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Associations of common variants in genes involved in metabolism and response to exogenous chemicals with risk of multiple myeloma

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Abstract

Background—We examined risk of multiple myeloma (MM) associated with variants in genes involved in metabolism and response to exogenous chemicals [cytochrome P450 enzymes (*CYP1B1*, *CYP2C9*), epoxide hydrolase (*EPHX1*), paraoxonase 1 (*PON1*), arylhydrocarbon hydroxylase receptor (*AHR*), and NAD(P)H:quinone oxidoreductase (*NQO1*)].

Methods—This study included 279 MM cases and 782 controls in a pooled analysis of two population-based case control studies. One common variant from each candidate gene was genotyped using DNA from blood or buccal cells. We estimated risk of MM associated with each genotype, controlling for race, gender, study site, and age, using odds ratios (OR) and 95% confidence intervals (CI).

Results—Evaluations of the *CYP1B1* V432L variant (rs1056836) suggested increased risk of MM among persons with the CG and GG genotypes compared to the CC genotype [OR (95% CI) = 1.4 (1.0–2.0)]. Similar results were seen in analyses stratified by race and gender. We did not find any associations between MM and the *CYP2C9*, *EPHX1*, *NQO1*, or *PON1* genes.

Conclusions—*CYP1B1* activates chemicals such as polycyclic aromatic hydrocarbons and dioxins to create oxidized, reactive intermediates, and higher gene activity has been shown for the G allele. We conducted the largest analysis to date on MM and these genetic variants and our results provide preliminary evidence that variation in *CYP1B1* may influence susceptibility to MM.

Author's Keywords

arylhydrocarbon hydroxylase receptor (AHR); cytochrome P450 enzymes (CYP1B1, CYP2C9); epoxide hydrolase (EPHX1); multiple myeloma; NAD (P) H: quinone oxidoreductase (NQO1); paraoxonase 1 (PON1)

INTRODUCTION

Genetic factors have been implicated in MM etiology from several family- and population-based studies [1–3]. In addition, African Americans are two times more likely to develop MM and are more likely to die of this disease than Caucasians, also suggesting that genetic factors may play a role in the incidence and progression of MM [4].

Several occupational exposures have also been identified as risk factors for MM, albeit with conflicting results. For example, farmers consistently have been found to be at increased risk [5–10] and exposure to pesticides has been associated with MM in some studies [11–19] but not in others [20–22]. Organic solvents [23–25], particularly benzene [26–28], have been associated with MM in several studies, but again, others have had conflicting results [29–32]. The toxicological effects of exogenous chemicals are dependent on genes that affect their metabolism and biologic responses and therefore polymorphisms in these genes may alter risk of MM.

To gain new insight into the etiology of MM, we analyzed variants in several candidate genes that are involved in metabolism or biological response to exogenous chemicals that are under investigation as possible risk factors for MM. The genes we selected included arylhydrocarbon hydroxylase receptor (*AHR*), two cytochrome P450 enzymes (*CYP1B1*, *CYP2C9*), epoxide hydrolase (*EPHX1*), NAD (P) H: quinone oxidoreductase (*NQO1*), and paraoxonase 1 (*PON1*). *AHR* is involved in biological response to organochlorine hydrocarbons by affecting transcriptional regulation of *CYP1A1*, *CYP1A2*, *CYP1B1*, and several other genes [33]. Similarly, *CYP1B1*, *CYP2C9*, and *EPHX1* take part in the metabolism of a variety of chemicals encountered occupationally and environmentally such as pesticides, solvents, and polycyclic aromatic hydrocarbons (PAHs) [34]. *PON1* metabolizes organophosphate pesticides to which farm workers and gardeners are commonly exposed. *NQO1* metabolizes benzene, which is used in a variety of industrial processes, particularly manufacturing, and PAHs, commonly found in the metal-working and textile industries, among others [35–37]. We aimed to estimate the main effects of the gene variants with MM, regardless of chemical exposures, to determine the importance of the genotypes in the context of population-wide MM etiology.

MATERIALS AND METHODS

Study population

Our analysis included data and specimens with cases identified from the Surveillance, Epidemiology, and End Results (SEER) programs of the greater Seattle/Puget Sound and Detroit regions, as well as the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource, a component of the Connecticut Tumor Registry [38,39]. Eligible cases were residents of the Seattle/Puget Sound region, Detroit metropolitan area, or the state of Connecticut, aged 35–74 years, with a diagnosis of MM (ICD-O-2 M9731:2) made between 2000 and 2002 in Seattle and Detroit and between 1996 and 2002 in Connecticut. Cases with reported diagnoses of HIV or non-Hodgkin's lymphoma (NHL) in Detroit and Seattle or any cancer except non-melanoma skin cancer in Connecticut were ineligible for these studies. In Connecticut, only women were enrolled because the original

purpose of that study was to examine risks involved with exposure to hair dye products among women. Of the potential total of 775 eligible MM cases identified, 150 (19%) died before they were contacted for an interview and 232 (30%) refused to participate (145 (19%) were patient refusals and 87 (11%) were physician refusals). A total of 365 eligible MM cases agreed to participate from all study sites, corresponding to a response rate of 58% among survivors. Of these, 294 (81%) were successfully genotyped for at least one candidate gene. To minimize confounding due to population stratification, we excluded 15 cases with who did not report race or who reported a race other than African American or Caucasian, leaving 279 MM cases that were included in this study.

A population-based control group (n=948) was originally enrolled for a study of NHL [40–44] using random digit dialing for controls less than 65 years or Medicare files for those who were older than 65. Controls were age-matched to the NHL cases, but were not matched specifically to the MM cases. The participation rate of all controls was 54%. Of the control population, 799 (84%) were successfully genotyped for at least one variant and 17 of these were excluded because they did not report race or reported race other than African American or Caucasian, leaving 782 total controls in this study. The case-control studies and related materials were approved by the appropriate Institutional Review Boards.

Genotyping

DNA was extracted using phenol-chloroform extraction [45] and genotyped by TaqMan-based real-time PCR on an ABI 7900HT sequence detection system at the Core Genotyping Facility of the National Cancer Institute as described on the SNP500 website (<http://www.snp500cancer.nci.nih.gov>) [46]. We genotyped samples for the following variants: *AHR* R554K (rs#2066853), *CYP1B1* V432L (rs#1056836), *CYP2C9* R144C (rs#1799853), *EPHX1* H139R (rs#2234922), *NQO1* P187S (rs#1800566), and *PON1* Q192R (rs#662). These were chosen because the rarity of MM required pooling of cases across multiple sites and these were the variants that were common at all sites in our study. Quality control was checked by a blinded duplicate analysis of 10% of study samples, which demonstrated greater than 99% concordance with original analyses.

Statistical Analysis

Departure from Hardy-Weinberg proportions was examined separately among African American and Caucasian controls using the Pearson chi-square test. We calculated odds ratios (OR) and 95% confidence intervals (CI) associated with each genotype using unconditional logistic regression separately among African American and Caucasian participants (controlling for sex, age, and study site [Detroit, Seattle, and Connecticut]), by sex (controlling for race, age, and study site), and then for all subjects combined, adjusting for age, race, sex, and study site. Common homozygote genotypes served as the reference group in each model and codominant and dominant genetic models were examined. Tests of trend were calculated for each variant by modeling the genotype as a continuous variable (0=wild-type; 1=heterozygote; 2=homozygous variant). We conducted Breslow-Day tests for heterogeneity for each SNP across the three study sites; none were significant, so we present results with all study sites combined. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Demographic characteristics of the study population, stratified by study site, are shown in Table 1. As expected since the controls were age-matched to NHL cases and MM tends to occur at later ages than NHL, cases tended to be older than controls. Few African Americans participated in Connecticut and Seattle. Education levels also differed among cases and

controls; cases in Connecticut tended to have fewer years of education than controls, whereas the opposite trend was observed in Seattle.

Risk estimates for MM with each gene variant, stratified by race, are listed in Table 2. Allelic frequencies among controls were consistent with those expected under the assumptions of Hardy-Weinberg equilibrium (Table 2; $p \geq 0.01$). Both African American and Caucasian subjects with the cytochrome P450 gene variant *CYP1B1*-V432L (rs1056836) were at greater risk of MM than the homozygous wild-types, but no significant trend was seen with increasing G alleles among African Americans (heterozygotes: OR (95% CI) = 6.5 (1.1–38.4); homozygous variants: OR (95% CI) = 5.5 (0.9–32.2); p-value for trend=0.16) or among Caucasians (heterozygotes: OR (95% CI) = 1.5 (1.1–2.2); homozygous variants OR (95% CI) = 1.4 (0.9–2.2); p-value for trend=0.09).

Caucasian participants with *AHR* R554K (rs#2066853) A-containing alleles were at increased risk of MM compared to the homozygous wild types (heterozygotes: OR (95% CI) = 1.3 (0.9–2.0); homozygous-variants: OR (95% CI) = 4.7 (1.0–22.5); p-value for trend=0.04). This finding was not seen among African American participants.

Females (with both races combined) with G alleles in *CYP1B1* V432L were at increased risk of MM compared to non-carriers (Supplementary Table A; heterozygotes: OR (95% CI) = 1.6 (1.1–2.4); homozygous-variants: OR (95% CI) = 1.6 (1.0–2.7)), with a significant trend of increasing risk with increasing number of variant alleles ($p=0.04$). We did not observe an association between the *CYP1B1* V432L variant and MM in men (African Americans and Caucasians combined) (Supplementary Table B).

An increase in risk was seen among females (African Americans and Caucasians combined) with variant alleles in *AHR* R554K (Supplementary Table A; heterozygotes: OR (95% CI) = 1.6 (1.1–2.4); homozygous-variants: OR (95% CI) = 1.4 (0.4–5.3); p-value for trend=0.03). No analogous increase in risk was seen among males (Supplementary Table B).

For the other variants besides *CYP1B1* V432L, we saw similar patterns of association among African Americans and Caucasians, so we also performed analyses with the races combined (Supplementary Table C). Again, study participants with G alleles in *CYP1B1* V432L were at increased risk of MM (heterozygotes: OR (95% CI) = 1.6 (1.1–2.3); homozygous-variants: OR (95% CI) = 1.4 (0.9–2.2)), but no significant trend was seen with increasing G alleles ($p=0.08$).

We saw no other statistically significant associations or trends with variants in the *CYP2C9*, *EPHX1*, *NQO1*, or *PON1* genes for risk of MM.

DISCUSSION

The increased risk of MM that this population-based case control study observed among participants, especially African Americans, with *CYP1B1* V432L G-alleles warrants further investigation. Analyses restricted to Caucasian participants as well as those restricted to female study subjects showed associations between MM and those with *AHR* R554K A-containing alleles. However, these associations were imprecise and we did not observe associations between *AHR* R554K A-containing alleles and MM in African American or male participants. Additionally, our results suggest that common variants in the *CYP2C9*, *EPHX1*, *NQO1*, or *PON1* genes are not strongly associated with susceptibility to MM.

CYP1B1 is a Phase 1 enzyme that is involved in the activation of several carcinogens that have been linked to MM, including arylamines [47] and dioxins [48]. *CYP1B1* is also responsible for oxidative metabolism of exogenous chemicals, including estrogens [49].

The V432L G (Val) allele of this gene has been associated with higher activity than the C (Leu) allele on several substrates, including procarcinogens [50], which could result in greater likelihood of activation of carcinogenic compounds in individuals with G (Val) alleles [51]. Further, having more G (Val) alleles on *CYP1B1* has been linked to prostate cancer [52] and breast cancer [53]. We observed an association between the G (Val) allele and MM in an analysis restricted to females, contributing support to the hypothesis that the increased activity of *CYP1B1* leads to toxic intermediates that may increase cancer risk in a sex-steroid dependent manner.

Few previous studies examining metabolic gene variants in MM cases have been reported. Lincz et al. [54] found a significant two-fold increased risk of MM in participants who had the homozygous variant genotype (Arg/Arg) of Q192R *PON1*, the same variant of *PON1* that we investigated. Earlier work by these authors also showed a three-fold increase in NHL in homozygous variants of this gene [55]. However, we found no statistically significant relation between the *PON1* variant and MM. Another investigation by Lincz et al. that used most of the same subjects found a five-fold increased risk in Australian Caucasians with homozygous variants (Arg/Arg) in the H139R *EPHX1* gene [56], the same variant we analyzed. Again, we detected no statistically significant relation between the *EPHX1* variant and MM, even when the analysis included only Caucasian participants. The disparities between our findings and these highlight the need for further studies involving MM cases from multiple study sites.

By combining three study sites, we were able to collect data on the largest number of MM patients to date for the genes we analyzed. However, our study had several weaknesses. Although the results seen in African American participants were interesting, our study did not include large numbers of this racial group and our estimates were imprecise. Furthermore, we also cannot rule out residual confounding by race because we simplified race into a binary variable. However, African Americans have been shown to be more likely to have higher activity variants in *CYP1B1* relative to Caucasians and Asian Americans; a meta-analysis including twenty studies showed that 91.5% of African Americans had at least one Val (G) allele compared to 69% of Caucasians and 29.5% of Asian Americans [48]. The fact that African Americans are twice as likely as Caucasians to be diagnosed with MM means that genetic variants that are more common in African Americans should be investigated further to determine the etiology of MM. Additional studies will need to include sufficient numbers of African American participants to determine whether an association exists between MM and genetic variants in the *CYP1B1* gene.

Another limitation of this study is the fairly low response rate from both cases and controls. A recent study, however, found little evidence for differences between variant DNA repair and growth factor genotypes in responders versus non-responders in a breast cancer case-control study [57]. We were unable to determine the extent of the differences between participants and non-participants in our study but we did examine whether cases and controls who provided bio-samples differed with respect to age, gender and race, and education compared to those who did not. We did not find any significant differences in terms of age, gender, or race, but in the highest education category, controls were slightly more likely to have provided samples than cases (88% of controls provided samples compared to 80% of cases). Furthermore, 19% of the eligible cases for this study died before they could be contacted, indicating that the relationships we found may be more applicable to those who live longer with MM. Additionally, we cannot rule out that the associations found in this study were due to chance, especially in sub-analyses by race and gender that had low power, which could possibly have resulted in false positive or false negative findings [58]. We also were unable to address potentially carcinogenic environmental exposures that these participants may have experienced that might have interacted with

genetic variations and affected development of MM. Finally, due to the inherent limitations of the candidate gene approach, we may not have selected the correct genes or variants within genes to determine relationships with MM.

CONCLUSIONS

MM is characterized by cytogenic chromosomal abnormalities and whether exposures to toxins that are metabolized by the genes that we examined in this study contribute to malignant transformations of plasma cells in the bone marrow remains unclear. Studies that delineate the complex relationships between the independent and joint effects of environmental and genetic exposures will be critical to our understanding of MM etiology. In order to obtain adequate power, this will likely require pooling MM cases across several study sites.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of multiple myeloma cases and controls.

Characteristic	All sites			Detroit			Connecticut			Seattle		
	Cases (n=279)	Controls (n=782)	p- value *	Cases (n=77)	Controls (n=96)	p- value *	Cases (n=151)	Controls (n=564)	p- value *	Cases (n=51)	Controls (n=122)	p- value *
Age at diagnosis or selection, yrs												
35–49	30 (11%)	172 (22%)		14 (18%)	27 (28%)		9 (6.0%)	115 (20%)		7 (14%)	30 (25%)	
50–59	73 (26%)	159 (20%)		29 (38%)	23 (24%)		33 (22%)	101 (18%)		11 (22%)	35 (29%)	
60–69	88 (32%)	203 (26%)		21 (27%)	36 (38%)		45 (30%)	128 (23%)		22 (43%)	39 (32%)	
70–75	88 (32%)	248 (32%)	0.0002	13 (17%)	10 (10%)	0.07	64 (42%)	220 (39%)	0.0004	11 (22%)	18 (15%)	0.18
Gender												
Male	77 (28%)	117 (15%)		48 (62%)	52 (54%)		0	0		29 (57%)	65 (53%)	
Female	202 (72%)	665 (85%)	<0.0001	29 (38%)	44 (46%)	0.28	151	564	--	22 (43%)	65 (47%)	0.67
Race												
Caucasian	233 (84%)	726 (93%)		52 (68%)	60 (63%)		131 (87%)	548 (97%)		50 (98%)	118 (97%)	
African American	46 (16%)	56 (7.2%)	<0.0001	25 (32%)	36 (37%)	0.49	20 (13%)	16 (2.8%)	<0.0001	1 (2.0%)	4 (3.3%)	0.99
Education, yrs												
0–11	47 (17%)	80 (10%)		12 (16%)	14 (15%)		28 (19%)	63 (11%)		7 (14%)	3 (2.5%)	
12–15	160 (58%)	429 (55%)		46 (60%)	48 (50%)		92 (61%)	308 (55%)		22 (43%)	73 (60%)	
16 or more	71 (25%)	273 (35%)	0.001	18 (24%)	34 (35%)	0.24	31 (20%)	193 (34%)	0.002	22 (43%)	46 (38%)	0.007

* p-value from chi-square or Fisher's exact statistic comparing case and control distributions

Odds ratios (OR) and 95% confidence intervals (95% CI) for associations between candidate genes and multiple myeloma for African Americans and Caucasians.

Table II

Gene / Locus (alias)	dbSNP Identifier	Genotype	Amino acid change	African Americans					Caucasians				
				Case No. (%)	Control No. (%)	P _{HWE} *	OR (95% CI) [†]	p-value for trend	Case No. (%)	Control No. (%)	P _{HWE} *	OR (95% CI) [†]	p-value for trend
CYP1B1 V432L	rs1056836	CC	Leu/Leu	2 (5%)	10 (19%)		Referent		60 (27%)	237 (34%)		Referent	
		CG	Leu/Val	17 (45%)	17 (31%)		6.50 (1.10–38.4)		113 (52%)	321 (47%)		1.53 (1.05–2.22)	
		GG	Val/Val	19 (50%)	27 (50%)	0.03	5.49 (0.93–32.2)	0.16	45 (21%)	131 (19%)	0.23	1.40 (0.88–2.21)	0.09
		CG/GG		36 (95%)	44 (81%)		2.43 (0.65–9.05)		158 (73%)	452 (66%)		1.42 (0.98–2.04)	
AHR R554K	rs2066853	GG	Arg/Arg	25 (54%)	29 (52%)		Referent		174 (77%)	584 (82%)		Referent	
		AG	Arg/Lys	14 (31%)	16 (29%)		0.99 (0.37–2.65)		49 (21%)	128 (18%)		1.33 (0.91–1.96)	
		AA	Lys/Lys	7 (15%)	11 (20%)	0.01	0.77 (0.22–2.66)	0.72	4 (2%)	3 (0.5%)	0.15	4.71 (0.99–22.5)	0.04
		AG/AA		21 (46%)	27 (49%)		0.91 (0.38–2.23)		53 (23%)	131 (19%)		1.41 (0.97–2.06)	
CYP2C9 R144C	rs1799853	CC	Arg/Arg	39 (87%)	53 (95%)		Referent		171 (75%)	541 (75%)		Referent	
		CT	Arg/Cys	6 (13%)	3 (5%)		1.95 (0.37–10.3)		52 (23%)	169 (23%)		0.93 (0.64–1.35)	
		TT	Cys/Cys	0 (0%)	0 (0%)	0.84	NA	NA	6 (2.5%)	12 (2%)	0.77	1.48 (0.53–4.15)	0.95
		CT/TT							58 (25.5%)	181 (25%)		0.97 (0.68–1.38)	
EPHX1 H139R	rs2234922	AA	His/His	17 (45%)	26 (48%)		Referent		148 (66%)	426 (62%)		Referent	
		AG	His/Arg	20 (53%)	22 (41%)		1.72 (0.68–4.34)		64 (29%)	226 (33%)		0.85 (0.60–1.20)	
		GG	Arg/Arg	1 (2.5%)	6 (11%)	0.68	0.22 (0.02–2.53)	0.98	10 (4.5%)	30 (4%)	0.99	0.84 (0.39–1.84)	0.36
		AG/GG		21 (55.5%)	28 (52%)		1.38 (0.57–3.37)		74 (33.5%)	256 (37%)		0.85 (0.61–1.18)	
NQO1 P187S	rs1800566	CC	Pro/Pro	32 (70%)	43 (78%)		Referent		142 (62%)	466 (65%)		Referent	
		CT	Pro/Ser	13 (28%)	11 (20%)		1.79 (0.66–4.85)		80 (35%)	223 (31%)		1.14 (0.82–1.59)	
		TT	Ser/Ser	1 (2%)	1 (2%)	0.76	0.98 (0.06–17.2)	0.36	8 (3.5%)	31 (4%)	0.51	0.90 (0.39–2.05)	0.65
		CT/TT		14 (30%)	12 (22%)		1.70 (0.65–4.46)		88 (38.5%)	254 (35%)		1.12 (0.81–1.53)	

Gene/ Locus (alias)	dbSNP Identifier	Genotype	Amino acid change	African Americans					Caucasians				
				Case No. (%)	Control No. (%)	P _{HWE} [*]	OR (95% CI) ^I	P- value for trend	Case No. (%)	Control No. (%)	P _{HWE} [*]	OR (95% CI) ^I	P- value for trend
PON1 Q192R	rs662	AA	Gln/Gln	10 (24%)	9 (16%)		Referent		105 (47%)	354 (51%)		Referent	
		AG	Gln/Arg	19 (45%)	27 (49%)		0.68 (0.20–2.26)		96 (43%)	288 (41%)		1.15 (0.82–1.59)	
		GG	Arg/Arg	13 (31%)	19 (35%)	0.91	0.75 (0.20–2.75)	0.74	24 (11%)	56 (8%)	0.81	1.47 (0.85–2.52)	0.16
		AG/GG		32 (76%)	46 (84%)		0.70 (0.22–2.21)		120 (54%)	344 (49%)		1.20 (0.88–1.64)	

^{*} P_{HWE}=p-value for chi-square test of Hardy-Weinberg equilibrium

^I Odds ratios adjusted for age, gender, study site