

# Familial Waldenstrom's Macroglobulinemia

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The etiology of Waldenstrom's macroglobulinemia (WM) is unknown. A possible role for genetic factors has been suggested by reports of familial clustering of WM. However, it is not yet possible to define the proportion of all WM that occurs in the familial setting. Review of the data on the 12 families published since 1962 suggests that familial WM may differ from sporadic disease in certain respects. Among these families, there is a pronounced occurrence of a variety of immunologic abnormalities in the relatives of WM cases. Notably, the prevalence of IgM monoclonal gammopathy (IgM MG) in first-degree relatives of WM cases was reported to be as high as 6.3%, representing a 10-fold increase relative to general population estimates. IgM MG has been shown to progress to WM at a rate of approximately 1.5% per year in a large case series; whether this rate of progression is altered in familial WM is unknown. Although limited by small numbers and a lack of systematic ascertainment and evaluation, these data are intriguing and provide a compelling basis for further study and systematic investigation of WM in families.

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**T**HE ETIOLOGY OF Waldenstrom's macroglobulinemia (WM) is unknown. A possible role for genetic factors has been suggested by reports of familial clustering of WM. However, the spectrum of familial WM remains undefined and may include not only families with multiple cases of WM, but also families with a single case of WM accompanied by relatives with IgM monoclonal gammopathy (IgM MG)<sup>1</sup> or related lymphoproliferative disorders (LPD). Because family studies can provide important tools for understanding both genetic and environmental determinants of neoplastic disease, systematic evaluation of WM families would be a useful adjunct to other investigations of WM etiology. Since the definitive

spectrum of familial WM has yet to be established, this review will adhere to conservative criteria, considering only families with multiple cases of WM.

## EPIDEMIOLOGY OF WM

Epidemiologic data for WM, particularly pertaining to potential risk factors, are sparse. In the United States, population-based studies have confirmed the rarity of WM.<sup>2,3</sup> Incidence rates are 3.4 per million in males and 1.7 per million in females and increase geometrically with advancing age. Median age at diagnosis is 72 years. WM is substantially more common in white males than in other race/gender groups and is nearly twice as common in whites as in blacks, in contradistinction to multiple myeloma, for which the rate ratio is reversed. Suggestions of a possible occupational or environmental association have been based on a handful of case reports,<sup>4-6</sup> but these have not been corroborated. The sole published case-control study<sup>7</sup> found cases to be better educated, but otherwise found no significant differences in other sociodemographic indicators, specific occupational exposures or employment, tobacco or alcohol use, medication use, or history of prior medical conditions.

## CHARACTERISTICS OF FAMILIAL WM

To date, 12 families containing 31 cases of WM have been reported<sup>1,8-17</sup> (Table 1); these have been characterized with variable detail, making systematic analysis difficult. Numbers are small, but the familial cases differ markedly from sporadic WM in age and gender distribution, being diagnosed at least a decade earlier and much more likely to be male than sporadic cases. The earlier age at diagnosis is unlikely to be explained by ascertainment bias, since it is unchanged when probands are excluded, but numbers are small. Younger age at diagnosis has been recognized as a marker of genetic propensity in other familial cancer syndromes (eg, breast,<sup>18</sup> prostate,<sup>19</sup> colon<sup>20</sup>), although the age disparity is sometimes greater. The gender difference is not readily explained and may reflect small sample size or as yet unrecognized endocrine or genetic factors. The typical reported WM family has only two cases, although up to four

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cases have been identified in selected families. The most commonly reported pedigree configuration is two affected siblings (including one set of monozygotic twins); only three families published exhibit parent to offspring transmission. Whether this represents the true pedigree distribution or a problem of ascertainment is unclear, given the late age of disease onset in combination with the fact that WM was first described in 1944<sup>21</sup> and not universally regarded as a malignancy until 1988.<sup>22</sup>

Bone marrow confirmation was reported in 21 patients; the histological pattern was reportedly discordant (diffuse v nodular) in half the families for whom the information was available. Presenting symptoms and signs were reported in about half the families and were generally similar to those found in sporadic WM.<sup>23</sup> A bleeding diathesis (33.3%) or malaise and/or weakness (33.3%) were the most common symptoms, followed by weight loss (22.2%). Anemia (72.2%) was common, and examination revealed hepatosplenomegaly (33.3%), lymphadenopathy (27.8%), retinal dysproteinemic findings (22.2%), and/or peripheral lymphocytosis (16.7%). Nearly all patients (94.4%) had an elevated erythrocyte sedimentation rate (ESR), and Bence-Jones proteinuria was reported in half. When other immunoglobulins were evaluated, most patients (84.2%) had some abnormality (Table 1), usually deficiencies of IgG alone (31.2%) or in combination with IgA (50.0%). There was wide variation in spectrum of autoantibodies examined among the various kindreds. When sought, 41.2% had evidence of autoantibodies, but definite clinical autoimmune disease was rare. Thirteen cases had a pre-existing IgM MG. Most of these were diagnosed with WM within 2 years. However, four patients had a prolonged history of gammopathy documented 3,<sup>14</sup> 7,<sup>15</sup> 10,<sup>16</sup> and 15<sup>15</sup> years prior to diagnosis of WM.

Several studies examined characteristics of the IgM molecule itself. Cases studied in two families shared a human constant region gene allele, *inv3*. Sixteen cases (69.6%) had kappa light chains, seven (30.4%) had lambda, and light chain typing was discordant in five of eight families. Furthermore, idiotypic determinants were found to be discordant among cases in all five of the families in which this was examined.

As has been historically true for sporadic WM, conventional cytogenetic studies in familial WM have been inconsistent. Cytogenetics were re-

ported specifically in a minority of families, and only one case was found to have a clonal abnormality. Unfortunately, no reported families have yet had cytogenetic analysis using more sensitive molecular techniques. Human leukocyte antigen (HLA) typing was performed in four families and was similarly inconsistent. Several cases were noted to have either A9, B7, or B15 antigens, all of which have been reported to be associated with monoclonal components in some studies<sup>24-26</sup> but not in others.<sup>27,28</sup> Only one family shared a haplotype<sup>14</sup> that cosegregated with B-cell immune response alloantigens Ia 172 and 350, which have been linked to certain autoimmune syndromes,<sup>29</sup> including Hashimoto's thyroiditis.<sup>30</sup> However, in this family, which included individuals with either WM, autoimmune thyroiditis, or serologic autoantibodies, analysis strongly favored linkage to these antigens.

#### IMMUNOLOGIC CHARACTERIZATION OF RELATIVES OF FAMILIAL WM PATIENTS

Family studies of WM are replete with evidence of a plethora of immunologic abnormalities in the relatives of WM cases. In 10 of the families, 121 relatives were studied (Table 2). Because of the late age of WM diagnosis, parents were available for study in only two families, including a parent (family no. 7) diagnosed with WM during study evaluation. Moreover, in these 10 families a notable number of cases ( $n = 8$ , 29.6%) had no offspring. Family members were evaluated for the presence of immunoglobulin abnormalities in all nine families and for various autoantibodies in six. A conservative estimate of the frequency of IgM MG (range, 3.2% to 6.3%) in first-degree relatives at initial evaluation remains much higher than expected from population estimates. Despite significant geographic variation, the highest population prevalence rates of IgM MG reported to date range from 0.25% (Western France<sup>31</sup>) to 0.64% (Southeast United States<sup>32</sup>). In contrast, no cases of IgG or IgA MG were identified in this series, although it has been reported rarely in relatives of sporadic cases of WM.<sup>33</sup> IgM MG progresses to WM at a rate of 1.5% per year.<sup>34</sup> Whether this risk of progression is altered in WM families is unknown, but it may be substantial, as evidenced by family no. 8, in which two of the three WM cases had originally been diagnosed with IgM MG and progressed over 7 and 15 years of observation.<sup>15</sup> In

Family No.	Reference	Case No.	Family Relation	Age (yr)	Clinical Findings				IgM Characteristics					
					Symptoms	Signs	ESR	BJP	Light Chain	Isootypes	AutoAbs (type)*	Other Igs	Cyrot	HLA Typing
1	Massari <sup>11</sup>	1 (P)	Brother	61	Epistaxis, hematomas, melena	Anemia, LN, splenomegaly, retinal	140	Yes	κ	Different	No	↑ G ↓ A	NR <sup>‡</sup>	NR
		2	Brother	61	Epistaxis, hematomas	Anemia, lymphocytosis, retinal	140	Yes	κ	Different	+ (AγG)	↓ G ↓ A	NR <sup>‡</sup>	NR
2	Costa <sup>9</sup> in Seligmann <sup>11</sup>	1 (P)	Brother	61	Gingival bleeding, epistaxis	Anemia, retinal	138	Yes	κ	Different	No	NG NA	NR <sup>‡</sup>	NR
		2	Sister	54	NR	NR	NR	NR	κ		+ (AγG)	↓ G ↓ A	NR <sup>‡</sup>	NR
3	Jacquot <sup>10</sup> in Seligmann <sup>11</sup>	1	Father	74	Anorexia, malaise	Anemia, ↓ Ptc LN	124	No	IgM	NR	NR	NR	NR	NR
		2	Son	49	Chest pain	Neuropathy, urticaria, leukocytosis	75	NR	IgM	—	NR	NR	NR	NR
4	Drivsholm, in Seligmann <sup>11</sup>	1 (P)	Brother	NR	NR	NR			IgM	NR	NR	NR	NR	NR
		2	Brother	NR	NR	NR			IgM	NR	NR	NR	NR	NR
5	Youinou <sup>1,2,5</sup>	1 (P)	Brother	61	NR	NR	NR	NR	κ	Different	No (RF)	↓ G/A	+	ND
		2	Brother	68	NR	NR	NR	NR	κ		No (RF)	↓ G/A	+	A9, B7
		3	Brother	64	NR	NR	NR	NR	κ		No (RF)	↓ G NA	+	A9, B7
		4	Brother	62	NR	NR	NR	NR	κ		No (RF)	↓ G ↑ A	ND	A9, B7
6	Géaz <sup>3</sup>	1	Father	70	Malaise, irritability, anorexia, weight loss	Anemia, HSM	130	No	IgM	NR	NR	NR	NR	NR
		2	Son	47	Myalgia, malaise	None	40	NR	IgM	NR	NR	NG NA	NR	NR

7	Blattner <sup>14</sup>	1	Father	84	NR	NR	NR	NR	κ	NR	NR	NR	NR	A9 B8 DRw3
		2 (P)	Son	53	NR	NR	NR	NR	λ	NR	NR	NR	NR	A9 B8 DRw3
		3	Son	43	NR	NR	NR	NR	λ	NR	NR	NR	NR	A9 B8 DRw3
		4	Daughter	57	NR	NR	NR	NR	κ	NR	NR	NR	NR	A9 B8 DRw3
8	Fine <sup>15,16</sup>	1 (P)	Brother	61	Epistaxis	Anemia, LN, HSM, lymphocytosis, retinal	105	NR	κ	NR	NR	NR	NR	NR
		2	Brother	65	Weakness	Anemia	120	NR	λ	NR	↓G	NR	NR	NR
		3	Sister	61	Weakness, weight loss, abdominal pain, dyspnea	Anemia, HSM	135	NR	κ,κ	NR	↓G	NR	NR	NR
9	Fine <sup>15</sup>	1 (P)	MZ brother	75	None	Anemia	100	NR	κ	Different	NR	↓G	↓A	NR
		2	MZ brother	75	None	Anemia	82	NR	λ	NR	NR	NG	NA	NR
		1 (P)	Brother	74	Epistaxis	Anemia	NR	NR	κ	Different	NR	↓G	↓A	NR
		2	Brother	75	None	None	NR	NR	κ	Yes	No	↓G	NA	NR
		3	Brother	68	Epistaxis	Pancytopenia	NR	NR	λ	Yes	No	↓G	↓A	NR
		4	Brother	68	None	LN	NR	NR	λ	Yes	NR	NG	↓A	NR
		1	Mother	74	NR	NR	NR	NR	κ	NR	NR	Normal	NR	NR
		2	Daughter	52	NR	NR	NR	NR	λ	NR	No	Normal	NR	NR
		1 (P)	Sister	64	Weight loss, diarrhea	Anemia, splenomegaly, LN	140	NR	κ	NR	NR	↓G	NA	NR
		2	Sister	43	Asthenia, weight loss, fever	Anemia, lymphocytosis, HSM	60	NR	λ	NR	NR	↓G	↓A	NR

\*Various autoantibodies were sought in different studies, including ANA, AmdA, ASM, AGA, ARA, and AMA.

†Cytogenetic studies: +, indicates procedure performed and results reported.

‡Seigmann et al<sup>11</sup> reported that "most" of the individuals in their series had cytogenetic studies that were normal; however, specific results were not reported for these individuals.

Abbreviations: ESR, erythrocyte sedimentation rate; BJP, Bence-Jones proteinuria; AutoAbs, autoantibodies; Igs, immunoglobulins; Cyto, cytogenetics; P, proband; LN, lymphadenopathy; Retinal, retinal dysproteinemia; HSM, hepatosplenomegaly; Ptt, platelets; AYG, anti-gamma-globulin; RF, rheumatoid factor; ANA, antinuclear antibody; AGA, antigastic antibody; ASM, antismooth muscle antibody; ARA, antireticulin antibody; AMA, antimyelin antibody; G, IgG; A, IgA; M, IgM; NG, normal IgG level; NR, not reported; ND, not determined.

Table 2. Characteristics of Immunologic Studies in Relatives of Familial WM Cases in Nine Families

Family No.	No. of Relatives Studied	Age Range (yr)	AutoAbs*	Immunoglobulins					Comment
				MC	Increased	(type)	Decreased	(type)	
1	1	82	0	1	1	(1 G/A)	0		MC found to be transient on follow-up <sup>8,11</sup>
2	17	17-69	3 A $\gamma$ G 1 A $\gamma$ G/RF	0	8	(2 M, 4 A, 2 G/A/M)	2	(2M)	$\uparrow$ M/A/G in 17 yo
3	3	NR	NR	0	0		0		
5	35	1-65	4 RF 1 ANA	1	3	(2 M, 1 A)	13	(13G)	1 $\uparrow$ A in 1 yo; 1 $\uparrow$ M in 30 yo
7	16	NR	3 RF 2 AMC 3 ATM $\pm$ ATG	1 $\dagger$	0		0		
8	26	1-67	NR	1 $\dagger$	0		13	(13G)	1 $\downarrow$ G in 1 yo
9	6	NR	NR	0	0		0		
10	2	NR	0	0	0		0		
11	12	21-63	1 ATA 1 ANA	0	6	(1 M, 2 G, 1 A, 1 G/A, 1 G/A/M)	0		
12	7	8-67	NR	0	4	(4 M)	0		

\* A variety of autoantibodies were studied in different families. Only those for which any positive titer was discovered are reported here.  
 $\dagger$  In families no. 7 and 8, monoclonal components were identified in two patients during initial study evaluation and following documentation of familiarity (ie, after at least two family members had been diagnosed with WM); both patients were eventually diagnosed with WM.  
Abbreviations: AutoAbs, autoantibodies; MC, monoclonal component; A $\gamma$ G, anti-gamma-globulin; RF, rheumatoid factor; AMC, antimyocardial antibody; ATM, antimicrosomal antibody; ATG, antithyroglobulin antibody; G, IgG; A, IgA; M, IgM; yo, years old; NR, not reported.

contrast, the IgM MG was transient in one relative in family no. 1. Overall, 40.5% of relatives had evidence of some immunoglobulin abnormality, including 9.9% with polyclonal IgM elevations (IgM PG). The frequency of IgM PG was highest in siblings (30.0%) and correlated with degree of relationship (14.3% and 7.3% in first- and second-degree relatives, respectively). In addition, 23.4% of tested relatives had autoantibodies, the presence of which was also correlated with degree of relationship (Table 3).

### CONCLUSIONS

An empirical risk study has not been conducted to determine what percentage of WM cases is familial. Thus it is not possible to define the proportion of all WM that occurs in the familial setting, although it appears to be small. Nonetheless, the data provided by these initial family studies are intriguing. For example, these reports, as well as descriptions of familial IgM MG, have provided much of the evidence suggesting a role

for an underlying defect in immune regulation as a contributing factor in the development of WM. It is clear, however, that our understanding of WM, both familial and sporadic, remains limited. This series has several limitations, including small numbers of families studied by several different investigators using variable study designs, methodologies, and endpoints, and it is hampered further by wide inconsistencies in data reporting and an overall lack of prospective follow-up. Moreover, the extent to which the published families are representative of familial WM in the general population is not certain. For instance, the male-to-female case ratio in an unpublished series of US families is 1.9 (M.L.M., unpublished observations), which is more consistent than the current series with the gender ratio observed in registry-based sporadic WM cases.<sup>2</sup> To address these limitations, we have undertaken a prospective investigation designed to recruit a large number of WM families from across the United States, employing an array of epidemiologic tools, molecular genetic

Table 3. Frequency of Immunologic Abnormalities in Relatives of WM Cases in Nine Families

Relationship of Studied Family Members to Cases	No. Studied		No. Found to Have Any Abnormality				
	Total	AutoAbs	Igs	Autoantibody		Immunoglobulin	
				n	%	n	%
First-degree relative	63	40	63	12	30.0	21	33.3
Second-degree relative	41	27	41	6	22.2	24	58.5
Other	17	14	17	1	7.1	4	23.5
Parents	1	1	1	0	0.0	1	100.0
Siblings	20	13	20	5	38.5	9	45.0
Offspring	42	26	42	7	26.9	11	26.2
Other	58	41	58	7	17.1	28	48.3
Total	121	81	121	19	23.4	49	40.5

Abbreviations: AutoAbs, autoantibodies; Igs, immunoglobulins.

technologies, and statistical genetic techniques for the systematic evaluation of clinicopathologic, epidemiologic, and laboratory parameters. This study of familial WM may elucidate the genetic and/or environmental determinants of this rare, distinctive disorder.

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