Familial monoclonal gammopathy of undetermined significance and multiple myeloma: epidemiology, risk factors, and biological characteristics

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Monoclonal gammopathy of undetermined significance (MGUS), a precursor to multiple myeloma (MM), is one of the most common premalignant conditions in the general population. The cause of MGUS is largely unknown. Recent studies show that there is an increased prevalence of MGUS in blood relatives of persons with lymphoproliferative and plasma cell proliferative disorders, suggesting presence of shared underlying genetic influences. In the past few years, additional studies have examined risk factors and biologic characteristics that may contribute to the increased prevalence of MGUS among relatives of probands with MGUS, MM, and other blood malignancies. This article reviews the known epidemiology and risk factors for familial MGUS and myeloma, the risk of lymphoproliferative disorders and other malignancies among blood-relatives of patients with MGUS and MM, and discusses future directions for research. (*Blood*. 2012; 119(23):5359-5366)

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is one of the most common premalignant plasma cell disorders. It is a precursor for multiple myeloma (MM) and other related plasma cell malignancies. MGUS is defined by a serum monoclonal (M) protein level of < 3 g/dL, $< 10\%$ of clonal plasma cells in the bone marrow and absence of clinical characteristics of hypercalcemia, renal insufficiency, anemia, and/or bone lesions that can be attributable to a plasma cell proliferative disorder.[1]

Approximately 3% of the general population aged 50 years and older have MGUS.[2] The prevalence increases with age, ranging from 1.7% in those 50-59 years of age, to $> 5\%$ in those older than 70 years.[2] The rate of progression of MGUS to malignancy is $\sim 1\%$ per year.[2] MGUS is more prevalent in men (4.0% older than age 50 years) than in women (2.7% older than age 50 years).[2] Differences in prevalence have also been seen across racial and ethnic groups. For example, reports indicate that persons of Asian descent have a lower prevalence of MGUS than do their white counterparts.[3] In addition, persons of African and African American descent have been reported to have an $\sim$ 2- to 3-fold increased prevalence compared with white populations.[4,5] These differential rates of MGUS by race suggest possible differences in environmental and/or genetic risk factors for MGUS.

A few studies have indicated that there is an increased prevalence of MM among blood relatives of probands with MM.[6,7] From recent data, there also appears to be an increased prevalence of MGUS in families containing ≥ 1 person with a lymphoid or plasma cell proliferative disorder.[8] Investigations have been performed to estimate the magnitude of the excess risk in first-degree relatives and to explore possible underlying mechanisms.[9] The purpose of this review is to summarize the current literature on familial MGUS and MM and to discuss future directions for research.

Epidemiology of familial MGUS and MM

Most studies of familial MGUS and MM have been case studies of a collection of families with multiple cases of MGUS, MM, and other hematologic malignancies. Furthermore, most of these investigations have been conducted in white populations. One of these earliest studies to examine familial aggregation of MGUS and MM described one family in which 2 siblings were diagnosed with MGUS.[10] On further investigation, it was found that a total of 5 of the 7 siblings had a monoclonal gammopathy (4 cases of MGUS and 1 case of MM). Another study described 8 families with 2 probands with a monoclonal gammopathy (with MGUS, MM, or Waldenstrom macroglobulinemia [WM]).[11] Relatives were traced back 2 generations before the proband; in addition, any person from a younger generation older than 20 years was included, yielding 4370 family members total. Linkage of these family members with the Icelandic Cancer Registry found 22 clinically diagnosed cases of monoclonal gammopathies. Of the 4370 family members, 350 first- and second-degree relatives contributed serum for additional screening, resulting in the discovery of 9 additional cases of monoclonal gammopathies (8 from first-degree relatives, 1 from a second-degree relative; Table 1). The above-mentioned studies were hypothesis-generating and found the presence of familial clustering in the monoclonal gammopathies but could not address whether the clustering was greater than expected by chance because a reference population was not examined.

The largest study to date that provided comparative data was an investigation of a Swedish population that examined the increased risk of both plasma cell and lymphoproliferative disorders among first-degree blood relatives of persons with and without MGUS.[8] This population-based investigation involved 14 621 relatives of 4458 patients with MGUS and found an increased risk of MGUS

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Table 1. Summary of family studies with MGUS and MM probands

Reference	Study type	Population details	No. of probands	No. of relatives of probands	No. of affected relatives	Risk of MGUS or MM (95% CI)‡
MGUS probands						
Steingrímsdóttir et al[11]*	Registry-based family study	Iceland	16 with either MGUS or MM (2 in each family)	4370 total; 350 first-degree	31 (22 identified by registry, 9 by screening)	
Landgren et al[8]	Population-based case-control study	Sweden	4458 (matched with 17 505 controls)	14 621 (58 387 relatives of controls)	22 MGUS/41 MM (vs 31 MGUS/57 MM in controls)	RR = 2.8 (1.4-5.6)/2.9 (1.9-4.3)§
Vachon et al [9]	Population-based prevalence study	United States (Olmsted County, white)	97 MGUS/232 MM	247 MGUS relatives/ 664 MM relatives	30 of MGUS cases/ 53 of MM cases	RR = 3.3 (2.1-4.8)/2.0 (1.4-2.8)§
Jain et al[12]	Family case study	United States (black)	2	10†	2 MM†	
Lynch et al[13]	Family case study	United States (black)	3	11	3 MGUS with abnormal FLC ratios; (5 MM previously identified)	
Multiple myeloma probands						
Kristinsson et al[14]	Registry-based case-control study	Sweden	13 896 (matched with 54 365 controls)	37 838 (151,068 relatives of controls)	42 MGUS/94 MM	RR = 2.1 (1.5-3.1)/2.1 (1.6-2.9)§
Hemminki et al[15]	Family study	Sweden	23 parents with MM (of 754 165 parents)		23 familial cases (878 sporadic) in offspring	SIR = 3.33 (2.1-5.0)§
Brown et al[6]	Case-control	United States (blacks and whites)	565 (2104 controls)			OR = 3.7 (1.2-12.0)§
Grosbois et al[16]	Registry-based family study	104 Intergroupe Francophone du Myelome centers	15	25	15	
Eriksson et al[17]	Case-control	Sweden	239 (220 matched controls)	NA	NA	RR = 2.36 (0.90-6.15)‖
Bourguet et al[7]	Case-control	Duke University Medical Center	439 (1317 matched controls)	NA	3 (4 in controls)	RR = 2.4 (1.4-4.0)§

SIR indicates standardized incidence ratio; and NA, not available.
*Also included WM and MM myeloma cases in probands.
†MGUS families only.
‡Risk of MGUS listed, followed by risk of MM, if any given.
§Risk of developing multiple myeloma.
‖Risk of all hematologic malignancies.

among relatives of probands, compared with 58 387 relatives of 17 505 controls without MGUS (relative risk [RR] = 2.8; 95% CI, 1.4-5.6). In addition, increased risks were found in relatives of MGUS probands for MM (RR = 2.9; 95% CI, 1.9-4.3; Table 1). These findings suggest that either genetic susceptibility factors or shared environmental risk factors (or both) were involved in this phenomenon. A main limitation of this study was that ascertainment of MGUS in the probands and relatives was by clinical diagnosis, and not all relatives were tested for the presence or absence of MGUS.

A similar study was conducted at the Mayo Clinic to assess the prevalence of MGUS in first-degree blood relatives of MM and MGUS probands.[9] Relatives of 232 MM and 97 MGUS probands were studied. Serum samples from 911 blood relatives were screened for MGUS with the use of electrophoresis and immunofixation. MGUS was detected in 6% of relatives (age- and sex-adjusted prevalence of 8.1%; 95% CI, 6.3-9.8). With the use of the Olmsted County MGUS prevalence study as a reference, it was found that relatives had a higher prevalence of MGUS, with a risk ratio of 2.6 (95% CI, 1.9-3.4) compared with the general population. This increased risk was seen both in relatives of MM probands (RR = 2.0; 95% CI, 1.4-2.8) and MGUS probands (RR = 3.3; 95% CI, 2.1-4.8). The prevalence of MGUS in first-degree relatives did not differ significantly on the basis of the isotype of the proband. In addition, it was found that the prevalence of MGUS increased with age, similar to the trend seen in the reference population. Unlike the previous studies, all family members of known MGUS probands as well as the comparison group were tested for the presence or absence of MGUS. Therefore, the study provided strong evidence that the risk of MGUS was significantly increased in first-degree relatives.

Although most of these studies focused on white populations, a handful of smaller studies in African Americans have also found evidence to support the concept of an underlying familial predisposition. In a single family case study, Lynch et al reported 5 persons with MM and 3 with MGUS across 2 generations.[13] One of the persons had offspring who developed MM and MGUS with 2 different partners, providing further evidence for an underlying genetic component. Another investigation focused on examining the pedigrees of 6 African American patients with MM and 2 with MGUS.[12] Of the 58 first-degree blood relatives, 21 were found to have a plasma cell disorder (12 MM, 8 MGUS, 1 amyloidosis; Table 1). Despite the small sample size in both of these studies and lack of comparison groups, both indicate possible underlying genetic factors that could play a role in susceptibility in African American populations. In these studies, no evidence was reported for clustering of cases by isotype, age, or other potential risk factors. Given the relative paucity of knowledge of familial aggregation of MGUS in African Americans and those of African descent and the previously established elevated risk of monoclonal gammopathies in these populations,[4,5] this is a high priority area of research.

Familial aggregation of MGUS and other lymphoproliferative disorders

Certain subtypes of MGUS have been associated with disorders other than MM, such as IgM MGUS with WM; as a result, some studies haves examined the relation between MGUS and familial clustering with lymphoproliferative conditions other than MM. Kristinsson et al sought to determine familial risk of lymphoproliferative disorders in first-degree blood relatives of probands with either WM or lymphoplasmacytic lymphoma (LPL) in another linkage study in a Swedish population.[18] Probands included 1539 patients with WM and 605 patients with LPL whose conditions were previously diagnosed between years 1958 and 2005 and 8279 population-based matched controls. First-degree relatives of the probands (n = 6177) and controls (n = 24 609) were included in the study. It is important to note that disease status of the relatives was assessed with clinical diagnosis rather than with screening; hence, these data may not represent the true risk. Relatives of probands had increased risks of LPL/WM (RR = 20; 95% CI, 1.4-98.4), non-Hodgkin lymphoma (NHL; RR = 3.0; 95% CI, 2.0-4.4), chronic lymphocytic leukemia (CLL; RR = 3.4; 95% CI, 1.7-6.6), and MGUS (RR = 5.0; 95% CI, 1.3-18.9). No significant differences were reported by the relative examined (parent, offspring, and sibling).

In a previously discussed Swedish population-based study of family members of 4458 MGUS probands, increased prevalence of other lymphoproliferative conditions in addition to MM and MGUS were identified.[8] An increased prevalence of LPL/WM (RR = 4.0; 95% CI, 1.5-11) and CLL (RR = 2.0; 95% CI, 1.2-2.3) was found for relatives of MGUS probands compared with relatives of controls. In addition, when probands were stratified by type of immunoglobulin, relatives of those with IgA/IgG MGUS had elevated risks of LPL and WM; relatives of those with IgM MGUS had an increased risk of CLL but nonsignificant increased risks of other conditions. As with the aforementioned study of probands with WM/LPL, no significant differences were found according to the specific blood relative examined.

Several other Swedish registry-based studies, such as the one by Lindqvist et al,[19] have been conducted and found familial clustering of both immune-related and plasma cell dyscrasias. This study showed evidence of an association of personal and family history of autoimmune disease with MGUS, indicating the potential for shared susceptibility for these conditions. An additional Swedish registry-based study conducted by the same group examined the risk of solid tumors and hematologic malignancies in first-degree blood relatives of MGUS probands.[20] The study examined 4458 MGUS probands and 17 505 controls and their first-degree relatives (14 621 and 58 387, respectively). First-degree relatives of patients with MGUS were found to have a slight increase in prevalence of any solid tumor (RR = 1.1; 95% CI, 1.04-1.21), with bladder cancer, spinal cancer, malignant melanoma, and lung cancer showing significantly increased risks individually. In this particular investigation, no significantly increased risk of myeloid malignancy, myeloproliferative disorders, or chronic myeloid leukemia were found. This study is intriguing but similar to the other Swedish population studies, is limited by the fact that MGUS in the probands was not detected by screening; therefore, the population of patients with MGUS represents a group that sought medical attention for some clinical problem or ailment resulting in testing for a monoclonal protein. Further, the absolute excess risk of solid tumors is small (5%-20%).

Taken together, our review of the literature suggests that, besides myeloma and related disorders, first-degree relatives of persons with monoclonal gammopathies have a 2- to 4-fold increase in the risk of certain lymphoproliferative disorders such as LPL/WM and CLL and that this risk depends on the type of the M protein in the proband. In contrast there appears to be a smaller and, in our opinion, not a clinically significant increase in the risk of other cancers.

Genetics and biologic mechanisms of familial MGUS and other monoclonal gammopathies

Genome-wide linkage analysis

Few studies to date have investigated genetic influence on MGUS. One genome-wide linkage analysis has been conducted on 11 families of probands with WM. Of the 122 family members included in the study, 10 were confirmed cases of IgM MGUS and an additional 34 had WM.[21] Investigators genotyped and analyzed 1058 microsatellite markers using both parametric and nonparametric methods. In an analysis in which those with MGUS and WM were labeled as "affected," linkage was found on chromosomes 1q and 4q. The nonparametric linkage scores reported were 2.5 for 1q and 3.1 for 4q ($P = .0089$ and .004, respectively). The investigators propose that this information could be useful in identifying genes that function as susceptibility factors for both conditions. However, these data are preliminary, and no genes for either WM or MGUS have been identified in these regions to date.

Biologic factors underlying familial MGUS

A recent series of investigations conducted by Grass et al has shown hyperphosphorylation of paraproteins to be linked with both familial and nonfamilial MGUS and MM.[22] In a case-control study, serum samples were collected from 252 consecutive patients with MGUS/MM and 252 healthy blood donors.[22] Paratag-7 (P-7), one of the targets of IgA and IgG paratag proteins with unknown function, was analyzed with DNA sequencing, SDS-PAGE, Western blotting, and isoelectric focusing. No significant DNA mutations were found in P-7 in either cases or controls; however, of the 252 cases, 35 (13.9%) had hyperphosphorylation of P-7 and a specific P-7 protein. Within this study, 8 families were assessed (7 MM and 1 with 2 cases of MGUS); the results showed that this hyperphosphorylation is inherited dominantly. Follow-up conducted by the researchers confirmed this inheritance pattern.[23] The researchers proposed that this hyperphosphorylation may induce autoimmunity, which, in turn, could lead to the development of MGUS or MM.

When specifically investigating 161 persons with IgM MGUS or WM from 3 sites (the Saarland University Medical School, the Bing Center for Waldenstrom Macroglobulinemia at Dana-Farber Cancer Institute at Harvard Medical School, and the Department of Clinical Therapeutics at the University of Athens School of Medicine), serum for 18 persons (11%) of those with IgM or WM (9 MGUS, 9 WM) reacted positively for P-7, but only for 4 of the healthy controls (2%).[24] Results led investigators to conclude that this marker is associated with a 6.2-fold increased risk ($P = .001$) of IgM MGUS or WM. Investigating the 161 persons further, 4 families with multiple cases of MGUS/WM were identified. All 25 first- and second-degree relatives were tested and were found to have hyperphosphorylated P-7. Examination of inheritance in the 4 families tested also found hyperphosphorylated P-7 to be a dominantly inherited trait.

A final study was conducted to assess the prevalence of hyperphosphorylated P-7 within families with a history of MGUS/MM.[25] Using 31 unaffected and 10 persons with MGUS/MM from 4 families, Grass et al determined that hyperphosphorylated P-7 was a target for the paratag proteins of 2 affected family members.[25] In addition, it was found that paratag protein-8 (P-8) was an antigenic target from 4 affected members of one family; this paraprotein was also hyperphosphorylated and inherited in a dominant fashion. Additional hyperphosphorylated nonfamilial paratag proteins were found in affected persons, leading to the conclusion that hyperphosphorylation of paratag proteins may underlie the pathogenesis of MGUS and/or MM, and that hyperphosphorylated P-7 and P-8 specifically may be more prevalent in familial MGUS/MM.

The above studies are limited because they do not systematically compare the prevalence of hyperphosphorylated P-7 (or P-8) in sporadic versus familial MGUS in well-defined cohorts. Thus, although interesting and hypothesis generating, additional confirmatory evidence and mechanistic studies are needed.

Hyperresponsive B cells

One of the proposed phenotypes that may underlie familial MGUS is the hyperresponsive B-cell phenotype, seen when pokeweed mitogen is applied in vitro, causing increased production of IgA, IgG, and IgM. Persons from 8 families with multiple cases of either MGUS or MM were examined for this phenotype with the use of blood samples cultured and stimulated by pokeweed mitogen.[11] One unaffected control was chosen for each of the cases and was matched on age and sex. Of the 62 healthy family members, 7 were IgG hyperresponders; 4 were IgM hyperresponders; and 1 person was hyperresponsive with increased production of both IgG and IgM. Eight of these hyperresponders were from one family, 2 came from another family, and the final 2 were each from a unique family. In addition, 10 persons had increased production of Ab production, but not enough to be classified as hyperresponders. Among the controls, only 2 were classified as hyperresponders. These results suggest that hyperresponsive B cells could be a potential novel endophenotype for familial monoclonal gammopathies. They are of particular interest because they provide a rational mechanistic basis for the generation of monoclonal plasma cell populations in close family members who share an inherited hyperresponsive B-cell phenotype.

Familial MM and other cancers

Aggregation of MM in families

Interest in examining familial MGUS arose partly from findings of familial aggregation in MM and other blood cancers. In a review of the literature documenting siblings with plasma cell disorders and monoclonal gammopathies before 1985, of the 38 pairs of affected siblings reported, 8 families had an additional sibling affected and 4 had a fourth affected relative.[26] Additional reports since the 1980s have reported several cases of MM in siblings as well as in parents and children.[27-30] The above-mentioned studies reported the presence of familial clustering in myeloma and laid the foundation for subsequent confirmatory studies. Of note, patterns of MM and other hematologic malignancies have been found anecdotally in spouses, suggestive of environmental influences.[31]

A retrospective study of 104 Intergroupe Francophone du Myelome centers examined the incidence of MM in siblings of patients with MM as well as other close relatives.[16] Of the participating centers, 14 reported 15 cases of familial MM. Of these, 10 cases involved siblings, 4 involved parents and children, and 1 involved an aunt and nephew. It was also noted that among these families, there were also 3 cases of MGUS. A subsequent study of the Swedish Family Cancer Database found a clear increase in the incidence of MM in offspring of persons with a previous diagnosis of MM (standardized incidence ratio = 3.33;

95% CI, 2.11-5.00).[15] Overall, several family studies have documented aggregation of MM in first-degree blood relatives (Table 1).[7,13,17,32] It is important to note that a limitation of some of these studies is the lack of comparison group. Together, though, these studies imply an increased risk of MM exists in first-degree relatives of patients with MM. In concert with the epidemiologic and biologic studies of familial MGUS they suggest that this increased risk is probably the result of inherited genetic susceptibility factors.

Given the increased risk of developing MM in persons of African and African American descent, Brown et al undertook a study to investigate whether the risk of familial MM was the same among blacks and whites.[6] Through interviews with 565 cases with MM (of whom 361 were white and 204 were black) and 2104 control subjects (of whom 1150 were white and 954 were black), investigators examined whether differences in family history of cancer and MM could explain the disparity between ethnicities. Analysis of the 2 races combined found that there was a significant elevated risk of MM in persons who reported a first-degree blood relative with the disease (odds ratio [OR] = 3.7; 95% CI, 1.2-12.0), any history of a hematolymphoproliferative cancer (OR = 1.7; 95% CI, 1.0-2.8), and an hematolymphoproliferative cancer in a sibling (OR = 2.3; 95% CI, 1.1-4.5). Blacks had a higher risk of MM associated with family history; however, the ORs were not significantly different between blacks (2.2; 95% CI, 0.9-5.1) and whites (1.3; 95% CI, 0.6-2.5) for any relative with any prior hematolymphoproliferative malignancy, indicating that family history may not explain the disparity in risk.

Hematologic malignancies and other cancers associated with familial MM

As with MGUS, several other hematologic conditions aggregate in families of persons with MM, including various other paraprotinemias.[33] Eriksson and Hallberg led a case-control study in Sweden in which a survey was sent to potential participants identified with MM and controls through the Swedish Cancer Register and parochial authorities inquiring about family history of hematologic malignancies and other diseases.[17] Analyses of 239 cases with MM and 220 controls found an increased risk of MM in those with first-degree blood relatives with hematologic malignancies (RR = 2.36; 90% CI, 0.9-6.15); this held true for first-degree relatives of patients with MM (RR = 5.64; 90% CI, 1.16-27.51). Additional investigation conducted by Domingo-Domènech et al examined 588 consecutive patients with newly diagnosed lymphoid neoplasms across 4 study centers and 631 hospital controls from the same study centers; controls were randomly selected and frequency matched on age, sex, and study center.[34] Data on family history of cancer was collected from the study subjects. Investigators found a significantly increased risk of hematologic cancers in relatives of those with lymphoid neoplasms, including a 2-fold increased risk of MM in probands and a 4-fold increased risk of CLL in probands, compared with controls.[34]

In another study, conducted by Ogmundsdóttir et al, a family registry of patients with MM was compared with the population-based Icelandic Cancer Registry to assess the prevalence of hematologic malignancies in relatives of patients with MM.[35] Data found almost a 2-fold increased risk for first-degree female relatives of MM probands for a grouping of hematologic malignancies (codes C81-C96 I the International Classification of Diseases and Related Health Problems, 10th Ed; RR = 1.95; 95% CI, 1.1-3.2). From the 218 MM probands, 8 families were identified in which the proband had > 1 relative with MGUS and > 1 relative with another hematologic malignancy; in 4 of these families, another relative had MM, and in 3, both myeloid and lymphoid conditions were found.

An investigation by Landgren et al examined MM risk in conjunction with individual history of autoimmune conditions and the occurrence of autoimmune and hematologic conditions in first-degree blood relatives.[36] From 8406 cases of MM and 16 543 matched controls with linkable relatives, information was obtained on 22 490 and 44 436 first-degree relatives (respectively) for information about history of autoimmune and hematologic disorders, both personal and familial. Similar to studies discussed, an increased risk of MM was found in relatives of MM cases (RR = 1.67; 95% CI, 1.02-2.73) compared with relatives of controls. Risk was even greater for relatives of cases 65 years or older (RR = 2.5; 95% CI, 1.19-5.27) and female relatives (RR = 3.97; 95% CI, 1.54-10.2). No significant increase in risk of MM was found in probands whose first-degree blood relatives had other blood cancers; however, some studies have found higher incidence of Hodgkin lymphoma, MM, NHL, and soft tissue sarcoma in persons with ≥ 1 relative with a prior malignancy.[37,38]

Some small studies have identified associations between MM probands and certain solid tissue tumors in first-degree blood relatives.[13,39] More recently, these findings were validated in a study conducted by Kristinsson et al using Swedish population-based data and family linkage.[14] Risks for hematologic malignancies and solid tumors, as well as MGUS, were assessed for first-degree blood relatives of 13 896 MM probands (37 838 relatives) and 54 365 matched controls (151 068 relatives). Family members of MM probands were at a small but increased risk of developing any solid tumor (RR = 1.1; 95% CI, 1.0-1.1), most notably bladder cancer (RR = 1.3; 95% CI, 1.0-1.5). In terms of hematologic malignancies, the Swedish study found that first-degree relatives had an increased risk of MM (RR = 2.1; 95% CI, 1.6-2.9), MGUS (RR = 2.1; 95% CI, 1.5-3.1), and acute lymphoblastic leukemia (ALL; RR = 2.1; 95% CI, 1.0-4.2). Overall, the absolute excess risk of solid tumors in first-degree relatives of patients with MM is small (10%) relative to the excess seen for MM, MGUS, and ALL.

Despite inherent limitations of retrospective cohort and registry studies, our overall interpretation of the literature is that first-degree relatives of patients with MM have a 2-fold higher risk of certain hematologic malignancies, including MM. In contrast there appears to be a less pronounced but in our opinion not a clinically significant increase in the risk of solid tumors.

Genetic variation associated with MM

Although there have been no studies of genetic variation and MGUS or progression of MGUS to MM, numerous studies have been conducted on the genetic epidemiology of MM. These range from early studies of regions of gain/loss and loss of heterozygosity to the first genome-wide association study (GWAS) of MM, to sequencing studies of germline and tumor DNA. For example, a recent study by Chapman et al examined tumor genome sequences of patients with MM and matched healthy controls and found mutations in key genes, such as those involved in histone methylation and in the NF-κB pathway.[40] To date, nearly 30 studies have been conducted that examined associations between polymorphisms and risk of MM; however, few have been replicated.

Table 2 summarizes the significant published associations between genetic variants and MM. The most comprehensive evaluation of genetic variation and MM to date is the recently published GWAS of MM conducted in United Kingdom and

Table 2. Genetic variation associated with MM

Gene	Genetic variant	Associated variation	Reference	OR Ratio (95% CI)*	*P*
BAX	rs1042265	G > A	Hosgood et al[41]	GA+AA = 0.40 (0.21-0.78)	.007
CASP9	rs7516435	A > G	Hosgood et al[41]	AG (vs AA) = 1.48, (0.94-2.32); GG (vs AA) = 2.59 (1.30-5.15)	.005
CD4	rs1075838	T > C	Lee et al[42]	1.44 (1.05-1.97)	.02
CD4	rs11064392	A > G	Lee et al[42]	2.36 (1.53-3.63)	.0001
CD4	rs2707212	C > T	Lee et al[42]	0.68 (0.49-0.96)	.03
CD4	rs7296859	C > G	Lee et al[42]	0.67 (0.48-0.94)	.02
CYP1A1	CYP1A1*2A	*2A	Kang et al[43]	0.57 (0.33-0.995)	
HGF	rs17501108	G > T	Purdue et al[44]	GT (vs GG) = 2.65 (1.62-4.35)	< .0001
HPSE	rs4693602	A > G	Ostrovsky et al[45]	χ^2 statistic = 7.276	.026
IL1A	−889 C/T	C > T	Abazis-Stamboulieh et al[46]	CT = 4.18 (2.58-6.55)	< .0001
IL1B	−511 C/T	C > T	Abazis-Stamboulieh et al[46]	CT = 1.54 (1.20-1.98)	< .0001
IL1B	+3954 T/C	T > C	Abazis-Stamboulieh et al[46]	CT = 1.38 (1.03-1.84)	< .0001
IL-1RN	*Msp*a1 +11100		Abazis-Stamboulieh et al[46]	TT = 1.35 (1.02-1.79)†	< .0001
IL-6	rs6684439	T > C	Birmann et al[47]	TT (vs CC) = 2.9 (1.2-7.0)	.048
IL-6	rs7529229	C > T	Birmann et al[47]	CC (vs TT) = 2.5 (1.1-6.0)	.08
IL-6	rs8192284	C > A	Birmann et al[47]	CC (vs AA) = 2.5 (1.1-6.0)	.038
IRS1	rs1801278	C > T	Birmann et al[47]	CT (vs CC) = 4.3 (1.5-12.1)	.68
ITGA6	rs12621278	A > G	Cooper et al[48]	11.19 (1.56-80.35)	.04
KLK3	rs2735839	G > A	Cooper et al[48]	0.05 (0.00-0.50)	.07
LAG3	rs2365094	G > C	Lee et al[42]	1.49 (1.08-2.04)	.01
LAG3	rs3782735	G > A	Lee et al[42]	0.67 (0.48-0.93)	.02
RIPK1	rs9391981	G > C	Hosgood et al[41]	0.32 (0.12-0.81)	.005
SERPINE1	rs2227667	A > G	Purdue et al[44]	AG (vs AA) = 0.43 (0.26-0.70)	< .0001
TRAF3	rs12147254	G > A	Du et al[49]	AG (vs GG) = 1 (0.62-0.82)	.001
VCAM1	rs3783605	A > G	Idelman et al[50]	NA	.001
XRCC4	rs963248	A > G	Hayden et al[50]	1.51 (1.10-2.08)	.0133
ULK4	rs1052501	G > A	Broderick et al[51]	1.32 (1.20-1.45)	< .0001
DNAH11	rs4487645	C > A	Broderick et al[51]	1.38 (1.28-1.50)	< .0001
DNTB	rs6746082	A > C	Broderick et al[51]	1.29 (1.17-1.42)	< .0001
	rs9364554	G > T	Cooper et al[48]	20.89 (1.88-232.43)	.02
	rs2660753	C > T	Cooper et al[48]	24.33 (2.39-247.56)	.07
	rs5759167	G > T	Cooper et al[48]	11.50 (1.04-127.69)	.06

*OR unless otherwise noted.

German populations, comprising 1675 cases and 5903 controls. Three novel loci were identified; 2 reached genome-wide significance ($P < 5 \times 10^{-8}$) at 3p22.1 (rs1052501 in *ULK4*) and 7p15.3 (rs4487645).[51] agnostic approach to identification of genetic variants for MM could lead to new insight into the biology of this disease and potential targets for therapy. For example, rs4487645 at the 7p15.3 region maps to an intron in *DNAH11* (dynein, axonemal, heavy chain 11) but the 88-kb region of linkage disequilibrium also contains the 3′ end of *CDCA7L*, or cell division cycle-associated 7-like, which is a MYC interacting protein. As noted by the investigators, fine mapping and functional analysis will be necessary to determine the causal candidates and potential therapeutic targets. However, in contrast to the GWAS, numerous studies focusing on candidate single nucleotide polymorphisms in genes in targeted pathways, including DNA repair and immune response, have been conducted and show significant associations, but replication is needed in additional populations.[41,50]

Common genetic predisposition

As discussed earlier, studies suggest clustering of MGUS with CLL, LPL/WM, and NHL[8,18-20] and MM with ALL and CLL in families.[17,33-38] The increased risk of hematologic malignancies, in particular B cell, in first-degree relatives of both MM and MGUS probands supports a common genetic predisposition. Recently several genetic variants have been identified for CLL and other subtypes of NHL.[52-56] These variants, as well as those yet unidentified, may also contribute to familial MGUS and MM.

Future directions

Several aspects of familial MGUS and MM warrant continued investigation. First, priority needs to be placed on understanding familial aggregation of MGUS and MM in African Americans and those of African descent, especially given the elevated risk of disease in this demographic. Second, there is a need for additional work on identification of genes that could serve as markers of susceptibility for MGUS and MM, especially in light of the novel variants recently identified for MM using the GWAS approach; markers specific to familial disease are of particular importance. Third, further investigation into hyperresponsive B cells and hyperphosphorylated P-7 is necessary, because validation of these findings could have clinical relevance for testing in family members. Finally, examination of genetic variants found associated with MM, such as those identified in the recent GWAS (at 3p22.1 and 7p15.3) should be conducted in cohorts of patients with MGUS to understand whether some of these factors indicate a predisposition toward both MGUS and malignancy. Such studies could help to lay the groundwork for better clinical management of familial MGUS and MM, as well as identification of potential novel therapeutic targets.

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Authorship

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