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The Role of GPX4 rs713041 Polymorphism in Hypertension Susceptibility Among Iraqi Patients

Zahraa Suwaih Ghulam and Intisar Hussein Ahmed

Department of Biology, College of Education for Pure Sciences, University of Wasit, Iraq

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Abstract: Hypertension, a global health challenge and major contributor to cardiovascular disease, is influenced by both environmental and genetic factors. Among genetic regulators, the glutathione peroxidase 4 (GPX4) gene plays a critical role in antioxidant defense mechanisms, especially in lipid peroxidation and ferroptosis regulation. A functional single nucleotide polymorphism (SNP) in the 3′ untranslated region (3′UTR) of GPX4, rs713041 (C>T), has been linked to altered enzyme activity and increased oxidative stress. This study evaluated the association between GPX4 rs713041 polymorphism and hypertension in an Iraqi cohort, with emphasis on sex-specific effects and genetic models. A total of 45 hypertensive patients and 35 healthy controls aged 40–70 years were genotyped using TaqMan PCR assays. Results revealed that the TT and CT genotypes were more prevalent among hypertensive individuals, while the CC genotype was significantly more common in the control group. The T allele was associated with increased hypertension risk (63.33% in patients vs. 38.57% in controls; $P = 0.001$). Males with the TT genotype had a fivefold increased risk, while CC was protective. Under a dominant genetic model, individuals carrying at least one T allele (CT+TT) were nearly five times more likely to develop hypertension ($OR = 4.9$, $P = 0.004$). Additionally, GPX4 serum levels were significantly reduced in hypertensive patients and appeared to correlate with genotype. These findings suggest that the GPX4 rs713041 T allele is a genetic risk factor for hypertension in the Iraqi population, particularly among males. GPX4 polymorphism genotyping may serve as a potential biomarker for early identification of individuals at elevated risk.

Keywords: GPX4 rs713041, Polymorphism, Hypertension Susceptibility

INTRODUCTION

Hypertension is a prevalent, modifiable risk factor for cardiovascular disease and premature mortality, affecting millions globally (WHO, 2021). Although lifestyle and environmental factors play significant roles, genetic predisposition—particularly genes involved in redox homeostasis—has gained increasing attention. One such gene is **GPX4 (glutathione peroxidase 4)**, a selenium-dependent antioxidant enzyme critical for neutralizing lipid hydroperoxides in cellular membranes and for preventing ferroptosis (Brigelius-Flohé & Maiorino, 2013; Ursini et al., 2022).

Unique among glutathione peroxidases, GPX4 reduces complex lipid peroxides embedded within phospholipid bilayers, thereby maintaining vascular and cellular integrity under oxidative stress (Seibt et al., 2019). The activity of GPX4 depends on the correct incorporation of selenocysteine, a process regulated by a structural element in the gene's 3′UTR.

The **rs713041 SNP (C>T)** in the 3′UTR of GPX4 may disrupt the efficiency of selenocysteine incorporation, potentially reducing enzyme function. Prior studies have linked the T allele to increased susceptibility to oxidative stress-related conditions including ischemic stroke, pre-eclampsia, and cardiovascular disorders (Chen et al., 2020; Synowiec et

al., 2021). However, the relationship between rs713041 and hypertension remains underexplored, particularly in Middle Eastern populations.

This study aimed to investigate the association of GPX4 rs713041 polymorphism with hypertension risk in an Iraqi cohort, evaluating genotype and allele distributions, gender-specific risk patterns, genetic model implications, and corresponding serum GPX4 levels.

RESULTS

Genotype and Allele Distribution

Significant differences were observed in GPX4 rs713041 genotype frequencies between hypertensive patients and controls. The TT genotype was more prevalent among patients (41% vs. 20%), while the CC genotype was predominant in controls (43% vs. 13%). The T allele showed a strong association with hypertension (63.33% in patients vs. 38.57% in controls; $P = 0.001$), suggesting its role as a risk allele.

Hypertension Risk by Genotype

- **TT genotype**: $OR = 2.7$, $P = 0.05$ (borderline significant)
- **CC genotype**: $OR = 0.21$, $P = 0.004$ (protective effect)
- **CT genotype**: Not significantly associated

These findings suggest a dose-dependent relationship, with increased risk correlating with T allele presence.

Gender-Stratified Analysis

- **Males** with the TT genotype had a significantly elevated risk ($OR = 5.0$, $P = 0.03$), while CC conferred a strong protective effect ($OR = 0.09$, $P = 0.006$).
- In **females**, genotype distributions did not reach statistical significance, potentially due to smaller sample size or sex-related biological differences.

Genetic Model Assessment

The dominant model (CT+TT vs. CC) showed the strongest association ($OR = 4.9$, $P = 0.004$), indicating that even a single T allele increases susceptibility. Neither recessive nor over-dominant models yielded significant associations.

DISCUSSION

This study provides novel evidence supporting the involvement of the **GPX4 rs713041 polymorphism** in hypertension susceptibility among Iraqis. The T allele, especially in homozygous form, was associated with increased risk, particularly in males. These findings align with earlier research indicating that impaired GPX4 activity compromises vascular resilience by increasing lipid peroxidation and promoting ferroptosis (Ursini et al., 2022; Seibt et al., 2019).

Sex-specific effects observed in this study may relate to hormonal modulation of oxidative stress pathways or differential expression of antioxidant enzymes. Previous Iraqi studies examining other polymorphisms, such as those in the **ADAMTS-13** and **renalase** genes, have

similarly reported genetic links to hypertension (Hamed & Ghali, 2024; Tuama & Ghali, 2022), highlighting the complex genetic landscape contributing to this disease.

The dominant inheritance pattern underscores the importance of considering heterozygous individuals in hypertension screening.

CONCLUSION

1. The GPX4 rs713041 T allele is significantly associated with hypertension in the Iraqi population.
2. The TT genotype increases risk—especially in males—while the CC genotype appears protective.
3. A dominant genetic model best explains the observed association.

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