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Role of GSTM1 and GSTT1 polymorphism: Susceptibility to hypertension in Arabs residing in UAE

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Abstract

Hypertension is a multifactorial condition influenced by both genetic predisposition and environmental factors. Oxidative stress has been identified as a key contributor to the pathogenesis of hypertension. The present study aims to investigate the role of Glutathione-S-Transferase (GST) genes, specifically GSTM1 and GSTT1, in hypertensive patients from the Arab population residing in the United Arab Emirates. The study focuses on identifying the presence of these genes and genotyping null alleles to assess their potential association with hypertension risk. A cohort of 20 hypertensive patients was selected for genetic analysis using polymerase chain reaction (PCR) with specific primers. The presence and null alleles of the GSTM1 and GSTT1 genes were assessed and compared with age- and sex-matched control subjects. The data were statistically analyzed to determine the prevalence of null genotypes in hypertensive individuals versus the control group. Our analysis revealed that the GSTT1- and GSTM1-null genotypes were more prevalent in hypertensive patients (25%) compared to the control group (10%), although the difference did not reach statistical significance (p=0.172). These findings suggest a potential association between GST gene deletions and increased susceptibility to hypertension. The results indicate a possible link between GSTT1- and GSTM1-null genotypes and hypertension risk, supporting the role of oxidative stress-related genetic factors in disease development. However, due to the limited sample size, further research with larger cohorts is necessary to confirm these findings and explore additional genes involved in the antioxidant defense pathway. Understanding genetic predispositions related to oxidative stress may contribute to personalized hypertension risk assessments and targeted therapeutic strategies. Identifying genetic markers such as GSTT1 and GSTM1 null alleles could aid in early detection and the development of antioxidant-based interventions to mitigate hypertension risk in susceptible populations.

Keywords: Genetic susceptibility, glutathione S-transferase (GST) genes, GSTM1 and GSTT1 polymorphisms, hypertension, oxidative stress, polymerase chain reaction (PCR).

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1. Introduction

Hypertension is a complex and multifaceted condition characterized by elevated blood pressure, which serves as a significant risk factor for various cardiovascular and renal diseases. This condition arises from a combination of intrinsic factors, including genetic predispositions and racial background, as well as extrinsic influences such as smoking, physical inactivity, obesity, psychological stress, dyslipidemia, and dietary habits [1, 2]. Furthermore, hypertension is closely linked to oxidative stress, which results from the accumulation of reactive oxygen species (ROS) in the body. This oxidative stress can lead to cellular damage, affecting proteins, lipids, and DNA [3, 4]. Antioxidant enzymes, including manganese superoxide dismutase (MnSOD), catalase (CAT), and glutathione S-transferases (GSTs) such as GSTM1 and GSTT1, play crucial roles in detoxifying harmful compounds and mitigating oxidative damage [5, 6].

The involvement of ROS in the pathogenesis of hypertension is well-documented, with increased ROS levels contributing to vascular dysfunction and impaired nitric oxide synthesis [7]. A deficiency in antioxidant defenses, coupled with heightened ROS production, exacerbates oxidative stress, thereby promoting the development of hypertension [8]. Antioxidants such as glutathione, vitamins C and E, and beta-carotene are vital in neutralizing free radicals and preventing cellular damage [9]. The GST family, particularly GSTM1 and GSTT1, is integral to the detoxification processes that protect against oxidative stress and inflammation, with polymorphisms in these genes influencing individual susceptibility to hypertension and related complications [10, 11].

The GSTM1 gene is located on chromosome 1p13.3, while GSTT1 is found on chromosome 22q11.2. Deletions in these genes result in null genotypes, leading to a complete loss of enzymatic function [12, 13]. Individuals with homozygous deletions of GSTM1 and GSTT1 exhibit significantly reduced detoxification capabilities, which can result in increased oxidative stress and a higher risk of hypertension-related complications [14, 15]. The structural similarities between GSTT1 and GSTT2, both belonging to the theta class, further emphasize their collective role in detoxification and antioxidant defense mechanisms [16].

Research indicates that polymorphisms in genes such as eNOS, GSTM1, and GSTT1 are associated with an elevated risk of hypertension, with null genotypes of GSTM1 and GSTT1 correlating with diminished enzyme activity and increased oxidative stress [17, 18]. The implications of GST polymorphisms extend beyond hypertension, as they have been linked to various diseases, including cancer, neurodegenerative disorders, and metabolic syndromes [19, 20]. This study aims to investigate the potential relationship between the loss of enzymatic activity due to deletions in GSTT1 and GSTM1 and the increased risk of developing hypertension.

2. Materials and Methods

The objective of this study was to investigate the influence of genetic factors on the etiopathogenesis of hypertension, comparing hypertensive individuals with healthy controls and first-degree relatives of hypertensive patients.

2.1. Selection of Cases

Blood samples were collected from Arab nationals diagnosed with hypertension at the Dubai Specialized Medical and Research Center. Each case was evaluated by a qualified clinician. Sample collection occurred on Mondays and Tuesdays over a period spanning from September 2018 to November 2018. Control samples were obtained from voluntary blood donors who were healthy, matched for age and sex, and had no familial history of hypertension. Additionally, blood samples were collected from volunteered first-degree relatives of hypertensive patients for subsequent genetic analysis.

2.2. Ethical Considerations

The research was approved by the ethical research committee from Dubai Pharmacy College of Girls (DPC-REC), NO: REC/UG/2018/8. Confidentiality of the respondents' information was strictly maintained. Before participation, respondents were asked to provide informed written consent and were informed that their participation was entirely voluntary and that the study was conducted solely for academic purposes.

2.3. Blood Pressure Measurement

Blood pressure readings were taken while the subjects were seated, using a sphygmomanometer on the right arm. Each subject's blood pressure was recorded twice, with a five-minute interval between measurements, and the average of these readings was utilized. Individuals were classified as hypertensive if they were currently prescribed antihypertensive medications or if their systolic blood pressure (SBP) exceeded 140 mm Hg and diastolic blood pressure (DBP) exceeded 90 mm Hg. Systolic pressure was determined at the initial detection of Korotkoff sounds. Following the initial measurement, the cuff was deflated, and the measurement was repeated. The diagnosis of hypertension adhered to the criteria established by the Joint National Committee (JNC) in 2017.

2.4. Data Collection

Comprehensive data were gathered from all healthy subjects serving as controls, as well as from individuals with diabetes, utilizing a structured Performa designed for this purpose.

Epidemiological Parameters

Data regarding age, sex, height, weight, waist circumference, hip circumference, dietary habits, and physical activity levels were collected from all participants, as these variables are recognized to influence hypertension. Additionally, information concerning the age of onset of hypertension was documented.

Height Measurement: Height was assessed by affixing a tape measure to a wall and utilizing a movable headboard to determine the height.

Weight Measurement: Weight was recorded using a mechanical weighing scale, with measurements taken to the nearest 0.5 kg. According to the World Health Organization (WHO) guidelines, obesity was defined as a body mass index (BMI) greater than 25 kg/m² for both genders.

2.5. Familial Incidence

Familial incidence of hypertension was defined as the presence of the condition in first-degree or second-degree relatives of the patient. Conversely, patients without affected relatives were categorized as having a non-familial incidence of hypertension.

2.6. Collection of Blood Samples

Blood samples from hypertensive patients and healthy controls were collected from all participants in sterile vials containing anticoagulants for the purpose of DNA isolation and polymerase chain reaction (PCR) analysis. Samples exhibiting signs of hemolysis were discarded to ensure the integrity of the genetic analysis.

2.7. Genetic Parameters

1. Extraction of Genomic DNA
2. GSTM1 and GSTT1 genetic polymorphisms evaluation using the multiplex polymerase chain reaction (PCR) technique.
3. The amplified PCR products were subjected to electrophoresis in a 1.5% agarose gel and stained with 0.5 ug/ml ethidium bromide and simultaneously identified.

2.8. Extraction of Genomic DNA

Genomic DNA was isolated from 1 mL of whole blood collected in EDTA anticoagulated tubes using the Wizard genomic DNA purification kit (Promega, Madison, USA). GSTM1 and GSTT1 genetic polymorphism were evaluated using the multiplex polymerase chain reaction technique. The PCR primers were synthesized by Alpha DNA, Montreal, Quebec H4C3N9 [21].

Primers for GSTM1

Forward:

5'-GAA CTC CCT GAAA AGCTAAAG-3’

Reverse:

5'GTT GGG CTC AAA TAT ACG GT GG-3’

Primers for GSTT1

Forward:

5'-TTC CTT ACT GGT CCT CAC ATC TC-3’

Reverse:

5'-TCA CCG GACAT GGC CAG CA-3’

The B globin locus was used an internal control to avoid false negative results .

Primers for B globin:

Forward:

5'-CAA CTT CAT CCA CGT TCA CC-3’

Reverse:

5'-GAA GAG CCA AGG ACA GGT AC-3`

PCR reaction was carried out in a total volume of 50µl containing

1) 25µl of master mix containing 2.5mmol/L of MgCl2, 0.2mmol/L of each deoxyribonucleotide triphosphate.
2) (dNTP’s, dATP’s , dCTP’s , dGTP’s , dTTP’s) and 1 unit of Taq Polymerase
3) 30P moles of each primer.
4) 5µl of Template / Genomic DNA
5) 8µl of nuclease free water.

Implication was performed by initial denaturation at 94°C for 5 minutes, followed by 30 cycles at 94°C for 1 minute, 64°C for 1 minute and 72°C for 1 minute and a final extension of 72°C for 7 minutes.

The amplified products were identified by electrophoresis in a 2% agarose gel and stained with 0.5 mg/ml ethidium bromide. The product lengths were 210bp, 480bp and 260bp for GSTM1, GSTT1 and B globin, respectively.

Absence of PCR product for GSTM1 or GSTT1 in the presence of B globin band was indicative of a null genotype for GSTM1 or GSTT1.

Individuals with one or two copies of the relevant gene were classified as a positive genotype and individuals with homozygous deletions as a null genotype.

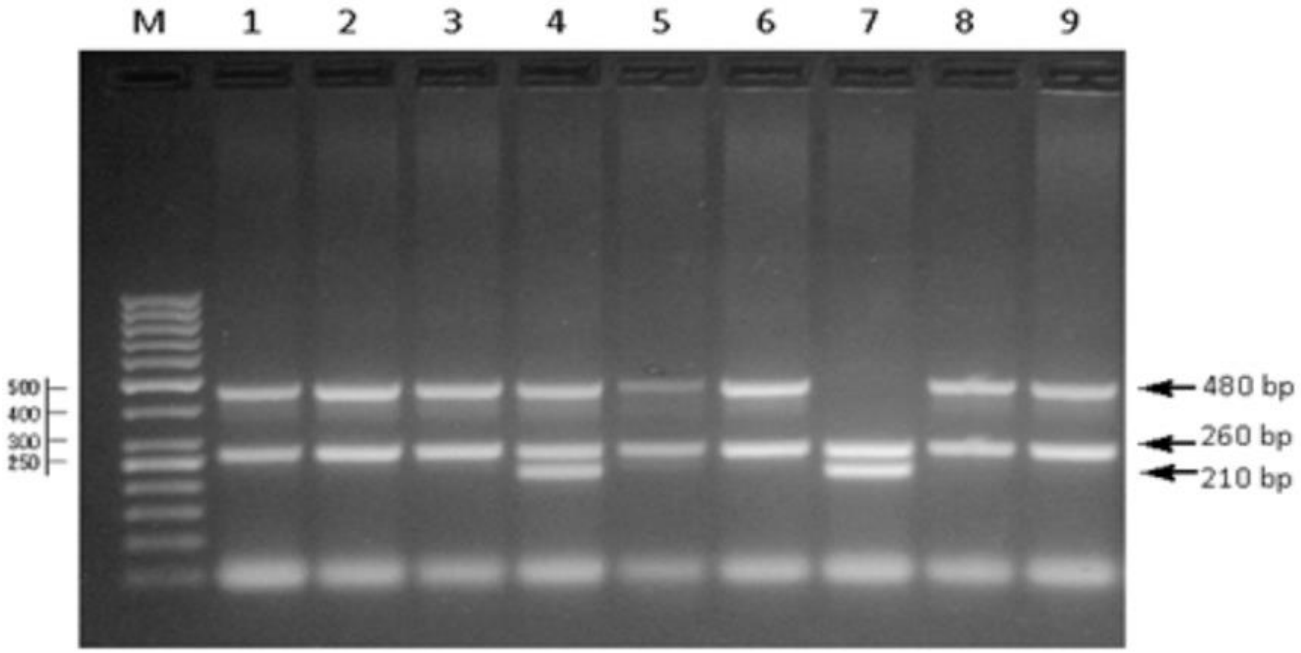

Figure 1.
PCR products evaluated on 2% agarose gel. The presence or absence (null) of GSTM1 and GSTT1 was identified by the presence or absence of a band at 480 bp (corresponding to GSTT1) and a band at 210 bp (corresponding to GSTM1). β-Globin is considered an internal control (260 bp). 50 bp ladder Lane 1; GSTM1 and GSTT1 wild type Lane 4; GSTM1 null Lanes 1-3, 5, 6, 8, 9; GSTT1 null genotype Lane 7.

2.9. Statistical Analysis

The statistical analysis was conducted using the SPSS software package (SPSS, Chicago, IL, USA), version 24.

2.10. Statistical Methods

To assess the differences in genotype prevalence and to evaluate the association between the case and control groups, the Chi-square test was employed. A p-value of less than 0.05 was considered indicative of statistical significance.

3. Results

T**able 1.**
Clinical Parameter Characteristics of control, First Degree Relatives (FDRs), and cases.

Clinical parameter	Controls n=20	Cases n=20	FDRs n=20	P value
Age (year)	58.2 ± 3.5	61.3 ± 4.9	21.5 ± 2.1	0.001*
Weight (kg)	71.08 ± 0.608	75.38 ± 5.03	58.08 ± 5.83	0.001*
Height (cm)	171.53 ± 5.18	172.17 ± 2.57	164 ± 6.08	0.59*
BMI (kg/m2)	23.82 ± 0.793	25.15 ± 2.49	22.8 ± 0.39	0.001*
Family history		18 (90%)	20 (100%)	
SBP (mmHg)	121.4 ± 15.43	145.61 ± 8.81	123.31 ± 4.43	0.005*
DBP (mmHg)	75.35 ± 7.86	95.35 ±7.36	81.4 ± 3.36	0.005*

Note: *Unpaired t test was used for analysis of clinical variable.
P < 0.05 is significant.

The results of anthropometric measurements among the cases FDRs and control are displayed in Table 1**.**

Significant differences exist between Cases, Controls, and FDRs in terms of age, weight, BMI, and blood pressure. Cases exhibit higher BMI, blood pressure, and weight, indicating metabolic or cardiovascular risk factors. FDRs are significantly younger and weigh less, suggesting they are at an earlier stage of disease development. Family history is strongly linked to disease occurrence in Cases and FDRs. Height does not significantly differ among groups, suggesting it does not contribute to the condition studied.

Table 2.
Distribution of GSTM1 and GSTT1 genotype among cases (essential hypertension) and controls.

Genotype	Cases (Hypertensive patients) (n=20)	Control group (n=20)	OR 95/CI	P value
GSTM1 no (%)				
Null (-)	12 (60%)	7 (35%)		
Non-null (+)	8 (40%)	13 (65%)		0.158
GSTT1 no (%)				
Null (-)	8 (40%)	2 (10%)	2.4	
Non-null (+)	12 (60%)	18 (90%)		0.184
GSTM1, GSTT1 no (%)	5 (25%)	2 (10%)	3.2	
Null both				0.172
Others ie	15(75%)	18 (90%)		
(GSTM1 +, GSTT1 -)				
Or				
(GSTM1 -, GSTT1 +)				

The distribution of GSTM1 and GSTT1 genotypes in cases and controls are shown in Table 2**,** Figure 2 & Figure 3**.**

GSTM1 Null Genotype and Hypertension: More frequent in hypertensive patients (60% cases vs. 35% controls). OR = 1.6, but p = 0.158 (not significant).

GSTT1 Null Genotype and Hypertension: More frequent in hypertensive patients (40% cases vs. 10% controls). OR = 2.4, but p = 0.184 (not significant).

GSTM1 & GSTT1 Dual Null Genotype: 25% of cases vs. 10% of controls had both genes null. OR = 3.2, but p = 0.172 (not significant).

The trends suggest that the null genotypes may increase the risk of hypertension, but larger sample sizes are needed to confirm this.

Table 3.
Distribution of GSTM1 and GSTT1 Genotype among FDR's (first degree relatives of hypertensive patients) and controls.

Genotype	FDR's (n=20)	Control group (n=20)
GSTM1 no (%)		
Null (-)	11 (55%)	7 (35%)
Non-null (+)	9 (45%)	13 (65%)
GSTT1 no (%)		
Null (-)	5 (25%)	2 (10%)
Non-null (+)	15 (75%)	18 (90%)
GSTM1, GSTT1 no (%)	4 (20%)	2 (10%)
Null both		
Others	16 (80%)	18 (90%)
(GSTM1 +, GSTT1 -)		
Or		
(GSTM1 -, GSTT1 +)		

Distribution of GSTM1 and GSTT1 Genotype among FDR's (first degree relatives of hypertensive patients) and controls. are shown in Table 3, Figures 4 & 5.

Higher GSTM1 Null Genotype Frequency in FDRs: 55% of FDRs vs. 35% of Controls have the GSTM1 null (-) genotype. This suggests a potential genetic predisposition to hypertension in first-degree relatives.

GSTT1 Null Genotype Shows a Weaker Association: 25% of FDRs vs. 10% of Controls have the GSTT1 null (-) genotype. The difference is less pronounced compared to GSTM1.

Combined GSTM1 and GSTT1 Null Genotype Could Be a Risk Factor: 20% of FDRs vs. 10% of Controls had both GSTM1 and GSTT1 null genotypes. This might indicate a higher genetic risk for hypertension.

Genetic Influence on Hypertension Risk: Since FDRs of hypertensive patients exhibit a higher prevalence of GSTM1 and GSTT1 null genotypes compared to controls, this supports the hypothesis that these deletions may contribute to hypertension susceptibility.

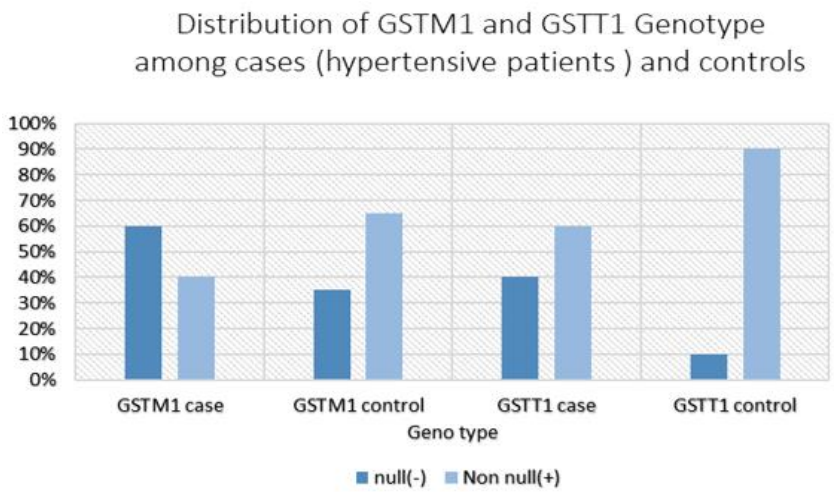

Figure 2.
Genotypic Distribution of GSTM1 and GSTT1 among Cases and Controls.

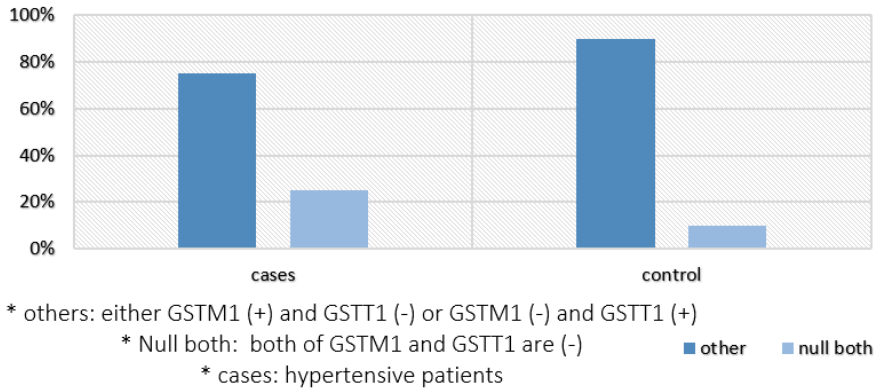

Figure 3.
Genotypic Distribution of GSTM1 and GSTT1 among Cases and Controls.

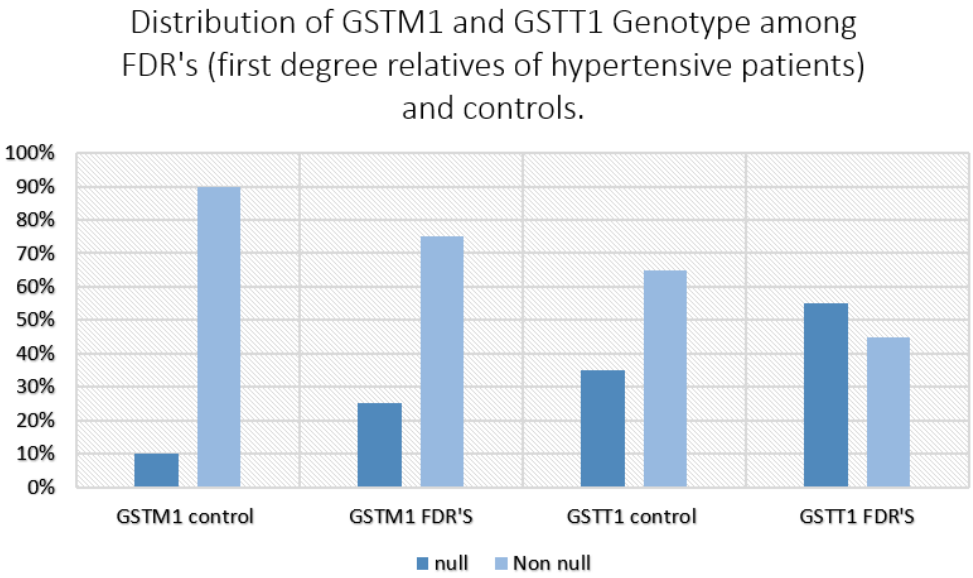

Figure 4.
Genotypic Distribution of GSTM1 and GSTT1 among FDRs (First Degree relatives of Cases) and Controls.

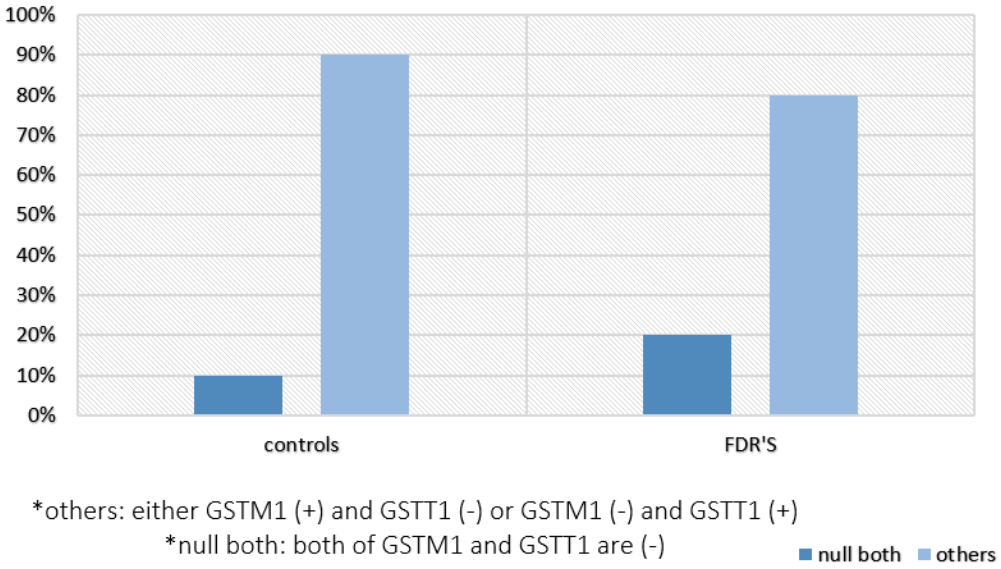

Figure 5.
Genotypic Distribution of GSTM1 and GSTT1 among FDRs (First Degree relatives of Cases) and Controls.

4. Discussion

Oxidative stress has been increasingly recognized as a significant contributor to the pathophysiology of hypertension, with various mechanisms implicated in this relationship. The evidence supporting the role of oxidative stress in hypertension is multifaceted, encompassing alterations in antioxidant defense systems and genetic polymorphisms associated with glutathione S-transferases (GSTs) [22, 23]. Numerous studies have highlighted the influence of GST polymorphisms on oxidative stress levels, suggesting that genetic variations in these enzymes may predispose individuals to hypertension. For instance, research conducted by Heslop et al. demonstrated that individuals with the GSTM1 null genotype exhibited significantly lower total antioxidant capacity compared to those possessing the wild-type GSTM1+ allele, reinforcing the potential role of GST polymorphisms in modulating oxidative stress and blood pressure regulation [24]. Moreover, it has been observed that hypertensive patients undergoing antihypertensive therapy experienced improvements in their glutathione-related antioxidant defense systems, indicating a possible therapeutic avenue for managing oxidative stress in this population [25]. Conversely, another study reported diminished GST enzyme activity and reduced plasma glutathione levels in hypertensive individuals; however, it found no significant correlation between these findings and the deletion polymorphisms of GSTM1 and GSTT1 [26]. This suggests that while oxidative stress is a critical factor in hypertension, the genetic predisposition may not be as straightforward as initially thought. In our investigation, we did not find GSTM1 null and GSTT1 null genotypes to be significant risk factors for hypertension. This contrasts with findings from other research, which identified the GSTM1 null genotype as a notable risk factor for hypertension, with an odds ratio (OR) of 2.25 (95% CI = 1.36–3.72; P = 0.005) [23]. In this study, the GSTT1 null genotype did not demonstrate a significant association with hypertension (OR = 1.24, 95% CI = 0.67-2.29, P = 0.52). Furthermore, the potential synergistic effect of having both GSTM1 null and GSTT1 null genotypes on hypertension risk remains to be fully elucidated [27]. Additionally, another study indicated that the presence of both GSTM1 and GSTT1 null genotypes could increase the likelihood of developing hypertension, reporting an adjusted odds ratio of 3.1 (95% CI: 1.0-9.5) [27]. This complexity in the relationship between GST polymorphisms and hypertension highlights the need for further research to clarify these associations and their underlying mechanisms. It is important to note that our pilot study was conducted with a limited sample size, which may have constrained our ability to detect significant associations. Therefore, we recommend that future research involve larger cohorts to better assess the relationship between GST polymorphisms, oxidative stress, and hypertension. Such studies could provide more definitive insights into the genetic factors contributing to hypertension and the potential for targeted interventions based on individual genetic profiles. In conclusion, while the interplay between oxidative stress and hypertension is supported by various studies, the role of GST polymorphisms remains complex and warrants further investigation [22, 23, 25, 26].

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