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Association Between Polymorphisms of *Alpha-Adducin* Gene Polymorphisms (rs4961, rs4963) and Essential Hypertension in Baghdad Population

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Abstract: Essential hypertension (EH), a leading risk factor for cardiovascular morbidity and mortality, remains poorly understood genetically. This case-control study investigated associations between *ADD1* gene polymorphisms (rs4961 G>T and rs4963 C>G), serum alpha-adducin levels, and EH risk in a Baghdad population (75 patients, 75 controls; June 2024–January 2025). Genotyping was performed via TaqMan assays, and serum alpha-adducin was quantified via ELISA. No significant difference in serum alpha-adducin levels was observed between patients and controls (36.03 ± 1.25 vs. 32.98 ± 1.05; $p > 0.05$). For rs4961 G>T, the TT and GT genotypes were significantly more frequent in patients ($p < 0.05$), while the GG genotype predominated in controls. For rs4963 C>G, the CG genotype was elevated in patients ($p < 0.05$), whereas the GG genotype was absent in both groups. Haplotype analysis revealed three combinations: GC, TC, and TG. The GC haplotype correlated with reduced EH risk ($p < 0.05$), while TC and TG were linked to increased susceptibility. Serum alpha-adducin levels showed no association with either SNP ($p > 0.05$). These findings suggest rs4961 G>T is significantly associated with EH risk in this population, whereas rs4963 C>G and alpha-adducin levels lack such association. Further studies are warranted to validate these results and explore *ADD1* mechanistic role in hypertension pathogenesis.

Keywords: Essential hypertension, , *ADD1* gene ,rs4961 and rs4963.

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Introduction:

Essential hypertension(EH) is a very common disorder with diverse causes, resulting from the interaction of genetic factors with environmental factors, and is cause of kidney disease and cardiovascular diseases such as myocardial infarction, stroke, and coronary artery disease (1,2,3,4).

Its prevalence rate reached about 30-45% of the total population in the world (5). In this study the statistics were issued by the Iraqi Ministry of Health for the years 2015-2022 indicating that the number of people suffering from high blood pressure in Baghdad reached (1,859,928) cases (6).

There are also risk factors associated with it that are not modifiable (such as gender, age, and genetics) and modifiable factors (such as overweight, obesity, smoking, alcohol consumption, high salt intake, stress, etc.) (7,8,9,10).

Epidemiological studies have found that approximately 20-40% of blood pressure variability is genetically

determined (11,12) Several genetic factors responsible for blood pressure regulation and essential hypertension have been identified (13). Adducin is one of the important candidate genes for essential hypertension. ADD is a heterodimeric or heterotetrameric protein that consists of alpha, beta, and gamma subunits; the three subunits are encoded by genes (*ADD1, ADD2*, and *ADD3*) that map to three different chromosomes (14).

ADD1 is located on chromosome 4 at position 4p16.3(15). It spans approximately 85 kb and contains 16 exons, ranging from 34 to 1892 base pairs (16). Adducin plays an important role in cell structure, especially in the kidneys, by maintaining them. It also helps bind other proteins to maintain cell stability and function(17). It also helps regulate blood pressure by controlling fluid and electrolyte balance by interacting with several proteins that help transport sodium in and out of cells, thus contributing to the reabsorption of the correct amount of sodium in the kidneys (18,19). However, if there are mutations in the *ADD1* gene, this process can be disrupted, leading to increased sodium reabsorption and high blood pressure. Common molecular variants of the *ADD1* gene that cause the substitution of glycine to tryptophan (Gly460Trp) at amino acid position 460 and serine to cysteine (Ser586Cys) at amino acid position 586 in exons 10 and 13, respectively, have an effect on the surface expression and maximum velocity of Na+-K+ ATPase and thus rapid reabsorption of renal tubular sodium (11). The difference in Blood pressure (BP) between normotensive rat strains and hypertensive melano mouse strains is due to mutations in the α and β subunits of ADD (20) Most clinical and experimental studies have implicated *ADD1* in essential hypertension in both humans and animals (21).

There are studies that indicate a role between the *ADD1* gene SNPs and susceptibility to EH, while other studies do not indicate this. In response to these findings, the current study investigated the role of between *ADD1* gene (rs4961, rs4963) polymorphisms and their seurm levels and susceptibility of EH in Baghdad Governorate EH patients.

Materials and methods

- Study design

The present study was conducted on 150 individuals, where 75 patients were diagnosed with the disease (mean age 50.36 ± 1.0 years) and 75 healthy people with normal blood pressure (mean age 50.40 ± 1.0 years). The present study was approved by the Training and Human Development Centre in the Baghdad Health Directorate – Karkh.

-Serum Alpha Adducin Level

The determination of alpha adducin protein levels in serum, it was done using ELISA devices produced by Bioassay Technology Laboratory / China, where:

The wavelength used in the spectrometer is 450 nm for the purpose of measuring the optical density (OD), which is directly proportional to the concentration of alpha adducin protein. The value of OD was compared with the standard curve for the purpose of calculating the protein concentration in the samples.

-Genotype analysis

The favorgen kit was used for the extraction of total genomic DNA from blood. A nanodrop device (model 2000 C, Thermo Scientific, USA) was used for the determination and purity of DNA between 1.7 and 1.9 (22). Labeled probes and primers from the supplier (TaqMan SNP Genotyping Assays, Applied Biosystems) were used for

determination of the *ADD1* genotype under TaqMan technology. For amplification and detection of genotypic interaction, the Applied Biosystems 7300 real-time PCR system was used. Table (1) shows the sequences of probes and primers used in allele determination experiments, including SNPs in the *ADD1* gene rs4961 in exon 10 (G to T mutation) and rs4963 in exon 13 (C to G mutation).

The figures (1 and 2) also show the heat cycle result of the Taqman analysis process for DNA amplification. NCBI Bioinformatics software was used to match the sequences of primers and probes. The 5′ and 3′ ends of the wild-type probe were marked with FAM and MGB, respectively. The 5′ and 3′ ends of the SNP probe were marked with VIC and MGB, respectively.

Table (1): Primers and Probes used in the study:

Primer/probe	Sequence (5′ →3′ direction)	Reference
*ADD1*gene (rs4961) CGGGGCGACGAAGCTTCCGAGGAA (G/T) GGCAGAATGGAAGCAGTCCCAAGT		(23)
Forword	GCTCCCCACTCAGACACAGTTTT	
Reverse	AGAGACTGCAGCAAGGGTTTCAC	
FAM-probe	TTCTGCCCTTCCTCGG	
VIC-probe	ATTCTGCCATTCCTCGGA	
*ADD1*gene (rs4963) GTGGAGAGGAAGCAGAAGGGCT(C/G) TGAAGGTGAGTGCTTGTGGTCCTGGG		Designed by this study
Forword	GCCCCAACCCCTTCACCACACT	
Reverse	GACCACAAAGAAGCTCCCAGA	
FAM-probe	CTCACCTTCAGAGCCCTTCTGC	
VIC-probe	CTCACCTTCACAGCCCTTCTGC	

Statistical analysis

SPSS version 30.0 (released in 2023) was used to calculate the mean and standard error of the parametric data, and the independent t-test and analysis of variance table were used to calculate the probability. To examine the association between the studied parameters, Pearson correlation was used. Pearson chi-square was used to calculate the probability for non-parametric data. The probability was considered significant when it was less than 0.05. To calculate the odds ratio, 95% CI and Fisher's exact probability, the online HWE Calculator was used. For the genotype, the SHEsisPlus website was used. (24).

Results and discussion

Estimation of serum level of the alpha adducin

Alpha adducin levels in serum were estimated in 150 participants (75 hypertension patients and 75 apparently healthy controls) using an ELISA kit. The results of alpha adducin levels in serum are shown in Table 2. The results of the present study indicated that there was no increase in serum alpha adducin levels in hypertensive patients compared with serum levels in the apparently healthy control group ((36.03 ± 1.25 vs. 32.98 ± 1.05, $p<0.05$).

Table (2): The alpha adducin level in serum median in the EH patients and control group.

Proteins	Mean ± SE (ng/L)		Probability
	Patients group	Control groups	
Alpha adducin	36.03 ± 1.25	32.98 ± 1.05	0.064 NS
NS: not significant (P > 0.05)			

Adducin interacts with membrane structural components and various membrane proteins to exert effects on ion transport, especially with sodium transport, e.g., Na+K+-ATPase, and is associated with human EH (17, 25–26). Point mutations in α *ADD* affect Na+K+ATPase activity and alter sodium reabsorption by renal tubules (17, 27, 28). Consequently, hypertension is caused by altered phosphorylation pattern of tyrosine kinase to PKA site (29).

Molecular study:

This study investigated the *ADD1* gene polymorphisms (rs4961 G>T in exon 10, rs4963 C>G in exon 13) among hypertensive patients and apparently healthy controls in Baghdad. It tested their association with the essential hypertension phenotype. The genotype distribution and allele frequency of each of *ADD1* gene polymorphisms, Hardy-Weinberg equilibrium and haplotype were tested as shown in tables (2,3,4,5 and 6).

Rs4961 G>T polymorphism:

The distribution of genotype allele frequencies at the rs4961 SNP of the *ADD1* gene is presented in table (3), and Figure (1) also shows the heat cycle result of the Taqman analysis process for DNA amplification. As related to GG, GT and TT genotypes, significant differences in frequency percentage were found between patients and apparently healthy subjects. Whereas the frequency of TT genotype was significantly ($p<0.05$) higher in patients with EH than in apparently healthy subjects (28% versus 10.7%, respectively, OR = 3.26; 95% CI, 1.35-7.88, $p<0.05$). While the GT genotype showed a significant increase (48.0 versus 28.0 %; OR = 2.37; 95% CI, 1.21-4.65, $p<0.05$) in the patient group with hypertension compared with the control group. While the GG genotype showed a significant increase (61.3 versus 24.0 %; OR = 0.20; 95% CI, 0.10-0.40, $p<0.001$) in the control group with hypertension compared with the patient group.

Table (3): The distribution of genotypes and allelic frequency of *ADD1* gene polymorphism (rs4961) in the study group.

Genotypes of rs4961	Patients group No.	Control group No.	Odd ratio	95% confidence intervals	Probability
GG	18 (24.0)	46 (61.3)	0.20	0.10 – 0.40	6.4×10^{-6} ***
GT	36 (48.0)	21 (28.0)	2.37	1.21 – 4.65	0.018
TT	21 (28.0)	8 (10.7)	3.26	1.35 – 7.88	0.012
Total	75 (100.0)	75 (100.0)			
Alleles frequencies					
G	72 (48.0)	113 (75.0)	0.30	0.19 – 0.49	1.7×10^{-6} ***
T	78 (52.0)	37 (25.0)	3.31	2.03 – 5.39	1.7×10^{-6} ***

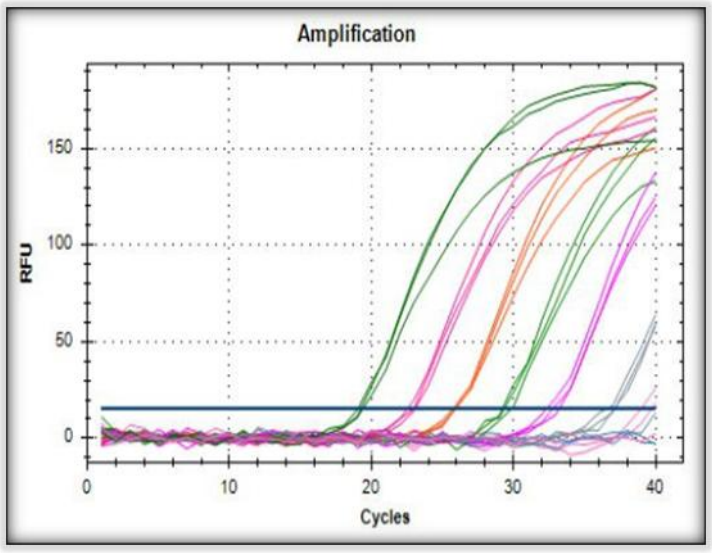

Figure (1): Amplification of DNA for the *ADD1* gene (rs4961), the picture was taken directly from Taqman analysis software.

Generally, the genotypes of *ADD1* at rs4961 SNP have a role in the incidence of EH in Baghdad. The T allele showed significantly increased frequency in hypertension patients versus the control group (52.0 % versus 25.0 %; OR= 3.31; 95% CI, 2.03-5.39, p<0.001). According to these results, the T allele seems to be a risk allele. The G allele frequency observed a significantly decreased frequency in patients versus the control group (48.0 versus 0 %; OR = 0.30; 95% CI, 0.19-0.49, p<0.001). The results of the current study are consistent with the study conducted by Sidorchuk *et al*. (30) regarding the relationship of the T allele with EH, as they observed that the T allele of the *ADD1* gene polymorphism (rs4961) is associated with sodium sensitivity in patients with EH. This indicates that the genetic variant plays an important role with sodium in hypertensive individuals. Jin *et al*. (31) conducted a study in which they found that the *ADD1* gene rs4961 polymorphism is involved in hypertension, especially in Asian populations. The research included 33 studies in the analysis, covering more than 40,000 individuals. The large sample size enhances the reliability of the results, as it gives a more comprehensive view of the potential association between the *ADD1* gene rs4961 polymorphism and hypertension. It was concluded that the genetic variant is significantly associated with an increased risk of hypertension. This indicates that genetic factors can influence EH.

Studies in North Indian and Tunisian populations found a significant association between the rs4961 polymorphism in the *ADD1* gene and EH. They concluded that individuals carrying the Trp allele have a higher risk of EH than those without it (32,33). These findings are consistent with our findings in this study. There is also a study conducted in China (34) in which they indicated that there was no association between the *ADD1* rs4961 polymorphism and EH, although previous studies have reported such associations in other populations as in our current study.

A Hardy-Weinberg equilibrium (HWE) analysis was performed for the *ADD1* gene SNP, rs4961, as shown in table 3. The HWE assessment showed that there was non-significant variation ($p > 0.05$) between the observed and expected frequencies of these genotypes in patients, while in the control group there was significant variation between the expected and observed. Regarding the analysis of the *ADD1* gene rs4961 SNP as shown in table (4). The deviation of control individuals from HWE might be caused by a variety of causes, the most important of which is that the control group was randomly selected and the control group was not clinically examined to confirm that the person is free from the disease, and that's because HWE deviation has been proposed as a measure of disease (35).

Table (4): Hardy-Weinberg equilibrium analysis of *ADD1*gene single nucleotide polymorphism (rs4961) in total hypertension patients and controls.

Genotypes of rs4961	Patients group		Control group	
	Observed No.	Expected No.	Observed No.	Expected No.
GG	18 (24.0)	17.28 (23.04)	46 (61.3)	42.56 (56.75)
GT	36 (48.0)	37.44 (49.92)	21 (28.0)	27.87 (37.16
TT	21 (28.0)	20.28 (27.04)	8 (10.7)	4.56 (6.08)
Total	75 (100.0)	75 (100.0)	75 (100.0)	75 (100.0)
Probability of Hardy-Weinberg	0.7391 NS		0.0327	

Rs4963 C>G polymorphism:

The results in table 5 refer to genotype CC (78.7% versus 90.7; OR = 0.38; 95% CI, 0.15-0.89, $p<0.05$); there was a decreased frequency in patients than the control group. In contrast, the CG genotype showed a significant increase (21.3 versus 9.3%; OR = 2.63; 95% CI, 1.02; 6.80 $p < 0.05$) in the patient group with hypertension compared with the control group. While the GG genotype does not appear in any groups of patients and controls. The findings of the current investigation indicate that CG was a risk factor for hypertension. The G allele showed significantly increased frequency in hypertension patients versus the control group (11.0 versus 5.0) %; OR= 2.44; 95% CI, 0.98-6.10 $p<0.05$). According to these results, the G allele seems to be a risk allele. The C allele frequency observed a significantly decreased frequency in patients versus the control group (89.0 versus 95.0; OR = 0.41; 95% CI 0.16-1.02; $p < 0.05$).

Table (5): The distribution of genotypes and allelic frequency of *ADD1* gene polymorphism (rs4963) in the study group.

Genotypes of rs4963	Patients group No.	Control group No.	Odd ratio	95% confidence intervals	Probability
CC	59 (78.7)	68 (90.7)	0.38	0.15 – 0.98	0.068
CG	16 (21.3)	7 (9.3)	2.63	1.02 – 6.80	0.068
GG	0 (0.0)	0 (0.0)	-	-	-
Total	75 (100.0)	75 (100.0)			
Alleles frequencies					
C	134 (89.0)	143 (95.0)	0.41	0.16 – 1.02	0.081
G	16 (11.0)	7 (5.0)	2.44	0.98 – 6.10	0.081

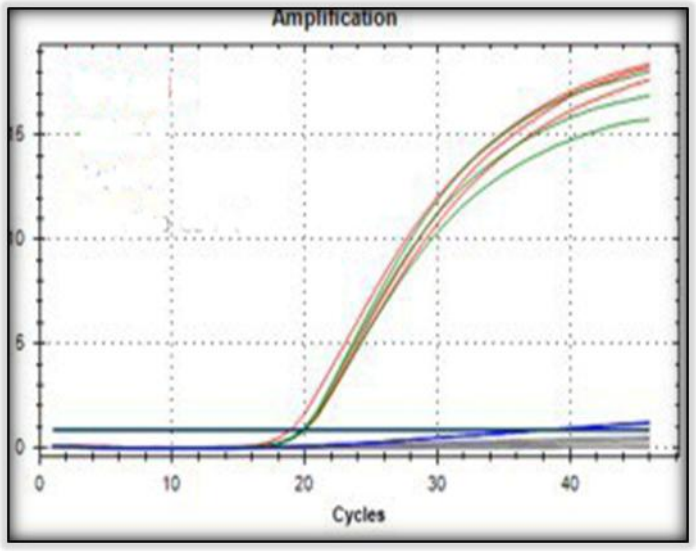

Figure (2): Amplification of DNA for the *ADD1* gene (rs4963), the picture was taken directly from Taqman analysis software.

The results of this study differ from the study conducted by Zhang *et al*. (36). The study found a significant association between a specific genetic variation (SNP rs4963) in the *ADD1* gene and EH in the Chinese population. This suggests that this genetic factor may increase the risk of developing high blood pressure, particularly in males. The study involved a well-defined population of Han Chinese individuals, which helps ensure that the findings are relevant to this specific group. The findings suggest that the rs4963 SNP may disrupt normal gene function, potentially leading to increased sodium reabsorption in the kidneys, which is a known contributor to high blood pressure. This is consistent with the study Cusi *et al*. (37), which indicated that the missense mutation in strong linkage disequilibrium association to hypertension in sib-pair and case-control analyses.

According to Hardy-Weinberg equilibrium (HWE) analysis, table 6 shows that there is a non-significant difference ($p > 0.05$) between the observed and expected frequencies of these genotypes in the apparently healthy control group and the control group.

Table (6): Hardy-Weinberg equilibrium analysis of *ADD1*gene single nucleotide polymorphism (rs4963) in total hypertension patients and controls.

Genotypes of rs4963	Patients group		Control group	
	Observed No.	Expected No.	Observed No.	Expected No.
CC	59 (78.7)	59.85 (79.80)	68 (90.7)	68.16 (90.88)
CG	16 (21.3)	14.29 (19.06)	7 (9.3)	6.67 (8.90)
GG	0 (0.0)	0.85 (1.14)	0 (0.0)	0.16 (0.22)
Total	75 (100.0)	75 (100.0)	75 (100.0)	75 (100.0)
Probability of Hardy-Weinberg	0.3011		0.6716	

Haplotypes

Haplotype frequencies of *ADD1* tagSNPs (rs4961 and rs4963) were estimated using the ShEsisPlus website. The D' value = 0.57 indicates a moderate association between the two

gene loci (rs4961 and rs4963). This suggests that changes at one locus can be used to predict changes at the other locus, but the association is not strong enough to consider one as a complete alternative to the other. The linkage disequilibrium block for two tagSNPs in the *ADD1* gene is shown in figure 3.

Haplotype combination

Haplotype analysis for *ADD1* gene tagSNPs is listed in table 7. We observed three possible haplotypes of the *ADD1* gene: GC, TC, and TG. The frequency of the GC genotype in patients and healthy individuals was: 0.466 vs. 0.726; OR = 0.329 (95% CI: 0.20-0.53), respectively. This indicates that the GC genotype is associated with a lower risk of hypertension. That is, people with this genotype are less likely to develop hypertension than those without it. As for the TC genotype frequency in patients and healthy individuals: 0.426 vs. 0.226; OR = 2.538 (95% CI: 1.54-4.19), respectively. This indicates that TC increases the risk of hypertension. That is, people with this genotype are more likely to develop hypertension than those without it. As for the TG genotype, its frequency in patients vs. healthy controls: 0.086 vs. 0.026; OR = 3.463 (95% CI: 1.10-10.89), respectively. This indicates that TG increases the risk of hypertension, but the association is weaker than that of the TC genotype.

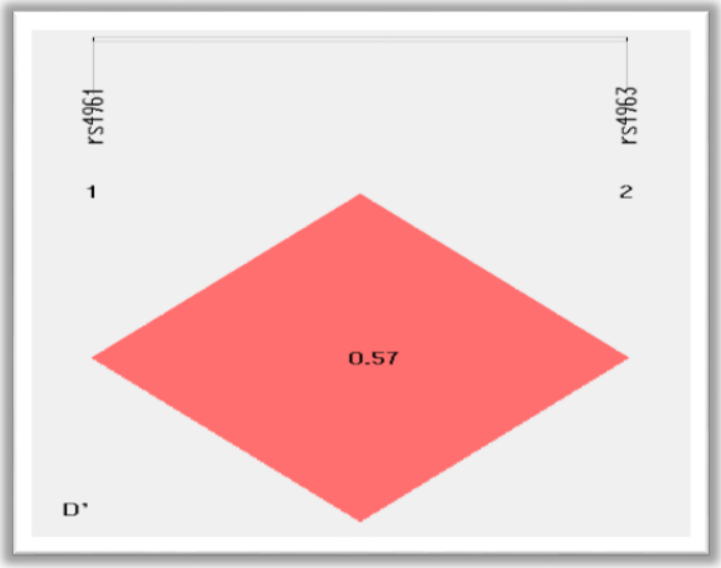

Figure (3): Linkage disequilibrium tests (D') map of two SNPs rs4961 and rs4963.

Table (7): Haplotype analysis loci of *ADD1* gene (rs4961 and rs4963).

Haplotype	Case (freq.)	Control (freq.)	Chi^2	Fisher's p	Pearson's p	OR [95% CI]
GC	70 (0.466)	109 (0.726)	21.067	6.78 x 10^{-6}	4.43 x 10^{-6}	0.329 [0.20~0.53]
TC	64 (0.426)	34 (0.226)	13.639	3.33 x 10^{-4}	2.22 x10^{-4}	2.538 [1.54~4.19]
TG	13 (0.086)	4 (0.026)	5.05	0.042	0.024	3.463 [1.10~10.89]

Correlation between SNP rs4961 and rs4963 of *ADD1*gene and serum level of alpha adducin:

Evaluation of alpha adducin serum levels in the rs4963 and rs4961 genotypes did not show different results in hypertensive patients and controls (Table 8). Alpha adducin levels between the two groups, patients and controls, there were no differences within the two groups. For rs4961 and rs4963, there were no significant differences between alpha adducin levels in the hypertensive group versus the control group. Mutations in the *ADD1* gene can significantly affect the function of the protein by changing the structure and activity of the protein, not its quantity, leading to increased sodium retention in the kidneys, which ultimately leads to hypertension (38,39). The ADD1 is responsible for producing a protein that helps maintain cell structure and a role in regulating sodium levels in the body. This regulation is important because sodium levels directly affect blood pressure. The functional alteration of ADD1 resulting from the mutation leads to increased sodium reabsorption through the protein's interaction with the action network and the sodium/potassium pump, which increases the efficiency of sodium transport, without necessarily increasing protein levels. Therefore, measuring seurm protein levels may not be an appropriate measure to assess the effect of genetic mutations on protein function (40,41,42).

Table (8): The *ADD1* level median distribution according to the genotyping of rs4961 and rs4963 of the studied groups.

Genotypes	*ADD1* mean ± SE (ng /L)		Probability
rs4963	Patients group	Control group	
CC	35.60 ± 1.29 ^{A}	32.84 ± 1.13 ^{A}	0.769 NS
CG	37.62 ± 3.51 ^{A}	34.42 ± 2.08 ^{A}	0.482 NS
GG	-	-	-
rs4961			
GG	40.79 ± 2.72 ^{A}	35.14 ± 1.90 ^{A}	0.374 NS
GT	33.21 ± 1.46 ^{A}	34.65 ± 1.82 ^{A}	0.361 NS
TT	38.49 ± 2.52 ^{A}	33.46 ± 8.64 ^{A}	0.215 NS

Conclusion

In this study, we found an association between rs4961 of the *ADD1* gene and the risk of essential hypertension, while rs4963 of the *ADD1* gene showed no association with essential hypertension, as well as no association between serum alpha-adducin levels of the SNPs *ADD1* rs4961 and rs4963 in the patient group and healthy individuals.

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