RESEARCH ARTICLE

Distribution of rs1801279 and rs1799930 Polymorphisms in *NAT2* Gene among Population in Kupang, Nusa Tenggara Timur, Indonesia

Edhyana Sahiratmadja[1,*], Simeon Penggoam[2], Ani Melani Maskoen[1,3], Alvinsyah Adhityo Pramono[4], Dias Aryani[5], Nurul Setia Rahayu[4], Ramdan Panigoro[1]

[1]Department of Biochemistry & Molecular Biology, Faculty of Medicine Universitas Padjadjaran, Jl. Eijkman No.38, Bandung, Indonesia
[2]Laboratorium Mikrobiologi, Prof. Dr. W.Z. Johannes Hospital, Jl. Dr. Muh. Hatta 19, Fontein Oebobo, Kupang, Indonesia
[3]Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Jl. Eijkman No.38, Bandung, Indonesia
[4]Health Research Unit, Faculty of Medicine Universitas Padjadjaran, Jl. Eijkman No.38, Bandung, Indonesia
[5]Department of Biology, Faculty of Natural Sciences, Universitas Padjadjaran, Jl. Eijkman No.38, Bandung, Indonesia

*Corresponding author. E-mail: e.sahiratmadja@unpad.ac.id

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Abstract

BACKGROUND: N-acetyltransferase-2 (NAT2) enzyme, encoded by *NAT2* gene, plays a key role in metabolism of anti-tuberculosis (TB) drug isoniazid. Polymorphisms in *NAT2* gene may result in different responses to TB therapy. Since TB prevalence in the eastern part of Indonesia is high, the aim of this study is to explore the distribution of *NAT2* gene polymorphisms among population from Kupang, Nusa Tenggara Timur.

METHODS: A total of 234 respondents were included from Kupang in 2012. Polymorphisms of *NAT2* gene were examined using mass screening platform and the genotypes distribution were presented in percentage. To confirm *NAT2* gene polymorphisms, polymerase chain reaction (PCR)-sequencing was performed in a subset of population.

RESULTS: The polymorphisms of *NAT2* gene showed that the distribution of rs1801279 for GG genotype was 100%; whereas the genotype distribution of rs1799930 for GG, GA and AA was 57%, 35.1% and 7.9%, respectively. In a subset of individuals (n13), acetylator status was well determined by PCR-sequencing, resulting in individual with wild type fast acetylator (NAT2*4; n4), intermediate (NAT2*4/*5 or NAT2*4/*6 or NAT2*4/*7; n7) and poor acetylators (NAT2*6/*6 or NAT2*7/*7; n2).

CONCLUSION: The amino acid change in rs1799930 result in intermediate and poor acetylator status in Kupang population. This may lead to suboptimal response of TB therapy. Assessing acetylator status before TB therapy is important and may serve as personalized INH therapy.

KEYWORDS: *NAT2* gene, polymorphism, acetylator status, Kupang

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Introduction

N-acetyltransferase-2 (NAT2) enzyme plays a key role in metabolism of a variety of drugs, including anti-tuberculosis (TB) drug isoniazid (INH).(1) This enzyme is encoded by polymorphic *NAT2* gene which is located at chromosome 8, identified as 8p22. There are at least 7 single nucleotide polymorphisms (SNPs) in *NAT2* gene, *i.e.,* nucleotide (nt) change of 191G>A at rs1801279, nt282C>T at rs1041983, nt341T>C at rs1801280, nt481C>T at rs1799929, nt590G>A at rs1799930, nt803A>G at rs1208, and nt857G>A at rs1799931, respectively. The distribution of these SNPs is listed in the International data base and has been reported differently in various ethnicities around the globe.(2)

Of note, the nucleotide change does not always result in a change of coded amino acid, for example at the position nt282C>T and nt481C>T; whereas in other positions amino acid do change, for example at the position nt590G>A there is a change from arginine (Arg) to glutamine (Gln)

or at the position nt857 there is a change from glycine (Gly) to glutamic acid (Glu). Combination of these SNPs determines haplotypes of *NAT2* gene result in various host acetylator status, that influences the NAT2 enzyme activity. For example, two normal allele of NAT2*4 or homozygous wild-type, designated as NAT2*4/*4 genotypes has fast or rapid enzyme activity, and this individual is identified as rapid or fast acetylator; whereas poor or slow acetylator has two mutant alleles with possible combination of genotypes such as nt481C>T, nt590G>A or nt857G>A, designated as NAT2*5, NAT2*6 or NAT2*7, respectively. Intermediate acetylator has one normal allele NAT2*4 in combination with one mutant allele NAT2*5, NAT2*6 or NAT2*7.(3) Rapid acetylator may develop in a suboptimal dose of drugs. In the other side of the coin, slow acetylator individuals may develop in an overdose leading to drug-induced hepatotoxicity or adverse drugs response. Therefore, adjustment of INH dose in TB therapy might be needed and serve as a personalized medicine.(4) Likewise the distribution of NAT2 polymorphisms, the prevalence of acetylator status have been reported differently in various ethnicities.(5,6,7)

A study in Java island, located in the western part of Indonesia, has shown that slow acetylator is occurred in 35% of the population.(8) This might have an impact in the management of TB therapy, especially since Indonesia ranks second in TB prevalence in the world.(9) The high frequency of slow acetylators in this western part of Indonesia raises some concerns for TB therapy complication resulting in INH-induced hepatitis. INH has been used as preventive therapy according to National TB Program in high burden TB countries, and this may increase the role of screening of the acetylator status in the population. Therefore, acetylator status detection is needed since this acetylator status is clinically relevant prior to INH therapy to adjust the dose of treatment.

There are several methods to determine the host acetylator status (l) *i.e.,* polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP), PCR-direct sequencing and many other recent new techniques using automatic genotyping SNP platform for robust mass screening.(10) The aim of this study was to explore the *NAT2* gene polymorphisms and to determine the acetylator status by using mass screening platform among population in Kupang, a region in the eastern part of Indonesia where TB prevalence is higher compared to the west.(11) Moreover, the ethnicity in Kupang is originally different compared to ethnicity in Java. Therefore, acetylator status study in the eastern part of Indonesia might give valuable information for TB control program in Indonesia.

Methods

This study was part of a larger study identifying susceptibility genes related to TB infection in the city of Kupang, Nusa Tenggara Timur, Indonesia. The initial study recruited newly TB patients (n124) diagnosed from Prof. Dr. W. Z. Johannes Hospital in Kupang and their healthy controls (n124) from the same house where TB patients lived. In brief, TB patients were diagnosed according to the standard hospital procedure as directed in WHO guideline, including history taking of TB infection, physical examination, chest X-ray, positive sputum, and positive mycobacterial culture. Patients with HIV and Diabetes Mellitus (n14) were excluded previously in the susceptibility study to TB.

This study explored *NAT2* gene polymorhpisms in the population, thus both patients and control (n234) who were originally 'by saying' from ethnicity in the Timor island, where Kupang is located, were included in this current *NAT2* gene study. The last name of the respondents would confirm the ethnicity from Timor island. No further exclusion criteria in this study since all participants with the same ethnicity would represent the genetic background of population. After reading and explaining the information of the study, all participants signed informed consent. The ethical clearance was approved by the Ethical Committee from Faculty of Medicine Universitas Padjadjaran Bandung under No.136/UN6.C2.1.2/KEPK/PN/2012.

Vein blood was drawn and collected in a 3mL EDTA tube and stored in cold condition (+4C) prior sending to Bandung located in Java island, in the Western part of Indonesia, where DNA was isolated according to the manufacturer's protocol (QIAamp DNA Blood Mini Kit, Cat No.51104, Qiagen).

Genotyping of Single Nucleotide Polymorphisms in NAT2 Gene

In total, 7 polymorphisms in *NAT2* gene, including 191G>A at rs1801279, nt282C>T at rs1041983, nt341T>C at rs1801280, nt481C>T at rs1799929, nt590G>A at rs1799930, nt803A>G at rs1208, and nt857G>A at rs1799931, were examined (the GoldenGate® Genotyping Assay for VeraCode®/BeadXpress Illumina®). The machine used in this study can mass screen of 96 participants in each plate and detect up to 48 SNPs. In brief, DNA was activated to bind to paramagnetic samples, and hybridization was followed according to manufacturer's protocol. Microbead code was then identified and fluorescent signal was detected (BeadXpress® Reader). During scanning, a laser beam penetrates the digitally inscribed to generate a unique code

image. Data was generated and analyzed by data analysis software (Illumina's GenomeStudio®). The distribution of each allele and genotype of each rs number were counted for the frequency and compared to published global frequency.(16,19)

NAT2 Gene Sequencing

To confirm the polymorphisms in *NAT2* gene, *NAT2* gene was sequenced. In brief, forward primer of 5'-GGG ATC ATG GAC ATT GAA GC-3' and reverse primer of 5'-GGG TGA TAC ATA CAC AAG GGT TTA-3' were self-designed. The total volume of 50µL PCR solution consisting of 25µL Master Mix solution (Kappa2G Fast, Kapabiosystems), 19µL deionized water, 2µL forward primer, 2µL reverse primer, and 2 µL of the DNA. The PCR condition was initial denaturation at 94°C for 3 min, followed by 30 cycles of denaturation at 94°C for 30 sec, annealing at 55°C for 30 sec, and extension at 72°C for 1 min with the final extension at 72°C for 5 min. PCR product of 870 bp was visualized on 1% agarose gel running for 20 min at 90V before further sequencing process (BigDye® Terminator v3.1 cycle sequencing, done by the 1st BASE, Kuala Lumpur).

Acetylator Status Determination from 7 Polymorphisms in NAT2 Gene

The acetylator status determination was assessed using 7 most important *NAT2* SNP *i.e.,* rs1801279 for 191G>A, rs1041983 for 282C>T, rs1801280 for 341T>C, rs1799929 for 481C>T, rs1799930 for 590G>A, rs1208 for 803A>G, and rs1799931 for 857G>A. Individual is classified as fast, intermediate, or slow acetylator, depending on *NAT2* diplotypes, as published elsewhere.(12) The nucleotide change at rs1801280 341 T>C, rs1799930 590 G>A, and rs1799931 857 G>A, were designated as NAT2*5, NAT2*6, NAT2*7, respectively.

Result

In total, 234 participants with ethnicity from Timor island area were included in this study, consisting of 107 male (45.7%) and 127 female (54.3%) with mean age of 36.7 years old (SD 13.6 years old). In a mass screening of 7 polymorphisms in *NAT2* gene, only 2 of 7 positions were detected *i.e.,* rs1801279 or nt191 for nucleotide change of G>A and rs1799930 or nt590 for nucleotide change of G>A. The genotype frequency of rs1801279 showed 100% GG, thus it was monomorphic; whereas rs1799930 showed genotype frequency of GG, GA and AA for 57%, 35,1%,7.9%, respectively, as summarized in Table 1.

Table 1. Distribution of SNPs *NAT2* gene at rs1801279 and rs1799930 in population from Kupang.

rs number	Nucleotide	GG (%)	GA (%)	AA (%)
rs1801279	nt191 G>A	100	0	0
rs1799930	nt590 G>A	57	35.1	7.9

Frequencies of the genotypes in one plate of 96 individual were also depicted for rs1801279 (Figure1) and for rs1799930 (Figure 2) as shown using GenomeStudio®. Furthermore, rs1801279 and rs1799930 genotype distribution in Kupang was compared to other population, showing similarity to population studied in East Asian countries (Figure 3) (16,19).

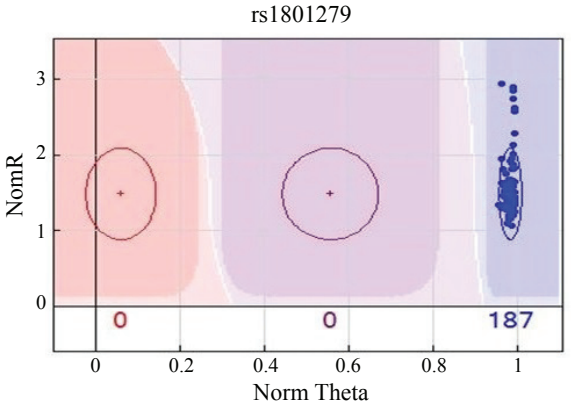

Figure 1. Distribution of SNP *NAT2* gene rs 1801279 in population from Kupang, as shown using Illumina's GenomeStudio®. Every single dot represents individuals genotyped in one plate for 96 individuals. Pink area is designated as genotype AA, purple area as GA, blue area as GG (wild type), respectively.

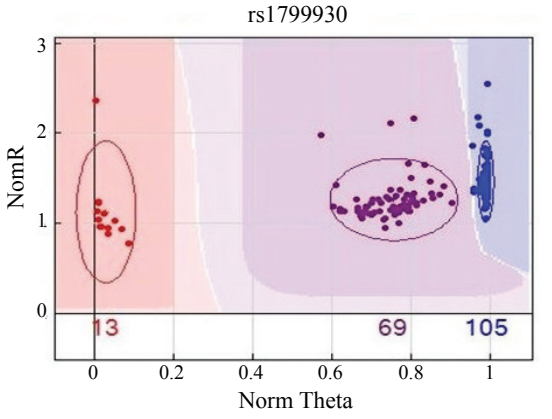

Figure 2. Distribution of SNP NAT2 gene rs 1799930 in population from Kupang, as shown using Illumina's GenomeStudio®. Every single dot represents individuals genotyped in one plate for 96 individuals. Pink area is designated as genotype AA, purple area as GA, blue area as GG (wild type), respectively.

Figure 3. The distribution of rs180279 and rs1799930 in population from Kupang compared to other populations.

In a subset of the population (n13), acetylator status was well determined using PCR-sequencing method, resulting in individuals with rapid acetylators (NAT2*4/*4; n=4), intermediate acetylators (n7, including NAT2*4/*5 n=1; NAT2*4/*6 n=1; NAT2*4/*7 n=5) and poor acetylators (n2, including NAT2*6/*6 n=1; NAT2*7/*7 n=1) as detailed in Table 2. Furthermore, we have assessed the results of rs1801279 and rs1799930 using PCR-sequencing and using mass-screening, and verified that both results were similar.

Discussion

TB is an infectious disease, caused by *mycobacterium tuberculosis*. INH has been used as one of the anti-TB therapy according to WHO guideline (9) and also encouraged for preventive drug in children.(13) NAT2 enzyme plays a key role in metabolism of INH. To control the TB prevalence in high burden area, host genetic factor, among others *NAT2* gene polymorphisms may play an

Table 2. The polymorphisms in NAT2 gene and acetylator status determination in a subset of population from Kupang, East Nusa Tenggara, using PCR-sequencing method.

	rs1801279	rs1041983	rs1801280	rs1799929	rs1799930	rs1208	rs1799931	Acetylator phenotype
Nucleotide change	**191 G>A**	**282 C>T**	**341 T>C**	**481 C>T**	**590 G>A**	**803 A>G**	**857 G>A**	
Amino acid change	**R64Q**	**Y94Y (synonymous)**	**I114T**	**L161L (synonymous)**	**R197Q**	**K268R**	**G286E**	
NAT2 haplotype			**NAT2*5**		**NAT2*6**		**NAT2*7**	
NAT2*4	.	.	.	.	.	.	.	Fast/Rapid
NAT2*4	.	.	.	.	.	.	.	Fast/Rapid
NAT2*4	.	.	.	.	.	.	.	Fast/Rapid
NAT2*4	.	.	.	.	.	.	.	Fast/Rapid
NAT2*4/*5	.	CT	TC	CT	.	.	.	Intermediate
NAT2*4/*6	.	CT	.	.	GA	.	.	Intermediate
NAT2*4/*7	.	CT	.	.	.	.	GA	Intermediate
NAT2*4/*7	.	CT	.	.	.	.	GA	Intermediate
NAT2*4/*7	.	TT	.	.	GA	.	GA	Intermediate
NAT2*4/*7	.	TT	.	.	GA	.	GA	Intermediate
NAT2*4/*7	.	TT	.	.	GA	.	GA	Intermediate
NAT2*6/*6	.	TT	.	.	AA	.	.	Poor
NAT2*7/*7	.	TT	.	.	.	.	AA	Poor

important role in response to TB therapy. Our study describes the distribution of *NAT2* gene polymorphisms in population in Kupang, Nusa Tenggara Timur, Indonesia, where TB prevalence in this area is high. Ideally, to have *NAT2* prevalence in an particular area or community, randomized community samples should be used. However, since *NAT2* gene is close related to pharmacogenomics in TB, we have used the respondents consisting of TB patients and their controls to represent the prevalence in Kupang, that limits our current study. Nevertheless, assessing the *NAT2* gene polymorphisms and thus the acetylator status in an area where TB prevalence is high, may optimize the strategy of TB control.

The *NAT2* gene polymorphisms distribution has been reported differently in various ethnicities worldwide and this *NAT2* gene diversity may have implications for *NAT2* evolutionary history.(14) Our result has shown that the monomorphic rs1801279 genotype distribution in Kupang was similar to population studied in the neighbor land Thailand (15) and many other East Asian population.(16) Interestingly, the study from Africa showed a very different distribution compared to the Kupang population.(16) In the case of population from Kupang and Timor island, this may be not true since the genetic background of this population is presumed to be derived from the African origin. African genetic diversity in human and pathogen may have implications for human demographic history, modern human origins, and complex disease mapping.(17) Previous group in Kupang has showed that m*ycobacterium tuberculosis* Family F (East African-Indian) and family D (Latin American and Mediterranean) were more prevalent to infect the population in Timor (33.3% and 20.0%, respectively), suggesting a host-pathogen relation.(18) As for rs1799930, genotype distribution from Kupang does not differ that much compared to global population.(19)

Ebeshi, *et al.,* has shown that the most common SNPs in *NAT2* gene that play a key role are the nucleotide change at rs1801279 or 191G>A, rs1801280 341 T>C, rs1799930 590 G>A, and rs1799931 857 G>A, as those mutations alone or in combination might have changes in activity, stability or specificity of NAT2 enzyme.(7) Since only 2 polymorphisms data were available in our study, the complete acetylator status of these population could not be determined. The monomorphic rs1801279 genotype in this study does not account for the acetylator status determination. The rs1799930 polymorphisms in our study showed that there is a nucleotide change from guanine to adenine. This amino acid change from Arg to Gln at R197Q, designated as NAT2*6, indicating that the slow acetylators (AA genotype) and intermediate acetylators (GA genotype) in this population is accounted for at least 7.9% and 35.1%, respectively. If data of other SNP *i.e.,* rs1801280 341 T>C (NAT2*5) and rs1799931857 G>A (NAT2*7) available, the percentage of slow acetylator could be counted and compared with the study in Jakarta, which is around 40%.(8) The slow acetylator may develop drug induced liver intoxicity, therefore, this high percentage is alarming, since Indonesia has high TB prevalence, being the second worldwide.(9)

Furthermore, geographic and ethnic variation in the frequency of *NAT2* genotypes associated with rapid or intermediate acetylator (5,6), as well as slow acetylator (20) have been reported. Pharmacology study in Japan clearly showed, that the metabolism of INH by NAT2 enzyme is impaired in subjects with NAT2 gene mutations (21), however, study in Chinese population could not find any significant association between *NAT2* gene genotype and the hepatotoxicity.(22) Although it is still questionable, whether *NAT2* genotype is necessary for personalize INH doses (23), study in Indonesia confirms a significant association between slow acetylators and susceptibility to liver injury induced by INH.(24) Further pharmacogenetic study in Indonesia is needed to explore the association between *NAT2* gene polymorphisms and INH metabolism.

The limitation of this study is that the mass screening of *NAT2* gene polymorphism cannot be optimally conducted, however, individual screening by using PCR-sequencing method can still be well performed to determine acetylator status. Since the acetylator status is clinically relevant prior to INH therapy to adjust the dose of treatment, especially in the area where TB prevalence is high, we therefore suggest that individual *NAT2* PCR-sequencing method is suitable to guide for a personalized therapy for successful TB treatment.

Conclussion

The rs1801279 *NAT2* gene in population from Kupang is monomorphic, whereas based on the distribution of rs1799930 or nt590 polymorphism, it is predicted that the intermediate (GA genotype) and poor acetylator (AA genotype) in population from Kupang is as low as 35.1% and 7.9%, respectively. It is worthy noted that acetylator status determination is needed, especially in the high TB burden area. PCR-sequencing of *NAT2* gene is of great help in determining acetylator status.

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