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A Case Study of the Utility of the HapMap Database for Pharmacogenomic Haplotype Analysis in the Taiwanese Population

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Abstract

Background: Single nucleotide polymorphisms (SNPs) can be used in clinical association studies to determine the contribution of genes to drug efficacy. The goal of this work was to evaluate the feasibility of using SNP information of the Han Chinese in Beijing (CHB) population from the HapMap database for clinical association studies in the Taiwanese (TWN) population.

Methods: We compared the HapMap populations with our TWN study population with regard to allele frequencies for common SNPs in two candidate genes for antidepressant treatment response to determine the applicability of the HapMap CHB data for SNP selection in the TWN population.

Results and conclusion: Our preliminary results suggest that there was no significant difference, in terms of allele and haplotype frequencies, between the CHB population of the HapMap database and the TWN population collected by Vita Genomics Inc. Therefore, it is possible to use the CHB population of the HapMap database for SNP selection in association studies for the TWN population. Using haplotype analysis, we generated a panel of SNPs that may be strongly relevant to antidepressant response in this population.

Background

Depression is the most common psychiatric disorder worldwide. No single antidepressant has been shown to be more effective than any other in lifting depression, and the effectiveness of any particular antidepressant in an individual is difficult to predict. Thus, doctors must prescribe antidepressants based on trial and error. Evidence is accumulating to suggest that the efficacy of antidepressants results from the combined effects of a number of genetic variants, such as single nucleotide polymorphisms (SNPs).[1] Although there are not enough data currently available to prove this hypothesis, more and more genetic variants associated with antidepressant response are being discovered.[1-3]

In clinical association studies, SNPs can be used to understand the relationship between genetic variations and drug efficacy by comparing SNPs found in responders to a particular drug with those found in non-responders.[1] However, it would be extremely inefficient to test all of the 10 million common SNPs found in an individual's chromosomes. Genotypes at many of these sites are strongly correlated because genetic variants that are close to each other on the chromosome are often inherited together.[4,5] These regions of linked variants are known as haplotypes. Thus, it is not necessary to assay all common SNPs if we can obtain the patterns of haplotypes between common SNPs.

In this work, we utilized the HapMap database[6] to gain haplotype information in order to identify SNPs that may be relevant to the drug efficacy of antidepressants in the Taiwanese (TWN) population. The goal of this work was to provide a comparison between a TWN population and the four populations of the HapMap database (Han Chinese in Beijing, China [CHB]; CEPH, Utah, USA, residents with Northern and Western European ancestry [CEU]; Japanese in Tokyo, Japan [JPT]; and Yoruba in Ibadan, Nigeria [YRI]) in terms of allele and haplotype frequencies. We also evaluated the possibility of using SNPs from the

HapMap Han Chinese population for clinical association studies of the TWN population.

Materials and Methods

Subjects

Our study population consisted of 96 Taiwanese adults, with DNA samples collected by Vita Genomics, Inc. The SNP genetic markers of these subjects were generated at the high-throughput genomics laboratory of Vita Genomics Inc. Informed consent was obtained from each subject.

Identification of Tag Single Nucleotide Polymorphisms (SNPs) and Generation of the SNP Panel

Based on the findings in the literature relating to the pharmacogenomics of antidepressant response,[1-3] we focused our study on candidate genes. These included the brain-derived neurotrophic factor (*BDNF*) gene, the tryptophan hydroxylase 1 (*TPH1*) gene, and their corresponding candidate SNPs, which were found to be strongly associated with the drug efficacy of selective serotonin reuptake inhibitor (SSRI) antidepressants.[7-10] The *BDNF* gene encodes a protein in the nerve growth factor family and may be involved in both the pathophysiology of depression and the effects of antidepressants.[7] Tsai et al.[8] tested this hypothesis in a TWN population and found the *BDNF* Val66Met SNP to be associated with response to fluoxetine. The *TPH1* gene codes for the rate-limiting enzyme in serotonin biosynthesis and may also play a role in antidepressant response.[1] *TPH1* haplotypes have been associated with depression,[11] and recent studies found that a SNP of the *TPH1* gene was associated with fluvoxamine and paroxetine and treatment response.[9,10]

We utilized the common SNPs in these candidate genes from the HapMap database and compared the populations of HapMap with our TWN study population. This allowed us to evaluate similarities between the TWN population and the HapMap CHB population. The HapMap database is a catalog of common genetic variants for four populations (CHB, CEU, JPT, and YRI).

We employed a haplotype block definition, based on the four-gamete test,[12] to identify the patterns of linkage disequilibrium (LD) among the common SNPs of the candidate genes. According to this definition, a haplotype block is a region without recombination. Let us assume two loci, A and B, each with two alleles (denoted as A_1, A_2, B_1, and B_2). Recombination leads to all four gametes (A_1B_1, A_1B_2, A_2B_1, and A_2B_2) being observed between a pair of loci. In the iterative process, haplotype blocks are identified

Table I. The allele frequencies of single nucleotide polymorphisms (SNPs) in the *BDNF* gene and the *TPH1* gene for the Taiwanese (TWN) population collected by Vita Genomics Inc. and the four populations from the HapMap database. There was no significant difference between the two sets of allele frequencies for the CHB and TWN populations ($p > 0.05$)

Gene	SNP	Allele frequency				
		TWN	CHB[a]	CEU[b]	JPT[c]	YRI[d]
BDNF	rs6265	A: 0.516; G: 0.484	A: 0.631; G: 0.369	A: 0.175; G: 0.825	A: 0.337; G: 0.663	A: 0.000; G: 1.000
	rs11030104	G: 0.541; A: 0.459	G: 0.633; A: 0.367	G: 0.200; A: 0.800	G: 0.352; A: 0.648	G: 0.000; A: 1.000
TPH1	rs7110238	T: 0.700; G: 0.300	T: 0.744; G: 0.256	T: 0.559; G: 0.441	T: 0.761; G: 0.239	T: 0.322; G: 0.678
	rs7943884	C: 0.900; T: 0.100	C: 0.878; T: 0.122	C: 0.692; T: 0.308	C: 0.841; T: 0.159	C: 0.583; T: 0.417
	rs951624	A: 0.892; T: 0.108	A: 0.889; T: 0.111	A: 0.942; T: 0.058	A: 0.909; T: 0.091	A: 0.883; T: 0.117
	rs7939791	G: 0.707; A: 0.293	G: 0.756; A: 0.244	G: 0.578; A: 0.422	G: 0.768; A: 0.232	G: NA; A: NA

a *BDNF* p = 0.1466; *TPH1* p = 0.9721 vs allele frequencies in TWN.

b *BDNF* $p = 1.7 \times 10^{-15}$; *TPH1* $p = 7 \times 10^{-6}$ vs allele frequencies in TWN.

c *BDNF* p = 0.0009; *TPH1* p = 0.6871 vs allele frequencies in TWN.

d *BDNF* $p = 1.1 \times 10^{-39}$; *TPH1* $p = 1.3 \times 10^{-15}$ vs allele frequencies in TWN.

CEU = HapMap CEPH (Utah, US residents with ancestry from Europe) population; **CHB** = HapMap Han Chinese in Beijing, China, population; **JPT** = HapMap Japanese in Tokyo, Japan, population; **YRI** = HapMap Yoruba in Ibadan, Nigeria, population.

Table II. The haplotype frequencies in the *BDNF* gene and the *TPH1* gene for the Han Chinese in Beijing (CHB) population from the HapMap database and the Taiwanese (TWN) population collected by Vita Genomics Inc. There is no significant difference between the two sets of haplotype frequencies for the CHB and TWN populations ($p > 0.05$)

Gene	Haplotype	Haplotype frequency	
		CHB	TWN
BDNF[a]	AG	0.633	0.511
	GA	0.367	0.474
	AA	NA	0.010
TPH1[b]	TCAG	0.744	0.695
	GCTA	0.111	0.105
	GTAA	0.122	0.095
	GCAA	0.011	0.095

a SNPs = rs6265 (A/G); rs11030104 (G/A).

b SNPs = rs7110238 (T/G); rs7943884 (C/T); rs951624 (A/T); rs7939791 (G/A).

as a set of contiguous SNP markers if the number of gametes does not exceed three.[12]

We then generated a set of tag SNPs for each candidate SNP using Haploview[13] software. Finally, we combined the candidate SNPs and tag SNPs, creating the panel of SNPs for further investigation.

Results

In the SNP panel for our study, there were two genes and six SNPs (table I). To evaluate the feasibility of using SNPs from CHB population in the HapMap database for clinical association studies of the TWN population, we first performed the statistical analyses for allele frequencies of SNPs in the four HapMap populations (CHB, CEU, JPT, and YRI) and the TWN population collected by Vita Genomics Inc. Table I shows the allele frequencies of SNPs in the *BDNF* gene and the *TPH1* gene for the four populations of HapMap and the TWN population. We compared the allele frequencies between the TWN population and each of the four populations of HapMap (i.e. CHB and TWN, EUS and TWN, JPT and TWN, YRI and TWN) by the χ^2 test. Results were considered to be statistically significant if $p < 0.05$. For the CHB and TWN populations, we did not find a significant difference between allele frequencies in the candidate genes (*BDNF* [$p = 0.1466$] and *TPH1* [$p = 0.9721$]). Thus, our results indicate that it is feasible to use the HapMap CHB population SNP data for clinical association studies in the TWN population. As shown in table I, we found a significant difference between the CEU and TWN populations, as well as between the YRI and TWN populations, for both candidate genes. Although there was no significant difference between the JPT and TWN populations in the *TPH1* gene ($p = 0.6871$), we found a significant difference between these two populations in the *BDNF* gene ($p = 0.0009$). Thus, our results indicate that it is not appropriate to use the CEU, JPT, and YRI populations of the HapMap database for the SNP selection in the TWN population.

Table II shows the haplotype frequencies in the *BDNF* gene and the *TPH1* gene for the CHB and TWN populations. We compared the haplotype frequencies for the CHB and TWN populations by the χ^2 test. Results were considered to be statistically significant if $p < 0.05$. For the CHB and TWN populations, we did not find a significant difference between haplotype frequencies in the candidate genes (*BDNF* [$p = 0.0712$] and *TPH1* [$p = 0.2414$]). Thus, our results indicate that it was reasonable to utilize the CHB population of the HapMap database for the SNP selection in the TWN population.

Several studies have shown that LD estimates for SNPs with lower minor allele frequency (MAF) were unreliable unless large numbers of subjects were genotyped.[5,14] As shown in table I, we focused on SNPs with MAF ≥0.1 for the TWN population in the two candidate genes. In addition, we found that the MAFs of the rs951624 SNP in the *TPH1* gene were <0.1 for the CEU and JPT populations. Furthermore, the MAFs in the *BDNF* gene were <0.1 for the YRI population.

Conclusions

With the SNP information that we obtained from the HapMap database, we applied LD analysis based on the four-gamete test to determine SNPs that may be strongly correlated and associated with antidepressant responsiveness. We found that there was no significant difference in the allele and haplotype frequencies of the selected SNPs between the HapMap database CHB population and the TWN population collected by Vita Genomics Inc. These preliminary results suggest that we could utilize the CHB population of the HapMap database to select SNPs for the TWN population in association studies. In future empirical trials, we will select more candidate genes and SNPs from the HapMap CHB population data, based on the methodology of the present study, to validate the association of specific haplotypes with SSRI clinical response in the TWN population.

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