Investigation of Genetic Polymorphisms of Cytochrome P450 2C19 in Iranian Patients With Drug-Eluting Stents

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Abstract

Background: Cytochrome P450 2C19 (CYP2C19) exhibits polymorphism, with about 21 known allelic variants. Notably, the *17 allele is associated with increased enzymatic activity, culminating in enhanced CYP2C19 activity and the ultra-rapid metabolizer (UM) phenotype. This genetic variation has a profound impact on an individual's response to a wide range of medications. The primary objective of this study was to ascertain the prevalence of the CYP2C19*17 allele among Iranian patients who have received drug-eluting stents.

Methods: This study was conducted to examine the genetic polymorphism of the CYP2C19 enzyme in 100 patients with drug-eluting stents (DESs) at Imam Hossein Hospital, Tehran, Iran. All participants were selected based on pre-defined inclusion criteria. Blood samples were obtained for DNA extraction, and CYP2C19 genotypes were subsequently analyzed through polymerase chain reaction (PCR) and gel electrophoresis.

Results: The *17 polymorphism was detected in 11% of the cohort. Of this group, 11 individuals were heterozygous carriers of the CYP2C19*17 allele, whereas the homozygous *17/*17 genotype was not observed in any participant.

Conclusion: Our findings demonstrate a low prevalence of the CYP2C19*17 allele and an absence of the homozygous *17/*17 genotype in the Iranian population. Despite its lower prevalence compared to other populations, the clinical implications of this allele are still considered highly significant.

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Introduction

Cytochrome P450 2C19 (CYP2C19), a crucial polymorphic enzyme in the CYP2 family, plays a significant role in metabolizing numerous clinically vital drugs (1). The gene for CYP2C19, located on chromosome 10q24, shows extensive genetic diversity, with over 21 alleles currently identified (2–4). These genetic variations lead to different metabolic phenotypes among individuals, which, in turn, influence drug effectiveness and potential toxicity. Prior research has thoroughly documented common alleles like *2 and *3, which are linked to loss-of-function, and *17, which is associated with a gain-of-function variant (5).

The CYP superfamily is a primary component of drug metabolism, responsible for roughly 75% of all drug breakdowns (6). Inherited variations within CYP families can significantly alter how a large part of the population responds to many medications (7). A more recently identified allelic variant of CYP2C19, known as CYP2C19*17, has enhanced enzyme activity. This is caused by a mutation (−806C > T) that leads to increased transcription of CYP2C19 (8). Individuals can be classified into four metabolic phenotypes based on their metabolic capacity: Poor metabolizers (PMs), intermediate

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metabolizers (IMs), extensive metabolizers (EMs), and ultra-rapid metabolizers (UMs) (9).

Cardiovascular diseases (CVDs) are consistently one of the leading causes of death worldwide (10), making them a key area of focus for medical research and intervention. In the past two decades, therapeutic approaches for coronary artery disease (CAD) have undergone a major shift, largely due to the wider use of both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) (9). The development of drug-eluting stents (DESs) has been particularly impactful, significantly reducing restenosis rates following PCI procedures (11). Additionally, antiplatelet medications, such as aspirin and clopidogrel, are crucial complementary therapies that help lower ischemic complication risks in patients who have undergone PCI (12).

Clopidogrel is a widely used antiplatelet medication for patients with acute coronary syndrome (ACS) and those undergoing PCI. It requires metabolic activation by the enzyme CYP2C19 (13). Genetic variations in the CYP2C19 gene can cause significant differences in how individuals respond to clopidogrel (14, 15). Some patients have a suboptimal response, which increases their risk of thrombosis (16-18). Conversely, other patients are at a higher risk of bleeding, likely due to a greater rate of clopidogrel metabolism into its active form (19).

Given Iran's significant burden of CVD and the widespread use of clopidogrel, understanding the prevalence of CYP2C19*17 mutations within its population is of paramount importance. This insight can help healthcare professionals refine drug regimens and mitigate the risks associated with angiography and intervention (20). While research has explored CYP2C19*17 mutations in various global populations, underscoring the need for independent studies across different ethnic groups (21), the prevalence of this allele in Iranian patients undergoing PCI remains unexplored.

The primary objective of this study was to ascertain the prevalence of the CYP2C19*17 allele in Iranian patients who have received DESs, to characterize the presence of this specific genetic polymorphism within the Iranian population.

Methods

Study Population

The current study enrolled 100 participants who met the following inclusion criteria: 1) Receiving standard doses of clopidogrel and aspirin; 2) Undergoing PCI for non-ST-segment elevation ACS (NSTE-ACS). Participants were excluded from the study if they met any of the following criteria: 1) Cardiac arrest within the last 48 hours; 2) Unsuccessful PCI; 3) Age under 18 years; 4) A contraindication to antiplatelet medication; 5) A platelet count below 100,000 mm−3; 6) A hematocrit level below 25%; 7) Creatinine levels greater than 4 mg dL−1; 8) A history of bleeding diathesis; 9) A co-existing severe illness with a life expectancy of less than one month; 10) An international normalized ratio (INR) exceeding 1.5 times the control value.

Ethical Considerations

The study protocol received approval from the institution's ethics committee (IR.SBMU.PHARMACY.REC.1398.001), and all participants provided written informed consent.

Sample Collection and DNA Extraction

Five milliliters of venous blood were collected from each volunteer into tubes containing ethylenediaminetetraacetic acid (EDTA). DNA was then extracted from these samples using a Puregene Blood Core Kit C (Qiagen, Germantown, MD, USA). The concentration of the resulting DNA was quantified by measuring its absorbance at 260 nm and 280 nm. The extracted DNA was subsequently stored at -20 °C.

Genotyping of Cytochrome P450 2C19

In this study, genotyping of the CYP2C19 gene was performed using a two-stage polymerase chain reaction (PCR) technique known as nested PCR. Specific polymorphic single nucleotide polymorphisms (SNPs) were amplified in a 96-well fast thermal cycler. The total reaction volume was 25 µL, which included 28 ng of DNA, along with the manufacturer's recommended quantities of PCR Master Mix (SinaClon), primers (SinaClon), and Taq DNA polymerase (SinaClon). The PCR thermal cycling protocol was as follows: An initial denaturation at 94°C for 5 minutes, followed by 40 cycles of denaturation at 94°C for 30 seconds, annealing at 52°C for 30 seconds, and extension at 72°C for 30 seconds. A final extension step was then performed at 72°C for 7 minutes. The sequences for the primers used are detailed in Table 1. The amplified PCR products were then separated by electrophoresis on a 2% agarose gel, and the resulting bands were analyzed using gel imaging software.

In the second stage, previous products served as templates for the reaction. The cycling program was a touchdown

protocol that began with an initial denaturation at 94°C for 1 minute, followed by 15 cycles. Each cycle consisted of denaturation at 94°C for 15 seconds, annealing at 50°C for 20 seconds, and extension at 72°C for 30 seconds. A final extension step was performed at 72°C for 7 minutes, and the products were then cooled to 4°C. The resulting PCR products were then separated on a 3% agarose gel. Bands corresponding to both the mutant (*17) and wild-type (*1) alleles were observed at approximately 200 base pairs, and genotypes were determined based on the size of the PCR products.

Table1. Primer sequence used for gene amplification

PCR Stage	Primer
First	17* forward: GCCCTTAGCACCAAATTCTC
	17*reverse: ATTTAACCCCCTAAAAAAACACG
Second	wild-type Primer: TCTGTTCTCAAAGC
	Reverse Primer: ATTTAACCCCCTAAAAAAACACG

Genotype Assignment

Genotypes were determined by the presence or absence of specific bands following gel electrophoresis. The initial PCR yielded a 470 bp product, which was confirmed by gel electrophoresis (Figure 1). Subsequently, for the second-stage analysis, a 200 bp band indicated the presence of the mutation when the mutant primer was used. Conversely, the absence of the mutation was confirmed by the appearance of a 200 bp band in the PCR product when the wild-type primer was employed (Figure 2). Consequently, the final genotype assignments were made based on whether a 200 bp band was present or absent in the respective PCR products.

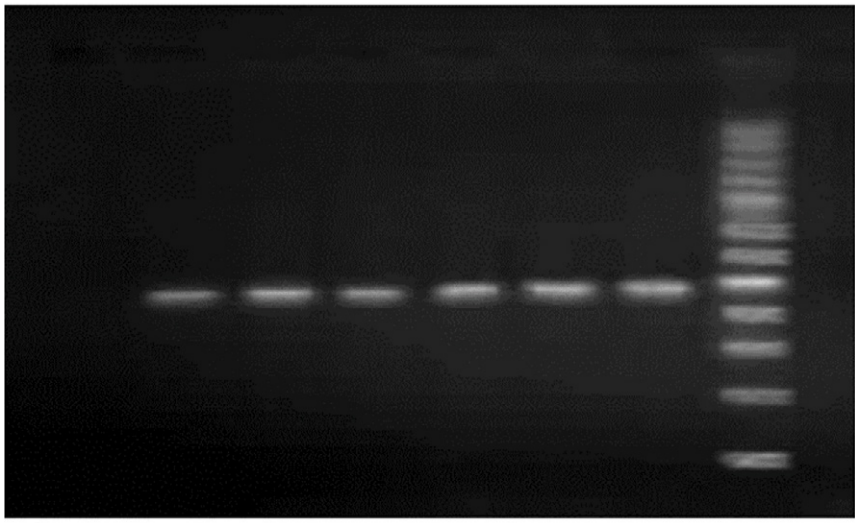

Figure 1. The first stage of PCR

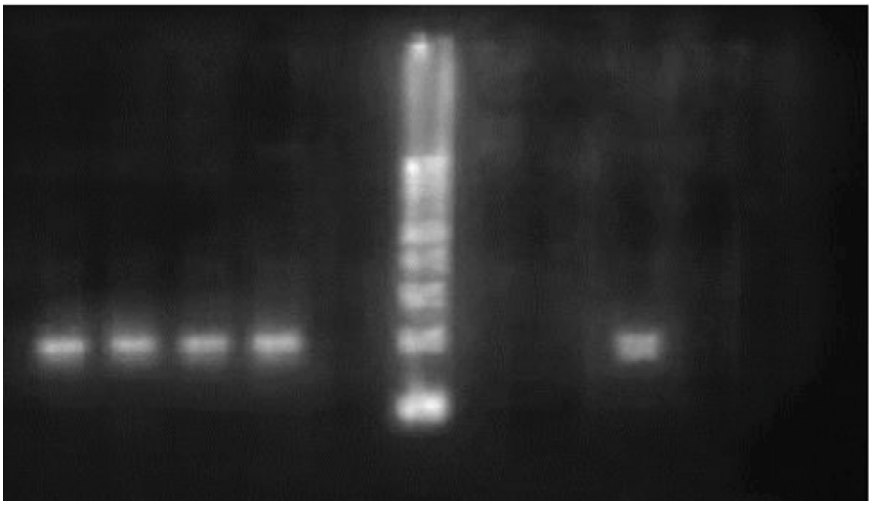

Figure 2. The second stage of PCR

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics. Continuous variables are reported as the mean ± standard deviation; the median and range were also included where relevant. Categorical variables are presented as counts and percentages. The Shapiro–Wilk test was used to evaluate the distribution of continuous variables. Given that age was approximately normally distributed, between-group comparisons (wild-type 1/1 versus heterozygous 1/17) were conducted using a two-tailed Student's t-test. For categorical variables, the Chi-square test was used for comparisons; however, Fisher's exact test was substituted when any expected cell count was less than 5. CYP2C1917 allele frequencies were determined through direct gene counting. Statistical significance was defined as a two-tailed $p < 0.05$.

Results

Patient Characteristics

In this cohort of 100 patients, continuous variables were summarized using the mean ± standard deviation, along with the median and range for age, while categorical variables were reported as counts and percentages. The patients had a mean age of 60.56 ± 12.22 years (median = 61; range = 29–82 years). The cohort was predominantly male, comprising 60% (60/100) of the total. Regarding lifestyle factors, 25.8% of the patients were current smokers, and 3.2% had a history of substance addiction. Of the comorbidities, hypertension was the most common at 64%, with diabetes being the next most frequent at 20%. Other conditions were less prevalent, including hyperlipidemia (15.7%), ischemic heart disease (8.9%), a history of myocardial infarction (6.7%), and prior PCI (5%). Consistent with their stent management, all patients (100%) were receiving dual antiplatelet therapy with aspirin and clopidogrel. The baseline medication profile of the cohort revealed that 60.6% of patients were receiving beta blockers and atorvastatin. Other common prescriptions included nitroglycerin (48.5%), pantoprazole (10.1%), and omeprazole (5.1%). A full summary of the cohort's demographic and clinical characteristics is presented in Table 2.

Table 2. Baseline demographic, clinical, and medication characteristics of the study population

Characteristic		Overall (N=100)
Age (years), mean±SD (median[range])		60.56 ± 12.22 (61[29–82])
Sex (Female), N (%)		40 (39.4%)
Smoking, N (%)		24 (25.8%)
Substance Addiction, N (%)		3 (3.2%)
Diabetes Mellitus, N (%)		20 (20.0%)
Hypertension, N (%)		64 (64.0%)
Hyperlipidemia, N (%)		15 (15.7%)
Ischemic Heart Disease, N (%)		8 (8.9%)
Prior MI , N (%)		6 (6.7%)
Prior PCI, N (%)		5 (5.0%)
Medication use, N (%)	**Aspirin**	100 (100%)
	Clopidogrel	100 (100%)
	Beta Blockers	60 (60.6%)
	Atorvastatin	60 (60.6%)
	Nitroglycerin	48 (48.5%)
	Pantoprazole	10 (10.1%)
	Omeprazole	5 (5.1%)

MI:Myocardial Infarction, PCI:Percutaneous Coronary Intervention. Continuous data are given as mean ± SD (median [range]); categorical data are given as n (%).

*CYP2C19*17 Genotype and Allele Frequencies*

Table 3 presents the genetic analysis of the CYP2C19 gene, showing that the wild-type *1/*1 genotype was present in 89 out of 100 patients (89%). The remaining 11 patients (11%) were heterozygous for the *17 allele, possessing the *1/*17 genotype. Notably, no patient was found to be homozygous for *17/17. This distribution indicates a CYP2C19*17 allele frequency of roughly 11% within the study cohort, meaning that 11 of the 200 alleles in the study population were the *17 variant. Thus, the *17 allele was relatively uncommon in this Iranian patient sample, with all carriers being in the heterozygous state. The frequencies of each genotype and the calculated allele frequencies are summarized in Table 3.

Table 3. Distribution of CYP2C19 genotypes and the derived allele frequencies in the study population

Genotype	Phenotype	No. of Patients (%) (N = 100)	Calculated Allele Frequency
*1/*1	(Extensive Metabolizer)	89 (89%)	*1 allele: 89% [a]
*1/*17	(Rapid Metabolizer)	11 (11%)	*17 allele: 11% [a]
*17/*17	(Ultra-Rapid Metabolizer)	0 (0%)	–

[a] Allele frequency is calculated as the percentage of all alleles in the population represented by the given allele. Here, 11 heterozygous *1/*17 individuals yield 11 *17 alleles out of 200 total alleles (~11%), with the remaining ~89% being 1 allele.

Comparison of Clinical Characteristics by Genotype

In Table 4, we conducted a comparative analysis of demographic and clinical variables between patients with the *1/*1 genotype (wild-type, n = 89) and those with the *1/*17 genotype (heterozygous mutant, n = 11). Continuous variables, such as age, were assessed for normality. Age showed an approximately normal distribution, as indicated by similar mean and median values. Therefore, a two-tailed Student's t-test was employed to compare mean ages between the two groups. Categorical variables, including gender, smoking status, comorbidities, and medication use, were compared using Chi-square tests. To ensure accuracy, Fisher's exact test was used instead of the Chi-square test when expected cell counts were < 5. A $p < 0.05$ was established as the threshold for statistical significance for all tests. Table 3 provides a detailed breakdown of patient clinical characteristics, organized by genotype, and highlights the statistical significance of any observed differences. Patients with the *1/*17 genotype exhibited no statistically significant differences when compared to those with the *1/*1 genotype in terms of age (mean 60.0 versus 60.6 years, P = 0.90) or gender distribution (45.5% versus 60.7% male, P = 0.35). Likewise, no significant differences were found regarding smoking status (9.1% versus 25.8% current smokers, P = 0.29) or a history of substance addiction (9.1% versus 2.2%, P = 0.30). The two genotype groups had a comparable prevalence of major cardiovascular risk factors and comorbidities. For example, hypertension was found in 54.6% of *1/*17 carriers compared to 65% of wild-types (P = 0.52). Similarly, diabetes was present in 27.3% of carriers versus 19.1% of wild-types (p = 0.69). None of these observed differences were statistically significant (all P values > 0.05). Medication usage patterns were comparable between the groups, irrespective of genotype. By study design, all patients with the *1/*17 and *1/*1 genotypes were on both aspirin and clopidogrel (100% in both groups). No significant differences were observed in the use of other medications, including beta-blockers (63.6% versus 59.5%), statins (54.6% versus 60.7%), nitrates (45.5% versus 48.3%), and proton pump inhibitors (PPIs) like omeprazole or pantoprazole, between *1/*17 and *1/1 patients (all P values > 0.05). In conclusion, carrying a single copy of the CYP2C1917 allele was not linked to any statistically significant differences in baseline demographic or clinical characteristics within this patient cohort. All P values were greater than the 0.05 significance level, which showed no statistically significant differences between the *1/*1 and *1/17 genotype groups for any of the characteristics measured. Each statistical test was two-tailed. Therefore, the analysis suggests that having a single CYP2C1917 allele (*1/*17 genotype) does not significantly affect the baseline demographic or clinical profiles of patients with DESs in this Iranian cohort.

Table 4. Comparison of patient characteristics by CYP2C19 genotype (*1/*1 vs. *1/17)

Characteristic	**Wild-Type *1/1* (n = 89)	**Heterozygous *1/17* (n = 11)	P value
Age (years), mean±SD	60.63 ± 11.86	60.00 ± 15.49	0.90[b]
Male Gender, N (%)	54 (60.7)	5 (45.5)	0.35
Smoking, N (%)	23 (25.8)	1 (9.1)	0.29
Substance Addiction, N (%)	2 (2.2)	1 (9.1)	0.30
Diabetes Mellitus, N (%)	17 (19.1)	3 (27.3)	0.69
Hypertension, N (%)	58 (65.2)	6 (54.6)	0.52
Hyperlipidemia, N (%)	14 (15.7)	1 (9.1)	1.00[c]
Ischemic Heart Disease, N (%)	8 (8.9)	0 (0)	0.59[c]
Prior MI, N (%)	6 (6.7)	0 (0)	1.00[c]
Prior PCI, N (%)	4 (4.5)	1 (9.1)	0.45[c]
Beta Blocker use, N (%)	53 (59.5)	7 (63.6)	1.00
Atorvastatin use, N (%)	54 (60.7)	6 (54.6)	0.75
Nitroglycerin use, N (%)	43 (48.3)	5 (45.5)	1.00
Pantoprazole use, N (%)	9 (10.1)	1 (9.1	1.00
Omeprazole use, N (%)	4 (5.1)	1 (9.1%)	0.45[c]

P values are from independent t-test (age) or Chi-square/Fisher's exact tests (categorical comparisons), as appropriate. MI: Myocardial Infarction, PCI:Percutaneous Coronary Intervention.b, P value from two-sample Welch's t-test for unequal variances (results were nearly identical to Student's t-test). Median ages were also similar between groups.c P value from Fisher's exact test (cell counts too small for Chi-square validity).

Discussion

Recent research has revealed notable variations in the prevalence of the CYP2C19*17 allele among diverse populations. These disparities underscore the critical importance of conducting population-specific studies to understand their distribution and clinical implications (Table 5).

Table 5. Allele frequencies of CYP2C19*17 in other ethnic groups

	Ethnicity	N	Allele frequency (-806C>T)	References
1	**Indian**	87	0.179	(28)
2	**Chinese**	68	0.044	(29)
3	**Japanese**	265	0.013	(30)
4	**Saudi Arabians**	184	0.269	(19)
5	**Norwegians**	332	0.22	(31)
6	**Poles**	125	0.272	(32)
7	**Swedes**	314	0.18	(29)
8	**Koreans**	271	0.015	(33)
9	**Brazilians**	183	0.158	(34)
10	**Ethiopians**	190	0.179	(29)
11	**Greeks**	283	0.1961	(35)
12	**Turkish**	54	0.157	(36)
13	**Iranians**	100	0.11	Current study

The current research revealed a relatively low frequency of the CYP2C19*17 (-806C > T, 5′-UTR) allele in the Iranian population. Approximately 11% of the volunteers examined were found to be carriers of the CYP2C1917 genotype, which was observed exclusively in its heterozygous form, with no homozygous cases identified. Mohammadi et al.'s (2019) study in Iran, entitled "Association between Cytochrome P450 2C19 Gene Polymorphisms and Hematological Malignancies in an Iranian Population" reported the presence of the CYP2C19*1/*17 and *17/17 genotypes in 37.3% of their patient cohort (22). Another study conducted in 2014 in Iran involving 180 healthy Iranians found the frequency of the CYP2C1917*/17 genotype to be approximately 5.5% (23). These findings collectively underscore the need for a comprehensive assessment of the 17 allele's prevalence across Iran.

Our results suggest that Iranians have a unique genetic profile concerning the CYP2C19*17 polymorphism compared to other nationalities. As documented in existing literature, the distribution of the CYP2C19*2, CYP2C19*3, and CYP2C19*17 variants shows considerable variation across different ethnic groups (24). The frequency of the CYP2C19*17 allele observed in the Iranian population is 11%, which is higher than in countries such as Japan (1.3%) but lower than in Sweden (18%) and Norway (22%). Genetic variations, specifically mutations like CYP2C19*17, have a significant impact on drug metabolism and subsequent patient outcomes. It is important to note that the occurrence of adverse drug reactions can differ among populations due to racial and ethnic backgrounds (25).

The CYP2C19 enzyme is the primary metabolic pathway for several drugs, and its function can be influenced by the CYP2C19*17 variant. Medications affected by this include clopidogrel, proton pump inhibitors (PPIs), antidepressants, antiepileptic drugs (such as phenytoin and diazepam), and propranolol (26).

Given the high rate of cardiovascular disease in the Iranian population and the widespread use of clopidogrel, understanding the clinical impact of the CYP2C19*17 mutation is critically important. The presence of this mutation may increase the risk of bleeding complications. Therefore, studies like this are crucial to determine the prevalence of this mutation, which can help guide drug dosage and reduce associated risks (9, 27).

While extensive research is still necessary including assessing the impact of mutations on drug metabolism, associated patient risks, population prevalence, and screening costs before mandating genetic assessments for treatment initiation, these initial findings are vital for advancing therapeutic strategies and the field of personalized medicine. Given the limitations of our participant size, we recommend broader studies involving larger patient populations. This would provide a more precise understanding of the prevalence of the CYP2C19*17 mutation within the Iranian population.

Conclusion

This study provides valuable insight into the prevalence of the CYP2C19*17 mutation within the Iranian population. The investigation found a frequency of 11% for the CYP2C19*17 variant among the participants. While this prevalence is relatively lower compared to certain other populations, its clinical implications are highly significant, particularly for individuals undergoing angiography. The associated risk of bleeding complications highlights the necessity for increased caution and a personalized therapeutic approach. As a result, a strong case can be made for additional genetic research in this area. Such investigations could enable the precise tailoring of medication dosages, thereby mitigating risks and improving patient care and treatment efficacy.

Conflict of Interest

The authors have no conflicts of interest to declare.

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None.

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