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Genetic polymorphisms of pharmacogenomic VIP variants in Li nationality of southern China

Yipeng Ding[a,*,1], Ping He[a,1], Na He[b,c], Quanni Li[a], Juan Sun[a], Jinjian Yao[a], Shengyang Yi[a], Heping Xu[a], Duoyi Wu[a], Xiang Wang[a], Tianbo Jin[b,c,d,**]

[a] Department of Emergency, People's Hospital of Hainan Province, Haikou, Hainan 570311, China
[b] School of Medicine, Xizang Minzu University, Xianyang, Shaanxi 712082, China
[c] National Engineering Research Center for Miniaturized Detection Systems, Xi'an 710069, China
[d] School of Life Sciences, Northwest University, Xi'an, Shaanxi 710069, China

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ABSTRACT

Objectives: The present study aimed to screen members of the Li nationality in southern China for genotype frequencies of VIP variants and to determine differences between the Li ethnicity and global human population samples in HapMap.
Methods: In this study, we genotyped 77 very important pharmacogenetic (VIP) variants selected from the pharmacogenomics knowledge base (PharmGKB) in members of the Li population and compared our data with other eleven populations from the HapMap data set.
Results: Our results showed that *VDR* rs1540339, *VKORC1* rs9934438, and *MTHFR* rs1801133 were most different in Li compared with most of the eleven populations from the HapMap data set. Furthermore, population structure and F-statistics (Fst) analysis also showed differences between the Li and other HapMap populations, and the results suggest that the Li are most genetically similar to the CHD population, and the least similar to the YRI in HapMap.
Conclusions: The findings of our study complement the pharmacogenomics database with information on members of the Li ethnicity and provide a stronger scientific basis for safer drug administration, which may help clinicians to predict individual drug responses, thereby avoiding the risk of adverse effects and optimizing efficacy in this population.

1. Introduction

The concept of pharmacogenetics originated as a result of clinical observations that showed there were patients with very high or very low plasma or urinary drug concentrations, suggesting inherited variation in drug metabolism (Weinshilboum, 2003). It is estimated that genetics can account for 20–95% of the variability in drug disposition and effects (Kalow et al., 1998). Pharmacogenetics relates to the inheritance of individual variation in drug response, whilst pharmacogenomics, the convergence of pharmacogenetics and rapid advances in human genomics, with the aim to ultimately identify the right drug for the right patient, leading to personalized medicine (March, 2000; Weinshilboum, 2003).

PharmGKB, the pharmacogenomics knowledge base (http://www.pharmgkb.org) is devoted to the dissemination of information related to how genetic variation results in the variation of drug responses. It mainly describes the association between genes, drugs and diseases. PharmGKB delivers knowledge in a number of forms, including very important pharmacogene (VIP) summaries, drug pathway diagrams, and curated literature annotations (Owen et al., 2008). It currently contains information for more than 26,000 genes and 3000 drug, including 54 VIP summaries, 113 pharmacokinetic and pharmacodynamic pathways (Zhang et al., 2015).

Recently, high-throughput experimental methods have provided a large quantity of genetic data that may permit us to improve pharmacogenomic research. These large-scale human data sets such as the HapMap Project, the Human Genome Diversity Project (HGDP) and the 1000 Genomes Project can be analyzed to discover sequence variants that affect common disease or drug responses. So this available information may be used

* Corresponding author at: #19, Xiuhua Road, Haikou 570102, Hainan, China.
** Corresponding author at: #229 North Taibai Road, Xi'an 710069, Shaanxi, China.
E-mail addresses: YipengDing_2009@163.com (Y. Ding), tianbo_xida75@163.com (T. Jin).
[1] These authors contribute equally to this work.

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to identify the health-related aspects most influenced by ethnicity. Now, global human population samples in HapMap are as following (http://hapmap.ncbi.nlm.nih.gov/biomart/martview/e4f42d4d0acde5ea6c35312381c1e461): African ancestry in southwest USA (ASW); Utah residents with Northern and Western European ancestry (CEU); Han Chinese in Beijing, China (CHB); Chinese in Metropolitan Denver, Colorado (CHD); Gujarati Indians in Houston, Texas (GIH); Japanese in Tokyo, Japan (JPT); Luhya in Webuye, Kenya (LWK); Mexican ancestry in Los Angeles, California (MEX); Maasai in Kinyawa, Kenya (MKK); Toscans in Italy (TSI); Yoruba in Ibadan, Nigeria (YRI).

The Li ethnic group has traditionally lived on Hainan Island in China for approximately 5000 years, and has a population of more than 1.28 million (2010 Census). As an ethnic minority in China, the Li population is a unique group who live only on Hainan Island. In recent years, pharmacogenomic studies have been conducted in several ethnic groups in China, however, we are unable to found any pharmacogenomic information in the Li ethnic group. Herein, we present the first study that systematically screens the Li ethnic group for genetic polymorphisms of pharmacogenomic VIP variants.

2. Materials and methods

2.1. Study participants

We randomly recruited participants in a healthy Li population of 100 unrelated subjects (50 males and 50 females) from Hainan province of China and determined their lineage and birthplace belong to the Li ethnicity. All subjects were healthy in terms of their medical history and physical examination. Besides, an explanation about the purpose and experimental procedures of the study were given to all individuals. Written informed consent was obtained from all subjects prior to sample donation, and the study protocol was performed in accordance with the Declaration of Helsinki and approved by the Human Research Committee of the People's Hospital of Hainan Province and Xizang Minzu University for Approval of Research Involving Human Subjects.

2.2. Variant selection and genotyping

We successfully genotyped 77 VIP variants selected from PharmGKB VIP in 100 Li population from Hainan. Genomic DNA was isolated from whole blood using the GoldMag nanoparticle method (GoldMag Ltd., Xi'an, China), in combination with liquid assistant, high performance composite magnetic particles can be specific adsorption of combined genomic DNA, and after elution can separate DNA. Compared with other traditional methods, the advantage lies in the extraction of genomic DNA fragments integrity, with high purity and high yield, and no protein and nucleic acid enzymes impurity pollution, can be directly for various downstream experiment, such as PCR and sequencing. DNA concentration was measured with the NanoDrop 2000C (Thermo Scientific, Waltham, MA, USA). The Sequenom MassARRAY Assay Design 3.0 Software (San Diego, CA, USA) was used to design Multiplexed SNP MassEXTEND assays (Gabriel et al., 2009). Single nucleotide polymorphism (SNP) genotyping was performed using the Sequenom MassARRAY RS1000 (San Diego, CA, USA) according to the standard protocol recommended. Sequenom Typer 4.0 Software (San Diego, CA, USA) was used to perform data management and analysis (Thomas et al., 2007).

2.3. Data analysis

Statistical calculations were performed with the help of Microsoft Excel (Redmond, WA, USA) and SPSS 19.0 statistical package (SPSS, Chicago, IL, USA). All statistical tests were two sided. After Bonferroni correction, $p \leq 5.9 \times 10^{-5}$ ($0.05/77 \times 11$) was indicated statistical significance. Genotype frequencies of Li and 11 HapMap populations were compared using the chi-squared test. Structure (version 2.3.4) and Arlequin (version 3.1) software were used to analyze the genetic structure within a hypothetical K number and F-statistics (Fst) in 12 populations, respectively.

3. Results

Table 1 lists the basic information of the selected variants in the selected study subjects of Li ethnicity. We successfully genotyped 77 VIP variants selected from PharmGKB VIP in 100 members of the Li population.

Table 2 displays only the significantly different loci ($p \leq 5.9 \times 10^{-5}$) between Li ethnicity and the 11 HapMap population groups. We used chi-squared test to compare differences between Li people and the 11 HapMap population groups in genotype frequency distribution of variants. The results showed there were only 1, 2, 2 and 3 of the selected VIP variant genotype frequencies in the Li that differed from those of the CHD, CHB, JPT and MEX, respectively. Differences among the selected Li group and GIH, TSI, LWK, ASW were found in 10, 10, 11 and 12 of the genotypes, respectively. When Li population was compared with the MKK, CEU, YRI groups, there were 15, 16, 19 different loci in frequency distribution, respectively. These variants were located in 16 genes, and the genotypes of *VDR*, *ABCB1*, *MTHFR*, *PGTS2* and *VKORC1* were significantly different between the Li and 11 other populations. We also found that the rs1540339 was most significantly different loci between the Li and 8 other populations.

The structure analysis of the genetic relationship among 12 populations is shown in Fig. 1, most suitable K was observed at $K = 3$, where the proportion of each ancestral component in a single individual is represented by a vertical bar divided into three colors, the results show that the Li population is most similar to the CHD, CHB and JPT populations. The results are in good agreement with those presented in Table 2.

On the basis of genetic structure, we further measured the genetic relationship throughout the population by using genetic distance, and calculated the distribution of pairwise Fst distances among the Li and all HapMap populations (Table 3). The Fst statistic is a measure of population differentiation, and the results showed that slight differences were observed between the Li group and CHB, CHD and JPT populations (Fst = 0.02488, 0.01363 and 0.02365, respectively). The minimum Fst distance was obtained between the Li and CHD (Fst = 0.01363), showed that the Li population is most similar to CHD, and least similar to the YRI populations in HapMap.

4. Discussion

Individual differences in drug metabolism and effects are due to polymorphisms in genes that encode drug metabolizing enzymes, drug transporters and drug targets (Evans and Johnson, 2001). It should be mentioned that to our knowledge, information on polymorphic distribution of pharmacogenomics VIP variants among the Li population is null.

It is generally appreciated that *VDR* gene binds the active form of vitamin D to modulate many of the neural, immune, and endocrine systems, containing calcium, phosphorous homeostasis, apoptosis and cell differentiation (Bikle, 2011; Hewison, 2010; Poon et al., 2012). Several reports have shown that the variant is associated with susceptibility to many diseases, such as type 1 diabetes mellitus (T1DM) (Wang et al., 2014), colorectal cancer (Wang et al., 2008) and asthma (Saadi et al., 2009). A Brazilian study demonstrated that rs1540339(C>T) was associated with T1DM (De Azevedo Silva et al.,