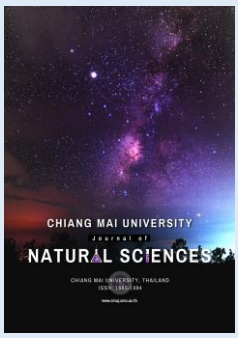

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Research article

The Frequencies of Allele Distribution of *CYP2C9* and *CYP2C19* Gene Polymorphisms in Healthy Papuan Population, Indonesia

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Abstract This study's objective was to determine the distribution of allele frequencies of *CYP2C9* and *CYP2C19* gene polymorphisms among the Papuan population, known as the second-largest ethnic group in Indonesia. According to recent research, there is a decrease in *CYP2C9* and *CYP2C19* produced by humans globally, including in Indonesia. These gene polymorphisms aid in the transmission of various endogenous and exogenous drugs in the human body. Material and Methods: A sum of 99 subjects, comprising 73 male and 26 female subjects aged 20-30 years, were used for this research. PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) analysis using AvaII, NsiI, and SfaNI enzymes tested for the genotypes *CYP2C9* and *CYP2C19* administered. The distribution of genotypes was calculated in the population (P<0.05) using the Hardy-Weinberg equilibrium. The Faculty of Medicine Gadjah Mada University's Medical and Health Research Ethics Committee (MHREC) accepted this research with written consent. The results revealed that in Papua subjects, *CYP2C9*2* (rs1799853) and *CYP2C19*17* (rs12248560) alleles were absent while in 17 percent of the population *CYP2C9*3* (rs1057910) allele frequency was. In conclusion, *CYP2C9*3* has the highest polymorphism rate in Indonesia, with the absence of *CYP2C9*2* and *CYP2C19*17*. Therefore, genetic drift can occur within this ethnic group.

Keywords: Genotyping; Papuan ethnic; Pharmacogenetics; Polymorphisms

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INTRODUCTION

The Papuan Past Project incorporates archaeological and genomic approaches to investigate the biological, cultural, and technological evolution of the human population occupation and adaptation modalities over the last 50,000 years. The ambiguity of the genetic environment present in Papuan populations has been explained by recent human genetic studies (https://papuanpast.hypotheses.org/194, accessed by 18 February 2021).

Variations in drug response among various people/populations are influenced by several factors, including differences in allele frequency of single nucleotide polymorphisms (SNPs) that affect drug-response genes functionally (Bachtiar et al., 2019). There were 70,187 adverse drug reactions (ADRs) cases, according to the 2007–2009 US FDA Adverse Event Reporting System (FAERS).

The CYP450 enzyme system's ability metabolism differs in all populations (Mcgraw & Waller, 2012). The CYP450 cytochrome group is thought to have an important role as a metabolizer of a phase I reaction drug that oxidizes over 90% of the drug. Over 90% of the oxidizing drug is identified with CYP1A2, 2A6, 2C9, 2C19, 2E1, 2D6, and 3A4 (Rendic & Guengerich, n.d.). One of the subfamilies of CYP2C is CYP2C9, a significant P450 cytochrome protein with an important function in oxidating xenobiotics and endogenous drugs. CYP2C9 can process around 100 remedial medications, for example, a limited restorative record including warfarin, phenytoin, and routinely endorsed medications, acenocoumarin, tolbutamide, losartan, glipizide, and some nonsteroidal calming drugs (Rettie & Jones, 2005). *CYP2C9* and *CYP2C19* genes have different capabilities in metabolizing individual drugs in the human body(Xie et al., 2002). Cytochrome P450 2C9 (CYP2C9) is an enzyme found in the human body encoded by the CYP2C9 gene (Romkes et al., 1993). These two subfamilies have a potent polymorphism in the human body, especially in the liver (Zanger & Klein, 2013). The second most noteworthy protein among all CYP isoforms is CYP2C9 and is integral to the digestion of numerous xenobiotics and different endogenous (Soares et al., 2008).

Currently, there are more than 60 alleles that have been identified in the human gene CYP2C9 (*1A to *60) (Lazar et al., 2004). The *CYP2C9*2* gene is a mutation (missense mutation) 430 T > C that causes R144C substitution associated with decreased CYP2C9 substrate enzyme activity. CYP2C9*3 is a mutation (missense mutation) 1075 A > C on exon 7, which causes I359L substitution at the CYP2C9 active point and is directly involved in the substrate. The performance of both CYP2C9*2 and CYP2C9*3 polymorphisms varies between communities. Not only are differences in the prevalence of each polymorphism, but one type may be more dominant than others. In the Caucasian population, the prevalence of CYP2C9*2 polymorphism varies from 8 to 19.1% and is higher than the native population of Canada, Afro-American and Asian (Table 1) (Saberi et al., 2020).

Table 1. The prevalence of *CYP2C9* polymorphs among different ethnic groups.

Ethnics	Polymorphism			
	*CYP2C9*2*	*CYP2C9*3*	*CYP2C9*4*	*CYP2C9*5*
	Point mutation			
	Cys144/lle359	Arg144/Leu359	Arg144/Thr359	Arg144/G1u360
Caucasia	8%-19.1%	6%-10%	nd	nd
Aborigine Canada	3%	6%	nd	nd
Africa-Americas	1%-3.6%	0.5%-1.5%	nd	2.3%
Asian	0%	1.7%-5%	0%-1.6%	0%

Note: nd-not determined

Conversely, *CYP2C9*3* polymorphism is more common in Asian populations (1.7-5 percent) than *CYP2C9*2* (0 percent) polymorphism. The prevalence of *CYP2C9*3* polymorphisms in Asia is still much lower than in the Caucasian population (6-10 percent). CYP2C19 is a quality that assumes a significant function in the digestion

of 25 significant sorts of medications, including psychotropic medications, proton inhibitor pump, and anticonvulsants, and accommodates the leeway of certain key medications, for example, S-mephenytoin, diazepam, omeprazole, proguanil, and R-warfarin (Scordo et al., 2001; Rosemary & Adithan, 2007). At present, more than 49 alleles in the CYP2C19 quality have been recognized and portrayed, including CYP2C19*17, which increment chemical movement. *CYP2C19*17* allele, with ultra-rapid metabolizer (UM) (Li-wan-po et al., 2010). This quality was somewhere in the range of 18 and 27 percent of the European population between 0.15-0.44 percent in Asia and 10 to 27 percent in Africa. The *CYP2C19*17* allele is firmly connected to a decrease in serum concentration of Pantoprazole (Gawroñska-Szklarz et al., 2012). Likewise has this impact on pharmaceutical medicines such as escitalopram, clopidogrel, and voriconazole (Hirota et al., 2013).

CYP2C9 and *CYP2C19* have primarily been carried out in polymorphic research in the Americas and the Caucasus and even in the East Asian (i.e., Chinese, Japanese, or Korean) populations. There is limited research on *CYP2C9* and *CYP2C19* in Southeast Asia. One work in the Indonesian community (Buginese in the South Sulawesi province) has been performed. This study was the first time to do in Papuan ethnic in Indonesia and to determine the Papuan population's genetic polymorphism. We hope to be able to conduct rigorous study for the next research about polymorphism genetics and toxicity in the Clinical Setting.

MATERIALS AND METHODS

In this study conducted in 2018, a total was collected whole blood samples of 99 healthy subjects (73 males and 26 females, aged 20-30 years old) and Papuan ethnicity determined from 3 descendants and above are origin ethnic Papuans (father-mother, grandparents, great-grandparents). All participants were healthy as described by medical history, physical examination, told them (both verbally and in writing), experimental procedures, and the study's purposes. According to the manufacturer's protocol, genetic DNA was extracted from blood samples by Genomic DNA Mini Kit (Blood) Blood Protocol (Geneaid, USA). Genotyping for *CYP2C9*2* (rs1799853, 430C>T)), *CYP2C9*3* (rs1057910, 1075A>C), *CYP2C19*17* (rs12248560, 806C>T) determined by techniques of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods. AvaII, NsiI, and SfaNI, respectively, have been used as restriction enzymes were obtained from New England Biolabs (Hitchin, UK). The distribution of genotypes was carried out by Hardy-Weinberg Equilibrium analysis to compare the observed and expected genotype frequencies using the chi-square test in the population (P<0.05).

Written informed consent for their involvement in the study was obtained from all of them and approved protocol by The Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Gadjah Mada University (KE/FK/0105/EC/2018).

CYP2C9 and *CYP2C19* Genotyping Procedures

PCR-RFLP analysis was performed to identify the *CYP2C9*2* (rs1799853, 430C>T)), *CYP2C9*3* (rs1057910, 1075A>C), *CYP2C19*17* (rs12248560, 806C>T). In brief (Table 2), PCR was done in a 50-µl last response volume including 2.5 mM $MgCl_2$, ten mM Tris-HCl, 50 mM KCl, ten mM dNTPs, 1.5 µL of AmpliTaq DNA polymerase, and around 200 ng of human genomic DNA, and the groundwork (0.32 µM). Aliquots of each PCR item (15 µl) were exposed to limitation catalyst examination with five µL of AvaII (*CYP2C9*2*), NsiI (*CYP2C9*3*), and SfaNI (*CYP2C19*17*) separately. Processed items detached by electrophoresis utilizing a 4 percent agarose gel after hatching at 70° C for around an hour.

Table 2. The condition about studied genes in the present study.

SNPs	Primer sequences	Annealing temperature	Restriction enzyme	Digestion products (bp)
CYP2C9*2 (rs1799853)	F:5'gTATTTTggCCTgAAACCCATA 3' R:5'ACCCTTggTTTTTCTCAACTC 3'	60.6 0C	AvaII	Wild (CC): 454 Mutant (TT): 57, 397
CYP2C9*3 (rs1057910)	F: 5'TgCACgAggTCCAgAgATgC 3' R:5'gATACTATgAATTTggggACTTC 3'	59 0C	NsiI	W (AA): 168 M (CC): 50, 118
CYP2C19*17 (rs12248560)	F: 5'gTgAAgCCTgTTTTATgAA 3' R: 5'gTggCgCATTATCTCTTA 3'	57.2 0C	SfaNI	W (CC): 165 M (TT): 20, 145

Note: bp=base pare

Statistical Analysis

Deviation from Hardy-Weinberg Equilibrium (HWE) tested using the online calculator (Rodriguez et al., 2009). Allele frequencies of various genotypes were compared using the x^2 test. *P-value* of < 0.05 considered statistically significant.

RESULTS

This study was the second time in the Indonesian population to test genetic polymorphism. The first was the Buginese population and the second for the Papuan population to assess the genes' genotype and genetic polymorphism *CYP2C9* and *CYP2C19*. The most common allele found in the Papuan population was *CYP2C9*3*. The *CYP2C9*3* allele frequency was 17 percent in stable Papuan subjects. Determination of the genotype showed that 68 of the PM were homozygous for C / C (69.4%), 27 were heterozygous for carrier A/C (27.6%), and three were wild for A/A (3%) (Table 3). Hence, the most popular allele is *CYP2C9*3* (*rs1057910, 1075A>C*) in the Papuan population. From the 98 subjects present in this study, *CYP2C9*2* (rs1799853, 430C>T) and *CYP2C19*17* (rs12248560, 806C>T) alleles were missing.

Table 3. The frequency of genotypes and alleles of *CYP2C9* and *CYP2C19* Papua subjects (n = 98)

Polymorphism *CYP2C9* and *CYP2C19*	Genotypes frequency % (95% CI)		Allele frequency % (95% CI)		
	Genotype	Subjects	Allele	Subjects	P-value
*CYP2C9*2 (rs1799853, 430C>T)*	CC CT TT	0 (0) 0 (0) 98 (100)	T C	100 (0) 0	-
*CYP2C9*3 (rs1057910, 1075A>C)*	AA AC CC	3 (3,06) 27 (27,55) 68 (69,39)	A C	0,17 (17) 0,83 (83)	0.100
*CYP2C19*17 (rs12248560, 806C > T)*	CC CT TT	0 (0) 0 (0) 98 (100)	C T	0 100 (0)	-

DISCUSSION

This research is the first to identify polymorphism in Papuan ethnicity, East Indonesia. Indonesia, an archipelago country in Southeast Asia, consisting of a variety of different ethnic groups. The database of gene polymorphisms encoding *CYP2C9* and *CYP2C19* enzyme protein expression in indigenous Indonesian tribes is still limited. One of the largest indigenous ethnic groups exists in Papua. This tribe is the second largest tribe in Indonesia after the Java tribe, with a phenotype and socio-cultural distinct from other tribes in Indonesia. The genetic drift of Papua's population could be a high differentiation between Indonesia's other ethnic groups.

The island of Papua located in Eastern Indonesia haves a unique characteristic to identify genetics ancestry in this reflects Austronesian migrations (https://papuanpast.hypotheses.org/194, accessed by 18 February 2021). Previous study involved Asian and Papuan genetic drift related to the mtDNA and Y-Chromosome (Wollstein et al., 2010; Reich et al., 2011). However, none of the previous polymorphism genetics of East Indonesia studied to apply in Clinical Setting.

The ancient migration wave was thought to have carried the ancestors of many "Australoid" groups in Southeast Asia and Australia, including the Papuans and Australian Aboriginals and any communities in the Andaman Philippines. The collective is known as Negritos in West Malaysia (Chisholm, 1995). Genetics Papuan ancestry is part of a New Guinea based on mtDNA and Y-chromosome studies found in East Indonesia (Cox et al., 2010). A study suggesting that East Indonesian, including Papuan ancestor, was descended from pre-Austronesian activity that started to migrate across eastern Indonesia, was mixed with occupant groups of Papuans from west to east around 4,000 years ago (Xu et al., 2012).

In the present study, the frequencies of the allele of *CYP2C9*2* and *CYP2C19*17* was 0%, while *CYP2C9*3* was 17%. Moreover, in the previous study of Buginese ethnic in Indonesia, the frequencies allele of *CYP2C9*2* was absent, *CYP2C9*3, CYP2C19*17* was 1.56, and 4.68%, respectively (Ikawati et al., 2014). According to the previous studies, the allele frequency of *CYP2C9*2* in European, Caucasian, Japan, Jahai (Malay) were 10, 7, 28, 0%, respectively. The frequencies of *CYP2C9*3* in Asian, European, Caucasian, Chinese, Japan, Jahai (Malay) were 6, 5.8, 7, 4, 2.7, 36.2% &, respectively (www.hapmap.org; (Allabi et al., 2003; Kimura et al., 1998; Ota et al., 2015; Rosdi et al., 2016; Sugimoto et al., 2008). And the values for *CYP2C19*17* in Caucasian, Chinese, Japan, and Macedonian were 18, 3, 1, and 20.1% (Allabi et al., 2003; Sugimoto et al., 2008; Zhou et al., 2010; Jakjovski et al., 2014; Ota et al., 2015).

Negritos studies in Malaysia ranked *CYP2C9*3* allele prevalence at 36.2 percent (Rosdi et al., 2016). The study argues that its proportion was the highest percentage of polymorphism in Malaysia regions while the Buginese population was absent (Indonesia's South Sulawesi) (Ikawati et al., 2014).

Besides, the lowest frequent polymorphism of *CYP2C9*3* was found in Papuan subjects at 17 percent. The statistical representation of the *CYP2C9*2* and *CYP2C19*17* alleles frequencies in this subject was null. The Pearson x^2 test was applied, examining differences among Buginese samples of the *CYP2C9* allele, and showing no significant differences.

CONCLUSION

To the high enrichment our knowledge, this is the first study to show on *CYP2C9 (CYP2C9*2, CYP2C9*3)* and *CYP2C19 (CYP2C19*17)* genotype and allele frequency in the Negrito tribe in Indonesia, in recording and exploring information related to gene polymorphism, this research offers a valuable database. The finding might also be valuable for the clinicians to determine a new diagnostic approach and clinical setting. The absence of frequency polymorphism distribution in the Papuan population may indicate that indigenous Papuans are not from the Asia region, this is in line with previous study and 1000 Genomes Browser data that the citizens of South Asia have around 3% and 15-20% of specific frequencies of allelic *CYP2C9*2* and *CYP2C19*17* (Hill et al., 2007), while Papuan population revealed the contradiction result which was an absence of the alleles from in this study.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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