predisposition for WM may in fact be higher than that which we have observed in this study.

While there is an argument to be made that some of the diagnostic ambivalences of the past may have led to misclassifications of the WM diagnosis among first-degree relatives of patients, nonetheless in most of these patients (usually siblings and children) we were able to confirm the diagnosis of non-WM B-cell disorders. Such clustering of non-WM B-cell disorders among relatives of WM patients has been reported as well by other investigators [7, 8, 10, 11, 19]. As others have also remarked, we also observed various types of monoclonal gammopathies among first degree relatives of WM patients which consisted of IgM, IgG, and light chain gammopathies [8, 10, 16, 17].

As part of these efforts, we also sought to delineate whether differences in disease presentation existed amongst patients with or without a familial predisposition. An important finding in this study was that patients who had a familial history of WM, and to a lesser extent any PCD, were diagnosed at a younger age with higher levels of bone marrow involvement, and among untreated patients were more likely to have higher IgM levels upon their initial clinical evaluation. In contrast, when patients with a familial history of non-PCD or non-WM B-cell disorders (i.e., those with ALL, CLL, NHL, or HD) were compared to patients without a family history, no significant differences in age and bone marrow involvement at diagnosis, and IgM levels at initial clinic presentation were observed (data not shown). Taken together, the above observations suggest differences in predisposition to familial WM may exist and that in certain family clusters there may be a generalized predisposition for a B-cell or plasma cell disorder, while for others a specific predilection for WM per se, may exist.

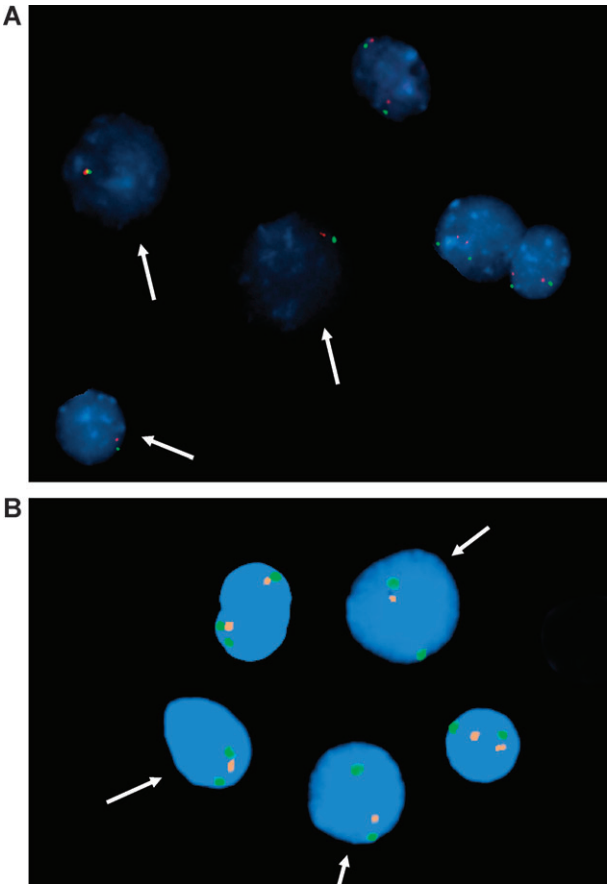

Figure 2. Interphase FISH analysis of bone marrow cells of WM patients using fluorescent probes to (**A**) RP11-91C23 (6q21-q22.1; red) and RP11-171J20 (6q22.1; green), and (**B**) RP11-79L7 (6q21; orange) and CEP6 (chromosome 6 centromere; green). Arrows depict cells showing loss of probe hybridization.

In an effort to delineate cytogenetic abnormalities that might distinguish patients with a familial versus non-familial predisposition to WM we performed extensive cytogenetic studies. To our knowledge these studies represent the largest series of patients with WM, and the only series since the consensus panel diagnosis for WM was adopted, in whom G-banding and FISH studies have been performed.

Deletions in 6q21–22.1 were confirmed by two distinct, non-overlapping probes and were present in most WM patients regardless of family history for any B-cell disorder, any PCD, or WM. Interstitial deletions of the long arm of chromosome 6 encompassing q13 to q22 have also been reported by other investigators in smaller series of WM patients, though these studies did not take into account familial predisposition to WM [22–26]. Deletions spanning 6q16–q27 are commonly present in various B-cell malignancies, and differences in the regions of minimal deletion have been reported, i.e., 6q21–q23 for ALL and 6q25–q27 for NHL [27–33]. Efforts to delineate the regions of minimal deletion, as well as the centromeric and telomeric borders for patients with or without a familial predilection for WM by use of interphase FISH are currently underway at our Institution. These studies may help shed further clues to the predilection for WM by identifying possible tumor suppressor

Table 4. Detection of 6q21–q22 deletions in bone marrow specimens of WM patients stratified on the presence or absence of a family history for any B-cell disorder

	All patients	No family history	Family history for any B-cell disorder	Family history for any PCD	Family history for WM
n =	66	48	18	13	7
% of patients with loss of RP11-91C23 (6q21–q22.1) hybridization	52 (78.8%)	37 (71.7%)	15 (83.3%)	11 (84.6%)	7 (100.0%)
% of patients with loss of RP11-171J20 (6q22.1) hybridization	44 (66.6%)	35 (72.9%)	9 (50.0%)	7 (53.8%)	3 (42.8%)
n =	20	14	6	5	2
% of patients with loss of RP11-79L7 (6q21) hybridization	9 (45%)	7 (50%)	2 (33.3%)	2 (40%)	1 (50%)
% of patients with loss of CEP6 (centromere 6) hybridization	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)

genes. Several candidate genes of interest have been localized to 6q21 including *BLIMP1*, *FOXO2*, *CD24*, cyclin C gene, and the AF6q21 gene [34–37]. BLIMP1, in particular, is an attractive tumor suppressor candidate gene for WM owing to its well established role as a master gene regulator for B-lymphocytic cell proliferation and differentiation [38–40]. *BLIMP1* facilitates transition from the mature B-cell to the plasma cell stage by inhibiting *C-MYC* and regulating directly and indirectly genes involved in plasma cell differentiation, including *PAX5*. Partial or whole losses in this master regulatory gene may in turn result in different functional capabilities for *BLIMP1*, and as such may differentially influence both the predilection for B-cell malignancies, and the propensity for WM itself. Genomic studies to further clarify a role for *BLIMP1*, as well as to identify other genomic differences between patients with and without a genetic predisposition to WM are underway.

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