Tumor Biol. (2016) 37:9549–9554
DOI 10.1007/s13277-015-4574-9

ORIGINAL ARTICLE

Association of *MDR1* single-nucleotide polymorphisms and haplotype variants with multiple myeloma in Chinese Jiangsu Han population

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Received: 5 November 2015 / Accepted: 1 December 2015 / Published online: 20 January 2016

Abstract Multidrug resistance 1 (*MDR1*) gene encodes P-glycoprotein (P-gp), which acts as an efflux pump and provides cell protection against various substances, and its single-nucleotide polymorphisms (SNPs) are associated with the development of malignant hematologic diseases. The present study aimed at investigating whether the *MDR1* SNPs and haplotype variants were correlated with the susceptibility to multiple myeloma (MM). A total of 115 MM patients and 153 healthy controls from Jiangsu Han population were enrolled and genotyped by polymerase chain reaction–allele-specific primer (PCR-ASP) method or DNA direct sequencing at *MDR1* loci of C1236T, G2677T/A, and C3435T. No significance was found in the distribution of alleles and genotypes in *MDR1* three loci. Diplotype analysis has also demonstrated no effect in susceptibility to MM. But, in haplotype analysis, the haplotype of T–G–T was significantly more common than healthy controls (12.6 % in MM group vs. 1.7 % in control group, odds ratios (ORs) = 8.7, 95 % confidence interval (CI) 3.3–22.8, $Pc < 0.01$). Our results pointed out that comparable allele, genotype, and diplotype frequencies among MM patients and controls in Chinese Jiangsu Han population were found; the frequency of T–G–T haplotype was significantly increased in MM group compared with the control group, which indicated that this haplotype might be associated with the susceptibility to MM.

Keywords Multiple myeloma (MM) · Multidrug resistance 1 (*MDR1*) · Single-nucleotide polymorphism (SNP)

Introduction

Multidrug resistance 1 (*MDR1*) gene is a member of the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily, and it encodes a 170-kDa membrane transporter named P-glycoprotein (P-gp), which acts as an efflux pump and provides cell protection against various substances, such as drugs and toxins, reducing the intercellular concentrations of different chemotherapeutic agents [1, 2]. It has been demonstrated that single-nucleotide polymorphisms (SNPs) in *MDR1* gene, such as C1236T (exon 12, rs1128503), G2677T/A (exon 21, rs2032582), and C3435T (exon 26, rs1045642), affect *MDR1* protein expression and function, which might be a protective or a risk factor in the development of many tumors, including hematologic malignant diseases [3–8].

Multiple myeloma (MM) is the second most common hematological malignancy and is characterized by accumulation of clonal plasma B cells in bone marrow, hypercalcemia, renal failure, anemia, and lytic bone lesions. The molecular pathogenesis of MM was still not clear, and lots of studies suggest that genetic component might play an important role in the etiology of MM [9]. As *MDR1* polymorphisms might be different in different ethnic and geographic populations for their unique genetic background, the possibility of an association of *MDR1* polymorphisms, at the three common loci C1236T (exon 12, rs1128503), G2677T/A (exon 21, rs2032582), and C3435T (exon 26, rs1045642), was assessed in a total of 115

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MM patients residing in Jiangsu Province, People's Republic of China.

Materials and methods

Subjects

In total, 115 cases of patients, Han ethnic, diagnosed with MM [10] were enrolled for *MDR1* association study. They consisted of 70 (60.9 %) males and 45 (39.1 %) females, with the median age of 68 years (range = 35–82 years). These patients were selected from Jiangsu population, and the details of their clinical characteristics are summarized in Table 1. DNA samples were also collected from 153 healthy volunteers as a control group from the same ethnic and geographical background in Jiangsu province. The informed written consents were obtained from each patient and control before blood collection, and this study was strictly adhered to the principles of the Helsinki Declaration.

Genotyping

Three interested SNPs in *MDR1* gene, including C1236T (rs1128503), G2677T/A (rs2032582), and C3435T (rs1045642), were genotyped by polymerase chain reaction–allele-specific primer (PCR-ASP) method and DNA direct sequencing for both patients and controls. Genomic DNA was isolated from peripheral blood in the light of the protocol provided by the manufacturer using salting-out method (Lot# N3113, Tiangen Company, Beijing, China) and then was stored at −70 °C before touchdown PCR-ASP program was initiated. PCR reactions were performed in the volume of 20-μl PCR mixture, composed of 10 μl PCR Master Mix reaction buffer (Lot# KT201-02, Tiangen Company, Beijing, China), 1 μl of each specific PCR primer, 1 μl Taq DNA polymerase, 1 μl genomic DNA template, and 7 μl ddH_2O. After the amplification was completed, PCR products were subjected to undergo electrophoresis on agarose gel with ethidium bromide (EB). *MDR1* genotypes in loci of C1236T (rs1128503) and C3435T (rs1045642) were identified by photographed picture of the EB-stained gel. PCR primers and reaction conditions were referenced in our previous literature [11]. Due to the genotype complexity of locus G2677T/A (rs2032582), DNA direct sequencing technique was employed to make out the genotype.

Table 1 The clinical characteristics of 115 patients with multiple myeloma enrolled in this study

Characteristics	Number of patients *n* (%)
Age (years)	
≥60	60 (52.2)
<60	55 (47.8)
Gender	
Male	70 (60.9)
Female	45 (39.1)
Staging	
DS I–II	27 (23.5)
DS III	88 (76.5)
ISS I–II	69 (60.0)
ISS III	46 (40.0)
Group	
A	99 (86.1)
B	16 (13.9)
Subtype	
IgG	51 (44.4)
IgA	18 (15.7)
κ light chain	15 (13.0)
λ light chain	22 (19.1)
Others	9 (7.8)

DS Durie-Salmon, *ISS* international staging system, *IgG* immunoglobulin G, *IgA* immunoglobulin A

Statistical analysis

Frequencies of allele, genotype, and diplotype were calculated directly, and the maximum likelihood haplotype frequencies were computed by the expectation–maximization (EM) algorithm using Arlequin software 3.01 [12], as well as the Hardy–Weinberg equilibrium test. Chi-squared test was employed to examine the statistical significance in the distributions of allele, genotype, diplotype, and haplotype between MM patients and controls, evaluated by odds ratios (ORs) with 95 % confidence interval (CI). Fisher's exact test was also used to evaluate the differences in *MDR1* SNPs when cells having expected count less than 1 were existed. Bonferroni inequality method [13] was employed to correct the original *P* value (*Pc*) to overcome the error when one of the alleles, genotypes, diplotypes, or haplotypes could have deviated significantly by chance. All statistical tests were two sided, and a *p* value of <0.05 was defined as the criterion of statistical significance.

Results

Hardy–Weinberg equilibrium examination

Distributions of the interested *MDR1* SNPs, C1236T at rs1128503, G2677T/A at rs2032582, and C3435T at rs1045642, were tested in Hardy–Weinberg formula, and the results indicated that they were in Hardy–Weinberg equilibrium ($p > 0.05$) (Table 2).

Table 2 Examination of Hardy–Weinberg equilibrium for three common *MDR1* SNPs in both MM and control groups

MDR1 SNPs	MM group ($N = 115$)				Control group ($N = 153$)			
	Observed heterozygosity	Expected heterozygosity	*Sd*	*P* value	Observed heterozygosity	Expected heterozygosity	*Sd*	*P* value
C1236T	0.38	0.44	0.001	0.20	0.45	0.46	0	1.00
G 2677T/A	0.66	0.61	0.002	0.63	0.63	0.61	0.001	0.49
C3435T	0.50	0.49	0.001	0.85	0.49	0.49	0	1.00

Sd standard deviation

Distributions of alleles and genotypes

The allelic and genotypic frequency distributions of three common SNPs (C1236T, G2677T/A, and C3435T) in *MDR1* gene between MM patients and healthy controls were analyzed and are presented in Table 3. The frequencies of each allelic variant did not show any statistical difference between MM group and control group. At locus G2677T/A, the G allele was detected relatively less frequent in MM patient cohorts than in control group (37.0 % in MM group vs. 43.5 % in control group, OR = 0.8, 95 % CI 0.5–1.1, $P = 0.13$), but the difference was not significant. In genotype analysis, the frequency of GG genotype at locus G2677T/A was decreased in MM group (12.2 % in MM group vs. 19.6 % in control group, OR = 0.6, 95 % CI 0.3–1.1, $p = 0.11$). There was also no significance in the distributions of three loci genotypes between MM patients and controls.

Diplotype association study

The distribution of diplotypes at the position of C1236T, G2677T/A, and C3435T was compared in MM patients and controls. Some common diplotypes (top seven in the rank of MM group) were demonstrated from all the diplotypes at any two of three loci. The most common diplotype was 2677GT/3435CT with a frequency of 28.7 %, followed by 1236TT/3435CT with a frequency of 23.5 % and 1236TT/2677GT with a frequency of 16.3 % in MM patients, while the most common diplotypes were 2677GT/3435CT (28.1 %), 1236CT/3435CT (22.9 %), and 1236TT/2677GT (21.6 %) in the control group (Table 4). No significance was found in the distribution of these diplotypes between MM patients and controls.

Haplotype association study

The distribution of all haplotypes computed by the EM algorithm is demonstrated in Table 5. When the three loci haplotype of 1236–2677–3435 were investigated, the most frequently observed haplotype was T–T–T in MM group with a frequency of 36.5 %, followed by T–G–C (28.7 %) and C–G–C (15.2 %). The T–G–C of 1236–2677–3435 showed an increased frequency in MM group compared with the control group, but the difference was not significant ($p = 0.058$). However, the haplotype of T–G–T was significantly more common than healthy controls (12.6 % in MM group vs. 1.7 % in control group, OR = 8.7, 95 % CI 3.3–22.8, $Pc < 0.01$). In MM group, the most common haplotype for two loci was T–T with a frequency of 44.9 % in 1236–2677, followed by T–T with a frequency of 39.2 % in 2677–3435, and T–T with a frequency of 37.7 % in 1236–3435. A comparison of two loci haplotype frequencies at 1236–2677, 2677–3435,

Table 3 Allele and genotype distributions at three common lociC1236T, G2677T/A, and C3435T in MM patients and controls

MDR1 allele/genotype	MM patients, *N* (%)	Controls, *N* (%)	OR	95 % CI	*P* value
C1236T					
C	74 (32.2)	107 (35.0)	0.9	0.6–1.3	0.50
T	156 (67.8)	199 (65.0)	1.1	0.80–1.6	0.50
CC	15 (13.0)	19 (12.4)	1.1	0.5–2.2	0.88
CT	44 (38.3)	69 (45.1)	0.8	0.5–1.2	0.26
TT	56 (48.7)	65 (42.5)	1.3	0.8–2.1	0.31
G2677T/A					
A	33 (14.3)	44 (14.4)	1.00	0.6–1.6	0.99
G	85 (37.0)	133 (43.5)	0.8	0.5–1.1	0.13
T	112 (48.7)	129 (42.2)	1.3	0.9–1.8	0.13
AA	1 (0.9)	3 (2.00)	0.4	0.1–4.3	0.47
AG	12 (10.4)	15 (9.8)	1.1	0.5–2.4	0.87
AT	19 (16.5)	23 (15.0)	1.1	0.6–2.2	0.74
GT	45 (39.1)	58 (37.3)	1.1	0.6–1.7	0.84
GG	14 (12.2)	30 (19.6)	0.6	0.3–1.1	0.11
TT	24 (20.9)	24 (16.3)	1.4	0.8–2.7	0.28
C3435T					
C	131 (57.0)	177 (57.8)	1.0	0.7–1.4	0.84
T	99 (43.0)	129 (42.2)	1.0	0.7–1.5	0.84
CC	36 (31.3)	51 (33.3)	0.9	0.5–1.5	0.73
CT	59 (51.3)	75 (49.0)	1.1	0.7–1.8	0.71
TT	20 (17.4)	27 (17.7)	1.0	0.5–1.9	0.96

OR odds ratio, *CI* confidence interval

Table 4 Distributions of diplotypes in *MDR1* three loci (C1236T, G2677T/A, and C3435T) and risk assessment of MM

Diplotype	MM *n* (%)	Controls *n* (%)	OR	95 % CI	*P* value
C1236T/C3435T					
1236TT/3435TT	18 (15.7)	21 (13.7)	1.2	0.6–2.3	0.65
1236TT/3435CT	27 (23.5)	34 (22.2)	1.1	0.6–1.9	0.80
1236TT/3435CC	6 (5.2)	10 (6.5)	0.8	0.4–1.3	0.65
1236CT/3435CT	26 (22.6)	35 (22.9)	1.0	0.6–1.8	0.95
1236CT/3435CC	17 (14.8)	28 (18.3)	0.8	0.4–1.5	0.45
1236CC/3435CC	9 (7.8)	13 (8.5)	0.9	0.4–2.2	0.84
1236CC/3435CT	5 (4.4)	6 (3.9)	1.1	0.3–3.7	0.86
C1236T/G2677T/A					
1236CC/2677GG	4 (2.6)	8 (5.2)	0.7	0.2–2.2	0.49
1236CT/2677GT	17 (11.1)	24 (15.7)	0.9	0.5–1.8	0.84
1236CT/2677GG	7 (4.6)	16 (10.5)	0.6	0.2–1.4	0.20
1236TT/2677GT	25 (16.3)	33 (21.6)	1.0	0.6–1.8	0.97
1236CC/2677AG	6 (3.9)	5 (3.3)	1.6	0.5–5.5	0.43
1236TT/2677TT	22 (14.4)	23 (15.0)	1.3	0.7–2.5	0.37
1236CT/2677AT	13 (8.5)	19 (12.4)	0.9	0.4–1.9	0.78
G2677T/A/C3435T					
2677GG/3435CC	12 (10.4)	24 (15.7)	0.6	0.3–1.3	0.21
2677GT/3435CT	33 (28.7)	43 (28.1)	1.0	0.6–1.8	0.91
2677TT/3435CT	4 (3.5)	7 (4.6)	0.8	0.2–2.6	0.65
2677GT/3435CC	10 (8.7)	7 (4.6)	2.0	0.7–5.4	0.17
2677AT/3435CT	16 (13.9)	17 (11.1)	1.3	0.6–2.7	0.49
2677TT/3435TT	18 (15.7)	17 (11.1)	1.5	0.7–3.0	0.27
2677AG/3435CC	9 (7.8)	14 (9.2)	0.8	0.4–2.0	0.70

Some common diplotypes (top seven in the rank of MM group) were demonstrated

OR odds ratio, *CI* confidence interval

Table 5 The haplotype association study between MM patients and controls

Haplotype	MM HF (%) (*N* = 230)	Controls HF (%) (*N* = 306)	OR	95 % CI	*P* value	*Pc*
1236–2677–3435						
T–T–T	36.5	35.1	1.1	0.8–1.5	0.71	
T–G–C	28.7	21.7	1.5	1.0–2.2	0.058	
C–G–C	15.2	16.6	0.9	0.6–1.4	0.65	
C–A–C	10.8	12.4	0.9	0.5–1.5	0.58	
T–T–C	8.3	5.4	1.5	0.8–3.0	0.22	
C–G–T	2.1	3.5	0.6	0.2–1.7	0.34	
T–G–T	*12.6*	*1.7*	*8.7*	*3.3–22.8*	*<0.01*	*<0.01*
C–T–T	0.9	0.8	1.3	0.2–9.5	0.77	
C–T–C	1.2	0.9	1.3	0.3–6.7	0.72	
T–A–C	3.2	0.8	4.8	1.0–23.2	0.03	
1236–2677						
T–T	44.9	40.5	1.2	0.8–1.7	0.32	
T–G	19.4	23.4	0.8	0.5–1.2	0.31	
C–G	17.6	20.1	0.8	0.5–1.3	0.40	
C–A	10.7	13.2	0.8	0.5–1.4	0.44	
C–T	3.8	1.7	2.5	0.8–7.4	0.11	
T–A	3.6	1.2	2.7	0.8–9.2	0.11	
2677–3435						
G–C	33.6	38.4	0.8	0.6–1.2	0.26	
T–T	39.2	35.9	1.2	0.8–1.6	0.45	
A–C	14.3	13.2	1.1	0.7–1.8	0.67	
A–T	0	1.2	NA	NA	NA	
T–C	9.5	6.3	1.6	0.8–3.0	0.15	
G–T	3.3	5.1	0.7	0.3–1.6	0.33	
1236–3435						
T–T	37.7	38.9	1.0	0.7–1.4	0.80	
T–C	30.1	28.2	1.1	0.8–1.6	0.63	
C–C	27.3	29.7	0.9	0.6–1.3	0.55	
C–T	4.9	5.3	0.9	0.4–2.0	0.82	

The significant haplotypes were italicized

HF haplotype frequency, *OR* odds ratio, *CI* confidence interval, *Pc* *P* corrected

and 1236–3435 revealed that no significant difference existed between MM patients and controls.

Discussion

Due to the fundamental role of transporting the cells' endogenous and exogenous harmful compounds outside to protect the cells, increasing evidences have suggested that *MDR1* SNPs are associated with cancer development, which might alter the *MDR1* expression and protein conformation [14–17]. *MDR1* SNPs may also influence the risk of malignant hematologic diseases, such as leukemia, lymphoma, and MM [16–18]. In our previous studies, *MDR1* correlations with chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), and diffuse large B cell lymphoma (DLBCL), as well as the prognostic value and drug resistance, have been explored and some risk or protective factors were revealed [7, 8, 19, 20]. Based on the association study of *MDR1* SNPs with MM was limited [21, 22] and the genetic background may alter the final associations, we focused on whether potentially functional polymorphisms in *MDR1* gene responsible for protection of the organisms against environmental carcinogens have an impact on the susceptibility to MM.

The alleles, genotypes, haplotypes, and diplotypes in *MDR1* three common positions, C1236T, G2677T/A, and C3435T, were focused on and compared in MM and control groups in this study. No significant allele or genotype was found in the distribution of three common *MDR1* loci between MM patients and controls. Jamroziak et al. [23] have also investigated whether three common *MDR1* SNPs (C1236T,

G2677T/A, and C3435T) affect predisposition to MM in 111 Caucasians, and they found comparable allele and genotype frequencies among MM patients and controls, which was in accordance with our results. In a CML association study [16], the 1236TT genotype was significantly associated with the susceptibility to CML when compared to the wild-type 1236CC (OR = 2.7, $p = 0.04$). In non-Hodgkin lymphoma (NHL), 1236CC genotype was associated with a decreased risk for NHL (OR = 0.74, $p = 0.04$) [6]. We have also focused on the associations of *MDR1* SNPs with DLBCL and found that allele G and genotype GT at locus G2677T/A were significantly more common in DLBCL (G: OR = 1.5, $p = 0.03$; GT: OR = 2.0, $p < 0.01$), while genotype AT seemed to be protective (OR = 0.3, $p = 0.03$) at this locus; TT genotype at locus C3435T showed a risk factor in DLBCL (OR = 2.4, $p < 0.01$) [20]. This discrepancy might be due to various factors, including the different ethnicity of the two populations, different environmental risk factors, different molecular pathogenesis in different tumors, or the difference in the sample size of the studies.

The distribution of diplotypes was similar between MM patients and controls. But, in haplotype association study, haplotype of T–G–T was significantly increased in MM group compared with the control group (12.6 % in MM group vs. 1.7 % in control group, $Pc < 0.01$). In a similar study, comparable genotype and haplotype frequencies among MM patients and controls were observed in Caucasians [23]. In a CML study, the frequency of T–G–T in CML group was higher than the control group (6.86 % in CML group vs. 2.46 % in control, $p = 0.11$) [16], indicating a potential trend in CML patients, which was in agreement with our findings.

It is generally accepted that inherited variation in *MDR1* involved in the transport and metabolism of environmental toxins in different genetic background and the tumor originations might determine the likelihood of malignant development [24]. A large meta-analysis of 39 independent studies conducted in relation with *MDR1* SNPs and cancer risk found an association between the 3435T allele and overall cancer risk (OR = 1.18, 95 % CI 1.04–1-34) [25]. However, *MDR1* mechanism associated with cancers or treatment response is surprisingly complex and poorly understood. It has been suggested that impaired *MDR1* expression and protein conformation can result in several cancer types or treatment response [6, 26–28]. For instance, Bellusci et al. [26] have reported that the *MDR1* C1236T SNP significantly reduces lopinavir plasma concentration affecting the virological response to treatment. Several other reports suggested that these significant associations might be due to linkage disequilibrium with the *MDR1* SNPs [29], allele-specific differences in mRNA folding [30], or numerous environmental factors [31].

In conclusion, our results pointed out that there was no significant allele, genotype, and diplotype in the distribution of three common *MDR1* loci between MM patients and controls in Chinese Jiangsu Han population. In haplotype analysis, the frequency of T–G–T haplotype was significantly increased in MM group compared with the control group, which indicated that this haplotype might be associated with the predisposition to MM. Further studies should be performed to explore the disease associations and establish the detailed molecular mechanisms, by which the *MDR1* SNPs modify the susceptibility to MM.

Acknowledgments This study was supported by grants from the National Natural Science Foundation of China (81470329, 81302040, 81372540), National Public Health Grand Research Foundation (No. 201202017), Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institute (No. JX10231801), Project of National Key Clinical Specialty, National Science & Technology Pillar Program (No. 2014BAI09B12), and Project Funded by Jiangsu Provincial Special Program of Medical Science (No. BL2014086).

Compliance with ethical standards

Conflicts of interest None.

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