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Research article

Allele and genotype frequencies of CYP2C19 in Sudanese patients undergoing percutaneous coronary intervention

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Abstract

Genetic variations among different ethnic groups result in variation of drug response. Several studies reported association between these variants and reduction of enzymatic function. Cytochrome P450, specifically CYP2C19 represent a major contributor in this variability. The present study aimed to determine the prevalence of CYP2C19 variants in Sudanese patients undergoing percutaneous coronary intervention (PCI).This prospective observational cohort study recruited 197 Sudanese patients with PCI taking clopidogrel from Wad Medani Heart Diseases and Surgery Center. Patients were genotyped for CYP2C19*2 and CYP2C19*3 using ASP-PCR and PCR-CTPP respectively. The frequency of CYP2C19*2, and *3 was 15%, and 1% respectively. The wild type (*1/*1) was the most frequent CYP2C19 *2 alleles (71.6%), followed by heterozygous mutant (*1/*2) 25.9%, and the least frequent was homozygous mutant (*2/*2) 2.5%. For CYP2C19 * 3, the wild type allele was the most frequent (98.0%), followed by heterozygous mutant (*1/*3) 2% and 0% for homozygous mutant(*3/*3). The overall distribution of CYP2C19 genotype revealed that 69.0% of patients were carriers of homozygotes wild allele *(*1/*1*); 28.4% were carriers of heterozygotes mutants *(1*/2*&1*/3*), and* 2.5% were carriers homozygotes mutant (2*/2*). Thus, 69.0% were classified as extensive metabolizers (EMs), 28.4% intermediate metabolizers (IMs) and 2.5% poor metabolizers (PMs). The finding of the present study was comparable to that obtained from several studies conducted in Arabs and African population. The wild type allele was the most prevalent, followed by heterozygotes mutants, and the least was homozygotes mutant. Accordingly the most frequent predicted phenotype was EMs followed by IMs and the least frequent was PMs.

Introduction

Cytochrome P450 (CYPP450) comprise diverse groups of CYP families that responsible for drug metabolism (CYP1-CYP4). The largest family is CYP2 and the main subfamily is CYP2C which include CYP2C8, CYP2C9, CYP2C18 and CYP2C19 [1]. The CYP2C family metabolize about 20% of the CYP450 substrates [2]. Genetic polymorphisms found in all CYP2C members, specifically CYP2C9 and CYP2C19 which considered the principal cytochrome P450 enzyme involved in clopidogrel activation [3, 4]. The most studied CYP2C19 variants were CYP2C19*2 and CYP2C19*3 [3], of which CYP2C19*2 represent the most prevalent lack of function allele (LOFA) and CYP2C19*3 the less common variant. CYP2C19*2 arises secondary to deviant link site in exon 5 (681G/A) resulting in a truncated nonfunctional protein, while CYP2C19*3 (636 G/A) occur secondary to early termination of the amino acid sequence resulting in loss of enzymatic activity [5-7].

The prevalence of *CYP2C19*2* allele is about 15% in Africans and Caucasians and, and 29–35% in Asians, while the less common LOFA *(CYP2C19*3*) is around 2–9% in Asian populations, but uncommon in other ethnic groups [8].

Inter patient differences in drug response a rises as a major health issue, since this variability result in failure of treatment or toxicity due to variation in plasma concentration of drugs or their active metabolite [9]. Polymorphisms of CYP2C19 plays a crucial role in this variability. Hence attract attention for clopidogrel pharmacogenetics and pharmacogenomics [10-12].

As prior knowledge of allelic and genotype frequencies of CYP2C19 variants aid in optimization of clopidogrel treatment, therefore this study aimed to determine the allelic and genotype distribution of CYP2C19 *2 and CYP2C19*3 among Sudanese patients with PCI and receiving clopidogrel.

Methods

Study subjects

This prospective observational cohort study recruited one hundred and ninety seven Sudanese patients with PCI from Wad Medani Heart Diseases and Surgery Center. The eligibility criteria involve both sex of age ≥18 years old, PCI with drug eluting stent implantation and being managed with clopidogrel. Patients were excluded if they have severe cardiac or renal abnormalities, hepatic failure and serious infection. All study participants received clopidogrel loading dose (300mg or 600mg) within 12 hours from hospitalization, and discharged on maintenance dose of clopidogrel (75mg twice daily) for 12 months and aspirin 100mg/day.

The study protocol was approved by Ministry of Health ethics committee and University of Gezira Research Ethics Committee. Patients were informed about the study, and the reason for blood sampling, and that the participation is voluntarily.

Molecular analysis

DNA extraction

Venous blood samples (3 ml) were collected from study subjects and transferred into tubes containing ethylene diamine tetra-acetic acid. The DNA was obtained from peripheral blood leucocytes by G-spin™ Extraction Kit using manufacturer instructions

Design of PCR Primers

PCR primers were designed for CYP2C19*2 rs4244285 (G/A) and CYP2C19*3 rs4986893 (G/A) using Gene Runner software program (Figure 1 & Figure 2).

Genotyping of CYP2C19*2 rs4244285 (G/A)

Allele Specific Primer PCR (ASP-PCR) was used for genotyping of CYP2C19*2 [13]. The ASP-PCR amplification reaction mixture contained 3µL DNA template, 5µL master mix, 0.5µ L for allele-specific primers (ASP 285G/ ASP285A), 0.5µL control primer (CP285), 0.2µLfor each internal control primers (Hb1&Hb2), and 1.0µL distilled H2O. Each allele was screened in separate tube reaction. The PCR cycling conditions were as follow: Initial denaturation at 95°C for 2 min then denaturation at 95°C for 30 sec, followed by annealing at 58°C for 45 sec, 72°C for 45 sec extension for 35 cycles and final extension step at 72°C for 2 min.

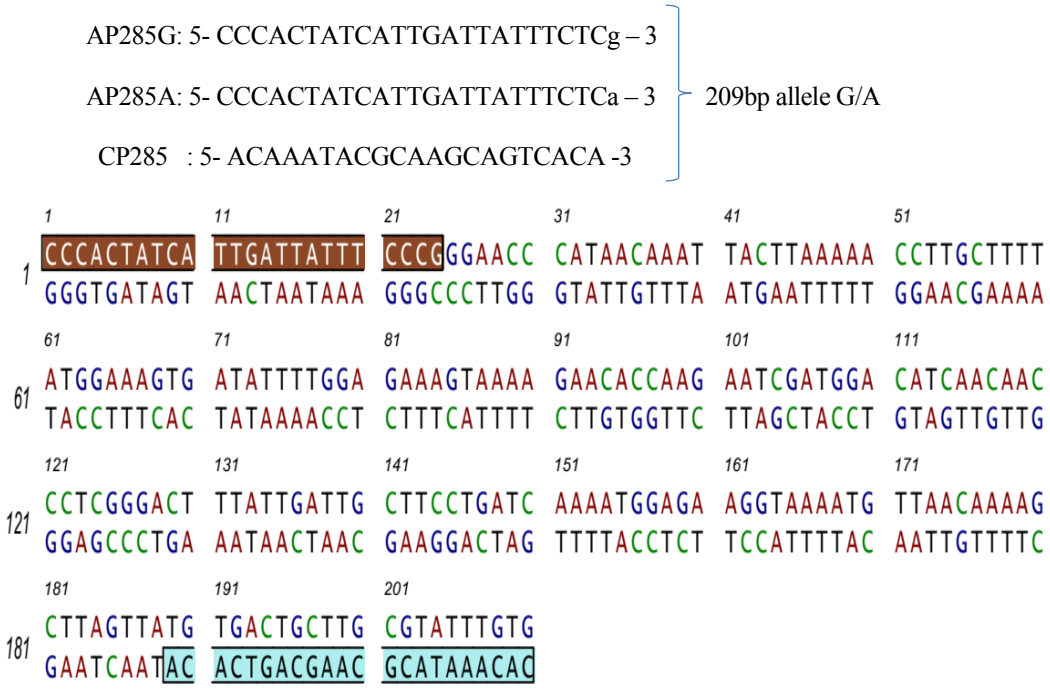

Figure 1. Primer sequence for CYP2C19*2 rs4244285 (G/A).

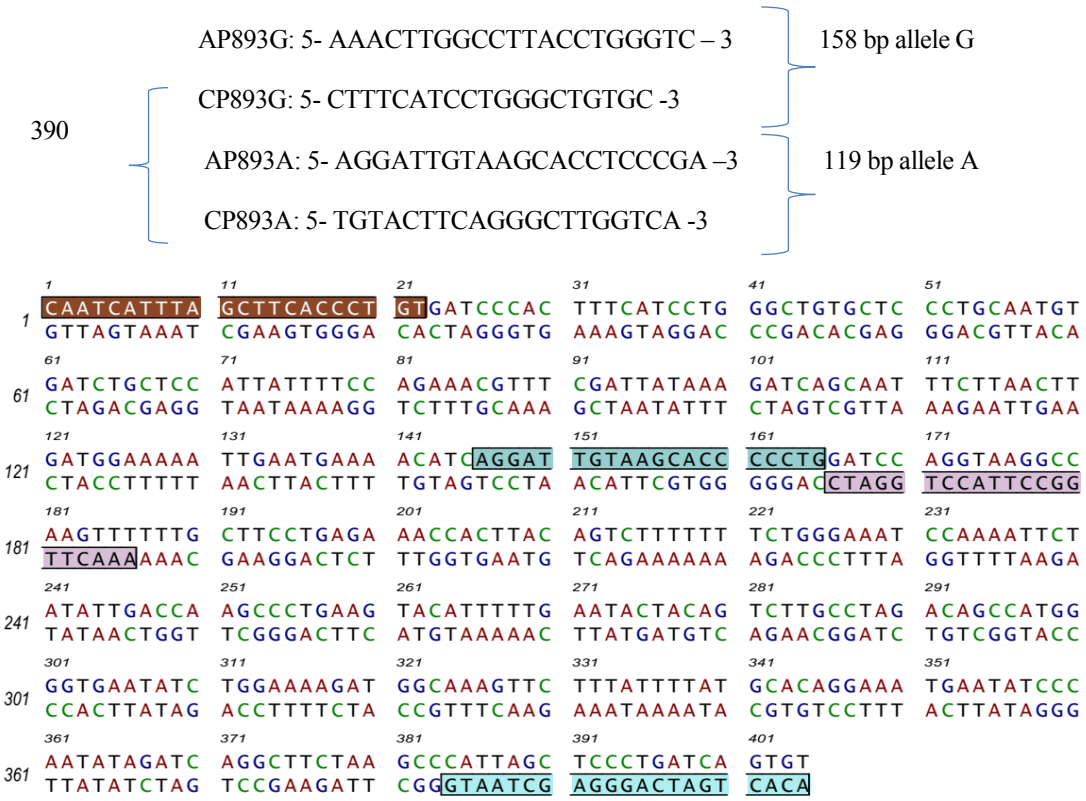

Figure 2. Primer sequence for CYP2C19*3 rs4986893 (G/A).

Genotyping of CYP2C19*3 rs4986893 (G/A)

Polymerase chain reaction with confronting two-pair primers technique (PCR-CTPP) was used for genotyping of CYP2C19*3 rs4986893 [14]. The PCR amplification reaction mixture contained 3µL DNA template, 6 µL master mix, 0.5 µL of each common primers (CP893G, CP893A) and 1 µL for each allele specific primer (ASP893G, ASP893A), H_2O 0.5 µ. The procedure involved initial denaturation at 95°C for 2 min then denaturation at 95°C for 45 sec, followed by annealing at 58°C for 45 sec, 72°C for 45 sec, extension for 35 cycles and final elongation at 72°C for 2 min.

Agarose gel electrophoresis

In the current study the gel was prepared by dissolving 2.5% of agarose gel in 100 mL 1× Tris-borate EDTA buffer and stained with 0.5 µg/ml ethidium bromide for visualization purposes. Then 15 µL PCR product and 5 µL of DNA ladder (100 bp) was loaded into gel wells and the gel was run at constant voltage (120 V) for approximately 45 minutes to permit adequate separation of bands. Then the bands were visualized UV light source. The presence of a 210 bp indicates the existence of CYP2C19*2 variant in the respective tube reaction together with a PCR product of 268 correspond to the internal control. On the other hand, the product size of G and A alleles for CYP2C19*3 were as follows: 158 bp, 119 bp, 390 bp for G allele, A allele, and internal control respectively.

Interpretation of the results

The presence of 390bp, 158bp and 119 bp indicate that the tested DNA sample is heterozygous (G/A), The presence of 390bp and 158bp indicate that the tested DNA is homozygous for the wild type allele (G/G) and The presence of 390bp and 119bp indicate that the tested DNA is homozygous for the mutant allele (A/A).

Predicted phenotypes based on CYP2C19 genotypes

According to *CYP2C19* genotypes, the study cohort were classified into three predicted metabolizer phenotypes as follow [8]: Extensive metabolizers (EMs) for those who harbor two copies of the **1* wild type alleles; Intermediate metabolizers (IMs), who have one copy of wild type allele and one nonfunctional allele (either **2* or **3*); and Poor metabolizers (PMs) harbor two copies of nonfunctional allele (**2* and **3).*

Statistical analysis

Statistical analysis was performed using SPSS version 22 and Online SNPStats program (http://bioinfo.iconcologia.net/ SNPStats) [15].

Results

Genotyping Frequency of CYP2C19*2 and *3 allele

Table 1 and table 2 illustrates allele and genotype frequency of the genetic variances of CYP2C19. The frequency of CYP2C19*2, and CYP2C19*3 was 15%, and 1% respectively with minor allele frequency 0.18 for *2 and

0.05 for *3. The most frequent CYP2C19 *2 genotype was *1/*1 the wild type (71.6%), followed by heterozygous *1/*2 (25.9%), and the least frequent was homozygous variance *2/*2 (2.5%). Similarly, the most frequent CYP2C19 * 3 genotype was the wild type *1/*1 (98.0%), followed by heterozygous variance *1/*3 (2%) with no detection for *3/*3 homozygous variant.

Overall distribution of CYP2C19 genotype Star allele diplotype

The overall distribution of CYP2C19 genotype revealed that 69.0% of study cohort were harbor homozygotes wild type allele *(*1/*1*); 28.4% harbor heterozygotes mutant alleles *(1*/2* and 1*/3*), and* 2.5% harbor homozygotes mutant allele (2*/2*). Accordingly, carriers of normal function variant *CYP2C19*1/*1* were classified as extensive metabolizers , carriers of one lack of function allele **1/*2 or *1/*3* were intermediate metabolizers *(*1/*2 or *1/*3*) and carriers of two lack of function alleles were poor metabolizers *(*2/*2*) as seen in figure 3, table 3.

Discussion

Numerous endogenous and exogenous substances undergoes phase one metabolism utilizing Cytochrome P450 enzymes system. CYP2C19 which belong to CYP2C subfamily, is highly polymorphic and play principal role in bioactivation of clopidogrel [3, 4, 16]. CYP2C19*2 and CYP2C19*3 alleles diminish the ability to metabolize drugs [17]. To our knowledge, there is no sufficient data about the prevalence of CYP2C19*2 and *3 among Sudanese, hence the present study conducted to determine the prevalence of CY2C19*2 and CYP2C19*3 alleles.

The frequency of CYP2C19*2 allele is widely spread among Asians (~30%), followed by African-Americans (~18%) and Caucasians (~13%) and. On the other hand, the CYP2C19*3 allele is highly prevalent in Asians (~10%) but lower in other ethnic groups (1%) [18, 19].

Table 1. Allele and genotype frequencies of CYP2C19*2 (N=197).

Allele / Genotype	Allele/ Genotype Frequency, N (%)	Minor allele frequency
G *1	333(85)	A (0.18)
A *2	61(15)	
G/G *1/*1	141(71.6)	
G/A*1/*2	51(25.9)	
A/A*2/*2	5(2.5)	

Table 2. Allele and genotype frequencies of CYP2C19*3 (N=197).

Allele / Genotype	Genotype frequency, N (%)	Minor allele frequency
G *1	390(99)	A(0.05)
A *3	4(1)	
G/G*1/*1	193(98)	
G/A*1/*3	4(2)	
A/A*3/*3	0(0)	

Table 3. Overall distribution of CYP2C19 genotypes and predicted phenotypes (N=197).

CYP2C19 Star allele diplotype / Phenotypes	Frequency	Percent %
Star allele diplotype		
*1/*1	136	69.0
*1/*2	52	26.4
*1/*3	4	2.0
*2/*2	5	2.5
CYP2C19 phenotype		
EMs (*1/*1)	136	69.0
IMs (*1/*2, *1/*3)	56	28.4
PMs (*2/*2)	5	2.5

EMs:Extensive Metabolizers; IMs: Intermediate Metabolizers; PMs:Poor Metabolizers.

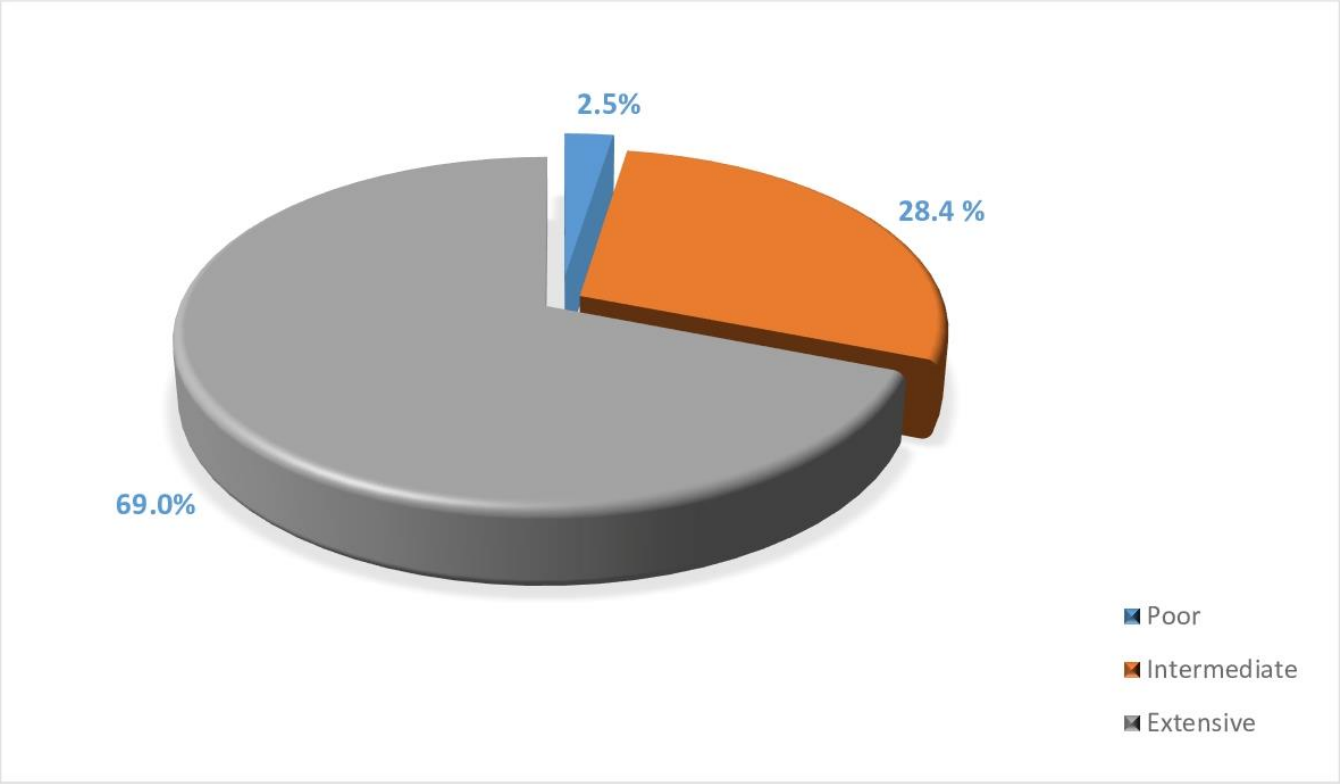

Figure 3. Distribution of metabolizer phenotypes among study cohort.

The present study revealed that the allelic frequency of CYP2C19*2 and CYP2C19 * 3 in our subjects was 15% and 1% respectively. Our finding was approximately similar to study conducted in Sudanese patients infected with *Helicobacter pylori* [20], and comparable to that reported in Palestinian 15.5% [21], German 15% [22], Danish 15% [23], Ethiopian 14% [24], Lebanese 13% [25], and Jordanian 12.5 to 16 % [26, 27], however it was slightly higher than that in Turkish 12%, Tunisian 11.5%, Saudi Arabian 11.2,and Egyptians 11% [28-31], and slightly lower than that in Tanzanian& African American (18%) [32, 33]. These result was not surprising as the most racial groups in Sudan were Arabs, and the lesser were from African descent.

Previous studies demonstrated that CYP2C19*3 allele is higher in Asian populations (~10%) in comparison to other ethnic groups (1%) [18, 19]. The prevalence of this variant in our participants was 1% which was higher than that reported in Egyptian 0.2% [31]. Moreover, this variant was not detected in Jordanians, Saudi Arabian, and Ghanaian [26, 34, 35].

In this study, the genotype results of CYP2C19 indicate 69.0% of study cohort were homozygotes wild type allele *(*1/*1)*; 28.4% were heterozygotes mutants (*1*/2** and *1*/3*),* and 2.5% were homozygotes for 2*/2* mutant allele. The most frequently predicted phenotype was EMs, followed by IMs and the least frequent was PMs. This frequency distribution of genotype results were in agreement with a study done in Palestinian subjects which concluded that 67.3% of the participants were homozygotes for wild type allele *(*1/*1)*, 27.3% and 2.7% were heterozygotes mutants for *1*/2** and *1*/3** respectively, and 0.9% were *2/*2 ,and 1.8% were *2/*3 [21]. Another study performed in East and Southern African populations including psychiatric Tanzanian, South African Venda and Zimbabweans, reported that the frequency distribution of CYP2C19 EMs (*1/*) was 65.1% for Tanzanian, 61.8% Venda ,and Zimbabweans 77.4%. While the frequency of IMs were 31.4%, 32.9%, 19.1% respectively. The lowest frequency of PMs is attributed to CYP2C19* 2 homozygote mutant since no detection of homozygous *3/*3 or *2/*3 (2.3% Tanzanian, 5.3% Venda, 3.5% Zimbabweans) [36]. These finding was consistent with ours as 2.5% of our subjects were classified as PMs according to presences of *2/*2 mutant. Scott and his collogues stated that the distribution of CYP2C19 PMs is lower among Caucasians and Africans (2-5%),and higher among Asians (15%) [37].

Conclusion

This study revealed that our finding was comparable to that obtained from several studies conducted in Arabs and African population. The prevalence of CYP2C19*2 and CYP2C19*3 was 15% and 1% respectively. 69.0% of study cohort harbor wild type allele; 28.4% harbor heterozygotes mutants (*1/*2; *1/*3), *and* 2.5% harbor homozygotes mutant (2*/2*). Consequently the most frequent predicted phenotype was EMs followed by IMs and the least frequent was PMs.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this article.

Author's contribution

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

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