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Analysis of CYP2C19 Genetic Polymorphism in a Large Ethnic Hakka Population in Southern China

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Manuscript Preparation E
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Background: Cytochrome P450 (CYP) 2C19 is an enzyme involved in the bioactivation of various important therapeutic drugs, from pro-drugs to an active inhibitor of platelet action. Variants in the CYP2C19 gene influence the pharmacokinetics and clinical response to antiplatelet drugs such as clopidogrel; however, there is no available data about the genetic variation of CYP2C19 in the Hakka population in China.

Material/Methods: A total of 6686 unrelated participants (ages 17–98 years) of self-reported Hakka ancestry admitted at an inpatient department in a hospital in southern China were successfully genotyped by the gene chip platform.

Results: The identified allele frequencies were CYP2C19*1 (64.33%), *2 (31.06%) and *3 (4.61%). The major prevalent genotype combinations were CYP2C19 *1/*1 (41.73%) and *1/*2 (39.65%). The distribution of CYP2C19 phenotypes was divided into extensive metabolizers (EM) (41.73%), intermediate metabolizers (IM) (45.21%), and poor metabolizers (PM) (13.06%). In the Hakka population, frequencies of the CYP2C19 *2 and *3 variants were observed to be close to those previously identified in Chinese and several other Asian populations.

Conclusions: Our study is the first to report on CYP2C19 polymorphisms in the Hakka population, and may help to optimize pharmacotherapy effectiveness by providing personalized medicine to this ethnic group in the near future.

MeSH Keywords: China • Pharmacogenetics • Polymorphism, Genetic

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Background

Advances in personalized medicine have been notable, as the role of inheritance in variable drug response are being unraveled and pharmacogenetics are being applied to develop individual-specific therapies. Inter-individual variability in drug dosage response or lack of response to a drug, as well as drug toxicity, can maximize drug efficacy and avoid adverse drug reactions and therapeutic failures [1,2]. The availability of genetic variation in genes encoding for drug metabolizing enzymes is a key element of individualized care. Cytochrome P450 (CYP) is a superfamily of phase I metabolizing enzymes, which play a critical role in biosynthesis and degradation of drugs, endogenic substances, and toxins [3]. Over the past few years, a variety of cytochrome P450 (CYP) enzymes that participate in phase I reactions of drug metabolism, including CYP1A2, CYP2C9, CYP2C19, and CYP2D6, have been described [4,5].

CYP2C19 is an important member of the CYP450 superfamily, which plays a substantial role in the metabolism of approximately 10% of commonly prescribed drugs such as proton pump inhibitors, antipsychotics, antidepressants, and clopidogrel [6]. Like many other CYP450 superfamily members, inter-individual variability in response to CYP2C19 substrate can be explained satisfactorily by factors such as highly polymorphic of CYP2C19 genes, and individuals can be classified into predicted phenotypes of poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), or ultrarapid metabolizers (UM) [7,8]. Currently, at least 34 known variant alleles and numerous subvariants have been identified within the CYP2C19 gene. Many studies have focused on the association between genetic polymorphisms and clopidogrel resistance.

Multiple mechanisms have been proposed for the clopidogrel antiplatelet response variability, and substantial evidence has linked the CYP2C19 genotype with the clinical response among clopidogrel-treated patients. Accumulating evidence has demonstrated that both heterozygotes and homozygotes for loss-of-function alleles, particularly CYP2C19*2 (c.681G>A; rs4244285) and CYP2C19*3 (c.636G>A; rs4986893), are responsible for reduced activation of clopidogrel and an increased rate of recurrent cardiovascular events [9–11]. In 2010, the US Food and Drug Administration (FDA) added a black-box warning about the diminished effectiveness of clopidogrel, which suggests that individuals with poor metabolizer genotypes may be at increased risk for adverse cardiovascular outcomes [12]. The use of CYP2C19 genetic testing to guide antiplatelet therapy in these high-risk patients with cardiovascular diseases appears to be an appealing strategy. Moreover, the polymorphism of CYP2C19 varies considerably with both geographical location and ethnic group [13]. To date, numerous investigations of the differences in allele frequencies of the CYP2C19 gene in various ethnic populations worldwide have been reported.

Prior knowledge of the genetic variants that are present in a population may facilitate the revision and optimization of existing medication choices and doses. China is a multi-ethnic country with 55 ethnic minorities. Hakka is an intriguing Han Chinese ethnic group that has a population living in southern China, which is characteristic of their unique culture with similarities to northern Han populations. More than 95% of people who live in the Meizhou region of Guangdong province are Hakka and possess some unique features in culture, language, diet, lifestyle, and environment [14]. To the best of our knowledge, no data is available on CYP2C19 polymorphism in the Hakka population. The aim of this study was to describe CYP2C19 genetic variants in Hakka people in our population. The present study investigated the incidences of different CYP2C19 mutant allele (*2 and *3) frequencies in the Hakka population attending an inpatient department of a hospital in southern China and to determine genotype frequencies for these mutations. The CYP2C19 genotypes were then classified into phenotypes. We also compared genetic polymorphisms of CYP2C19 with previous observations in other ethnic groups.

Material and Methods

Study subjects

This was a retrospective study. The study protocol conformed to the principles of the Declaration of Helsinki, and was approved by the Ethics Committee of Meizhou People's Hospital. In total, 6686 unrelated subjects (ages 17–98 years) who visited Meizhou People's Hospital, Guangdong, Republic of China, were enrolled in the study from November 2015 to April 2017. Written informed consent was obtained from all participants prior to enrollment in the study.

DNA extractions

Blood samples from a peripheral vein were collected from each participant and stored in 6-ml evacuated vacuum tubes containing ethylenediaminetetraacetic acid (EDTA). Genomic DNA extraction was carried out using the Puregene Blood Core Kit C (Qiagen, Germantown, MD, USA) following the manufacturer's instructions, and DNA concentration was quantified using the Nanodrop 2000™ Spectrophotometer (ThermoFisher Scientific, Waltham, MA). Only quality DNA (A260/280 ratio >1.7) was stored at –80°C until analysis.

Polymerase chain reaction and DNA sequencing

The single-nucleotide polymorphisms CYP2C19*2 and CYP2C19*3 were genotyped using a commercially available kit (BaiO Technology Co, Ltd, Shanghai, China). Polymerase chain reaction (PCR) was performed according to the following

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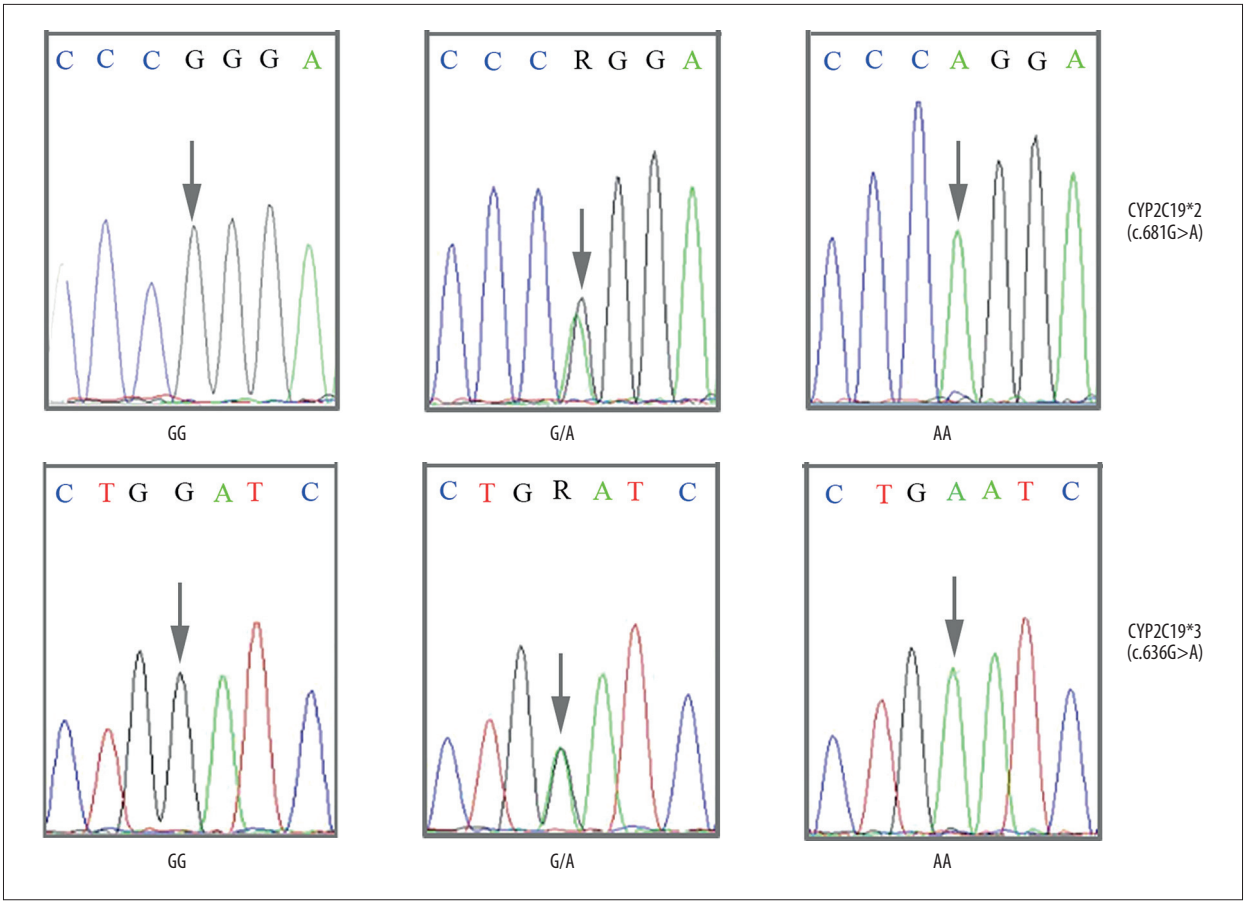

Figure 1. Sequence chromatogram of *CYP2C19**2(c.681G>A; rs4244285) (up) and CYP2C19*3 (c.636G>A; rs4986893) (down). SNPs are indicated by arrows.

protocol: 50°C for 5 min, pre-denaturation at 94°C for 5 min, followed by 35 cycles of denaturing at 94°C for 25 s, annealing at 48°C for 40 s, and extension at 72°C for 30 s, and a final elongation at 72°C for 5 min. The amplification products were subsequently dispensed into a hybridization reaction chamber to hybridize reactions. BaiO Array Doctor Version 2.0 (BaiO Technology Co, Ltd, Shanghai, China) software and BaiO®BE-2.0 (BaiO Technology Co, Ltd, Shanghai, China) software were utilized to analyze the images of the hybridization of the amplification products with the gene probes according to the instructions of the manufacturer.

Sanger sequencing was performed to confirm the different allelic variants of CYP2C19*2 and CYP2C19*3. Sequencing of the purified products using reverse primers was conducted with the sequencing kit according to the instructions of the manufacturer (SinoMDgene Technology Co., Ltd, Beijing, China). The DNA sequencing was performed on an ABI 3500xL Genetic Analyzer (Applied Biosystems). The sequencing results were assembled using ABI PRISM sequencing analysis software version 5.4 (Applied Biosystems). The chromatograms of different SNP variants using reverse primers for sequencing are presented in Figure 1.

Statistics

SPSS statistical software version 19.0 was used for data analysis. Chi-square and Fisher's exact tests were used to compare the allele and genotype frequencies and descriptive analysis was used to compare allele frequencies between the Hakka population and published data of other ethnic groups. A value of $P<0.05$ was considered as statistically significant.

Results

Genotype and allelic frequencies of CYP2C19 *1, *2, *3 in 6686 subjects of the Hakka population attending an inpatient department of a hospital in southern China were successfully obtained and are shown in Tables 1 and 2. The allelic frequency of CYP2C19*2 was 0.31, with 652 individuals homozygous for this defective allele resulting in a frequency of 9.57% for the *2/*2 genotype. The frequency of CYP2C19*3 allele was 0.05, with 0.35% of the Hakka population harboring the homozygous *3/*3 genotype; therefore, the wild-type allele CYP2C19*1 exhibited the highest frequency at 0.64. The observed frequencies of

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Table 1. Genotype frequencies of *CYP2C19* in 6,686 subjects of Hakka ethnic population.

CYP2C19		Observed number	Expected number	Frequency (%)
Phenotypes	Genotype			
Extensive metabolizer	*1/*1	2,790	2,767	41.73
Intermediate metabolizer	*1/*2	2,651	2,672	39.65
	*1/*3	372	396	5.56
Poor metabolizer	*2/*2	652	645	9.75
	*2/*3	198	191	2.96
	*3/*3	23	14	0.35
Total		6,686		100.00

Table 2. Ethnic variation of CYP2C19 (*1, *2, *3) in the present study and previous studies.

Populations	Number	Alleles frequency of CYP2C19			Reference
		*1	*2	*3	
Hakka	6,686	0.6433	0.3106	0.0461	
Chinese-Dai	193	0.66	0.30	0.03	33
Chinese Li	100	0.74	0.25	0.01	25
Chinese-Han	101	0.56	0.37	0.07	34
Koreans	103	0.67	0.21	0.12	22
Japanese	1,003	0.59	0.30	0.11	24
Vietnamese	90	0.62	0.24	0.14	22
Thai	1,051	0.63	0.27	0.10	30
Malaysian	54	0.72	0.23	0.05	21
Turkish	404	0.88	0.12	0.00	35
Saudi Arabians	97	0.85	0.15	0.13	40
Iranians	140	0.56	0.24	0.20	44
Mexican	238	0.77	0.08	–	23
Macedonian	184	0.65	0.14	–	22
Swedish	175	0.77	0.23	0.00	36
Russian	290	0.88	0.11	0.00	32
Italian	360	0.89	0.11	0.00	28
Bolivian	778	0.92	0.08	0.00	37
Faroese	312	0.97	0.03	0.00	38
Tanzanian	251	0.81	0.18	0.01	41
Ethiopian	114	0.84	0.14	0.02	42
Zimbabwean	84	0.87	0.13	0.00	43

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Table 3. Alleles and genotypes frequencies for the two SNPs in the Hakka population.

Gene	Genotype				Gene frequency	
	GG	GA	AA	Total	G	A
CYP2C19*2 (rs4244285)	3,185 (47.64)	2,849 (42.61)	652 (9.75)	6,686	9,219 (68.94)	4,153 (31.06)
CYP2C19*3 (rs4986893)	6,093 (91.13)	570 (8.53)	23 (0.34)	6,686	12,756 (95.39)	616 (4.61)

CYP2C19 genotypes in the Hakka ethnic group were in Hardy-Weinberg equilibrium (χ^2=7.62, P>0.05).

The frequencies and genotypes of CYP2C19*2 and CYP2C19*3 alleles in Chinese Hakka subjects are summarized in Table 3. The frequency of mutant allele CYP2C19*2 was almost 6-fold higher than that of mutant allele CYP2C19*3. Among the 6686 subjects, there were 3185 (47.64%) with wild-type homozygous, 2849 (42.61%) with heterozygous, and 652 (9.75%) with mutant homozygous CYP2C19*2. There were 6093 (91.13%) with wild-type homozygous, 570 (8.53%) with heterozygous, and 23 (0.34%) with mutant homozygous CYP2C19*3. We divided these 6686 subjects into 3 phenotypes based on CYP2C19*2 and CYP2C19*3 genotypes in the present study (Table 1). The normal metabolizer genotype was the extensive metabolizer (EM; 41.73%), followed by intermediate metabolizer (IM; 45.21%) and poor metabolizer (PM; 13.06%) genotypes.

To ensure accuracy, 300 samples were re-genotyped by Sanger sequencing. We obtained the same genotyping result for each selected sample by both methods (Gene chip method and Sanger sequencing).

Discussion

Numerous lines of evidence strongly suggest that inter-individual, ethnic, and racial differences in drug metabolism are due to polymorphic expression of metabolizing enzymes, especially cytochrome P450 (CYP) [15,16]. Recent data demonstrate significant alteration in the enzyme activity result in variable drug responses and increased rates of thrombotic events in patients harboring hepatic cytochrome gene variants [10,17–19]. CYP2C19*2 and CYP2C19*3 alleles, which result in the aberrant splicing and a premature stop codon, respectively, have been extensively studied in populations of different ethnicities and geographic origin [20–23]. Since CYP2C19*2 and *3 cover >90% of the poor metabolism population, the mutation genotype contained *1/*2, *1/*3, *2/*2, *2/*3, and *3/*3. The allele frequency of Asian backgrounds has been reported to have a substantially greater prevalence of CYP2C19 polymorphisms associated with loss-of-function of this enzyme when compared to other racial groups [22,24,25]. For the first time, we analyzed the frequency of CYP2C19 polymorphisms in the Hakka population and compared these results with racial populations from different continents. All genotype frequencies for both CYP2C19*2 and CYP2C19*3 alleles were consistent with Hardy-Weinberg equilibrium.

We compared the allele frequencies estimated for CYP2C19*2 and CYP2C19*3 with respect to previously published reports in other ethnic populations (Table 2). Previous studies have shown that the allelic frequency of CYP2C19*2 in Asian populations are up to 30.0%, and are 15.0–17.0% in Europeans and blacks [26–28]. The allelic frequencies of CYP2C19*2 in west Asian, European, South American, Scandinavian, and African-American populations are relatively low [29–32]. Compared to other ethnicities, the CYP2C19 loss-of-function alleles are notably higher in Asian populations. Overall, the allelic frequency of CYP2C19*2 of the Hakka subjects (31.06%) are closer to that of Chinese-Dai (30%), but are in between that of populations from Chinese Li (25%) and Chinese-Han ethnic groups (37%) [25,33,34]. The frequency of the CYP2C19*2 in our study was similar to that in studies of other Asian populations (Table 2).

On the other hand, the CYP2C19*3 allele was found with a frequency of 0.0461 in the Hakka population, which is consistent with findings within East Asian populations (Table 2). CYP2C19*3 is relatively common in Asians and accounted for the remaining defective alleles in Asian PMs after genotyping for CYP2C19*2. In contrast, previous reports suggested that CYP2C19*3 was present at a low frequency or nearly absent in Turkish, Swedish, Russian, Italian, Bolivian, Faroese, Tanzanian, Ethiopian, and Zimbabwean populations [32,35–38]. The prevalence of CYP2C19*3 presented in our study is consistent with previous reports on the Chinese population, but lower than that of Japanese, Koreans, Vietnamese, and Thai populations [22,39]. Despite this, no statistically significant difference in frequency of CYP2C19*3 was found between the Hakka and the populations mentioned above. In addition, more attention should be paid to populations that have a high frequency of the CYP2C19 loss-of-function alleles, especially in China, because people with the variants CYP2C19*2 or CYP2C19*3 can have abnormal in metabolism of drugs such as clopidogrel, with adverse drug reactions.

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As described earlier, several studies have provided evidence that CYP2C19*2 and CYP2C19*3 alleles are consistently associated with adverse cardiovascular events. Therefore, clinical use of the CYP2C19 genotype as a predictive biomarker for personalized therapy is crucial, and can be classified into the 3 following metabolizer phenotypes: poor metabolizers (PM), intermediate metabolizers (IM), and extensive metabolizers (EM). In the present study, the frequencies of extensive metabolizers and intermediate metabolizers were observed to be comparable, although the proportion of intermediate metabolizers (45.21%) was found at a slightly higher frequency than extensive metabolizers (41.73%). The most important mutated allele was CYP2C19*2, which was predominantly responsible for poor metabolizers and accounted for 86.03% of the study population. The frequencies of the mutant CYP2C19 alleles and genotypes showed large inter-ethnic differences. As with previous studies, poor metabolizers are significantly more frequent (12–23%) in the East Asian population, whereas the prevalence of poor metabolizers is estimated to be lower in West Asian, Europeans, South Americans, Scandinavians, and Africans [22,40–43]. In this study, we observed that the prevalence of the poor metabolizers' phenotype is 13.06%, which is similar to that of other Asian populations.

Conclusions

For the first time, we describe the genetic polymorphism of CYP2C19 (CYP2C19*2 and *3) in the Hakka ethnic population. The CYP2C19 allele and genotype frequencies were also compared to other populations. In particular, most of the previous studies were conducted with relatively low numbers of individuals. In comparison, a large sample size of 6686 subjects was genotyped in our study and the results may deepen our understanding of the basic genetic profile of CYP2C19 in the Hakka population. The results of the present study offer a preliminary basis for more rational use of drugs that are substrates for CYP2C19 in Hakka subjects. Further studies should focus on obtaining sufficient data on allelic frequencies related to drug response for their implementation in clinical practice.

Conflicts of interest

None.

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