

1 **Prevalence of the Genetic Mutation *CYP2C8*5* in Selected Ethnic** 2 **Groups in Southern Ghana**

3 **Abstract**

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

9 **Results**

10 Allelic frequency for *CYP2C8*5* was 0.8375 which was statistically significant ($p<0.05$).
11 There was no significant difference ($p> 0.05$) in the prevalence of *CYP2C8*5* allele within
12 the ethnic groups. Also, there was no significant association ($p >0.05$) between *CYP2C8*5*
13 allele and reported ADRs. Many (88.75%) of the study subjects depended highly (>1-3x in a
14 year) on drugs metabolized by CYP2C8.

15 **Conclusions**

16 The high prevalence of *CYP2C8*5* determined in the study population may indicate a high
17 risk of toxicity in using drugs metabolize by CYP2C8 since *CYP2C8*5* mutants have been
18 reported to have a reduced enzymatic activity. This is the first reported study on prevalence
19 of *CYP2C8*5* in Ghanaians.
20

21 Key words: CYP2C8, drug toxicity, ArtesunateAmodiaquine, malaria

22 **Background**

23 Cytochrome P450 (CYP) family enzymes are diverse group of haemoproteins bound to
24 membranes of the endoplasmic reticulum and mitochondria where they function in catalyzing
25 the oxidative metabolism of many endogenous and exogenous compounds such as drugs and
26 carcinogens (Redlich *et al.*, 2008). Based on sequence homology, 57 isoforms of CYPs have
27 been identified and classified in humans. CYPs are found in abundance in the liver and, to a
28 lesser extent, in extra hepatic tissues as such the kidney, salivary ducts, intestine and adrenal
29 cortical cells (Enayetallah *et al.*, 2004), with low expression of CYP2C8 protein in the
30 intestines (Lapple *et al.*, 2003). The CYP2C subfamily is responsible for catalyzing the
31 metabolism of about 20% of clinically prescribed drugs. Cytochrome P450 2C8 (CYP2C8) is
32 a member of the CYP2C subfamily and account for approximately 6% of the total CYP

content in liver (Rowland-Yeo, Rostami-Hodjegan, and Tucker, 2004). 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) (Rahman *et al.*, 1994), anti-diabetes drugs (rosiglitazone, pioglitazone and repaglinide) (Baldwin, Clarke, and Chenery, 1999; Yamazaki *et al.*, 2000); antiarrhythmic drug (amiodarone) (Ohya *et al.*, 2000), and HMG-CoA reductase inhibitor (cerivastatin) (Muck, 2000). Furthermore, CYP2C8 play a role in the metabolism of endogenous compounds such as lipids, steroidal hormones, retinoids and arachidonic acid (Capdevila *et al.*, 1981; Nadin and Murray, 1999; Zeldin *et al.*, 1996). The gene that code for the CYP2C8 enzyme is known as the *CYP2C8* gene which is 31KB in size consisting of 9 exons (Klose, Blaisdell, and Goldstein, 1999). It is located at chromosome 10q24 in a multigene cluster containing the other CYP2C subfamily members CYP2C9, CYP2C18 and CYP2C19 (Finta and Zaphiropoulos, 2000) prearranged as Cent–CYP2C18–CYP2C19–CYP2C9–CYP2C8–Tel (Gray *et al.*, 1995). The nucleotide sequences of CYP2C8 gene shares about 74% homology with CYP2C9 gene. The whole CYP2C gene family spans about 400kb and has linkage between its genes (Yasar *et al.*, 2002). The CYP2C8gene 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 Caucasian populations (Totah and Rettie, 2005). *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% (Totah and Rettie, 2005). 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 (Yasar *et al.*, 2002). *CYP2C8**4 (c.792C>G, p.Ile264Met) allele is also present in Caucasians with a frequency of about 8% (Totah and Rettie, 2005). *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 of during protein synthesis (Bahdur, 2002). The resulting product of the enzyme lacks 64% of normal enzymes protein structure affecting the substrate recognition (haem-binding) site and 5 of 6 substrate recognition sites of the enzyme (Nakajima *et al.*, 2003). 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 (Dai *et al.*, 2001).

Report indicates that the prevalence of *CYP2C8**2 mutation was determined to be 16.75% in northern Ghanaian populations (Rower *et al.*, 2005) and 17% in Southern Ghanaians (Kudzi, Dodoo, and Mills, 2009). 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 as well as the extent to which individuals with genotypes of mutant allele depend of drugs metabolized by CYP2C8.

Methods

Ethical Issues

The research work was approval by the Committee on Human Research, Publications and Ethics, Kwame Nkrumah University of Science and Technology, School of Medical Sciences and KomfoAnokye Teaching Hospital, Kumasi-Ghana (CHRPE/AP/089/14). An informed

84 written consent was also obtained from all the subjects who participated in this research
85 study.

86

87 **Study Design and Subjects**

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

95 **Blood Sample and Medical History Data Collection**

96 Peripheral blood samples were obtained from the study subjects and preserved on labelled
97 Whatman filter papers which were air dried and stored in a plastic bag until DNA was
98 extracted. A questionnaire was also administered for information on medical history with
99 respect to the common major diseases which require the use of drugs that the enzyme CYP
100 2C8 metabolizes as well as their general attitude toward chemotherapy as a treatment and
101 history of personal adverse drug reaction. The Body Mass Index of the study subjects was
102 also obtained.

103

104 **Molecular Analysis**

105 ***DNA Extraction from Blood Blot Samples***

106 The genomic DNA was extracted from the filter paper blood blots collected using the TE
107 buffer extraction method (Plowe *et al.*, 1995). The extract DNA was stored at -40 °C in the
108 DNA microtubes in a Deep freezer until use after quantification using spectrophotometric
109 analyses.

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) (Nakajima *et al.*, 2003). The DNA was amplified in 20µl reaction mix containing 1X PCR buffer (invitrogen, USA), 25mM MgCl₂ (Promega, USA), 10mM 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) (Nakajima *et al.*, 2003) and 5U/µl of DNA *Taq* Polymerase. An amount of 5µl extracted genomic DNA was used as template for the PCR reaction. Sterile double distilled water (sddH₂O) was added to the mix to make the volume up to 20µl. 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), Anealing (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.

Gel Electrophoresis

The PCR products were electrophoresed in 2% agarose gels prepared with 1x TAE buffer and stained with 0.5µg/ml ethidium bromide dye. About 8µl of each sample of DNA was added to 1µl 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.

134 The sizes of the PCR products were calculated using the mobility of a 100bp molecular
135 weight ladder of DNA (Promega, USA) as the reference.

136 **Statistical Analysis**

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

140 **Results and Discussion**

141 **Demographics of Study Subjects**

142 The age distribution of the study subjects ranged from 18 to 53 years with an average age of
143 30.63 ± 8.75 years. Majority of the study subjects had access to secondary (45%) and tertiary
144 education (42.5%). The Body Mass Index (BMI) distribution of the subjects ranged from of
145 15.78kg/m^2 to 36.75kg/m^2 with a mean of $22.36 \pm 3.20\text{kg/m}^2$.

146 **Genotyping of CYP2C8*5 and Ethnic Distribution**

147 DNA was extracted from all the samples ($n = 80$) and PCR was performed on the DNA
148 samples using primers specific for amplifying mutant allele of CYP 2C8*5. Figure 1 is an
149 ethidium bromide stained agarose gel electrophoregram showing the positive and negative
150 samples.

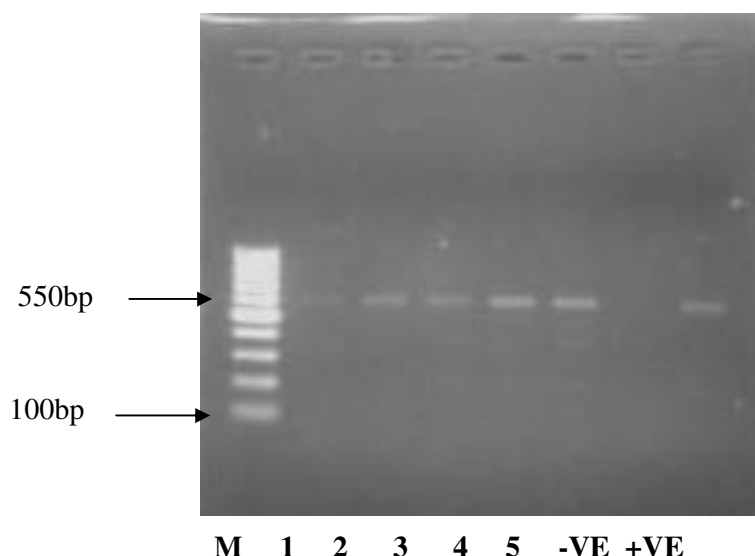


Figure 1: Ethidium bromide stained 2.0% agarose gel electrophoregram showing PCR amplified DNA sequences of CYP2C8*5 for the Ashanti Male Subjects.

The study determined the prevalence of *CYP2C8*5* allele as 0.8375 (Table 1). The overall prevalence of *CYP2C8*5* was observed to be in the study population was higher compared to that observed in the Japanese population as 0.025 involving 200 healthy subjects (Nakajima *et al.*, 2003) and Soyama *et al.* (2002) who also reported the heterozygote of *CYP2C8*5* in Japanese population to be 0.009 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* (0.17) in the same Ghanaian population (Kudzi *et al.*, 2009; Rower *et al.*, 2005). The result of this study supports and augments these findings that *CYP2C8* gene mutation is high in the population. In addition, the observed prevalence of 0.83 of *CYP2C8*5* in the study is higher than reported *CYP2C8* gene mutations in the African population such *CYP2C8*2* (0.12) in Burkinabes (Parikh *et al.*, 2007). It is also higher than *CYP2C8*2* (0.21), *CYP2C8*3* (0.021) and *CYP2C8*4* (0.006) reported by Cavaco *et al.* (2005) 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 1). As such, the information from some of these ethnic populations may be useful on populations or individuals that share a more close 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.

Table 1: 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)	
Total (80)	30 (75)	37 (92.5)	67 (83.75)	0.636

180

181 Statistically, there was no significant difference between the study subjects when their BMI
 182 was cross tabulated against presence or absence of the *CYP2C8*5* mutant allele ($p>0.05$).
 183 Most the participants having healthy BMI (Table 2) is a reflection of their health status as
 184 well the ability to dose drugs correctly. There are medications which accumulate in adipose
 185 tissue and will necessitate an adjusted weight for a better accurate dosing for such drugs since
 186 not all the drugs are bioavailable. An adjusted, or dosing weight, is calculated to account for
 187 obese patients exceeding >125% of their ideal body weight (Blouin and Warren, 1999;
 188 Cheymol, 2000; Wurtz, Itokazu, and Rodvold, 1997). Individuals who are underweight are
 189 less likely to tolerate drug while individuals who are overweight are prone to experiencing
 190 therapeutic failure and will require more dosage compared to the normal weight individuals.

191 **Table 2: Body Mass Index (BMI) and *2C8*5* Status of Study Subjects.**

BMI Status	CYP 2C8*5Mutant Allele Status		<i>P-value</i>
	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)	
Total	66 (83.75)	14 (16.25)	0.007

192

193 Adverse Drug Reactions and *CYP2C8*5* Mutant Allele Status

194

195 Table 3 shows the cross tabulation of *CYP2C8*5* against reported history of adverse drug
 196 reaction. Statistically, there was no significant difference between study subjects having the
 197 *CYP2C8*5* mutant allele and reported history of adverse drug reactions ($p>0.05$).

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.

Table 3: *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	
Total	33 (41.25)	43(53.75)	4(5.0)	80(100)	0.323

Also some drug substrate have multiple enzymes involved in their metabolism (Glamočlija and Jevrić-Čaušević, 2010). The similarity in size accounts partly for the observation of *CYP2C8* and *CYP3A4* having many related substrates compared to other CYPs (Jaakkola *et al.*, 2006). 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 (Adjei *et al.*, 2009). 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.

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). Considering the high presence of the *CYP2C8*5* allele in the study population and the high level of dependency the study population may be at risk of using drugs metabolised by CYP2C8 even though 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 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 (%)	<i>P-value</i>
0x	9 (11.25)	
1-3x	69 (86.25)	
4-6x	2 (2.50)	
7-9x	0 (0.00)	
>10x	0 (0.00)	
Total	80 (100)	0.000

Conclusions

The prevalence of *CYP2C8*5* mutant allele in selected ethnic groups in Southern Ghana is high (0.83). 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.

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