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## Prevalence of the Genetic Mutation *CYP2C8\*5* in Selected Ethnic Groups in Southern Ghana

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### Authors' contributions

*This work was carried out in collaboration between all authors. Authors CB, CL and DSYA designed the study and wrote the protocol. Authors CB and CL supervised the work. Author DSYA carried out all laboratory works. Authors CL and DSYA performed the statistical analysis. Authors CB, CL and DSYA managed the analyses of the study. Authors CL and DSYA wrote the first draft of the manuscript. Author DSYA managed the literature searches. Authors CB, CL and DSYA edited the manuscript. All authors read and approved the final manuscript.*

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### ABSTRACT

**Aim:** The study determined prevalence of clinically relevant *CYP2C8\*5* polymorphism in 80 unrelated individuals, from selected ethnic groups in Southern Ghana. Medical history on adverse drug reactions of the subjects and level of dependency on drugs metabolized by *CYP2C8* enzyme was obtained by questionnaire. Allele Specific-PCR analyses were used to genotype *CYP2C8\*5* alleles in the study subjects.

**Results:** Allelic frequency for *CYP2C8\*5* was 83.75% which was statistically significant ( $p < 0.05$ ). There was no significant difference ( $p > 0.05$ ) in the prevalence of *CYP2C8\*5* allele within the ethnic groups. Also, there was no significant association ( $p > 0.05$ ) between *CYP2C8\*5* allele and reported

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ADRs. Many (88.75%) of the study subjects depended highly (>1-3x in a year) on drugs metabolized by CYP2C8.

**Conclusions:** The high prevalence of *CYP2C8\*5* determined in the study population may indicate a high risk of toxicity in using drugs metabolize by CYP2C8 since *CYP2C8\*5* mutants have been reported to have a reduced enzymatic activity. This is the first reported study on prevalence of *CYP2C8\*5* in Ghanaians.

**Keywords:** *CYP2C8* mutation; drug toxicity; artesunate amodiaquine; chloroquine; malaria.

## 1. BACKGROUND

Cytochrome P450 (CYP) family enzymes are diverse group of haemoproteins bound to membranes of the endoplasmic reticulum and mitochondria where they function in catalyzing the oxidative metabolism of many endogenous and exogenous compounds such as drugs and carcinogens [1]. Based on sequence homology, 57 isoforms of CYPs have been identified and classified in humans. CYPs are found in abundance in the liver and, to a lesser extent, in extra hepatic tissues such as the kidney, salivary ducts, intestine and adrenal cortical cells [2] as well as low expression of CYP2C8 protein in the intestines [3]. The CYP2C subfamily is responsible for catalyzing the metabolism of about 20% of clinically prescribed drugs. Cytochrome P450 2C8 (CYP2C8) is a member of the CYP2C subfamily and account for approximately 6% of the total CYP content in liver [4]. CYP2C8 plays important roles in the metabolism of about 5% of therapeutic drugs in phase I processes such as anti-malaria drugs (amodiaquine, chloroquine and dapsone); anti-cancer drug (paclitaxel) [5], anti-diabetes drugs (rosiglitazone, pioglitazone and repaglinide) [6,7]; antiarrhythmic drug (amiodarone) [8], and HMG-CoA reductase inhibitor (cerivastatin) [9]. Furthermore, CYP2C8 play a role in the metabolism of endogenous compounds such as lipids, steroidal hormones, retinoids and arachidonic acid [10-12]. The gene that code for the CYP2C8 enzyme is known as the *CYP2C8* gene which is 31KB in size consisting of 9 exons [13]. It is located at chromosome 10q24 in a multigene cluster containing the other CYP2C subfamily members CYP2C9, CYP2C18 and CYP2C19 [14] prearranged as Cent-CYP2C18-CYP2C19-CYP2C9-CYP2C8-Tel [15]. The nucleotide sequences of CYP2C8 gene shares about 74% homology with CYP2C9 gene. The whole CYP2C gene family spans about 400 kb and has linkage between its genes [16]. The CYP2C8 gene is polymorphic, and the distribution of variant alleles differs among ethnic populations. The wild-type gene of CYP2C8 is

referred to as *CYP2C8\*1* (*\*1A*, *\*1B* and *\*1C*) and although there are about 15 identified variants of CYP2C8, studies have shown only *CYP2C8\*2*, *CYP2C8\*3*, *CYP2C8\*4* and *CYP2C8\*5* to have altered enzyme activity with respect to *CYP2C8\*1*. *CYP2C8\*2* (c.805A>T, p.Ile269Phe) is the most common in blacks although it is very rare in Caucasians [17]. *CYP2C8\*3* (c.416G>A, p.Arg139Lys and c.1196A>G, p.Lys399Arg) results in the change in the amino acid sequence of CYP2C8 and is mostly found in Caucasians, with an allele frequency of approximately 10-20% [17]. There is a link between *CYP2C9\*2* (c.430C>T, p.Arg144Cys) and *CYP2C8\*3* variant alleles, where about 95% of phenotypes having the *CYP2C8\*3* variant allele have also been reported to be with the *CYP2C9\*2* variant allele [16]. *CYP2C8\*4* (c.792C>G, p.Ile264Met) allele is also present in Caucasians with a frequency of about 8% [17]. *CYP2C8\*5* results from a deletion of adenine (471) on exon 3 which lead to a frame shift in the mRNA which in turn leads to an early stop codon at residue 177 during protein synthesis (Bahdur, 2002). The resulting product of the enzyme lacks 64% of its normal protein structure affecting the haem-binding site and 5 out of 6 substrate recognition sites on the enzyme [18]. This implies that individuals homozygous for *CYP2C8\*5* who are poor metabolizers (PM) may find it difficult to tolerate drugs metabolized by CYP2C8 and suffer Adverse Drug Reactions [19].

Report indicates that the prevalence of *CYP2C8\*2* mutation was determined to be 16.75% in northern Ghanaian populations [20] and 17% in Southern Ghanaians [21].

### 1.1 Aims

This study determined the allele frequency of *CYP2C8\*5* variant in selected ethnic groups in southern part of the Ghanaian population by estimating the distribution of *CYP2C8\*5* genotype frequencies in the Ashanti, Fanti, Anlo, Ewes and Ga ethnic groups in Southern Ghana. The study also determined association between

the *CYP2C8\*5* genotype and reported adverse drug reactions in the study subjects with respect to drugs metabolised by the enzyme. Finally the study determined the extent to which individuals with genotypes of the mutant allele depended of drugs metabolized by CYP2C8 enzyme.

## 2. MATERIALS AND METHODS

### 2.1 Ethical Issues

The research work was approved by the Committee on Human Research, Publications and Ethics, Kwame Nkrumah University of Science and Technology, School of Medical Sciences and Komfo Anokye Teaching Hospital, Kumasi-Ghana (CHRPE/AP/089/14). The participants were all fully briefed on the importance of the study and written informed consent was obtained from all the study subjects who participated in the research.

### 2.2 Study Design and Subjects

The study was cross-sectional involving 80 study subjects comprising of 40 males and 40 females with 10 subjects from each ethnic group being Akyem, Ashanti, Fanti, Eve, Anlo, Ga, Krobo and Nzema in Southern Ghana. They were healthy individual blood donors at Blood Units of Korle-Bu Teaching Hospital (Accra), Komfo Anokye Teaching Hospital Transfusion Medicine Unit (Kumasi), Hohoe Municipal Hospital (Hohoe) and Winneba Municipal Hospital (Winneba), who were willing to participate in the study. Only individuals whose grandparents are of the same ethnic background were considered for the study. Participation was entirely voluntarily.

### 2.3 Blood Sample Collection

Peripheral blood samples were obtained from the study subjects and preserved on labelled Whatman No 3 filter papers which were air dried and stored in plastic bags until DNA was extracted.

### 2.4 Medical History Data Collection Questionnaire

A questionnaire was also administered for information on medical history of the study subjects. They were asked if they have any history of adverse drug reactions and if yes then they indicate which drugs were involved. The study subjects were also given a list of common

drugs metabolised by CYP2C8 enzyme and asked to indicate how often they use any of these drugs. The Body Mass Index of the study subjects was also obtained to reflect the health status of the study subjects.

## 2.5 Molecular Analysis

### 2.5.1 DNA extraction from blood blot samples

The genomic DNA was extracted from the filter paper blood blots collected using the TE buffer extraction method [22]. The extract DNA was stored at -40°C in the DNA microtubes in a Deep freezer until use after quantification using spectrophotometric analyses.

### 2.5.2 AS-PCR A475 del (Frameshift, CYP2C8\*5)

Allele specific (AS) PCR analysis was used for the analysis of A475 del (Frameshift, *CYP2C8\*5*) with the primers 5'-AGG CAA TTC CCC AAT ATC TC-3' (3S) and 5'-TCA CCC ACC CTT GGT TTT C-3' (mutant) [18]. The DNA was amplified in 20 µl reaction mix containing 1X PCR buffer (Invitrogen, USA), 25 mM MgCl<sub>2</sub> (Promega, USA), 10 mM DNTP mix containing each of the four different forms of deoxyribonucleotide triphosphates (DNTPs), 10µM of the primers 5'-AGG CAA TTC CCC AAT ATC TC-3' (3S), 5'-TCA CCC ACC CTT GGT TTT C-3' (mutant) [18] and 5U/µl of DNA *Taq* Polymerase. An amount of 5 µl extracted genomic DNA was used as template for the PCR reaction. Sterile double distilled water (sddH<sub>2</sub>O) was added to the mix to make the volume up to 20 µl. For each reaction, a non-DNA negative control and positive control containing the expected DNA was also used in the set up. The PCR was run in Gene Amp PCR System 9700 thermo-cycler using cycling conditions as follows: initial denaturation (94°C for 4 minutes), followed by 40 cycles of denaturing (94°C for 1 minute), Annealing (51°C at 1 minute), Extension (72°C for 2 minutes) and Final Extension of cycle (72°C for 7 minutes). The final reaction volume of 20µl contained 8-10 µl of the amplified products. The PCR machine was set keep the PCR products at 4°C until they were removed from thermo-cycler for storage and further analysis.

### 2.5.3 Gel electrophoresis

The PCR products were electrophoresed in 2% agarose gels prepared with 1x TAE buffer and stained with 0.5 µg/ml ethidium bromide dye.

About 8 µl of each sample of DNA was added to 1 µl of 10x bromothymol blue gel loading dye. The gels were run in a 1x TAE buffer at 100V for 45 minutes using mini gel system (BIORAD, USA), visualized by ultraviolet transillumination and photographed using a Sony Toyobo FASIII gel documentation system. The sizes of the PCR products were calculated using the mobility of a 100bp molecular weight ladder of DNA (Promega, USA) as the reference.

## 2.6 Statistical Analysis

For the analysis of the data Chi-square ( $\chi^2$ ) and Student t-test analyses were performed with SPSS version 20.0 using a confidence interval of 5% and graph plotted using Microsoft Excel version 2007.

## 3. RESULTS

### 3.1 Demographics of Study Subjects

The age distribution of the study subjects ranged from 18 to 53 years with an average age of 30.63±8.75 years. Majority of the study subjects had access to secondary (45%) and tertiary education (42.5%). The Body Mass Index (BMI) distribution of the subjects ranged from 15.78 kg/m<sup>2</sup> to 36.75 kg/m<sup>2</sup> with a mean of 22.36±3.20 kg/m<sup>2</sup>.

### 3.2 Distribution of BMI of Study Subjects

Statistically, there was no significant difference between the study subjects when their BMI was cross tabulated against presence or absence of the *CYP2C8\*5* mutant allele ( $p>0.05$ ).

### 3.3 Genotyping of *CYP2C8\*5* and Ethnic Distribution

DNA was extracted from all the samples (n = 80) and PCR was performed on the DNA samples using primers specific for amplifying mutant allele of *CYP2C8\*5*. Fig. 1 is an ethidium bromide

stained agarose gel electrophoregram showing the positive and negative samples.

The study determined the prevalence of *CYP2C8\*5* allele as 83.75% (Table 2). There was no significant difference between the selected ethnic groups with respect to the observed prevalence of *CYP2C8\*5* in the study population ( $p>0.05$ ) (Table 2).

### 3.4 Adverse Drug Reactions and *CYP2C8\*5* Mutant Allele Status

Table 3a shows reported history of adverse drug reactions by the study subjects. Thirty-three (41.25%) of the respondents indicated they had a history of adverse drug reaction, while 4 (5%) were not sure whether they had a history of adverse drug reaction. Table 3a further shows the drugs involved in the adverse drug reactions among the study subjects. Eighteen (22.5%) of the study subjects reported that they have reacted to Chloroquine CQ, while 4 (5%) reacted to only Amodiaquine (AQ) and 5 (6.25%) reacted to both CQ and AQ.

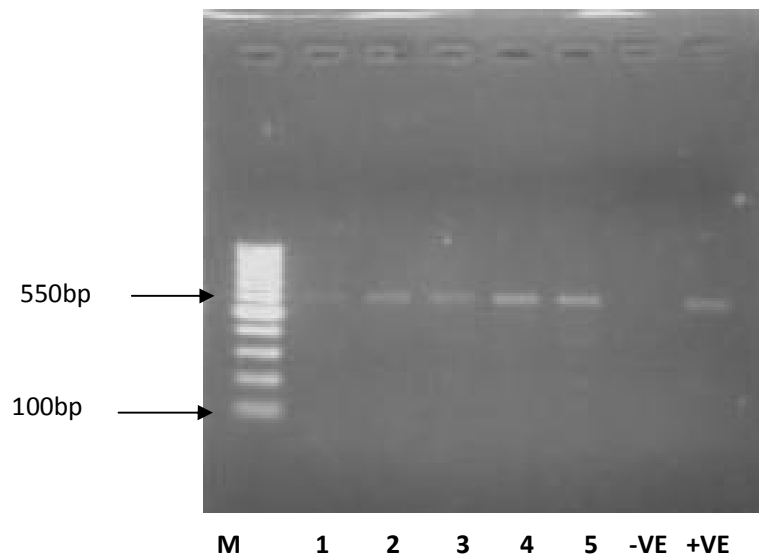
Table 3b shows the cross tabulation of *CYP2C8\*5* against reported history of adverse drug reaction. The study subjects reported that they react to the drugs Chloroquine and Amodiaquine (both antimalarial drugs) as well as Aspirin. Statistically, there was no significant association between having *CYP2C8\*5* allele and reported history of adverse drug reactions ( $p>0.05$ ).

### 3.5 Extent of Dependency on Drugs Metabolized by *CYP2C8* Enzymes

In generally many of the study subjects (88.75%) depend highly (1-3x in the past 5 years) on drugs metabolized by the *CYP2C8* enzyme (Table 4). There was no significant association between the presence of the *CYP2C8\*5* mutant allele and reported history of adverse drug reactions ( $p >0.323$ ).

**Table 1. Body Mass Index (BMI) and *CYP2C8\*5* status of study subjects**

BMI status	CYP 2C8*5 mutant allele status		P-value
	Presence (%)	Absence (%)	
<18.50	3 (4.54)	2 (14.28)	
18.50 - 24.90	54 (81.81)	8 (57.1)	
25.00 - 29.90	9 (13.63)	2 (14.28)	
>=30.00	0 (0)	2 (14.28)	
<b>Total</b>	<b>66 (83.75)</b>	<b>14 (16.25)</b>	<b>0.007</b>



**Fig. 1.** Ethidium bromide stained 2.0% agarose gel electrophoregram showing PCR amplified DNA sequences of CYP2C8\*5 for the Ashanti Male Subjects

**Table 2.** Frequency of CYP2C8\*5 distribution in study population

Ethnicity	Positive CYP2C8*5 mutants (%)			P-value
	Females (5)	Males (5)	Overall (10)	
Akyem	3 (60)	5 (100)	8 (80)	
Ashanti	4 (80)	4 (80)	8 (80)	
Fanti	3 (60)	4 (80)	7 (70)	
Anlo	4 (80)	4 (80)	8 (80)	
Eve	4 (80)	5 (100)	9 (90)	
Ga	5 (100)	5 (100)	10 (100)	
Krobo	5 (100)	5 (100)	10 (100)	
Nzema	2 (40)	5 (100)	7 (70)	
<b>Total (80)</b>	<b>30 (75)</b>	<b>37 (92.5)</b>	<b>67 (83.75)</b>	<b>0.636</b>

**Table 3a.** History of adverse drugs reactions and drugs involved

Variable	Category	Frequency (%)	p-value
History of adverse drug reaction by study subjects	Yes	33(41.25)	<b>0.000</b>
	No	43(53.75)	
	Not Sure	4(5)	
	<b>Total</b>	<b>80 (100)</b>	
Drugs reacted to by study subjects	Amodiaquine (AQ)	4 (5)	
	Chloroquine (CQ)	18 (22.5)	
	CQ and AQ	5 (6.25)	
	Aspirin	1 (1.25)	
	Other	6 (7.5)	
	<b>Total</b>	<b>33 (41.25)</b>	

**Table 3b.** CYP2C8\*5 mutant allele and history of adverse drug reactions

CYP 2C8*5 allele status	History of adverse drug reaction			Total	P-value
	Yes (%)	No (%)	Not Sure (%)		
Presence	25 (37.87)	37 (56.06)	4(6.06)	66	
Absence	8 (57.1)	6 (42.86)	0(0)	14	
<b>Total</b>	<b>33 (41.25)</b>	<b>43(53.75)</b>	<b>4(5.0)</b>	<b>80(100)</b>	<b>0.323</b>

**Table 4. Extent of dependency on drugs metabolized by CYP2C8 in past 5 years**

Extent of dependency on CYP2C8 drugs substrates in 5 years (%)		
Category	Frequency (%)	P-value
0x	9 (11.25)	
1-3x	69 (86.25)	
4-6x	2 (2.50)	
7-9x	0 (0.00)	
>10x	0 (0.00)	
<b>Total</b>	<b>80 (100)</b>	<b>0.000</b>

## 4. DISCUSSION

### 4.1 Distribution of CYP2C8\*5 Genotype

The overall prevalence of CYP2C8\*5 observed in the study population was 83.75%. This was higher compared to that observed in the Japanese population as 2.5% involving 200 healthy subjects [18] and Soyama, Saito [23] who also reported the heterozygote of CYP2C8\*5 in Japanese population to be 0.9% involving 54 subjects. Apart from the Japanese population, there is not much information on the allele frequency of CYP2C8\*5 in other populations. The prevalence of CYP2C8\*5 observed is also higher than the reported prevalence of CYP2C8\*2 (16-17.0%) in the same Ghanaian population [20,21]. The result of this study supports and augments the findings that CYP2C8 gene mutation is high in the Ghanaian population. In addition, the observed prevalence (83.75%) of CYP2C8\*5 in the study is higher than other reported CYP2C8 gene mutations in the African population such CYP2C8\*2 (12.0%) in Burkinabes [24]. It is also higher than CYP2C8\*2 (21.0%), CYP2C8\*3 (2.1%) and CYP2C8\*4 (0.6%) reported by Cavaco, Stromberg-Norklit [25] in 165 paediatric malaria patients in Zanzibar Islands which has a mixed race population of both Arabs and Asians.

There was no significant difference between the selected ethnic groups with respect to the observed prevalence of CYP2C8\*5 in the study population ( $p>0.05$ ) (Table 2) As such, the information from some of these ethnic populations may be useful on populations or individuals that share a close blood relation with those in the selected study populations but are outside Ghana such as the Ewes whose population extend from Ghana through Togo and Benin to Nigerian and Cameroun. These also include the Nzemas, Fantis and Ashantis whose

population extends into Ivory Coast as well as individuals abroad.

### 4.2 Distribution of BMI and CYP2C8\*5

Most the participants having healthy BMI (Table 1) is a reflection of their health status as well the ability to dose drugs correctly. There are medications which accumulate in adipose tissue and will necessitate an adjusted weight for a better accurate dosing for such drugs since not all the drugs are bioavailable. An adjusted, or dosing weight, is calculated to account for obese patients exceeding >125% of their ideal body weight [26-28]. Individuals who are underweight are less likely to tolerate drug while individuals who are overweight are prone to experiencing therapeutic failure and will require more dosage compared to the normal weight individuals. Despite the healthy BMI in the study population, individuals may still be at risk of having adverse reactions from normal dosing of drugs since the calculation for the dosing does not take into consideration the high prevalence of the CYP2C8\*5 mutation observed. Rather dosing is based on the assumption that the population has normal individuals having the correct CYP2C8 wild type allele.

### 4.3 Adverse Drug Reaction and CYP2C8\*5n

The study population resides in an area where malaria is endemic with 3,415,912 confirmed cases in 2013 [29, p. 119]. As such most of the study subjects who have them use antimalarial drugs such as Amodiaquine and Chloroquine which they have a history of adverse reaction. Antimalarial treatment courses distributed as a proportion of estimated malaria cases in the public sector in 2014 was 100% for Ghana [29, p. 69]. The WHO recommended treatment for uncomplicated malaria is the artemisinin-based combination therapy (ACT) which most of the study subjects have been using to combat malaria [30, p. 9].

Considering the structure of protein product of CYP2C8\*5 and the lack of enzyme activity, it would have been expected that majority of the study subjects would report a history of adverse drug reactions but this was not observed in the study. This implies that the study subjects could be heterozygous individuals with one correct allele (CYP2C8\*1) and one mutant allele (CYP2C8\*5) or they could even have two different mutant alleles (CYP2C8\*2 and

*CYP2C8\*5*) such that the activity of the enzyme is still present but at reduced levels. With previous works conducted indicating that *CYP2C8\*2* is the most predominant (17%) of *CYP2C8* mutation in the Ghanaian population, this is more likely to be the case.

Also some drug substrate have multiple enzymes involved in their metabolism [31]. The similarity in size accounts partly for the observation of *CYP2C8* and *CYP3A4* having many related substrates compared to other CYPs [32]. Hence although the frequency of *CYP2C8\*5* was observed to be high in the population, if the wild type of another enzyme which metabolizes the same drug is present, the effect of the active enzyme will mask the absence of activity of the other enzyme to some extent. Studies conducted in Ghana however observed that individuals using Artesunate Amodiaquine, when it was first introduced were having Adverse drug reactions [33]. Nevertheless, due to the heterozygosity of *CYP2C8* gene, individuals having the *CYP2C8\*5* may still produce a functional enzyme from the non-mutant *CYP2C8\*5* allele and tolerate certain drugs. Such individuals are still at risk of drug toxicity since most of those heterozygous for the mutation will be considered as partial metabolizers. Such individual will have both a functional and non-functional enzymes.

#### 4.4 Extent of Dependency on Drugs Metabolized by *CYP2C8* Enzyme

Although there was no significant association between the presence of the *CYP2C8\*5* mutant allele and reported history of adverse drug reactions ( $p > 0.323$ ), the study population may be at risk of using drugs metabolised by *CYP2C8* enzyme. This may be true considering the high presence of the *CYP2C8\*5* allele in the study population and the high level of dependency on drugs metabolized by *CYP2C8* by the study subjects.

### 5. CONCLUSIONS

The prevalence of *CYP2C8\*5* mutant allele in selected ethnic groups in Southern Ghana is high (83.75%). There was no significant difference in the prevalence of *CYP2C8\*5* allele between the selected ethnic groups being Ashanti, Akyem, Fanti, Ewe, Anlo, Ga, Krobo and Nzema. Also there was no significant association between individuals with *CYP2C8\*5* mutant allele and reported history of adverse drug reactions. Much of the study subjects (88.75%) depend highly

(>1-3x in year) on drugs metabolized by *CYP2C8*. The study population may be at risk of using drugs metabolised by *CYP2C8* although no statistically significant association between presence of the *CYP2C8\*5* allele and reported history of ADRs ( $p > 0.323$ ) was observed in the study.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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