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Variability in the Frequency of Single Nucleotide Polymorphisms of N-acetyl Transferase 2 (*NAT2*) Gene among the Different Ethnic Groups in Taiwan

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ABSTRACT

Significant variations in the frequency of single nucleotide polymorphisms (SNPs) of human leukocyte antigen among Taiwan's aboriginal tribes and high homogeneity within each tribe have been reported. To identify variations in genetic polymorphisms of drug-metabolizing enzyme in seven of Taiwan's ethnic groups, the SNPs of N-acetyl transferase 2, a conjugation enzyme in phase II metabolism, were investigated. Methods: Three SNPs of *NAT2*, *NAT2**5, *NAT2**6, and *NAT2**7, were determined by the TaqMan® method and subsequently confirmed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Our results showed statistically significant variations in the frequency of *NAT2* genotype categories according to the 3 SNPs of *NAT2* within 7 Taiwanese ethnic groups (Chi-square = 32.08, $p<0.05$). The distribution of the frequency of the slow acetylator genotype ranged from 32.0% in the Hakka population to 75.5% in the Paiwan population. A lack of *NAT2**5 SNP alleles was found in the Atayal population, while a *NAT2**5 allele frequency of 31.6% was observed in the Paiwan group. The frequencies of allele *NAT2**6 and *NAT2**7 in the investigated ethnic groups ranged from 11.2-37.0% and 17.0-53%, respectively. Our results also showed the considerable variations in drug-metabolizing enzyme *NAT2* genotypes among Taiwan's aboriginal and general population. The variation in the genetic polymorphisms of drug-metabolizing enzyme in Taiwan's groups is worthy of further study to understand different therapeutic and adverse drug responses in ethnic groups.

Key words: N-acetyltransferase 2, aboriginal, single nucleotide polylmorphism, Taiwan

INTRODUCTION

Arylamine N-acetyltransferase 2 (NAT2), a xenobiotic metabolizing enzyme in *O*- or *N*-acetylation of aromatic and heterocyclic amines, has been demonstrated to be associated with drug response and cancer development[1-6]. Patients with low NAT2 activity have a higher risk of developing severe skin reactions and hepatitis when treated with sulphonamide and isoniazid, respectively[4,5]. In addition, some evidence suggests that people with the slow acetylation genotype had the risk of colorectal and breast cancers[2,6]. Therefore, it may be important to understand the functional NAT2 activity in each individual to avoid excessive exposure to certain drugs and environments.

The relationships between genotypes and phenotypes have been elucidated via recombinant human *NAT2* alleles with specific nucleotide substitutions in an *Escherichia coli* expression system[7]. A number of single nucleotide polymorphisms (SNPs) of *NAT2* that influence NAT2 activity has been systematically classified and applied in the human clinical studies[8,9]. Reduced enzyme activity is associated with some SNPs of *NAT2*, such as *NAT2**5 (C341T, rs1801280), *NAT2**6 (G590A, rs1799930), *NAT2**7 (G857A, rs1799931), and *NAT2**14 (G191A, rs1801279), compared to the wild-type allele *NAT2**4[7]. NAT2 acetylation activity can be divided into 3 classes, namely rapid, intermediate, or slow acetylation, when the genotypes contain two alleles, one allele or none allele of *NAT2**4, respectively[9,10]. Nevertheless, the first two categories were combined as the rapid acetylation classification in some reports. Because the *NAT2**14 genotype is rare in the Asian population[11,12], only 3 SNPs, *NAT2**5, *6, and *7, were examined in this study.

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The ethnic difference in the *NAT2* polymorphism has been observed in several studies[2,12-20]. Various frequencies of slow acetylators have been reported from 6.1%, 16.6-24.1%, 44.3%, and 55.0% in the Japanese, Taiwanese, North Indian, and Caucasian populations, respectively. Taiwan's population is composed of 1.5% aboriginal people, 7.5% mainland Chinese from China after War World II, and 91% Minnan and Hakka from southeast coast of China since the 17th century[21]. Researchers often use Chinese as representatives of Asian people and the Minnan/Hakka or so-called Han people as subjects in clinical studies. However, genetic variations in metabolizing enzymes among Taiwan's indigenous tribes and Minnan/Hakka were poorly investigated. On the other side, remarkable genetic variations in human leukocyte antigen (HLA) between Taiwan aborigines and Minnan/Hakka have been reported by Lin *et al*.[22,23]. Their results showed homogeneity in each tribe and heterogeneity among the different tribes with respect to HLA SNPs, due to long-term geographical isolation. Taiwan aborigines were divided into nine ethnic groups according to their linguistic, cultural, and geographical features. Different hypotheses regarding the origin of Taiwan aboriginal ethnic groups have been raised from the approaches of archaeology and linguistics[24,25]. Until recently, genetic distances by mitochondria DNA polymorphisms were employed to investigate the origin of Taiwan aboriginal populations from the genetic viewpoint[26,27]. Taiwan aboriginal populations appeared closer to island Southern Asian populations, e.g. Philippines, Indonesia, etc., than to the population from mainland East Asia, e.g. Minnan/Hakka, South-China, North-China, etc., according to the results of the principle component analysis[27]. Furthermore, the geographical feature was correspondent with the map of genetic markers in Taiwanese aboriginal ethnic groups, i.e., genetic distances revealed distinct clusters that were composed of the southernmost populations (Paiwan, Puyuma, and Rukai), Yami from the Orchid Island, and the northern (Atayal, Saisiat), and central/east coast populations (Tsou, Bunun, and Ami)[27]. However, Ami showed closer to the southern than to the central/east coast populations by the other haplogroup frequencies[27]. Although mitochondrial DNA polymorphisms analysis provided useful information to understand the origin of Taiwan ethnic groups, the results remained inconsistent with other research group[26].

Therefore, we hypothesized that the frequency of *NAT2* SNPs is varied among Taiwan ethnic groups, which may contribute to the variant responses to the medications involving NAT2 metabolism. To test our hypothesis, the *NAT2* genotype in Taiwan ethnic groups, 5 aboriginal groups and 2 general populations were included in this study. This is the first study to explore SNPs distribution of the drug metabolizing enzyme, NAT2, among Taiwan's ethnic groups.

MATERIALS AND METHODS

I. *Subjects*

Human DNA samples were collected at Transfusion Medicine Research Laboratory of the Mackay Memorial Hospital in Taipei, Taiwan[22]. The recruited subjects have signed the consents to participate in the study. The research was also approved by the Institutional Review Board, Mackay Memorial Hospital, Taipei, Taiwan, under clinical trial number NCT00459251. The aboriginal groups were defined by the geographical area where the aboriginal populations reside. In addition, only those whose parents were from the same tribes and who were unrelated to other participants as confirmed by the tribal chiefs, were included in our study. Five aboriginal tribes, Atayal (AT), Tsou (TS), Paiwan (PW), Ami (AM), and Yami (YM), and general Taiwanese groups, Hakka (HK) and Minna (MN), were included in this study. Five aboriginal groups were selected in our study because of their definite populations among the nine tribes with less effect of admixture by other surrounding populations and also representing different geographical areas. The Atayl, Tsou, and Paiwan inhabit the north, middle, and south of the central mountain area of Taiwan main island, respectively. The Ami lives the plains of the east coast surrounded by mountains and Pacific Ocean. The Yami resides Orchid Island, located off the eastern coast of the main island. If an aboriginal group spread in different areas, the participants were recruited from different areas in order to represent of a specific ethnic population in this study. Around 50 individual DNA samples from each ethnic group were analyzed to elucidate the allele frequency of *NAT2* genotypes.

II. *NAT2 Genotype Assay*

TaqMan® drug metabolism genotyping assays (Applied Biosystems, Foster City, CA, USA), using endpoint fluorescence (ABI Prism® 7900HT Sequence Detection System Software version 2.2.1), were used for high throughput determination of *NAT2* genotype polymorphisms, *NAT2**5, *NAT2**6, *NAT2**7.

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was also performed to confirm the results and identified the undetermined samples from TaqMan® drug metabolism genotyping assays[12]. Briefly, the *NAT2* gene was amplified by PCR with primers of sequences, 5'-GGAACAAATTGGACTTGG-3' and 5'-TCTAGCATGAATCACTCTGC-3' (Operon Biotechnologies, Cologne, Germany). PCR mixture was composed of 1X Colorless Gotaq® Reaction Buffer (Promega Corporation, Madison, WI, USA), 1 U Gotaq® DNA polymerase, 100 ng DNA template, 0.2 pmol of each primer, 0.4 mM dNTPs and deionized water in a final volume of 25 μL. PCR program settings were preheating at 95°C for 5 min, 35 cycle of 95°C for 40s,

62.5°C for 30s, 72°C for 90s, and then extension at 72°C for 10 min. A 25-μL aliquot of PCR product was digested with restriction enzymes *Kpn*I (C341T), *Taq*$^{\alpha}$I (G590A), or *Bam*HI (G857A) for 16 h. The digested products were resolved by electrophoresis in 2% agarose gel (AMRESCO® Agarose^{TM}) at 100 V for 35 min.

Each individual sample was classified into 3 classes (the rapid, intermediate, and slow *NAT2* acetylation genotypes) when carrying two wild alleles (*NAT2**4/*4), one wild allele (*NAT2**4/*5, *NAT2**4/*6, and *NAT2**4/*7), and two mutant allele (*NAT2**5/*5, *NAT2**5/*6, *NAT2**5/*7, *NAT2**6/*6, *NAT2**6/*7, and *NAT2**7/*7), respectively[9].

III. *Statistical Analysis.*

The statistical significance was evaluated by Chi-square test using the SPSS 11.5.0 (SPSS Inc. Chicago, IL, USA) program. A value of $p<0.05$ was considered statistically significant.

RESULTS

I. *NAT2*5 Allele*

The allele frequency of SNP of *NAT2**5 in studied Taiwan ethnic groups varied from 0.0 to 31.6% (Table 1). *NAT2**5 SNP allele was not detected in the Atayal tribe. In contrast, the high frequency, 31.6%, of *NAT2**5 SNP was observed in the Paiwan tribe. The percentages of wild type, heterozygote, and homozygote of *NAT2**5 populations were 42.9%, 51.0%, and 6.1%, respectively, in the Paiwan population. The allele frequency of *NAT2**5 in the other groups ranged from 6.0 to 11.0%. Individuals homozygous for *NAT2**5 were only identified in the Paiwan (3 persons) and Yami (1 person) populations.

II. *NAT2**6 Allele

The allele frequency of SNP of *NAT2**6 in investigated groups ranged from 11.2 to 37.0% (Table 1). The higher distribution of *NAT2**6, 37.0 and 33.0%, was observed in the Ami and Tsou tribes, respectively. On the other hand, lower frequencies of 15.0 and 11.2% were observed in the Atayal and Paiwan populations, respectively. The distribution of *NAT2**6 was similar in Yami, Hakka, and Minnan groups.

III. *NAT2**7 Allele

The allele frequency of *NAT2**7 varied in the Taiwanese ethnic groups (Table 1). The Paiwan and Atayal populations had higher proportions, 41.8 and 53.0%, respectively, relative to other groups. 7 of 49 and 16 of 50 persons are *NAT2**7 homozygous in the Paiwan and Atayal tribes, respectively.

IV. *NAT2* Genotypes Classification

The *NAT2* phenotypes in the studied population according to the genotype classification of *NAT2**4, *5, *6, and *7 are depicted in Table 2. The difference in the three genotype categories (rapid, intermediate, and slow acetylator) among each of 7 Taiwanese ethnic populations was statistical significant by Chi-square test (Chi-square = 32.08, DF=12, $p < 0.05$). Only 6.1% of the Paiwan population was classified as the rapid acetylation genotype, *NAT2**4/*4. However, the rapid acetylation genotype were observed in 28% of the Hakka and Minnan populations. Among the aboriginal groups, the frequency of rapid acetylator varied from 6.1 to 20%. The low proportions of intermediate acetylation genotypes, 18.4% and 28%, represent in the Paiwan and Ami populations, respectively. The high proportion of intermediate acetylation genotypes in the other groups ranging from 34 to 40% was observed. Obviously, very high percentage of slow acetylators (75.5%) were observed in the Paiwan population in our study with statistical significance comparing to other ethnic groups. Subsequently, 56%, 48%, and 43.8% of Ami, Atayal, and Yami tribes, respectively, were reported as slow acetylators. Similar distributions of the slow acetylation genotypes in Tsou, Hakka, and Minnan tribes were observed. In addition, the distribution of the combined NAT2 genotypes in each ethnic population did not differ significantly, as derived from Hardy-Weinberg equilibrium at significant level $\alpha = 10^{-3}$[28].

Table 1. Frequency distribution of NAT2 genotypes in Taiwanese ethnic populations

Groups / Allele frequency*	Ami	Atayal	Paiwan	Tsou	Yami	Hakka	Minnan
*NAT2**4	30/100 (30)	32/100 (32)	15/98 (15.3)	43/100 (43)	36/96 (37.5)	48/100 (48)	45/100 (45)
*NAT2**5	11/100 (11)	0/100 (0)	31/98 (31.6)	7/100 (7)	9/96 (9.4)	6/100 (6)	6/100 (6)
*NAT2**6	37/100 (37)	15/100 (15)	11/98 (11.2)	33/100 (33)	19/96 (19.8)	21/100 (21)	27/100 (27)
*NAT2**7	22/100 (22)	53/100 (53)	41/98 (41.8)	17/100 (17)	32/96 (33.3)	25/100 (25)	22/100 (22)

Allele frequency* was calculated according to a formula: (2nx/x + nx/-)/2n, where nx/x is the number of individuals homozygous for X and nx/- heterozygous for X. X stands for each single nucleotide polymorphism of NAT2.

Table 2. Distribution of NAT2 phenotypes according to genotypes in Taiwanese ethnic populations

Groups / Genotypes	Ami n/total (%)	Atayal n/total (%)	Paiwan n/total (%)	Tsou n/total (%)	Yami n/total (%)	Hakka n/total (%)	Minnan n/total (%)
NAT2 rapid acetylator							
*NAT2**4/*4	8/ 50 (16)	6/ 50 (12)	3/ 49 (6.1)	10/ 50 (20)	9/ 48 (18.8)	14/ 50 (28)	14/ 50 (28)
Total	8/ 50 (16)	6/ 50 (12)	3/ 49 (6.1)	10/ 50 (20)	9/ 48 (18.8)	14/ 50 (28)	14/ 50 (28)
NAT2 intermediate acetylator							
*NAT2**4/*5	4/ 50 (8)	0/ 50 (0)	4/ 49 (8.2)	4/ 50 (8)	0/ 48 (0)	5/ 50 (10)	1/ 50 (2)
*NAT2**4/*6	10/ 50 (20)	5/ 50 (10)	2/ 49 (4.1)	13/ 50 (26)	6/ 48 (12.5)	9/ 50 (18)	11/ 50 (22)
*NAT2**4/*7	0/ 50 (0)	15/ 50 (30)	3/ 49 (6.1)	6/ 50 (12)	12/ 48 (25)	6/ 50 (12)	5/ 50 (10)
Total	14/ 50 (28)	20/ 50 (40)	9/ 49 (18.4)	23/ 50 (46)	18/48 (37.5)	20/ 50 (40)	17/ 50 (34)
NAT2 slow acetylator							
*NAT2**5/*5	0/ 50 (0)	0/ 50 (0)	3/ 49 (6.1)	0/ 50 (0)	1/ 48 (2.1)	0/ 50 (0)	0/ 50 (0)
*NAT2**5/*6	4/ 50 (8)	0/ 50 (0)	3/ 49 (12.2)	3/ 50 (6)	3/ 48 (6.3)	1/ 50 (2)	2/ 50 (4)
*NAT2**5/*7	3/ 50 (6)	0/ 50 (0)	18/ 49 (36.7)	0/ 50 (0)	4/ 48 (8.3)	0/ 50 (0)	3/ 50 (6)
*NAT2**6/*6	8/ 50 (16)	2/ 50 (4)	0/ 49 (0)	4/ 50 (8)	2/ 48 (4.2)	4/ 50 (8)	3/ 50 (6)
*NAT2**6/*7	7/ 50 (14)	6/ 50 (12)	6/ 49 (12.2)	9/ 50 (18)	6/ 48 (12.5)	3/ 50 (6)	8/ 50 (16)
*NAT2**7/*7	6/ 50 (12)	16/ 50 (32)	7/ 49 (14.3)	1/ 50 (2)	5/ 48 (10.4)	8/ 50 (16)	3/ 50 (6)
Total	28/ 50 (56)	24/ 50 (48)	37/ 49 (75.5)	17/ 50 (36)	21/48 (43.8)	16/ 50 (32)	19/50 (38)

The difference in three genotype categories (rapid, intermediate, and slow) among each of 7 Taiwanese ethnic populations was statistically significant by Chi-square test (Chi-square = 32.08, $p<0.05$)

DISCUSSION

The Taiwanese mountain aboriginal tribes have preserved their culture and languages because of geographical isolation. Paiwan is the southernmost tribe of Taiwan. The Atayal, Tsou, and Ami tribes are from the northern and central parts of Taiwan, respectively. The Yami tribe is on Orchid Island, which is 49 miles from Taiwan. In addition, the HLA genotyping among different tribes showed high homogeneity and heterogeneity in intra-tribes and inter-tribes, respectively, because of low levels of admixture[22]. Therefore, genetic polymorphisms of the drug metabolizing enzyme, NAT2, was analyzed to elucidate drug metabolizing enzyme genetic variation among Taiwan's aboriginal and general groups.

In general, the percentages of NAT2 slow acetylator were above 30% in the investigated aboriginal and general populations, which are different from the frequencies of 16.6-24.1% and 6.1% in Taiwanese and Japanese, respectively, in the previous reports[12,13,18,19]. In addition, the distribution of the *NAT2* genotype in Paiwan tribe revealed the highest proportion (75.5%) of slow acetylators in our study, even higher than the proportion in Caucasian, 55%[14,15]. The allelic prevalence of NAT2*5 and NAT2*7 in Paiwan and Atayal tribes was not close to general people (Hakka and Minna) compared to other aboriginal tribes (Table 1). It can be partially explained by the relationships of the Taiwanese aboriginal and general populations which have been investigated by neighbor-joining tree and principle components analysis[26,27]. Paiwan, the southernmost population, clearly differentiated from other aboriginal and general populations[27]. However, other possible explanations may remain as to the difference of allelic distribution among populations.

Our data showed significant difference in the *NAT2* genotypes within each of 7 Taiwanese ethnic populations (Table 2), which may cause problem in the appropriate dosing of specific medications, such as the anti-tuberculosis antibiotic, isoniazid[9]. The increased incidence and drug-resistance of tuberculosis has become an important infectious disease control issue in Taiwan[29], especially in the aboriginal mountain areas[30]. In addition, it has been reported that 83.3%, 2.3%, and 0% of isoniazid-induced, nausea/vomiting, fever, visual impairment, and peripheral neuritis is observed in slow acetylators, inter-

mediate acetylators, and rapid acetylators, respectively, by Hiratsuka M., *et al*.[9]. Isoniazid-induced hepatotoxicity was also found to a greater extent in slow acetylators as compared to rapid acetylators (26.4% vs. 11.1%) in the Taiwanese general population[4]. Therefore, our results demonstrated the existence of drug-metabolizing enzyme NAT2 genetic variation among aboriginal and general populations, which may contribute to the medication induced adverse drug reactions in some populations.

To reach the goal of individualized medicine, many studies have been focused on drug-metabolizing enzyme genetic variations among races or ethnicities[31,32]. Especially, information gleaned from SNP analysis provides an important basis for individualized medicine. NAT2 is one of the drug-metabolizing enzymes and its SNPs exert a remarkable effect on drug-metabolism. According to our findings, the therapeutic response and toxicity of isoniazid may vary significantly among Taiwan's ethnic groups, especially in the Paiwan tribe, which consists of a high percentage of slow acetylators. Further pharmacoepidemiology studies of isoniazid will be conducted to elucidate the clinical importance of *NAT2* genetic variations. In addition, SNPs analysis of other drug-metabolizing enzymes, such as cytochrome P450 2C9, 2C19, and 2D6, will be performed in our populations to explore important considerations for individualized medicine.

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