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Association of Renalase rs2296545 gene polymorphism to susceptibility of hypertension in Iraqi patients

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***Abstract*---**Hypertension is a major public health problem due to its high prevalence all around the globe. Renalase is involved in the regulation of blood pressure and cardiac function via degrading catecholamines in the blood circulation. This study aims to investigate the association of polymorphism of *renalase* gene rs(2296545) to the susceptibility of hypertension Iraqi hypertensive patients .The results of this study revealed that the proportion of hypertensive patients with GG genotype was markedly higher with significant difference compared to controls 40% vs.5%,p≤ 0.01, CC genotype revealed remarkable proportion among hypertensive patients.Genotype CC represented the highest percentage among patients and healthy subjects 46% vs.70, P> 0.05.The C allele was the major allele among hypertensive patients and controls. Susceptibility analysis of *renalase* gene (rs2296545) gene polymorphism with hypertension showed that GG genotype was significant risk association among hypertensive patients in both females and males OR =12.6 (CI 95%1.65-97.26) p≤ 0.01, while, rs2296545CG and CC are protective OR=0.41(CI95%0.11-1.50) OR=0.4 (CI95%0.13-1.17) ,P> 0.05 respectively. We conclude that The *renalase* rs2296545 GG genotype and G allele could be a risk factor for hypertensive patients .

***Keywords*---**Renalase, polymorphism, susceptibility, hypertension.

Introduction

Hypertension is a major public health problem due to its high prevalence all around the globe (Erem *etal.*,2009). It is predicted to be increased to 1.56 billion adults with hypertension in 2025 (Tabrizi *etal.*,2016). Renalase is a flavin adenine

dinucleotide dependent amine oxidase and secreted in the kidney. Renalase is involved in the regulation of blood pressure and cardiac function via degrading catecholamines in the blood circulation (Milani *etal.*,2011; Zbroch *etal.*,2013). Human renalase gene is mapped to 10q23.33 (Xu *etal.*,2005) and highly expressed in the kidney and heart (Hennebry *etal.*,2010; Fedchenko *etal.*,2013). To date, available studies focus on the role of renalase gene polymorphism in the hypertension, and the single nucleotide polymorphisms (SNP) studied in previous studies is usually localized at the potential functional domains. There is evidence showing that SNP of rs2296545 is associated with hypertension (Zhao *etal.*,2007) or hypertension and concomitant diabetes (Buraczynska *etal.*,2011). Genetic polymorphisms may contribute to the differences in disease risks amongst different individuals. Different forms of genetic variants are found in the human genome. Single-nucleotide polymorphisms (SNPs) account for more than 90% of genomic variants and are the major form of genetic polymorphisms (Collins *etal.*,1998).

This study aims to investigate the association of polymorphism of *renalase* gene rs(2296545) to the susceptibility of hypertension Iraqi hypertensive patients.

Objective of the current study

To investigate the polymorphism of *renalase* rs (2296545) using polymerase chain reaction –restriction fragment length polymorphism (PCR-RFLP) hypertensive patients and healthy controls.

Method

Materials and Methods

This study included70 participants 50 confirmed hypertensive patients whose their age range between 40–73 years and 20 apparently healthy individuals (controls) subjects (12males and 13 females) and their age range between 40–69 years were selected using a convenient sampling methods. Genetic polymorphism of renalase gene (rs2296545) was carried out using RFLP-PCR restriction enzyme *Bsu 36I* (BioLabs/ USA**)**. Two primers were used to detect the polymorphism of SNP of rs2296545. The sequences of these primers are Forward 5′GGAAGTCCCCGATCACGTGAC-3.Reverse 5′TGCTGTGTGGGACAAGGCTGA -3′. the optimal conditions of *renalase* gene detection by PCR . Initial denaturation 94^{o}C**,** 5 min. 1Cycle. Denaturation 9 4^{o}C,40 sec. Annealing 60,^{o}C40 sec**.** Extension-1,72^{o}C, 40 sec. 45 cycle . Extension -2 ,72^{o}C,10 min1 cycle .

Results

Frequency of *renalase* gene(rs2296545) genotypes

C allele is a major one in the studied groups. This allele is common in hypertensive patients (74%) and in controls (70%) with significant difference when compared patients with controls, P=0.002. The main genotype is CCin the investigated groups. The CC genotype percentages of hypertensive patients and

controls has non-significant difference when compared patients with controls ,the most frequent genotype detected among patients and controls groups was *renalase* homozygous allele (CC) 46% and 70% respectively, P=0.095 . The GG genotype his played high significant difference when comparing patients with controls, in hypertensive patients (40%) compared to controls (5%), P=0.004. CG genotype displayed non-significant difference when compared patients with control, (hypertensive patients (14%), control (25%) P= 0.177.

Table 1
Frequency distribution of *renalase* gene(rs2296545) genotypes and alleles among hypertensive patients and controls

Groups	***renalase* gene(rs2296545) genotypes no.(%)**			**Allele frequency (%)**	
	GG	**CG**	**CC**	**C**	**G**
Control	1(5)	5(25)	14(70)	70	**30**
Hypertensive Patients	20 (40)	7 (14)	23 (46)	74	**36**
Chi square	8.33	1.82	2.78		**9.09**
P-value	0.004	0.177	0.095		**0.002**
Statistical significance	**	**NS**	**NS**	**	

≤ 0.01 P **

NS: Non-significant P> 0.05

Susceptibility analysis of *renalase* gene (rs2296545) gene polymorphism with hypertension

The homozygous GG genotype of *renalase* showed significant risk association among hypertensive patients and controls with OR=12.6 (CI95% [1.65-97.26]) p-value =0.004. The CG genotype decreases the susceptibility of contracting the disease with OR=0. 41(CI95% [0.11-1.50]), P =0.274. The genotype CC reduces also the likelihood of

Hypertension OR=0.4 (CI95% [0.13-1.17]) ,P= 0.116.

Table 2
Odds ratio OR of *renalase* gene (rs2296545) among hypertensive patients and controls

Genotypes	controls	hypertensivepatients	P value	OR CI 95%	Statistical Significance
GG	**1(5)**	**20 (40)**	**0.004**	**12.6 (1.65-97.26)**	****
CG	**5(25)**	**7 (14)**	**0.274**	**0.41(0.11-1.50)**	**NS**
CC	**14 (70)**	**23 (46)**	**0.116**	**0.4 (0.13-1.17)**	**NS**

≤ 0.01 ** p
NS: Non-significant P> 0.05

Discussion

The renalase gene is a reasonable candidate to be potentially involved in blood pressure regulation.Gene polymorphism analysis in case-control studies has found that renalase gene is related to several diseases in humans. Renalase gene has been found to be involved in the regulation of blood pressure (Desir *etal.*,2012).

The proportion of hypertensive patients with GG genotype was markedly higher with significant difference compared to controls, CC genotype revealed remarkable proportion among hypertensive patients.Genotype CC represented the highest percentage among patients and healthy subjects.The C allele was the major allele among hypertensive patients and controls. The allele C frequency of rs2296545 are closely related to hypertension. In addition, there is evidence (Buraczynska *etal.*,2011; Stec *etal.*,2012) showing that the allele C frequency of rs2296545 of renalase gene might be associated with diabetes. The results of the present study are in consistence with Adel Abou Zaghla *etal.*, 2020 who found that that rs2296545 CC genotype showed significant increase in hypertensive patients when compared to healthy control .Furthermore ,the polymorphism of renalase rs2296545 of the current study are in agreement with Li *etal.*, 2014 and Buraczynska *etal.*,2011 . Susceptibility analysis of *renalase* gene (rs2296545) gene polymorphism with hypertension showed that GG genotype was significant risk association among hypertensive patients in both females and males.These results suggest that rs 2296545 GG genotype is a susceptibility factor of hypertension while, rs2296545CG and CC are protective. The results also are in agreement with Zhao *et* al., who studied the association of single nucleotide polymorphisms of the renalase gene with the primary hypertension in the northern Han Chinese population, in a group of 2586 subjects (1317 patients with essential hypertension and 1269 healthy controls) and found association

between rs2296545 and essential hypertension. Whereas Fava *et al.*, studied more than 5000 subjects in a Swedish urban-based cohort, found no relation between rs2296545 gene polymorphism and cardiovascular events as hypertension suggesting that in Caucasian population.In a meta study, Lv *etal.*,displayed that renalase gene rs2296545 polymorphism is significantly associated with increased risk of hypertension . Renalase (amine oxidase) acts as a regulator of blood pressure and can predict many diseases, such as preeclampsia and cardiovascular diseases especially in patients with hypertension especially among patients with hypertension, using renalase polymorphisms.

Recently, renalase acts as a cytokine or pro-survival signal that supplies protection to cells, tissues, and organs through binding to the receptor of the cell membrane. The plasma membrane calcium adenosine triphosphates isoform PMCA4, stimulates some intracellular signaling pathways such as the protein kinase B (AKT), extracellular- signal-regulated kinase (ERK), and signal transducer and activator of transcription 3 (STAT3) pathways(Guo *etal.*,2014).On the other hand, the fast growth of malignant cells in several tumors may be due to dysregulated in renalase signaling pathway that stimulates the growth-related gene expression. For instance, the mortality increased in pancreatic cancer and melanoma patients when renalase gene expression increased (Derosa *etal*,2006). Treatment with renalase decreased the damage in several cases such as myocardial infarction (Gu *etal.*,2011), ischemic tubular necrosis(Lee *etal.*,2013), and acute pancreatitis (Xu *etal.*,2005).To our knowledge, this is the first study to investigate the genetic polymorphism of renalase rs2296545 in Iraqi patients.

Conclusion

The *renalase* rs2296545 GG genotype and G allele could be a risk factor for hypertension in females and males.

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