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Differences in the distribution of cytogenetic subtypes between multiple myeloma patients with and without a family history of monoclonal gammopathy and multiple myeloma

Alexandra J. Greenberg^{1,2}, Margot Cousin², Shaji Kumar³, Rhett P. Ketterling⁴, Ryan A. Knudson⁴, Dirk Larson⁵, Colin Colby⁵, Christopher Scott⁵, Celine M. Vachon¹, and S. Vincent Rajkumar³

¹Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN

²Mayo Clinic Center for Translational Science Activities, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN

³Division of Hematology, Department of Internal Medicine, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN

⁴Division of Laboratory Genetics, Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN

⁵Division of Biomedical Statistics and Informatics, Department of Health Science Research, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN

Abstract

We previously reported an increased risk of monoclonal gammopathy of undetermined significance (MGUS) in first-degree relatives of MGUS and multiple myeloma patients. Here, we examine whether primary cytogenetic categories of myeloma differ between patients with and without a family history of MGUS or myeloma. We studied 201 myeloma patients with available data on family history and molecular cytogenetic classification. Myeloma with trisomies was more common in probands who had an affected first-degree relative with MGUS or myeloma compared to those without a family history (46.9% vs. 33.5%, $p=0.125$); however, the difference was not statistically significant. Additional studies on the cytogenetic types of myeloma associated with familial tendency are needed.

Keywords

Multiple myeloma; MGUS; family history; cytogenetics

Correspondence to: S. Vincent Rajkumar, MD, Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905 rajkumar.vincent@mayo.edu.

Contribution: A.J.G., M.C., C.M.V., and S.V.R. conceived of the study question and wrote the paper with comments from all coauthors; C.M.V. was responsible for study design and overseeing the project; R.A.K. and R.P.K. helped in strategizing the project, contributed study populations, and interpreted study findings; C.S., D.R.L., and C.L.C. performed all statistical analyses and contributed to their interpretation; S.K.K. provided scientific input and interpretation of analyses; all coauthors read and approved the paper.

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Introduction

Multiple myeloma (MM), a plasma cell cancer, is the third most prevalent hematologic malignancy worldwide. In the United States alone, there are 20,000 new cases of MM every year and 12,000 MM-associated deaths (1, 2). While the etiology of MM is not fully understood, one known risk factor is having a family history of either monoclonal gammopathy of undetermined significance (MGUS), a precursor for MM, or MM itself (3–5).

MM is cytogenetically and clinically heterogeneous, suggesting not a single disease, but rather a collection of six or more diseases (6). Different cytogenetic subtypes are associated with different prognoses; for example, patients with trisomies have a median overall survival of 7–10 years, while patients with t(14;16) and t(14;20) have a median overall survival of only 2–3 years, even with improvements in current therapy (7). The presence of trisomies ameliorates the adverse prognosis associated with some high risk cytogenetic subtypes (8). There is also a differential response to therapy based on underlying cytogenetic subtype. For example, bortezomib-based combinations appear to improve prognosis and survival for patients with t(4;14), while therapeutic regimens using immunomodulatory agents appear to be particularly effective in patients with t(11;14) or trisomies (6, 9–11). Furthermore, presentation is also clinically heterogeneous; whether this variation is associated with cytogenetic subtype is yet to be determined. (12)

While the distribution of cytogenetic subtypes and prognostic significance has been previously investigated, there are no data available on whether a difference exists in the distribution of cytogenetic subtypes between patients with and without a family history of MGUS and MM (13). Our aim was to estimate the prevalence of cytogenetic subtypes in MM probands with and without a family history of MGUS and/or MM, and to examine whether there is a higher prevalence of high-risk cytogenetic subtypes [t(4;14), t(14;16), and t(14;20)] in patients with a positive family history.

Methods

Study probands

MM probands were recruited from patients seen at the Mayo Clinic from February 2006 through September 2007. Eligible patients were invited to participate via a letter distributed during their clinical appointment (Vachon, *et al* 2009). Consent forms and questionnaires were sent to each consenting proband and solicited names and addresses of first-degree relatives for contact. Of these 232 MM probands, family history information regarding MGUS and MM status was available for 201 probands.

First-degree relatives

An invitation, risk factor questionnaire, and informed consent form were mailed to all first-degree relatives identified by probands. History of MM was self-reported on the questionnaire. Upon receipt of the completed consent form, a blood collection kit was mailed to relatives for blood to be collected at a local facility and returned to Mayo Clinic to determine presence or absence of MGUS by electrophoresis and immunofixation.

FISH and Cytogenetic Studies

All FISH and cytogenetic data were retrieved from the electronic medical record at the Mayo Clinic. All studies were completed at Mayo Medical Laboratories (Rochester, MN). Briefly, aspirate samples were enriched for mononuclear cells using the Ficoll method and

cytospin slides were prepared. FISH analysis was performed as previously described (14). Classical cytogenetic banded analysis was also performed on a subset of samples.

Statistical Analyses and Considerations

Based on the results of the FISH and cytogenetic studies, patients were divided into the various cytogenetic subtypes of MM (Table 1). Family history was categorized as “positive” if a first degree relative had MGUS or MM; and “negative” if no first degree relatives had MGUS or MM diagnosis (15). We examined whether distribution of the following subgroups differed by family history of MM or MGUS: trisomies, IgH translocation without trisomies, IgH translocation with trisomies, monosomies 13 and/or 14 in absence of translocations or trisomies, other, and normal. Patients who showed disruption of IGH, but had no identified translocation partner, were categorized as “other.” Fisher’s exact test was used to test for differences between cytogenetic subgroups and family history. Additional analyses were conducted to evaluate the possible confounding influence of age on the association between family history and cytogenetics. All analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria).

Results and Discussion

Of 201 eligible patients in the family study, the necessary FISH and/or cytogenetic data (with sufficient plasma cells) to establish the primary molecular cytogenetic classification of myeloma was available on 198 patients (96 had chromosome analysis only and 102 had both FISH and chromosome analysis). Of these, 49 (24.7%) had an affected first-degree relative with MGUS or MM. There was no association of age with cytogenetic subtype (data not shown).

The distribution of cytogenetic abnormalities between patients with and without a family history is shown in Table 1. Individuals with a family history of MGUS or MM had a higher rate of trisomies (with or without IgH translocations) compared with patients who did not have a family history of MGUS or MM (46.9% vs 33.5%), although this difference did not reach statistical significance ($p=0.125$). We found no significant difference in rates of IgH translocated MM (regardless of trisomy status) in myeloma patients with a positive family history of MGUS or MM than patients without a family history (22.4% vs. 19.1%, $p>0.05$).

Previously, we and others found an increased prevalence of heavy-chain MGUS in first-degree relatives of individuals with either heavy-chain MGUS or MM (Vachon, *et al*, 2009; Landgren, 2009). Here, we provide the first examination of the prevalence of the major cytogenetic translocations in MM patients with and without a family history of MGUS. We found that there is greater incidence of trisomies in patients with familial tendency compared to those without a family history. Although the difference did not reach statistical significance, this observation is intriguing and needs further study. Based on our argument that MM is not a single disease, we hypothesized that select cytogenetic subtypes of MM will be associated with a familial tendency. Our results lend some support to this hypothesis. Additional insight could also be gained by examining whether cytogenetic subtypes are shared in pairs of relatives with MGUS and/or MM to determine if specific abnormalities cluster in families, which could suggest a similar underlying genetic basis.

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References

1. Jemal A, Siegel R, Ward E. Cancer Statistics, 2010. *CA Cancer J Clin.* 2010; 60 (5):277–300. [PubMed: 20610543]
2. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc.* 2003; 78(1):21–33. [PubMed: 12528874]
3. Greenberg AJ, Rajkumar SV, Vachon CM. Familial monoclonal gammopathy of undetermined significance and multiple myeloma: epidemiology, risk factors, and biological characteristics. *Blood.* 2012; 119(23):5359–66. [PubMed: 22354002]
4. Greenberg AJ, Rajkumar SV, Larson DR, Dispenzieri A, Therneau TM, Colby CL, Phelps TK, Kumar SK, Katzmman JA, Kyle RA, Slager SL, Vachon CM. Increased prevalence of light chain monoclonal gammopathy of undetermined significance (LC-MGUS) in first-degree relatives of individuals with multiple myeloma. *Br J Haematol.* 2012; 157(4):472–5. [PubMed: 22629552]
5. Vachon CM, Kyle RA, Therneau TM, Foreman BJ, Larson DR, Colby CL, Phelps TK, Dispenzieri A, Kumar SK, Katzmman JA, Rajkumar SV. Increased risk of monoclonal gammopathy in first-degree relatives of patients with multiple myeloma or monoclonal gammopathy of undetermined significance. *Blood.* 2009; 114(4):785–90. [PubMed: 19179466]
6. Kumar S, Fonseca R, Ketterling RP, Dispenzieri A, Lacy MQ, Gertz MA, Hayman SR, Buadi FK, Dingli D, Knudson RA, Greenberg A, Russell SJ, Zeldenrust SR, Lust JA, Kyle RA, Bergsagel L, Rajkumar SV. Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics. *Blood.* 2012; 119(9):2100–5. [PubMed: 22234687]
7. Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2012; 87(1):78–88. [PubMed: 22180161]
8. Kumar S, Fonseca R, Ketterling R, Dispenzieri A, Lacy M, Gertz M, Hayman S, Buadi F, Dingli D, Knudson R, Greenberg A, Russell S, Zeldenrust S, Lust J, Kyle R, Bergsagel L, Rajkumar S. Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics. *Blood.* 2012; 119(9):2100–5. [PubMed: 22234687]
9. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Patani L, Galli M, Raimondo FD, Crippa C, Zamagni E, Palumbo A, Offidani M, Corradini P, Narni F, Spadano A, Pescosta N, Deliliers GL, Ledda A, Cellini C, Caravita T, Tosi P, Baccarani M. Network "GIM. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet.* 2010; 376(9758):2075–85. [PubMed: 21146205]
10. Barlogie B, Anaissie E, Rhee FV, Haessler J, Hollmig K, Pineda-Roman M, Cottler-Fox M, Mohiuddin A, Alsayed Y, Tricot G, Bolejack V, Zangari M, Epstein J, Petty N, Stewart D, Jenkins B, Gurley J, Sullican E, Crowley J, Shaughnessy JDJ. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. *Br J Haematol.* 2007; 138(2):176–85. [PubMed: 17593024]
11. Rajkumar SV. Treatment of multiple myeloma. *Nat Rev Clin Onc.* 2011; 8(8):497–1.
12. Talamo G, Farooq U, Zangari M, Liao J, Dolloff NG, Loughran TPJ, Epner E. Beyond the CRAB symptoms: a study of presenting clinical manifestations of multiple myeloma. *Clin Lymphoma Myeloma Leuk.* 2010; 10(6):464–8. [PubMed: 21156463]
13. Fonseca R, Bergsagel PL, Drach J, Shaughnessy J, Guterrez N, Stewart AK, Moran G, Ness BV, Chesi M, Minvielle S, Neri S, Barlogie B, Kuehl WM, Liesbisch P, Davies F, Chen-Kiang S, Durie BG, Carrasco R, Sezer O, Reiman T, Pilarski L, Avet-Loiseau H, Group IMW. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia.* 2009; 23(12):2210–21. [PubMed: 19798094]
14. Kumar S, Mikhael J, Buadi F, Dingli D, Dispenzieri A, Fonseca R, Gertz M, Greipp P, Hayman S, Kyle R, Lacy M, Lust J, Reeder C, Roy V, Russell S, Short K, Stewart A, Witzig T, Zeldenrust S, Dalton R, Rajkumar S, Bergsagel P. Management of newly diagnosed symptomatic multiple

myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. *Mayo Clin Proc.* 2009; 84(12):1095–110. [PubMed: 19955246]

15. Vachon CM, Kyle RA, Therneau TM, Foreman BJ, Larson DR, Colby CL, Phelps TK, Dispenzieri A, Kumar SK, Katzmann JA, Rajkumar SV. Increased risk of monoclonal gammopathy in first-degree relatives of patients with multiple myeloma or monoclonal gammopathy of undetermined significance. *Blood.* 2009; 114:785–90. [PubMed: 19179466]

Table 1

Distributions of cytogenetic abnormalities by family history of MGUS and/or MM based on FISH and cytogenetic testing.

Cytogenetic Abnormality	Myeloma probands with one or more affected first-degree relatives (n=49) n (%)	Myeloma probands with no affected first-degree relatives (n = 152) n (%)
Trisomy (ies)	20 (40.8%)	44 (28.9%)
IgH Translocation without trisomies	8 (16.3%)	22 (14.5%)
IgH Translocation with trisomies	3 (6.1%)	7 (4.6%)
Monosomy 13 and/or 14 in absence of translocations or trisomies	3 (6.1%)	10 (6.6%)
Other	2 (4.1%)	4 (2.6%)
Abnormal by chromosome studies/FISH not done	1 (2.0%)	2 (1.3%)
Normal by chromosome studies/FISH not done	11 (22.4%)	61 (40.1%)
No genetic studies done	1 (2.0%)	2 (1.3%)

* No probands were found to be normal by FISH studies or insufficient by FISH studies.