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Distribution of the functional *MDR1*^{C3435T} polymorphism in the Han population of China

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Summary

Principles: 3435C>T, a single nucleotide polymorphism (SNP) in exon 26 of the *MDR1* gene, is linked to the variability of P-gp expression and function among different individuals. It was found that ethnic differences exist in the polymorphism of the *MDR1*^{C3435T} gene. However, the distribution of 3435C>T genotypes in the Chinese Han population is not clear up till now.

Methods: In this study, the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was applied to assess 3435C>T genotypes in 265 healthy individuals of the Han population of China.

Results: The genotype frequencies were: *CC* 32% (n = 85), *CT* 48% (n = 127) and *TT* 20% (n = 53). C and T allele frequencies were 0.56 and 0.44 respectively. The C allelic frequency for female was 56.5% (T: 43.5%), and 55.9% (T: 44.1%) for male.

Conclusions: There was no significant difference between females and males (p = 0.92, OR = 1.02, 95%CI: 0.67–1.57) in the present study. The frequency of C-allele was similar to that of some populations in Asia/Europe and was lower than that of populations in Africa. When compared with the study on Singapore-Chinese, some differences were found. The results of this study would be useful for individualised therapy of some diseases, and could have a prognostic implication for the Chinese Han population.

Key words: P-glycoprotein (P-gp); MDR1; single nucleotide polymorphism (SNP); 3435C>T

Introduction

P-glycoprotein (P-gp), the product of the multidrug resistance gene *(MDR1/ABCB1)*, is an energy-dependent efflux pump that is involved in extrusion of a wide variety of drugs [1–7]. *MDR1*, located on chromosome 7q21.1, is composed of 28 exons and encodes a protein of 1280 amino acids [6]. Mutational analyses have revealed that the *MDR1* gene is highly polymorphic and it is extensively used to investigate P-gp structure-function relationships (more detailed information is shown on http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=5243). Among all single nucleotide polymorphisms (SNPs) of the *MDR1* gene, many researchers focused on position 3435 in exon 26 (3435C>T). Hoffmeyer et al. found a significant correlation of single nucleotide polymorphism (SNP) of the *MDR1*^{C3435T} with P-gp expression level and function [8]. The study of this site would be helpful for treatment of some diseases in the clinic [9–13]. Nowadays, it has been reported that the distribution of the 3435C>T polymorphism is significantly influenced by ethnicity [14–26]. These results suggest that the evaluation of *MDR1*^{C3435T} genotypes is of great importance for individualised pharmacotherapy.

As far as we know, three studies on the *MDR1C*^{3435T} polymorphism in Chinese people have been reported [19, 26, 27]. One investigated the southwest of China, and the other two investigated Singapore-Chinese. There is still lack of information for the central and northeast of China. In the present study, according to a set of strict criteria, 265 healthy subjects of Chinese Han nationality were selected from 2836 people. The genomic DNA was used as template for the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay for the 3435C>T genotypes. The results would be very

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useful for further analysing the deleterious SNPs of the *MDR1* gene, which could provide information for therapy of many diseases treated by drugs (P-gp substrates or inducers) in the Chinese Han population.

Material and methods

Study samples

The criteria for building the data set.

- Chinese Han nationality for at least 5 generations.
- No genetic disease reported.
- No diseases like cancer, hepatitis, organs transplant, neural diseases and HIV.
- No medications (substrates or inducers for P-gp) for a week in the last three months, including antidepressants, hypnotics, medications against tuberculosis, epilepsy, (bacterial) infections, and blood-clots, steroids, immunosuppressants, blood pressure-lowering agents, cardiac glycosides, narcotic analgesics, antipsychotics.
- Not hypersusceptible to penicillin, streptomycin, sulfanilamide.
- No smoking in the family.
- No touching chemicals in the last three years continuously, including pesticides and chemical reagents.
- The samples are Northeast native or Shandong native.
- Passing physical examination in the Second Affiliated Hospital of Dalian Medical University, China.
- Age ranges from 20 to 60 years old.

The subjects in our study have come from Dahua Group Dalian Chemical Industry Co. Ltd. In our investigations, 2836 subjects agreed to donate blood for our study in the Second Affiliated Hospital of Dalian Medical University. However, 89 suitable persons (56 females and 33 males) of the 354 planned samples refused to give informed consent for our study. Therefore, we only enrolled 265 healthy subjects (54 females and 211 males) in our study. All the volunteers have been informed that the samples would be used for analysis of the *MDR1*^{C3435T} genotypes. Their median age was 33 years old. Ethical approval for this study was obtained from the hospital where the samples were collected, and the documents of informed consent were obtained from all subjects.

Genotyping

100 µl of freshly withdrawn bloods with EDTA were used to isolate DNA using sodium iodide (NaI) [28, 29]. The amplification of exon 26 of the *MDR1* gene was carried out by the forward primer [20] 5'-TTG ATG GCA AAG AAA TAA AGC-3'; and the reverse primer 5'- CTT ACA TTA GGC AGT GAC TCG –3' (Genbank M29445). PCR was carried out in a total volume of 50 µl using about 50 ng of genomic DNA, 5 pM of each forward and reverse primer, 2.5 mM dNTP (TaKaRa Dalian Co. China), 10 × Buffer and 2.5 units of TaKaRa Ex Taq™ DNA polymerase (TaKaRa Dalian Co. China, Cat DR001A). The PCR process included initial denaturation at 94 °C for 5 minutes followed by 40 cycles of denaturation at 94 °C for 30 seconds, annealing at 55 °C for 30 seconds, and synthesis at 72 °C for 60s. The final synthesis

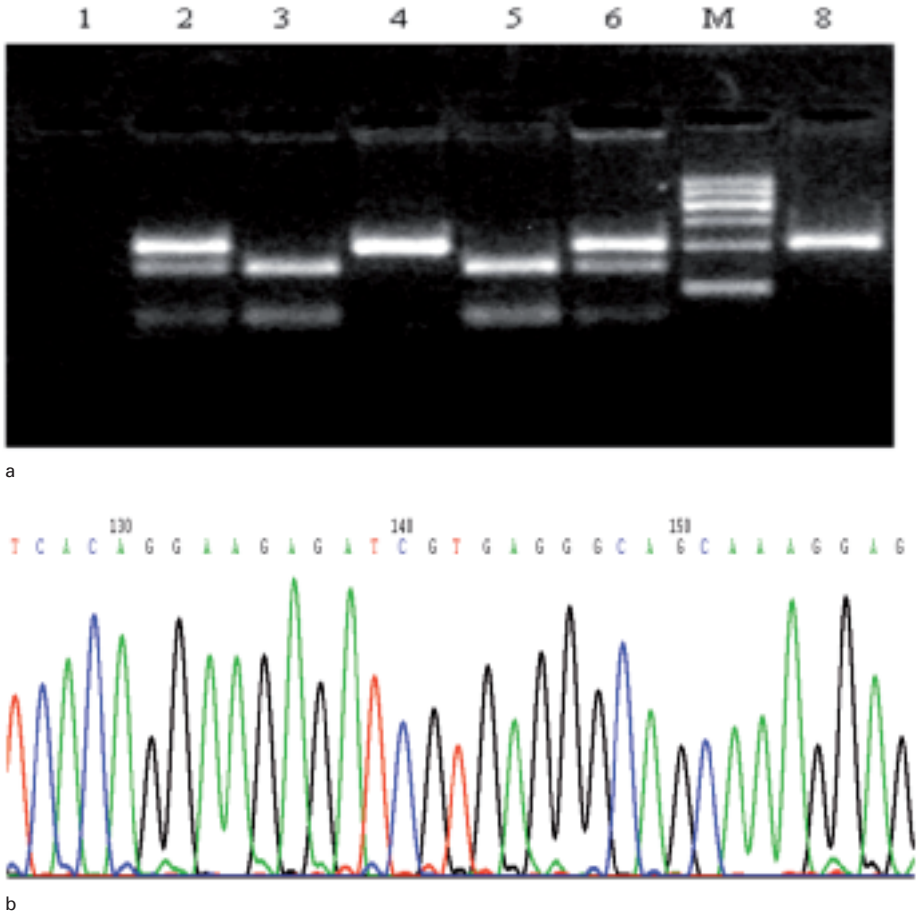

Figure 1

a Electrophoresis patterns for *MDR1* genotypes by PCR-RFLP based assay. Lane M: 100 bp DNA Marker; lane 8: uncut; lane 2, 6: heterozygous *CT* genotype; lane 4: homozygous T allele; lane 3, 5: homozygous C alleles; lane 1: control (water).
b Direct sequencing results for the *CC* genotype. No140 is the 3435C>T site.

was carried out for 5 minutes at 72 °C, and then a 207 bp PCR product was digested with restriction enzyme *MboI* (TaKaRa Dalian Co. China, Cat D1069A) for 16 h at 37 °C. The digested products were separated with a 3.0% agarose gel. The *MboI* digestion of wild homozygous *CC* genotype yielded fragments of 145 bp, and 62 bp. The heterozygous *CT* genotype was composed of one restriction site and yielded 207 bp, 145 bp and 62 bp fragments with *MboI* digestion. The homozygous of *TT* genotype had no restriction site (figure 1a). A random sample of homozygous *CC* genotype was sequenced to confirm the expected sequence of exon 26 (figure 1b). Automated sequencing of the PCR fragment confirmed that the expected sequence of the *MDR1* gene in exon 26 was amplified from genomic DNA with these primers.

Statistical analysis

In this study, the Chi-square test was used for comparison of the allele and genotype frequencies among different populations. According to Hardy-Weinberg equilibrium, statistical analysis was made on the observed genotype frequencies and the theoretical genotype frequencies. The C/T allele or *CC/CT/TT* genotype frequencies were analyzed between the Chinese Han population and different ethnical populations reported previously. The 95% confidence intervals were calculated for all observed allele frequencies. A $p < 0.05$ was considered to be statistically significant. Statistical analysis was carried out using STATA software package (StataCorp LP, College, TX, USA).

Results

This study emphasised the distribution of SNP of the *MDR1*^{C3435T} gene in the Chinese Han population. The *MDR1*^{C3435T} genotypes assessed by PCR-RFLP were done in 265 healthy individuals. In this study the allele and genotype frequencies of the *MDR1*^{C3435T} do not deviate from the Hardy-Weinberg equilibrium (more detailed information is shown in table 1). Figure 1a shows the electrophoresis patterns for the *MDR1*^{C3435T} genotypes analysed by PCR-RFLP. The subjects of *CC*, *CT* and *TT* genotype were 85 (32%), 127 (48%) and 53 (20%), respectively. There was no difference between females (C: 56.5% and T: 43.5%) and males (C: 55.9% and T: 44.1%) (p = 0.92, OR = 1.02, 95%CI: 0.67–1.57).

The comparisons of the *MDR1*^{C3435T} genotype analysis in this study with previous reports are presented in table 2, including some African, European and Asian. The C allelic frequency for the Chinese populations in this study and other reports, ie the Singapore-Chinese [26, 27] and the southwest of China [19], are shown in table 3.

Table 1

The statement for Hardy-Weinberg equilibrium about the allele and genotype frequencies of the *MDR1*^{C3435T}.

	N_{CC}	N_{CT}	N_{TT}	
A	85	127	53	
E	$(V_C{}^2 \times N_{total})$ 83.104	$(2\ V_C \times V_T \times N_{total})$ 130.592	$(V_T{}^2 \times N_{total})$ 51.304	
$(A-E)^2/E$	0.043	0.099	0.056	$\sum\sum 0.198$

$V_C = (2N_{CC}+N_{CT})/2N_{total} = (2\times85+127) / (2\times265) = 0.56$
$V_T = (2N_{TT}+N_{CT})/2\ N_{total} = (2\times53+127) / (2\times265) = 0.44$
N_{CC}, N_{CT} and N_{TT} represent the numbers of genotype *CC*, *CT* and *TT*, respectively; N_{total} represents the number of total samples; V_C and V_T represent the values for allele C and T;
A represents the actual number of each genotype;
E represents the theoretical number of each genotype.
$f = (2\text{-}1) \times (2\text{-}1) = 1$ (f: degree of freedom)
$\chi^2_{0.05}\ (1) = 3.841$ (from χ^2 table)
$\chi^2 = 0.198 < 3.841$

Table 2

The statistical results of C allelic frequencies of the *MDR1*^{C3435T} between the data in this study and the other published data (allele C and T; genotype *CC, CT* and *TT*)

Population samples (n)	Allele freq		Genotype freq			p Value	OR	95%CI	Ref
	C	T	CC	CT	TT				
Chinese (265)	0.56	0.44	0.32	0.48	0.2	/	/	/	This study
Ghanaian (206)	0.83	0.17	0.67	0.34	0	0.00	0.26	0.19–0.36*	[19]
Kenyan (80)	0.83	0.17	0.7	0.26	0.04	0.00	0.26	0.17–0.40*	[19]
Sudanese (51)	0.73	0.27	0.52	0.43	0.06	0.00	0.45	0.28–0.72*	[19]
Ashkenazi (100)	0.65	0.35	0.42	0.46	0.12	0.03	0.69	0.49–0.96*	[25]
Polish (122)	0.62	0.38	0.42	0.41	0.17	0.13	0.79	0.58–1.07	[44]
Japanese (114)	0.61	0.39	0.35	0.53	0.12	0.21	0.82	0.59–1.12	[47]
French (81)	0.57	0.43	0.36	0.42	0.22	0.87	0.97	0.68–1.38	[40]
Filipino (60)	0.56	0.41	0.38	0.42	0.2	0.74	0.93	0.62–1.40	[19]
Saudi (96)	0.55	0.45	0.37	0.38	0.26	0.84	1.03	0.74–1.44	[19]
Spanish (408)	0.52	0.48	0.26	0.52	0.22	0.14	1.18	0.95–1.47	[46]
German (188)	0.52	0.48	0.27	0.48	0.24	0.24	1.17	0.89–1.53	[8]
Caucasian (UK) (190)	0.48	0.42	0.24	0.48	0.28	0.41	1.12	0.85–1.47	[19]
Malay (99)	0.48	0.52	0.25	0.46	0.28	0.05	1.38	1.0–1.92	[26]
New Zealander (160)	0.47	0.53	0.21	0.52	0.27	0.01	1.44	1.09–1.91*	[24]
Indian (264)	0.38	0.62	0.25	0.46	0.28	0.00	2.07	1.62–2.65*	[26]

* Data showing significant significances are in bold print. The C allelic frequency of the Chinese serves as control.

Table 3

The C allelic differences of Chinese populations between the data in this study and those of other studies (allele C and T; genotype *CC, CT* and *TT*)

Chinese (n)	Allele freq		Genotype freq			p Value	OR	95%CI	Ref
	C	T	CC	CT	TT				
265	0.56	0.44	0.32	0.48	0.2	/	/	/	This study
Singapore (224)	0.59	0.41	0.28	0.50	0.22	0.33	0.88	0.68-1.14	[27]
Southwestern (132)	0.53	0.47	0.32	0.42	0.26	0.42	1.13	0.84-1.52	[19]
Singapore (98)	0.46	0.54	0.24	0.44	0.32	0.02	1.50	1.08-2.09*	[26]

* Data showing significant differences are in bold print. The C allelic frequency in this study serves as control

Discussion

In recent years the relationship between the *MDR1*^{C3435T} polymorphism and susceptibility to some diseases, such as gastrointestinal tract infections [30, 31], HIV [32], Parkinson's disease [12, 13, 27], nortriptyline-induced postural hypotension [24], renal epithelial tumours [33] and childhood acute lymphoblastic leukaemia (ALL) [34, 35] has been studied. Moreover, the 3435C>T, as well as 2677G>T/A polymorphism, showed a significantly lower incidence of non-traumatic necrosis of the femoral head (ONF) [23]. However, some contradictory results also exist [18, 36–39]. In summary, these reports suggested that an assessment of 3435C>T polymorphism could be useful for predicting some P-gp-dependent diseases.

However, the direct association between the 3435C>T polymorphism and the P-gp expression and function has not been very clear. The 3435C>T is a silent variation, so it does not result in any changes of amino acid. Some researchers proposed that it might link with other polymorphic sites in the *MDR1* gene to change P-gp activity and function [18, 20, 23, 27, 40], such as 2677G>T/A in exon 21, 1236C>T in exon 12 and *T-129* in exon 1b. Other researchers assumed that 1) the silent variation in the *MDR1*^{C3435T} might reduce translation efficiency influencing functional consequences [41], 2) it might alter or regulate the processing and translation of mRNA [42, 43], 3) it would have impact on posttranscriptional modifications or would be linked to an important sequence for mRNA processing [44]. In this paper, we have described the distribution of a functional SNP in the human *MDR1*^{C3435T} gene within the Chinese Han population, which might be helpful for individualised pharmatherapy.

Table 2 shows the differences in genotypes and allelic frequencies of the *MDR1*^{C3435T} polymorphism between the Chinese and different ethnic groups reported previously. For the C allelic frequency, the difference between the Chinese and African (Ghanaian, Kenyan and Sudanese) (table 2) [19] was statistically significant. The low T allelic frequency in African may explain the high incidence of resistance and aggressive tumours, such as breast cancer [45]. However, the C allelic frequency in this study was not significantly different from the European (German, French, Polish and Spanish) populations (table 2) [8, 40, 44, 46], with the exception of Ashkenazi [25] (p = 0.03, OR = 0.69, 95%CI: 0.49–0.96). New Zealand was different from the Chinese sample in the present study (p = 0.01, OR = 1.44, 95%CI: 1.09–2.91). This might be due to that New Zealand is a relatively multi-ethnic country, resulting in the difference of C allelic frequency. In Asia, there is no significant difference between Chinese and Filipino, Saudi Arabian, and Japanese (table 2), respectively, except between Chinese and Indian [19, 26, 47] (p = 0.00, OR = 2.07, 95%CI: 1.62–2.65). As there are more than ten large nationalities in India, as well as the lack of adequate information from the original paper [26], the reason for the difference between Chinese and Indian samples is still unclear. Interestingly, the difference in Malays is ambiguous [26] (p = 0.05, OR = 1.38, 95%CI: 1.00–1.92). Due to the limitation of the original data from the report [26], we could not explain it clearly. The comparison would be more reliable if the Malay study population were more randomly selected samples. Further investigations among ethnic populations of some countries will be difficult, as they are multi-ethnic countries, such as the UK, Malaysia and Germany.

The statistical results mentioned above are not surprising, as black populations were suggested to have diverged from Caucasoid and Mongoloid groups for over 100 000 years ago, whereas the Caucasoid and Mongoloid groups were thought to have diverged approximately 40 000 years ago [48]. Differences in ethnic origin, environmental and dietary factors may contribute to small differences between C allelic distributions of different populations.

Table 3 shows the statistical results between the different Chinese populations from different regions, involving two data sets of Singapore-Chinese and one of southwestern Chinese. The distribution of C allelic frequency in our study population and one set of Singapore-Chinese [26] (p = 0.02, OR = 1.50, 95%CI: 1.08–2.09) were considered significantly different. However, no significant statistical difference was observed between our report and the other report for Singapore-Chinese [27], with a 95% confidence interval of 0.68 to 1.14 and a p-value of 0.33. As can be seen from the two Singapore studies in table 3 (0.46 versus 0.59 for the C allele), the large difference might be

due to the sampling variability in the studies. However, there is no significant difference between our data and the data from the southwest of China, also a region with multiple nationalities [19] (p = 0.42, OR = 1.13, 95%CI: 0.84–1.52). Due to the wide variety of nationalities in China and wide regional differences, the study of the *MDR1*^{C3435T} polymorphism, especially for the Chinese Han population, is still needed.

In summary, this study investigated the allelic frequency distribution of 3435C>T polymorphism in the Chinese Han population for the first time. To perform our analysis, we applied the PCR-RLFP assay as an easy-to-use and relatively inexpensive method to detect known SNPs. The results of this study could serve as a basis for large-scale correlation studies on relevance of 3435C>T genotypes for individualised therapy of some diseases. It can be used to further understand the variability in individual drug response, and improve therapeutic and prognostic implications for the Chinese Han population. Further studies are still needed to elucidate the mechanism by which the 3435C>T polymorphism causes decreased P-gp expression and activity, and to define its role as a susceptible factor in infectious diseases and drug treatment with P-gp substrates and inducers.

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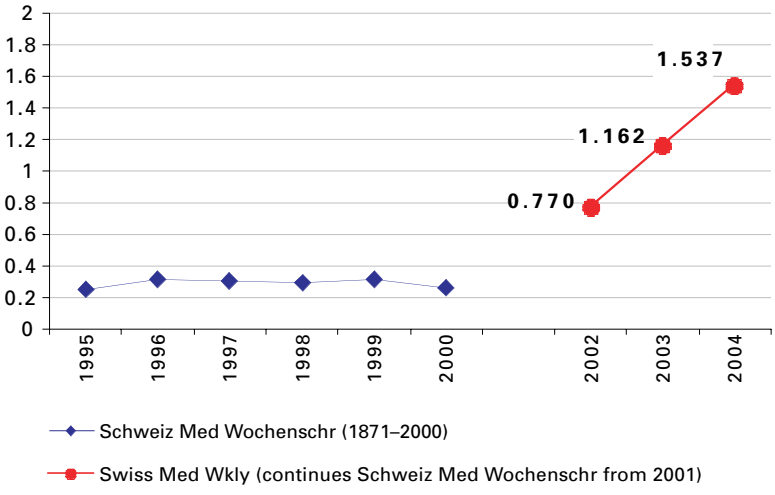

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