

Genetic Polymorphism of CYP2C19 in Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention (PCI) in Erbil

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Abstract

Introduction: CYP2C19 is an enzyme involved in the hepatic metabolism of many clinically important drugs, such as clopidogrel. CYP2C19 is highly polymorphic, and great inter-individual variability has been noticed among clopidogrel users, with many patients being resistant to clopidogrel, resulting in therapeutic failure. This study aims to investigate the distribution of CYP2C19 polymorphism among patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) in Erbil -Iraq.

Materials and methods: 70 patients (Kurdish and Arab) who had undergone PCI in Cardiac Center Surgical Specialty Hospital in Erbil were enrolled. DNA was extracted for each patient, and genotyping for CYP2C19*1, CYP2C19*2, CYP2C19*3, and CYP2C19*17 alleles was performed for each patient using real time-polymerase chain reaction (RT-PCR).

Results: The CYP2C19 allele frequencies were CYP2C19*1 (66%), CYP2C19*2 (13%), and CYP2C19*17 (21%). Five genotypes were identified among the studied samples including: CYP2C19*1/*1 (40%), CYP2C19*1/*2 (21.4%) CYP2C19*2/*17 (2.9%), CYP2C19*1/*17 (31.4%), and CYP2C19*17/*17 (4.3%).

Conclusion: The findings of the current study indicate that CYP2C19 gene variants are present among people in Erbil, and this study can serve as a foundation for further investigations, targeting different ethnicities with greater sample size.

Keywords: CYP2C, P2Y12-blocker, Pharmacogenetics, SNP.

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INTRODUCTION

Cytochrome P450 (CYP) is an enzyme superfamily responsible for metabolizing the majority of therapeutic agents.⁽¹⁾ It comprises 18 families and 43 subfamilies, among which CYP1, CYP2, and CYP3 are the most prominent ones.⁽²⁾ Genetic polymorphisms have been observed among most of the CYP450 isoenzymes leading to inter-individual variations in drugs pharmacokinetics and pharmacodynamics.⁽³⁾

An essential member of the CYP2 family, which is highly polymorphic, is CYP2C19.⁽⁴⁾ Although CYP2C19 has over two thousand single nucleotide polymorphisms (SNPs) and 35 variants of mutant alleles, only the loss-of-function (*2 and *3) and gain-of-function (*17) alleles have been studied extensively, given their allele frequency being >5%.^(4,5)

CYP2C19 enzyme is in charge of metabolizing many clinically significant medications, such as antidepressants

(Citalopram), anxiolytics (diazepam), anticonvulsants (Phenytoin), proton pump inhibitors (omeprazole), and antiplatelets (clopidogrel).^(6,7)

CYP2C19 plays an essential role in clopidogrel metabolism, which is a prodrug requiring enzymatic activation to its active metabolites.⁽⁸⁾

Clopidogrel (platelet P2Y12 adenosine diphosphate (ADP) receptor antagonist) is widely prescribed for patients with ischemic heart disease after percutaneous coronary interventions (PCIs).^(9,10) However, clopidogrel fails to produce a therapeutic response in one-fourth of its users, a phenomenon which is referred to as clopidogrel resistance (CR).⁽¹¹⁾ Although the exact mechanism of CR has not been fully identified, it is thought to be multifactorial, and genetic polymorphism is one of the factors.^(12,13)

Clopidogrel resistance has been observed among carriers of *2 and *3 loss of function alleles resulting in ischemic events and stent thrombosis.⁽¹⁴⁻¹⁶⁾ Moreover, CYP2C19*2 allele

carriers have a threefold higher risk of stent thrombosis than non-carriers.⁽¹⁷⁾ Therefore, Food and Drug Administration (FDA) has issued a black box warning recommending genotyping to guide clopidogrel therapy and using another antiplatelet agent in patients identified as poor metabolizers.^(18,19)

CYP2C19 SNPs have been studied extensively among nations to optimize antiplatelet therapy and reduce the risk of adverse ischemic events. To the best of our knowledge, the presence of CYP2C19 SNPs has not been studied among people in Erbil-Iraq. Therefore, we aimed to study the distribution of such polymorphisms among patients with acute coronary syndrome undergoing PCI to provide insight to clinicians regarding the genetic variations among people in Erbil.

MATERIALS AND METHODS

Sample collection

For the current study, 70 patients (25 female and 45 male, 40-75 years old), who had undergone PCI in Cardiac Center Surgical Specialty Hospital in Erbil, were enrolled. All the patients were prescribed 75mg Clopidogrel to be taken for one year post-PCI.

The inclusion criteria were Iraqi patients (Kurdish and Arab) living in Erbil, patients undergoing elective PCI, patients prescribed clopidogrel, and patients >18 years old.

Patients admitted to the ICU or those not consenting to the study were excluded.

A questionnaire was filled, and 2mL of whole blood in EDTA tubes was collected for each patient. Informed consent was obtained from all participants, and the study was approved by the Research and Ethical Committee of the College of Pharmacy at Hawler medical university (Reference no.: 1492021-233 Ph HMU EC).

Genomic Extraction

Genomic DNA was isolated from 2mL blood specimens using ThermoFisher (ThermoFisher Scientific, Wilmington, DE, USA) DNA extraction kit according to the manufacturer's instructions. NanoDrop (Biometrika, UK) was used for identifying DNA quality and quantity. An (A260–A320)/(A280–A320) ratio of 1.7-2 indicated high DNA quality.

CYP2C19 genotyping

DNA was amplified by real time-Polymerase Chain Reaction (RT-PCR) using a ready-to-use RT-PCR kit (SNP Biotechnology R&D Ltd. Hacettepe Technopolis – Ankara/Turkey, Cat. No: 113R-20-03) to detect 681 G>A (*2), 636 G>A (*3), and 806 C>T (*17) variants in CYP2C19 gene. The components of the RT-PCR reaction included 20µl ready-to-use Master Mix with 5 µl template DNA. The PCR reaction started with a 3 min initial denaturation at 95°C,

followed by 30 cycles of denaturation (95°C for 15s) and annealing (60°C for 1min).

Statistical analysis

Genotype and allele frequencies were calculated by counting. Hardy-Weinberg equation (HWE) was used to calculate expected genotype frequencies from the allele frequencies ($p^2 + 2pq + q^2 = 1$). Correlations were tested by using chi-square. Statistical Package for Social Sciences (SPSS) software (version 25, IBM Corporation) was used for data analysis.

RESULTS

The mean age of the participants was 59 ± 9.7 , and the main variant alleles detected in our study were *2 and *17, which presented at a frequency of 0.128 and 0.207 (Fig.1). Five CYP2C19 gene variants were found (*1/*1), (*1/*2), (*1/*17), (*17/*17), and (*2/*17), which were grouped to four phenotypes (Fig.2). The genotype frequencies are shown in (Table 1).

Most of the subjects (40%) were homozygous for the wild-type allele (CYP2C19*1/*1), which are considered normal or extensive metabolizers (NM). The CYP2C19*17 allele was profound among the participants, with 31.4% of the subjects being heterozygous (rapid metabolizers) and only 4.3% being homozygous (ultra-rapid metabolizers). 21.4% of the participants carried one wild-type allele and one loss of function allele (CYP2C19*1/*2) and were classified as intermediate metabolizers (IM). Three subjects showed compound heterozygosity by having one loss of function (*2) and one gain of function (*17) allele, which are also considered IM.

None of the studied participants were heterozygous for the CYP2C19*2 allele; thus, none were classified as poor metabolizers (PM). In addition, the CYP2C19*3 loss of function allele was absent. The CYP2C19 genotype frequencies were consistent with Hardy–Weinberg Equilibrium ($\Sigma x^2 = 2.053$).

Table 1: CYP2C19 genotype frequencies among patients in Erbil city and Hardy-Weinberg equilibrium values

Genotypes (phenotypes)	Frequency (%)	HWE
*1/*1	28 (40)	0.378
*1/*2	15 (21.4)	0.656
*1/*17	22 (31.4)	0.385
*2/*17	3 (2.9)	0.358
*17/*17	2 (4.3)	0.276

HWE: Hardy–Weinberg Equilibrium

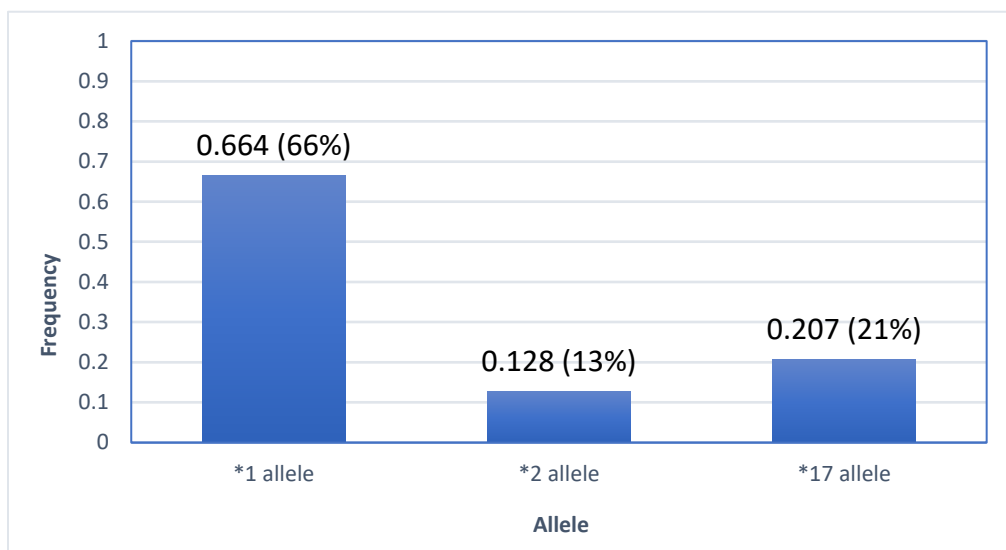


Figure 1: CYP2C19*1, *2, and *17 allelic frequencies among people in Erbil

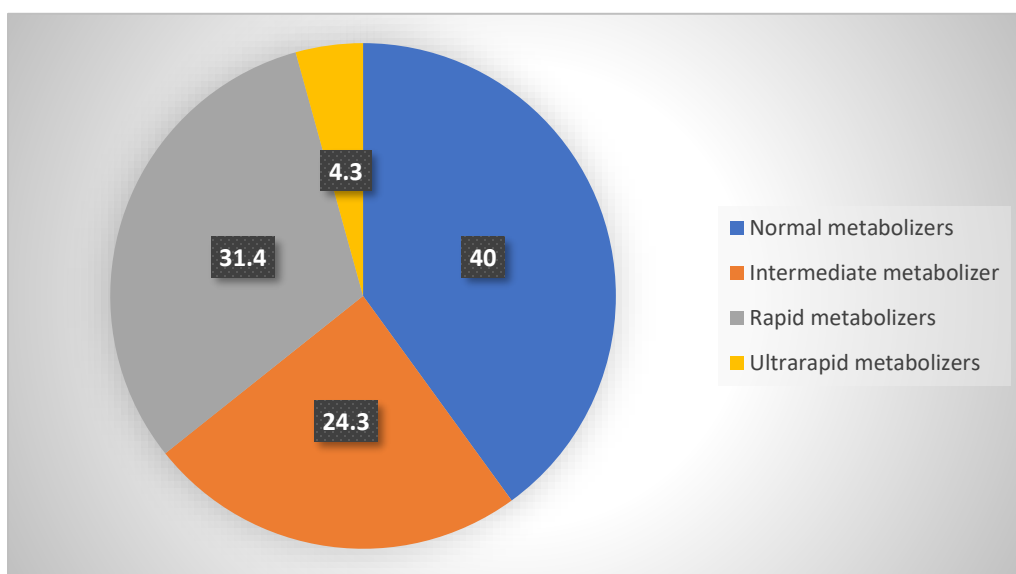


Figure 2: The percentage of CYP2C19 phenotypes

Table 2. shows the nonsignificant correlation ($p > 0.05$) between CYP2C19 genotypes with gender ($P= 0.5$) and

previous events of the acute coronary syndrome (ACS) such as myocardial infarction (MI) and unstable angina (UA) ($P=0.622$). A P-value of ≥ 0.05 was considered significant.

Table 2: Correlation of CYP2C19 genotypes with gender and previous ACS using person chi-square

Genotype						
Gender	*1/*1	*1/*2	*1/*17	*2/*17	*17/*17	Chi-square
Male	18 (64.3%)	9 (60%)	15 (68.2%)	1 (33.3%)	2 (100%)	2.628
Female	10 (35.7%)	6 (40%)	7 (31.8%)	2 (66.7%)	0	
Previous ACS events	14 (50%)	10 (66.7%)	12 (54.5%)	1 (33.3%)	2 (100%)	3.311
No previous ACS events	14 (50%)	5 (33.3%)	10 (45.5%)	2 (66.7%)	0 (0%)	

DISCUSSION

The present study determined the distribution of CYP2C19 allele variants among people in Erbil. The CYP2C19 *1 allele was the most frequent (0.664), followed by CYP2C19 *17 (0.207) and CYP2C19*2 (0.128). Compared to a number of studies performed in the middle east and north Africa (MENA) region, our results were close to that of Saudi Arabians,⁽²⁰⁾ Iranian,⁽²¹⁾ and Turkish,⁽²²⁾ people. This may be due to the fact that Iraq has borders with the aforementioned countries. In addition, Kurds, Iranians, and Turkish are genetically considered to be of Caucasian and Mediterranean origins.⁽²³⁾ In addition, our results were also consistent with a previous study performed in Iraq which included Arab ethnicity.⁽²⁴⁾

The frequency of the *1 allele was less than that of Lebanon (86.3%), Jordan (84%), Palestine (90.5%), and Egypt (88%), close to Iraq (65%), Iran (65.3%), Turkey (65.6%), Saudi Arabia (62.9%), and more than Pakistan (47.3%) which is known to have many ethnic groups.^(20-22,24-29)

The frequency of the *2 allele was close to the frequencies in Iraq (15.2%),⁽²⁴⁾ Iran (13.1%),⁽²¹⁾ Lebanon (13.4%),⁽²⁶⁾ Saudi Arabia (11.2%),⁽²⁰⁾ and Egypt (11%).⁽²⁵⁾

The *3 and *17 alleles were less frequently studied than the *2 allele. CYP2C19*3 allele, although absent in the current study, as well as among Iranian⁽²¹⁾ and Turkish people,⁽²²⁾ was observed in very low frequencies among Iraqi (0.1%),⁽²⁴⁾ Lebanese (0.3%),⁽²⁶⁾ and Egyptians (2%),⁽²⁵⁾ indicating the rareness of this allele in the region.

The *17 allele was only studied among Iraqi, Iranian, Turkish, Saudi Arabian, and Pakistani people and the frequencies were all close to each other (current study (21%); Iraq (19.5%); Iran (21.6%); Turkey (24.4%); Pakistan (23.7%); Saudi Arabian (25.7%).^(20-22,24,29)

Regarding the phenotype, most of the participants in our study had *1/*1 and *1/*17 genotypes, which were classified as extensive metabolizers (71.4%), and this result was consistent with the ones obtained from Iran (70.6%), Turkey (74.6%), and Saudi Arabia (70.7%).⁽²⁰⁻²²⁾ The next common genotype was (*1/*2), and the value (21.4%) was close to those observed in most of the countries, which scored (18.3%-20.5%), except for Turkey and Saudi Arabia, which were 12.3% and 14.5%.^(20-22,24-29)

The phenotype of *2/*17 carriers has become a source of conflict since some studies regard subjects possessing this genotype as extensive metabolizers,^(20,22,30) whereas some consider them as intermediate metabolizers.^(7,21,29) Few studies have observed that the *17 allele counterbalances the effect of the *2 allele by exerting a higher metabolic rate, thus, resulting in normal drug metabolism.⁽³⁰⁾ On the contrary, some believe that the effect of the *2 allele on CYP2C19 is superior to that of *17 and thus results in

reduced drug metabolism.⁽²¹⁾ This is further backed by some observations where carriers of this genotype have had a greater serum drug concentration than normal metabolizers of the same drug.⁽³¹⁾ In addition, Gurbel *et al.* had shown that both CYP2C19 *1/*2 and CYP2C19 *2/*17 had effects on CYP2C19 activity in clopidogrel-treated patients.⁽³²⁾ CPIC guideline has also classified these individuals as intermediate metabolizers.⁽³³⁾

This phenotype was the least observed among our sample (2.9%), which also occurred in low percentages among Iranians (3.3%), Turkish (5.3%), Iraqis (7.7%) and Saudi Arabians (7%), but was higher among Pakistanis (26.7%).^(20-22,24,29)

None of our studied subjects were classified as poor metabolizers, which was mostly present among the Jordanian (6.4%) and Pakistani (6.2%) people. However, the percentages among Iraqis, Iranians, Turkish, Lebanese, Palestinian, Saudi Arabians, and Egyptians were relatively low (0.4%-3.1%).^(20-22,24,29) The percentage of ultrarapid metabolizers among our samples was 4.3% and ranged from 2.3% to 7% among other nationalities.^(20-22,24,29)

Since some of the studied participants had experienced previous attacks of myocardial infarction and unstable angina, we investigated whether there is any correlation between these attacks and CYP2C19 genotypes. However, there was no correlation ($P=0.5$). A correlation was not found between gender and genotypes either ($P=0.622$).

CONCLUSION

The findings of the present study indicate that there is individual variability in response to clopidogrel and other drugs known to be CYP2C19 substrates among people in Erbil, and the patterns of genotype distribution were close to some of the MENA countries.

Although no correlation was observed between CYP2C19*2 allele carriers and patients with a history of MI or UA, a standard dose of clopidogrel might not be suitable for all the patients undergoing PCI. Routine genotyping for an individualized anti-platelet therapy might be of benefit in preventing stent thrombosis or bleeding risks following PCI. The current study can serve as a foundation for future investigations on larger sample size and different ethnic groups in Erbil.

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