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HLA polymorphism and Risk of Multiple Myeloma

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The 2-to-3-fold increased risk of multiple myeloma (MM) within families, and among African Americans vs. Whites support a role of genetic factors in disease development(1, 2). HLA proteins initiate immune surveillance through peptide presentation to T-cell receptors(3). Each HLA allele has the capability of presenting a differing limited repertoire of peptides derived from self and non-self proteins, therefore HLA polymorphim has been associated with numerous immune-mediated diseases(4).

A genome wide association study (GWAS) of MM identified a risk variant within the major histocompatibility complex (MHC) but the associated SNP (rs228580) was not directly characterized with classical HLA typing(5). GWAS has identified loci in the major histocompatibility region as the strong associations in other B cell malignancies, with p-

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Authorship Contributions:

All authors participated and co-wrote the manuscript. In addition MB and PH designed the study, analyzed the data and interpreted the results. LG, SF, MM, MA, XZ, MZ designed the methods for analysis and analyzed the data. WC, AD and SL interpreted the results and reviewed and edited the paper. MB and LG's contributions to the manuscript were equal.

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There are no conflicts of interest relevant to the content of this manuscript.

values of up to 10^{-60}(6). Previous MM association studies with HLA are limited by sample size(7). Building on work in chronic lymphocytic leukemia (CLL), where a similar analysis identified several HLA alleles associated with susceptibility(8), we comprehensively analyzed HLA associations with MM risk among White, African American, Hispanic, and Asian US populations.

Cases:US MM patients who searched National Marrow Donor Program (NMDP) for potential donors for hematopoietic cell transplantation (HSCT) or had HLA data collected by the Center for International Blood and Marrow Transplant Research (CIBMTR) after transplant (Table 1). HLA typing data were available on 2897 White, 569 African American, 184 Hispanic and 74 Asian / Pacific Islander patients. Independent association studies were conducted with 50,000 controls for each ethnic group. Controls were selected randomly from the NMDP volunteer adult donor registry recruited since 2005 and frequency-matched for patient age quartiles and gender proportions.. Cases and controls were HLA typed using DNA-based methods (Sanger sequence-based typing (SBT) or sequence-specific oligonucleotide (SSO))(9).

Predisposing or protective associations of HLA polymorphisms with MM were identified at: (1) the individual allele level (HLA-A,-C,-B,-DRB3/4/5,-DRB1,-DQB1 loci); (2) haplotype combinations of these loci; and (3) genotypes of the loci. Associations were tested at two levels of HLA typing resolution – allele family and high resolution. DRBX*NNNN designates absence of any DRB3/4/5 gene on the chromosome. Groups of alleles with identical amino acid sequence in the antigen recognition site, designated with a ‘g’ notation, were not distinguished(10).

We developed a novel statistical methodology for fine-mapping of HLA associations, previously applied in CLL(8). We incorporated HLA typing ambiguity into our statistical model, allowing reporting of high-resolution haplotype-level associations. We also employed factor analysis to group associated HLA variants that are highly correlated by linkage disequilibrium(11). Multivariate logistic regression on independent sets of cases and controls for each ethnic subgroup identifies HLA that are associated with MM. P-values were adjusted for multiple testing using False Discovery Rate (FDR) with a 5% threshold; associations for age and gender interactions were unadjusted(12).

Cases and Controls Were Younger than Typical MM Patients: Baseline demographics are summarized in Table 1. Cases and controls are younger (49 years) than the typical median age for MM incidence (69 years). Generalizability of our findings may be limited to younger MM patients and possibly higher risk disease where allogeneic HSCT was considered.

Allele-Level HLA Associations Identified in Whites and Asians: Figure 1 depicts the high resolution allele-level associations for Whites (3 predisposing or positively associated, 3 protective or negatively associated with MM) and Asians (4 predisposing). While no significant high resolution allelic associations were identified among Africans Americans and Hispanics, several allele-family-level and haplotypic associations were detected.

We list all associated haplotypes and alleles at both high-resolution and allele family level for each population, with correlated associations grouped by factor analysis in

Supplementary Table 1. The longest extended haplotypic association within each factor analysis group is provided in Table 1 for each population. Suggestive associations that were no longer significant after correction for multiple testing are listed in Supplementary Table 2.

C*07 Positively Associated with MM Risk: An increased MM risk was observed for both C*07:02g (OR=1.27,P=5.27×10^{-7}) and B*07:02g (OR=1.24,P=3.70×10^{-5}) in Whites. Because these two alleles are in extremely high linkage disequilibrium (D'>0.98)(10), it was not possible to disentangle effects of these alleles in Whites. We found three haplotypes containing these alleles independently associated with MM: A*03~C*07~B*07~DRB5*01~DRB1*15~DQB1*06 (OR=1.27,P=0.03), A*03:01g~C*07:02g~B*07:02g (OR=1.33,P=4.68×10^{-5}), and C*07:02g~B*07:02g~DRB4*01:01g~DRB1*04:01~DQB1*03:02g (OR=1.85,P=0.0497) (Table 1A).

While neither single allele C*07:02g nor B*07:02g was associated with MM in other populations, several extended haplotype associations containing C*07 were positively associated with MM in Hispanics and Asians also. Haplotypes A*24:02g~C*07:02g~B*39:06~DRB3*01:01~DRB1*14:06~DQB1*03:01g (OR=3.93,P=0.0016) and A*68:02~C*07:01g~B*57:03 (OR=2.94,P=0.039) in Hispanics (Table 1C) and haplotypes C*07~B*38~DRB5*01~DRB1*15~DQB1*05 (OR=3.91,P=0.0094) and C*07:02g~B*15:35 were associated in Asians (OR=8.99,P=2.23×10^{-5}) (Table 1D). Because C*07, but not B*07, was associated across populations, we infer that C*07 most likely drives the association with increased risk.

C*05:01g Negatively Associated with MM Risk: C*05:01g was negatively associated with MM in Whites (OR=0.85,P=0.039) along with B*44:02g (OR=0.85,P=0.044) on the same haplotype (Table 1A). The negative association of MM risk with C*05:01g, but not B*44:02g, was statistically significant in Hispanics and African Americans (Supplementary Table 2).

Many Other HLA Associations Were Unique to Single Populations: Differences in the frequency of HLA alleles, their underlying LD with other genes, and interactions with other genes that differ in LD and frequency across populations may account for heterogeneous HLA associations across populations[14]. For example, positively associated alleles A*34:01, B*15:35, B*27:05g, and DQB1*05:02g were not replicated across populations. C*02:02g was predisposing in Whites (OR=1.20,P=0.039) (Figure 1), with higher risk observed when C*02:02g occurred on a haplotype lacking a DRB3/4/5 gene, C*02:02g~DRBX*NNNN (OR=1.50,P=0.042) (Table 1A). Among African Americans, two independent haplotype associations (C*04~B*15 and DRB3*02~DRB1*11~DQB1*02) were associated with increased risk of MM (Table 1B).

We tested for interactions of HLA associations with age (Supplementary Table 3) and gender (Supplementary Table 4). None of the associations had a gender effect. Genotypic associations, grouped by factor analysis, are listed in Supplementary Table 5.

With the large numbers of cases/controls across four population groups, this study represents the most extensive examination of associations of HLA variants with MM risk. . Our results using classical HLA typing and haplotype inference clarify findings from a recent GWAS in Northern European Whites (4,692 MM cases and 10,990 controls) where HLA alleles were imputed from MHC region SNPs(5). The most significant GWAS association was DRB5*01 (OR 1.22,P=1.42×10^{-5}), while C*07:02g and B*07:02g were also listed as apparently independent MM risk factors in the GWAS. We confirmed these three risk alleles, and illustrate their high correlation by linkage disequilibrium in Whites. Cross-population analysis suggests C*07 as the independent risk allele, while B*07:02 and DRB5*01 are likely surfacing on the same haplotype rather than contributing to MM risk. Similarly confirmed were, the protective association with MM of C*05:01g and B*44:02g alleles occurring on the same haplotype in Whites and the predisposing associations of C*12:03g~B*38:01 haplotype and B*58:01g in Whites and Asians respectively (Supplementary Table 2). While the cause of the positive risk association for C*07:02 is unclear from our data, it is known that C*07 group alleles have the lowest levels of expression among HLA-C alleles, which reduces immune control of HIV and may likewise reduce control of MM(13). C*07:02 is also a C1 group ligand for inhibitory KIR2DL2/2DL3 receptors on natural killer cells, and this KIR/HLA genotype combination has been associated with increased risk of melanoma(14).

The HLA associations observed here and in GWAS demonstrate that the HLA region is a key risk locus for mature B-cell malignancies(15, 16). MM etiology often involves clonal immunoglobulin production directed against post-translationally modified human proteins, such as hyperphosphorylated paratarg-7 (P-7) or sumoylated Hsp90(17, 18). HLA presentation of altered self-antigens derived from these modified proteins within B cells to T cell receptors could stimulate production of autoantibodies. Additional research is needed to characterize differences among HLA alleles in presentation of these altered self-antigens and to identify additional antigenic targets of MM clones(19). While inherited variation in immunologic response to protein-derived peptides may explain some of the increased risk of MM, because odds ratios for HLA were modest, genetic differences within oncogenes probably account for most of this differing risk. Interactions between HLA variants and myeloma subtypes / somatic mutations may also impact efficacy of emerging immunotherapy in MM(20). Identification of MM associated peptides bound by HLA alleles would be important next steps in developing immune oncologic therapies in MM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

1. Inherited HLA polymorphisms influence risk for developing multiple myeloma
2. HLA variation impacts immune surveillance of cancer

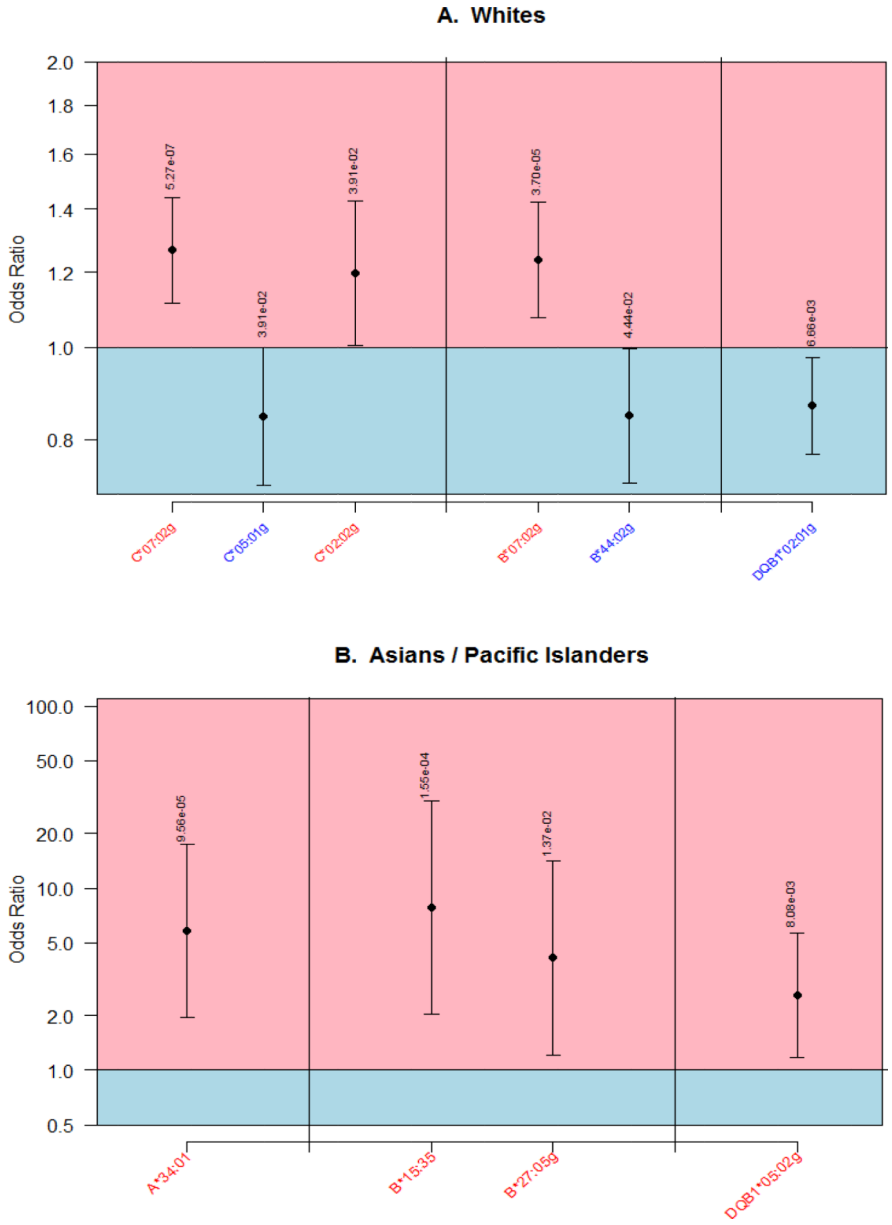

Figure 1.

High resolution HLA alleles associated with Multiple Myeloma among Whites (A) and Asian / Pacific Islanders (B)

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Table 1

Haplotype Associations:

Table 1A: Extended HLA Haplotype Associations from Factor Analysis for Whites						
Variant	**Control Frequency**	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**FDR P**	**Factor Analysis**
A*03~C*07~B*07~DRB5*01~DRB1*15~DQB1*06	0.030	1.27	1.01	1.61	3.00E-02	Group 1
A*02~C*05~B*44~DRB4*01~DRB1*04~DQB1*03	0.024	0.67	0.45	0.97	2.15E-02	Group 2
A*03:01g~C*07:02g~B*07:02g	0.051	1.33	1.10	1.61	4.68E-05	Group 3
C*05~B*44~DRB4*01~DRB1*04~DQB1*03	0.031	0.71	0.52	0.96	9.82E-03	Group 4
C*05:01g~B*44:02g	0.075	0.80	0.66	0.96	4.42E-03	Group 5
C*07:02g~B*07:02g~DRB4*01:01g~DRB1*04:01~DQB1*03:02g	0.003	1.85	1.00	3.43	4.97E-02	Group 6
C*06:02g~B*57:01g~DRB4*01:01g~DRB1*07:01g~DQB1*02:01g	0.005	0.41	0.17	1.03	4.97E-02	Group 7
C*05:01g~B*44:02g~DRB4*01:01g~DRB1*04:01	0.027	0.71	0.52	0.99	3.00E-02	Group 8
DRB1*15:01~DQB1*06:03g	0.001	5.31	1.75	16.15	5.00E-05	Group 9
C*02:02g	0.043	1.20	1.01	1.43	3.91E-02	Group 10
DQB1*02:01g	0.220	0.87	0.77	0.98	6.66E-03	Group 11
C*02:02g~DRBX*NNNN	0.007	1.50	1.01	2.24	4.20E-02	Group 12

Table 1B: Extended HLA Haplotype Associations from Factor Analysis for African Americans						
Variant	**Control Frequency**	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**FDR P**	**Factor Analysis**
C*04~B*15	0.003	2.87	1.01	8.19	4.57E-02	Group 1
DRB3*02~DRB1*11~DQB1*02	0.001	4.61	1.15	18.46	1.59E-02	Group 2

Table 1C: Extended HLA Haplotype Associations from Factor Analysis for Hispanics						
Variant	**Control Frequency**	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**FDR P**	**Factor Analysis**
A*02~C*04~B*35~DRB3*01~DRB1*14~DQB1*03	0.0035	5.43	1.88	15.69	2.74E-04	Group 1
A*24:02g~C*07:02g~B*39:06~DRB3*01:01~DRB1*14:06~DQB1*03:01g	0.0053	3.93	1.57	9.83	1.63E-03	Group 2
DRBX*NN NN~DRB1*08:04~DQB1*03:01g	0.0052	3.37	1.09	10.40	2.45E-02	Group 3
A*68:02~C*07:01g~B*57:03	0.0040	2.94	1.04	8.26	3.92E-02	Group 4

Table 1D: Extended HLA Haplotype Associations from Factor Analysis for Asians						
Variant	**Control Frequency**	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**FDR P**	**Factor Analysis**
C*03:02g~B*58:01g~DRB3*02:02g~DRB1*03:01~DQB1*02:01g	0.0269	2.40	1.04	5.58	3.91E-02	Group 1
DRB5*01~DRB1*15~DQB1*05	0.0497	2.98	1.26	7.08	3.85E-03	Group 2
B*27:05g	0.0074	4.14	1.21	14.17	2.29E-03	Group 3
A*34:01~DRB1*15:02	0.0074	7.68	2.66	22.12	3.17E-05	Group 4
C*07~B*38~DRB5*01~DRB1*15~DQB1*05	0.0135	3.91	1.30	11.82	9.38E-03	Group 5
DRB5*01~DRB1*15~DQB1*06	0.1251	0.39	0.16	0.97	3.90E-02	Group 6
C*07:02g~B*15:35	0.0060	8.99	2.53	31.97	2.23E-05	Group 7
DRBX*NN~DRB1*01~DQB1*05	0.0268	2.51	1.04	6.06	3.46E-02	Group 8

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