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

**Short running title:** Review: Familial MGUS and myeloma

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Abstract

Monoclonal gammopathy of undetermined significance (MGUS), a precursor to multiple myeloma, is one of the most common premalignant conditions in the general population. The etiology of MGUS is largely unknown. Recent studies show that there is an increased prevalence of MGUS in blood relatives of individuals 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 biological characteristics that may contribute to the increased prevalence of MGUS among relatives of probands with MGUS, multiple myeloma (MM), and other blood malignancies. This manuscript reviews the known epidemiology and risk factors of 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.
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 less than 3 grams per deciliter, less than 10% of clonal plasma cells in the bone marrow, and absence of clinical CRAB (hypercalcemia, renal insufficiency, anemia, and/or bone lesions) characteristics 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 greater than 5% in those older than 70.² The rate of progression of MGUS to malignancy is approximately 1% per year.² MGUS is more prevalent in men (4.0% over age 50) than in women (2.7% over age 50).² Differences in prevalence have also been seen across racial and ethnic groups. For example, reports indicate that individuals of Asian descent have a lower prevalence of MGUS compared with their white counterparts.³ Additionally, those of African and African-American descent have been reported to have approximately a two- to three-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. From recent data, there also appears to be an increased prevalence of MGUS in families containing at least one individual with a lymphoid or plasma cell proliferative disorder. Investigations have been performed to estimate the magnitude of the excess risk in first-degree relatives and explore possible underlying mechanisms. The purpose of this review is to summarize the current literature on familial MGUS and MM and discuss future directions for research.

Epidemiology of familial MGUS and MM

The majority of 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 two siblings were diagnosed with MGUS. Upon further investigation, it was found that a total of five of the seven siblings had a monoclonal gammopathy (four cases of MGUS and one case of MM). Another study described eight families with two probands with a monoclonal gammopathy (with MGUS, MM, or Waldenstrom’s macroglobulinemia (WM)). Relatives were traced back two generations prior to the proband; additionally, any individual from a younger generation over the age of twenty was included, yielding 4370 family members total. Linkage of these
family members with the Icelandic Cancer Registry revealed 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, one from a second-degree relative)
(Table 1). The above studies were hypothesis-generating and demonstrated the
presence of familial clustering in the monoclonal gammopathies but could not
address whether the clustering was greater than expected by chance since 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 individuals
with and without MGUS. This population-based investigation involved 14,621
relatives of 4,458 MGUS patients and found an increased risk of MGUS among
relatives of probands, compared with 58,387 relatives of 17,505 controls without
MGUS (relative risk [RR] = 2.8, 95% CI, 1.4 to 5.6). Additionally, increased risks
were found in relatives of MGUS probands for multiple myeloma (RR=2.9, 95%
CI, 1.9 to 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 major 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 Mayo Clinic to assess the prevalence of MGUS in first-degree blood-relatives of MM and MGUS probands. Relatives of 232 MM and 97 MGUS probands were studied. Serum samples from 911 blood-relatives were screened for MGUS using electrophoresis and immunofixation. MGUS was detected in 6% of relatives (age- and sex-adjusted prevalence of 8.1%, 95% CI, 6.3 to 9.8). Using 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 to 3.4) compared to the general population. This increased risk was seen both in relatives of MM probands (RR = 2.0, 95% CI, 1.4 to 2.8) and MGUS probands (RR = 3.3, 95% CI, 2.1 to 4.8). The prevalence of MGUS in first-degree relatives did not differ significantly based on the isotype of the proband. Additionally, it was found that 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.

While the majority of these studies focused on white populations, a handful of smaller studies in African Americans have also found evidence supporting the concept of an underlying familial component. In a single family case study, Lynch et al. reported five individuals diagnosed with MM and three with MGUS across two generations. One of the individuals had offspring who developed MM and MGUS with two different partners, providing further evidence for an underlying
genetic component. Another investigation focused on examining the pedigrees of six African American patients with MM and two with MGUS. 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, 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 Waldenstrom macroglobulinemia; as a result, some studies have examined the relationship 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 Waldenstrom macroglobulinemia (WM) or lymphoplasmacytic lymphoma (LPL) in another linkage study in a Swedish population. Probands included 1,539 WM and 605 LPL patients previously diagnosed between years 1958 and 2005 and 8,279 population-based matched
controls. First-degree relatives of the probands (n = 6,177) and controls (n = 24,609) were included in the study. It is important to note that disease status of the relatives was assessed via clinical diagnosis rather than screening, and hence these data may not represent the true risk. Relatives of probands had increased risks of LPL/WM (relative risk [RR] = 20, 95% CI, 1.4 to 98.4), non-Hodgkin lymphoma (RR = 3.0, 95% CI, 2.0 to 4.4), chronic lymphocytic leukemia (CLL) (RR = 3.4, 95% CI, 1.7 to 6.6), and MGUS (RR = 5.0, 95% CI, 1.3 to 18.9). No significant differences were reported regarding which relative was examined (parent, offspring, and sibling).

In a previously discussed Swedish population-based study of family members of 4,458 MGUS probands, increased prevalence of other lymphoproliferative conditions in addition to MM and MGUS were identified. An increased prevalence of LPL/WM (RR = 4.0, 95% CI, 1.5 to 11) and CLL (RR = 2.0, 95% CI, 1.2 to 2.3) was found for relatives of MGUS probands compared to relatives of controls. Additionally, 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 based on the specific blood-relative examined.

Several other Swedish registry-based studies, such as the one by Lindqvist et al., 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. The study examined 4,458 MGUS probands and 17,505 controls and their first-degree relatives (14,621 and 58,387, respectively). First-degree relatives of MGUS patients were found to have a slight increase in prevalence of any solid tumor (RR = 1.1, 95% CI, 1.04 to 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, and 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 very 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 two- to four-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 biological mechanisms of familial MGUS and other monoclonal gammopathies**

*Genome-wide linkage analysis*

There have been few studies to date investigating 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.\textsuperscript{17} Investigators genotyped and analyzed 1,058 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 (\(p = 0.0089\) and 0.004, respectively). The authors 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.


Biological 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. In a case-control study, serum samples were collected from 252 consecutive MGUS/MM patients and 252 healthy blood donors.\textsuperscript{18} Paratag-7 (P-7), one of the targets of IgA and IgG paratag proteins with unknown function, was analyzed using 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, eight families were assessed (seven MM and one with two cases of MGUS); the results revealed that this hyperphosphorylation is inherited dominantly. Follow-up conducted by the authors confirmed this inheritance pattern.\textsuperscript{19} The authors proposed that this hyperphosphorylation may induce auto-immunity, which, in turn, could lead to the development of MGUS or MM.

When specifically investigating 161 individuals with IgM MGUS or WM from three 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 University of Athens School of Medicine), serum for 18 individuals (11\%) of those with IgM or WM (9 MGUS, 9 WM) reacted positively for P-7, but only for four of the healthy controls (2\%).\textsuperscript{20} Results led investigators to conclude that this marker is
associated with a 6.2-fold increased risk (p=0.001) of IgM MGUS or WM.
Investigating the 161 individuals further, four 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 four families tested also found hyperphosphorylated P-7 to be a dominantly inherited trait.

A final study was conducted in order to assess the prevalence of hyperphosphorylated P-7 within families with a history of MGUS/MM. Using 31 unaffected and 10 individuals with MGUS/MM from four families, Grass et al. determined that hyperphosphorylated P-7 was a target for the paratag proteins of two affected family members. Additionally, 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 individuals, 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 by the fact that they do not systematically compare the prevalence of hyperphosphorylated P-7 (or P-8) in sporadic versus familial MGUS in well-defined cohorts. Thus while interesting and hypothesis-generating, additional confirmatory evidence and mechanistic studies are needed.
Hyper-responsive B-cells

One of the proposed phenotypes that may underlie familial MGUS is the hyper-responsive B-cell phenotype, seen when pokeweed mitogen is applied *in vitro*, causing increased production of IgA, IgG, and IgM. Individuals from eight families with multiple cases of either MGUS or MM were examined for this phenotype using blood samples cultured and stimulated by pokeweed mitogen. 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 hyper-responders; four were IgM hyper-responders; and one individual was hyper-responsive with increased production of both IgG and IgM. Eight of these hyper-responders were from one family, two came from another family, and the final two were each from a unique family. Additionally, 10 individuals had increased production of antibody production, but not enough to be classified as hyper-responders. Among the controls, only two were classified as hyper-responders. These results suggest that hyper-responsive B-cells could be a potential novel endophenotype for familial monoclonal gammopathies. They are of particular interest since they provide a rational mechanistic basis for the generation of monoclonal plasma cell populations in close family members who share an inherited hyper-responsive B cell phenotype.

Familial multiple myeloma and other cancers
Aggregation of multiple myeloma 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 gammapathies prior to 1985, of the 38 pairs of affected siblings reported, eight families had an additional sibling affected and 4 had a fourth affected relative. Additional reports since the 1980s have reported several cases of MM in siblings as well as in parents and children. The above studies demonstrated 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.

A retrospective study of 104 Intergroupe Francophone du Myelome centers examined the incidence of MM in siblings of MM patients as well as other close relatives. Of the participating centers, 14 reported 15 cases of familial MM. Of these, ten cases involved siblings, four involved parents and children, and one involved an aunt and nephew. It was also noted that among these families, there were also three cases of MGUS. A subsequent study of the Swedish Family Cancer Database, found a clear increase in the incidence of MM in offspring of individuals with a previous diagnosis of MM (SIR = 3.33, 95% CI, 2.11 to 5.00). Overall, several family studies have documented aggregation of MM in first-degree blood-relatives (Table 1). 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 likely the result of inherited genetic susceptibility factors.

Given the increased risk of developing multiple myeloma 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. 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 two races combined revealed that there was a significant elevated risk of MM in individuals who reported a first-degree blood-relative with the disease (odds ratio [OR] = 3.7, 95% CI, 1.2 to 12.0), any history of a hematolymphoproliferative cancer (HLC) (OR = 1.7, 95% CI, 1.0 to 2.8), and an HLC in a sibling (OR = 2.3, 95% CI, 1.1 to 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 to 5.1) and whites (1.3, 95% CI, 0.6 to 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 multiple myeloma

As with MGUS, several other hematologic conditions aggregate in families of individuals with MM, including various other paraprotinaemias.\textsuperscript{32} 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.\textsuperscript{33} Analyses of 239 cases with MM and 220 controls revealed an increased risk for MM in those with first-degree blood relatives with hematologic malignancies (RR = 2.36, 90\% CI, 0.9 to 6.15); this held true for first-degree relatives of MM patients (RR=5.64, 90\%CI, 1.16 to 27.51). Additional investigation conducted by Domingo-Domenech \textit{et al.} examined 588 consecutive newly diagnosed patients with 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. 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, as compared with controls.\textsuperscript{34}

In another study, conducted by Ogmundsdóttir \textit{et al.}, a family registry of MM patients was compared with the population-based Icelandic Cancer Registry in
order to assess the prevalence of hematologic malignancies in relatives of MM patients." Data revealed almost a two-fold increased risk for first-degree female relatives of MM probands for a grouping of hematologic malignancies (ICD-10 codes C81-C96) (RR = 1.95, 95% CI, 1.1 to 3.2). From the 218 MM probands, eight families were identified in which the proband had more than one relative with MGUS and more than one with another hematologic malignancy; in four of these families, another relative had MM, and in three, 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. From 8,406 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 regarding 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 to 2.73) vs. relatives of controls. Risk was even greater for relatives of cases 65 or older (RR = 2.5, 95% CI, 1.19 to 5.27) and female relatives (RR = 3.97, 95% CI, 1.54 to 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 (HL), Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), and Soft Tissue Sarcoma (STS) in individuals with at least one relative with a prior malignancy."
Some small studies have identified associations between MM probands and certain solid tissue tumors in first-degree blood-relatives.\textsuperscript{12,39} More recently, these findings were validated in a study conducted by Kristinsson and colleagues using Swedish population-based data and family linkage.\textsuperscript{40} 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 for developing any solid tumor (RR = 1.1, 95\% CI, 1.0 to 1.1), most notably bladder cancer (RR=1.3, 95\% CI, 1.0 to 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 to 2.9), MGUS (RR=2.1, 95\% CI, 1.5 to 3.1), and acute lymphoblastic leukemia (ALL) (RR=2.1, 95\% CI, 1.0 to 4.2). Overall, the absolute excess risk for solid tumors in first degree relatives of MM patients is very 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 MM patients have a two-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 multiple myeloma

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 (LOH) to the first genome-wide association study (GWAS) of multiple myeloma, to sequencing studies of germline and tumor DNA. For example, a recent paper by Chapman and colleagues examined tumor genome sequences of multiple myeloma patients and matched normals and found mutations in key genes, such as those involved in histone methylation and in the NF-κB pathway. To date, nearly 30 studies have been conducted examining associations between polymorphisms and risk of multiple myeloma; 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 UK and German populations, comprising 1675 cases and 5903 controls. Three novel loci were identified; two reached genome-wide significance (p<5x10^{-8}) at 3p22.1 (rs1052501 in ULK4) and 7p15.3 (rs4487645). This 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 authors, 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 SNPs 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.43,44

Common Genetic Predisposition

As discussed earlier, studies suggest clustering of MGUS with CLL, LPL/WM and NHL8,14-16 and MM with ALL and CLL in families.32-38 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. There have recently been several genetic variants identified for CLL and other subtypes of NHL.45-49 These variants as well as those yet unidentified, may also contribute to familial MGUS and MM.

Future Directions

There are several aspects of familial MGUS and MM that 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 hyper-responsive B-cells and hyperphosphorylated P-7 is necessary, as 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 MGUS patients in order to understand whether some of these factors indicate a predisposition towards 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

Contribution: A.J.G., S.V.R., and C.V.M. did the required background research for this manuscript and wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interest.
References


Table 1. Summary of family studies with monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) probands.6-9,11-13,28,29,31,40

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Population details</th>
<th>Number of probands</th>
<th>Number of relatives of probands</th>
<th>Number of affected relatives</th>
<th>Risk of MGUS/MM (95% CI)</th>
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<tr>
<td>Steingrimsdottir et al. (2011)*</td>
<td>Registry-based family study</td>
<td>Iceland 16 with either MGUS or MM (2 in each family)</td>
<td>4370 total; 350 first-degree</td>
<td>31 (22 identified via registry, 9 via screening)</td>
<td>22 MGUS/41 MM (versus 31 MGUS/57 MM in controls)</td>
<td>Relative risk = 2.8 (1.4-5.6) / 2.9 (1.9-4.3)</td>
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<td>Landgren et al. (2009)</td>
<td>Population-based case-control study</td>
<td>Sweden 4458 (matched with 17505 controls)</td>
<td>14621 (58387 control)</td>
<td>22 MGUS/41 MM (versus 31 MGUS/57 MM in controls)</td>
<td>Relative risk = 2.8 (1.4-5.6) / 2.9 (1.9-4.3)</td>
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<td>Population-based prevalence study</td>
<td>United States (Olmsted County, white) 97</td>
<td>247</td>
<td>30</td>
<td>Risk ratio = 3.3 (2.1-4.8)</td>
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<td>Jain et al. (2009)</td>
<td>Family case study</td>
<td>United States (African American) 2</td>
<td>10**</td>
<td>2 MM**</td>
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<td>Lynch et al. (2008)</td>
<td>Family case study</td>
<td>United States (African American) 3</td>
<td>11 (16 with those with prior MM diagnoses)</td>
<td>3 with abnormal FLC ratios; 5 MM previously identified</td>
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<td><strong>Multiple myeloma probands</strong></td>
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<td>Kristinsson et al. (2009)</td>
<td>Registry-based case-control study</td>
<td>Sweden 13896 (matched with 54,365 controls)</td>
<td>37838 (matched with 151,068 relatives of controls)</td>
<td>42 MGUS/94MM (versus controls)</td>
<td>Relative risk = 2.1 (1.5-3.1) / 2.1 (1.6-2.9)</td>
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<td>Hemminki et al. (2004)</td>
<td>Family study</td>
<td>Sweden 23 parents</td>
<td>-</td>
<td>878 sporadic cases in offspring</td>
<td>SIR = 3.33 (2.1 - 5.0)</td>
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<td>Brown et al. (1999)</td>
<td>Case-control</td>
<td>United States (blacks and whites) 565 (2104 controls)</td>
<td>-</td>
<td>-</td>
<td>Odds Ratio = 3.7 (1.2-12.0)</td>
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<td>Grosbois et al. (1999)</td>
<td>Registry-based family study</td>
<td>104 Intergroupe Francophone du Myelome centers 15</td>
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<tr>
<td>Eriksson et al. (1992)</td>
<td>Case-control</td>
<td>Sweden 239 (220 matched controls)</td>
<td>-</td>
<td>-</td>
<td>Relative risk = 2.36 (0.90-6.15)</td>
<td></td>
</tr>
<tr>
<td>Bourquet et al. (1985)</td>
<td>Case-control</td>
<td>Duke University Medical Center 439 (1317 matched controls)</td>
<td>-</td>
<td>3 (4 in controls)</td>
<td>Relative risk = 2.4 (1.4-4.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Also included Waldenstrom’s macroglobulinemia and multiple myeloma cases in probands

**MGUS families only
Table 2. Genetic variation associated with multiple myeloma.42-44,50-58

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genetic variant</th>
<th>Associated variation</th>
<th>Reference</th>
<th>Odds Ratio (95% CI) *</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAX</td>
<td>rs1042265</td>
<td>G &gt; A</td>
<td>Hosgood et al. (2009)</td>
<td>GA+AA = 0.40 (0.21–0.78)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2.59 (1.30–5.15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p(trend) = 0.005</td>
<td></td>
</tr>
<tr>
<td>CASP9</td>
<td>rs7516435</td>
<td>A &gt; G</td>
<td></td>
<td>AG = 1.48, (0.94–2.32);</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>rs1075838</td>
<td>T &gt; C</td>
<td></td>
<td>1.44 (1.05–1.97)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs11064392</td>
<td>A &gt; G</td>
<td>Lee et al. (2010)</td>
<td>2.36 (1.53–3.63)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>rs2707212</td>
<td>C &gt; T</td>
<td></td>
<td>0.68 (0.49–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>rs7296859</td>
<td>C &gt; G</td>
<td></td>
<td>0.67 (0.48–0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>CD4</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CYP1A1</td>
<td>CYP1A*1</td>
<td>1/*2A and 1/*2B</td>
<td>Kang et al. (2008)</td>
<td>0.43 (0.19-0.98) and 0.51 (0.26-0.98)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>rs17501108</td>
<td>G&gt;T</td>
<td>Purdue et al. (2011)</td>
<td>NA</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>rs46903608</td>
<td>A &gt; G</td>
<td>Ostrovsy et al. (2007)</td>
<td>Chi-squared statistic = 7.276</td>
<td>0.026</td>
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<tr>
<td></td>
<td>889</td>
<td>C &gt; T</td>
<td></td>
<td>5.660 (2.546–12.583)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>511</td>
<td>C &gt; T</td>
<td>Abazis-Stambouleh et al. (2007)</td>
<td>0.057 (0.019–0.186)</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>p3954</td>
<td>CC</td>
<td></td>
<td>0.057 (0.019–0.167)</td>
<td>&lt;0.0001</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IL-1RN</td>
<td>Mspa1 p11100</td>
<td>-</td>
<td></td>
<td>0.044 (0.011–0.171)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>rs6684439</td>
<td>T &gt; C</td>
<td></td>
<td>2.9 (1.2-7.0)</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>rs7529229</td>
<td>C &gt; T</td>
<td>Birmann et al. (2009)</td>
<td>2.5 (1.1-6.0)</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>rs8192284</td>
<td>C &gt; A</td>
<td></td>
<td>2.5 (1.1-6.0)</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>rs1801278</td>
<td>C &gt; T</td>
<td></td>
<td>4.3 (1.5-12.1)</td>
<td>0.68</td>
</tr>
<tr>
<td>IRS1</td>
<td>rs12621278</td>
<td>A &gt; G</td>
<td>Cooper et al. (2011)</td>
<td>11.19 (1.56-80.35)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>rs2735839</td>
<td>G&gt;A</td>
<td></td>
<td>0.05 (0.00-0.50)</td>
<td>0.07</td>
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<tr>
<td></td>
<td>rs2385094</td>
<td>G &gt; C</td>
<td>Lee et al. (2010)</td>
<td>1.49 (1.08–2.04)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>rs3782735</td>
<td>G &gt; A</td>
<td></td>
<td>0.67 (0.48-0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>rs9391981</td>
<td>G &gt; C</td>
<td>Hosgood et al. (2009)</td>
<td>0.32 (0.12 – 0.81)</td>
<td>0.005</td>
</tr>
<tr>
<td>SERPINE1</td>
<td>rs2227667</td>
<td>A &gt; G</td>
<td>Purdue et al. (2011)</td>
<td>NA</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>rs12147254</td>
<td>G &gt; A</td>
<td>Du et al. (2011)</td>
<td>0.709</td>
<td>0.001</td>
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<tr>
<td>TRAF3</td>
<td>rs3783605</td>
<td>A &gt; G</td>
<td>Idelman et al. (2007)</td>
<td>NA</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>rs963248</td>
<td>G &gt; C</td>
<td>Hayden et al. (2007)</td>
<td>1.51 (1.10-2.08)</td>
<td>0.0133</td>
</tr>
<tr>
<td>XRCC4</td>
<td>rs1052501</td>
<td>C &gt; A</td>
<td></td>
<td>1.5 (1.16–1.95)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ULK4</td>
<td>rs4487645</td>
<td>G &gt; A</td>
<td>Broderick et al. (2011)</td>
<td>1.34 (1.00–1.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DNAH11,</td>
<td>rs6746082</td>
<td>A &gt; C</td>
<td></td>
<td>1.22 (0.91–1.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intron 80</td>
<td>rs1859962</td>
<td>T &gt; G</td>
<td></td>
<td>6.89 (0.71-66.43)</td>
<td>0.09</td>
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<tr>
<td></td>
<td>rs2660753</td>
<td>C &gt; T</td>
<td>Cooper et al. (2011)</td>
<td>24.33 (2.39-247.56)</td>
<td>0.07</td>
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<tr>
<td></td>
<td>rs5759167</td>
<td>G &gt; T</td>
<td></td>
<td>11.50 (1.04-127.69)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Odds ratio unless otherwise noted
Familial monoclonal gammopathy of undetermined significance and multiple myeloma: epidemiology, risk factors, and biological characteristics

Alexandra J. Greenberg, S. Vincent Rajkumar and Celine M. Vachon