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Association of the CYP2C19 rs4244285 Polymorphism with Hypertension Susceptibility and Clopidogrel Response in an Iraqi Population

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ABSTRACT: CYP2C19 rs4244285 polymorphism plays an important role in drug metabolism and cardiovascular disease. This study aimed to investigate the association between CYP2C19 rs4244285 genotype distribution and hypertension susceptibility, as well as Clopidogrel treatment response in an Iraqi population from Wasit Governorate. A case-control study included (45) hypertensive patients and (35) healthy controls. The CYP2C19 rs4244285 polymorphism was evaluated in a case-control study involving 45 hypertensive patients and 35 healthy controls from Wasit Governorate, Iraq. Genotyping was carried out using the TaqMan SNP Genotyping Assay. The distribution of genotypes and alleles showed no significant differences between patients and controls and was in agreement with Hardy-Weinberg equilibrium. Although the GG genotype and G allele exhibited a protective tendency, while GA and AA genotypes were associated with increased risk, these findings were not statistically significant. A strong and statistically significant association was identified between rs4244285 genotypes and response to Clopidogrel. Individuals with normal metabolizer status demonstrated the most favorable response, whereas intermediate metabolizers showed partial response and poor metabolizers exhibited reduced or absent therapeutic effect. Conclusion: CYP2C19 rs4244285 does not significantly influence hypertension susceptibility but is a key determinant of clopidogrel treatment response.

1. INTRODUCTION

Hypertension is a complex condition arising from the interaction of genetic and environmental factors and represents a major global health challenge due to its contribution to cardiovascular morbidity and mortality (WHO, 2021). Patients reveal variable responses to antihypertensive medications, a phenomenon partly explained by genetic differences that affect drug metabolism and pharmacodynamics, forming the foundation of pharmacogenomics (Johnson et al., 2020). The *CYP2C19**2 allele (rs4244285) is known as the most common loss-of-function variant of the CYP2C19 gene, which has a significant impact on the metabolism of several important drugs, such as clopidogrel, proton pump inhibitors, and antidepressants (Fohner et al., 2018). Evidence suggests that CYP2C19 polymorphism not only influences clopidogrel response but may also contribute to the pathophysiology of hypertension through effects on endogenous vasoactive compounds (Scott et al., 2013). The current study aims to investigate the distribution of *CYP2C19* rs4244285 genotypes and evaluate their association with hypertension risk and drug response in an Iraqi population.

2. MATERIALS AND METHODS

2.1 Study Design

It was carried out as a case-control study, and 80 samples were collected, 45 samples were obtained from patients with hypertension as a (patient), and 35 samples obtained from healthy control as a (control). Samples were taken from Al-Zahraa

Teaching Hospital / Wasit Governorate from 1 st July 2025 to 15 th February 2026 after approval of the competent ethics committee and after taken informed consent consent from all participants.

2.2 Sample Collection and Processing

From each participant, 5 mL of blood was collected via venipuncture. The sample was placed into sterile EDTA tubes, labeled, and stored at -20°C pending DNA extraction and genotyping.

2.3 DNA Extraction and Genotyping

Blood samples were collected and processed to extract genomic DNA using Quick-gDNA™ Blood MiniPrep Kit (Zymo Research; Catalog Nos. D3072 and D3073) according to the manufacturer's protocol and instructions. Genotyping of *CYP2C19* rs4244285 (*CYP2C19**2) the single nucleotide polymorphism (SNP) was performed using a custom TaqMan® SNP Genotyping Assay (Thermo Fisher Scientific, USA). This assay is based on allele-specific discrimination technology and was conducted using real-time polymerase chain reaction (Real-Time PCR).

2.4 Statistical Analysis

The data were analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Allele and genotype frequencies were compared using the Chi-square test, and Hardy–Weinberg equilibrium was assessed. The level of significance was categorized as Sig. for significant difference ($P < 0.05$), HS for highly significant difference ($P < 0.01$), and NS for non-significant difference ($P > 0.05$).

3.RESULTS

Table3.1: Demographic variables of hypertension patients and healthy controls

variable	patients (n=45)	Healthy controls (n=35)
Age (years)($\pm$ SD)	53.27 $\pm$ 9.43	47.00 $\pm$ 7.42
Sex (male/female)	20/25	17/18

A total of 45 hypertension patients and 35 healthy controls were enrolled in this case control study. Among them, 20 (44.44%) were males, and 25 (55.56%) were females in the patient group, whereas 17 (48.57%) were males and 18 (51.43%) were females in the control group.

Table 3.2: Frequencies of *CYP2C19* rs4244285 G/A genotypes and alleles in Iraqi patients with hypertension

Groups	Genotype n.(%)			Allele frequency n.(%)	
	GG	GA	AA	G	A
Control	21(60)	13(37)	1(3)	(%78.57) 55	(%21.43) 15
Patients	23(51)	20(44)	2(5)	(%73.33) 66	(%26.67) 24
Chi square	0.669			0.586	
P-value	0.715			0.443	
Significance level	NS.				

The distribution of genotypes and alleles of *CYP2C19* rs4244285 G/A was similar between Iraqi hypertensive patients and healthy controls.

Table 3.3 :Hardy–Weinberg Equilibrium Analysis of *CYP2C19* rs4244285 G/A

Group	n	GG n (%)	AG n (%)	AA n (%)	G allele n (%)	A allele n (%)	χ^2 (HWE)	df	P-value	HWE status
Control	35	21 (60.0)	13 (37.0)	1 (3)	55 (78.57)	15 (21.43)	0.371	1	0.54	In equilibrium
Patients	45	23 (51)	20 (44)	2 (5)	66 (73.33)	24 (26.67)	0.836	1	0.36	In equilibrium

The G allele showed higher frequency than the A allele in both groups, and genotype distributions conformed to HWE equilibrium, suggesting no significant deviation from expected genotype frequencies.

Table 3.4: Distribution of *CYP2C19* rs4244285 G/A genotypes and allele frequencies with odds ratios in patients with hypertension and healthy controls

Significance level	P-value	OR95%CI	OR	Patients	Controls	Genotypes
Ns.	0.428	0.285 - 1.7038	0.697	23	21	GG
Ns.	0.51	0.548 - 3.3408	1.353	20	13	GA
Ns.	0.713	0.137 - 18.184	1.581	2	1	AA

The odds ratio for the GG genotype was 0.697 (95%CI 0.285 - 1.7038), $P = 0.428$ indicating that homozygous genotype GG was protective genotypes against hypertension.

The odds ratios for the GA and AA genotypes were 1.353 (95%CI 0.548 - 3.3408), $P = 0.510$ and 1.581 (95%CI 0.137 - 18.184), $P = 0.713$, respectively, revealing that these genotypes were a higher risk of hypertension. These results suggest that the A allele may be considered as risk allele of hypertension whereas the G allele is protective against the disease.

Table3.5: Association *CYP2C19* rs4244285 G/A polymorphism with hypertension in males and females : OR, 95% CI, and allele frequencies

Genotype	Males (n=)			Females (n=)		
	GG	GA	AA	GG	GA	AA
Patients	11	7	2	12	13	0
Controls	10	6	1	11	7	0
OR	0.855	0.987	1.777	0.587	1.702	-
OR (95% CI)	0.231 - 3.162	0.254 - 3.823	0.146 - 21.51	0.171 - 2.01	0.497 - 5.826	-
P-value	0.815	0.985	0.651	0.396	0.396	-
Sig.	Ns.	Ns.	Ns.	Ns.	Ns.	

The female group showed results consistent with the general results, while the male group showed a different pattern, as the GG and GA models reduced the risk of developing the disease, while AA was associated with an increased risk of hypertension.

Table 3.8 : Association between SNP Genotype/Phenotype (AA/PM, AG/IM, GG/NM) of *CYP2C19* rs4244285 G/A and Clinical Response to Clopidogrel .

Genotype / Phenotype	Responder n	Partial n	Non-responder n
GG /NM	13	1	0
GA/IM	5	3	0
AA/PM	0	1	1
χ^2 value	16.405		
P-value	0.0025		
Significance level	**Sig.		

The results displayed that the (GG) NM phenotype is associated to the best clinical response, whereas the (AA) PM phenotype is associated with reduced or absent response, highlighting the influence of metabolizer status on personalized therapy.

4. DISCUSSION

In term of baseline characteristics, patients with hypertension revealed a higher mean age compared to healthy subjects, this is in agreement with the widely recognize role of aging as a key risk factor for hypertension (Mills et al., 2020). No significance difference in sex distribution was observed between two groups, suggesting that gender had no apparent effect on disease prevalence in the current study.

The distribution of genotypes of *CYP2C19* rs4244285 in both groups were consistent with Hardy–Weinberg equilibrium, suggesting no deviation from expected genetic frequencies. This supports the reliability of the sampling and genotyping procedures and revealed that the study population is in genetic equilibrium (Nussbaum et al., 2016).

The association analysis showed a tendency toward increased risk among hypertensive patients carriers of the A allele (GA and AA genotypes), these results were not statistically significant. This may be attributed to the relatively small sample size and the low frequency of the AA genotype. pharmacogenetic studies have showed similar findings with *CYP2C19* variants affecting treatment response more significantly than disease susceptibility (Scott et al., 2013).

Gender-associated analysis also did not reveal significant associations between *CYP2C19* genotypes and hypertension in either males or females. However, slight differences in odds ratios between genders especially male patients who carry the genotype GA may suggest a potential tendency that requires further investigation in larger population. This variation in the pattern of gender correlation is due to a number of biological and methodological factors. Estrogen receptors bind to the promoter region of the *CYP2C19* gene and inhibit its activity in females, which means that females live under continuous hormonal inhibition of the activity of this enzyme regardless of the nature of their genotype, and this hormonal inhibition is reflected at the functional level that one normal copy of the gene (GA) may be sufficient to protect males from the risk of hypertension due to the absence of this hormonal inhibition in them, while this type of GA does not achieve the same protection in females due to interference. with the activity of this enzyme, several studies have also shown that oral contraceptive formulations significantly reduce the activity of the *CYP2C19* enzyme (Hagg et al., 2001; Palovaara et al., 2003)

where taking birth control pills in females may be one of the reasons for this disparity between males and females. The mechanism behind this is thought to be drug reactions at the active site of the enzyme (Laine et al., 2000)

A markedly significant association was found between CYP2C19 rs4244285 polymorphism and clopidogrel efficacy. The hypertensive patients carriers the GG genotype exhibited the most favorable therapeutic outcomes, while those with the AA genotype showed diminished or absent response. These results are in consistent with other studies. Mega et al., 2009 and Simon et al., 2009 observed that CYP2C19 polymorphism (loss- of- function alleles) are associated with impaired clopidogrel activation and poorer clinical outcomes. Similarly, Mohammad and Al-Allawi, 2018 reported that cardiovascular outcomes in patients receiving clopidogrel therapy influences by CYP2C19 genotype significantly.

Based on metabolizer phenotype, the classification of patients showed that normal metabolizers had the best response, whereas reduced drug efficacy was exhibited by poor metabolizers exhibited. This observation aligns with pharmacogenetics guidelines ,which highlight the crucial role of CYP2C19 genetic variation in modulating clopidogrel metabolism (Scott et al., 2013).

Previous studies, particularly local investigations conducted on population groups from the same region, have indicated that the SLC30A8 rs13266634 polymorphism—especially the TT genotype—may serve as a potential genetic marker for increased susceptibility to T2DM-related hypertension, particularly among specific subgroups such as males (Enad and Ghali, 2025). Ghulam and Ahmed ,2025 investigated the association between he glutathione peroxidase 4 (GPX4) genes 713041 polymorphism and hypertension in an Iraqi cohort, with emphasis on sex-specific effects and genetic models. They found that GPX4 rs713041 T allele is a genetic risk factor for hypertension in the Iraqi population, particularly among males. Previous Iraqi studies examining other polymorphisms, such as those in the ADAMTS-13 and renase genes, have similarly reported genetic links to hypertension (Tuama and Ghali, 2022), highlighting the complex genetic landscape contributing to this disease.

5. CONCLUSIONS

The *CYP2C19* rs4244285 G/A polymorphism showed no significant association with hypertension risk in this Iraqi population, although GG/G appeared protective and GA/AA (A allele) indicated increased risk, with some sex-specific variation. Genotypes were in Hardy–Weinberg equilibrium, confirming data reliability. In contrast, the polymorphism significantly affected response to Clopidogrel, with GG (normal metabolizers) showing the best response, AG intermediate, and AA (poor metabolizers) reduced or absent response, supporting genotype-guided therapy.

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