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Original Article

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# Evaluation of Renin, Aldosterone, Angiotensin, and Lipid Metabolism Genes and Genotype-Phenotype Relationship in Childhood Primary Hypertension Pathogenesis

Özgür Özdemir Şimşek[1], Afig Berdeli[2], Ahmet Keskinoğlu[2]

[1]Department of Pediatric Nephrology, University of Health Science, Izmir Tepecik Training and Research Hospital, İzmir, Türkiye
[2]Department of Pediatric Nephrology, Faculty of Medicine, Ege University, İzmir, Türkiye



## ABSTRACT

**Objective:** Childhood primary hypertension has been increasing in parallel with the increase in obesity prevalence in recent years. Hypertension is a polygenic disease in which epigenetic changes are also effective. In this study, factors and gene polymorphisms in hypertension etiology were evaluated.
**Methods:** Age, gender, body mass index, family history, blood glucose and lipid levels, blood pressure measurements and percentiles at the time of diagnosis, post-treatment blood pressure controls, and target organ involvement were examined. Polymorphisms of ACE, renin, angiotensin, aldosterone, FABP2, and ApoB100 were evaluated.
**Results:** A total of 100 patients, 50 patients (group 1) and 50 healthy controls (group 2), were included in the study. In terms of age distribution, the patient and control groups were not similar ($P$ =.040). Distributions by gender were similar. While the mean height as one of the anthropometric values of both groups was statistically similar, the body mass index of Group 1 was significantly higher than the control group ($P < .001$). In the biochemical tests, only the high-density lipoprotein (HDL) mean of Group 1 was significantly lower than that of Group 2 ($P < .001$). When the distribution difference of ACE, renin, angiotensin, aldosterone, FABP2, and ApoB100 polymorphism was examined, no statistically significant difference was observed.
**Conclusion:** In this study ACE, renin, angiotensin, aldosterone, FABP2, and ApoB100 gene polymorphisms were not identified as risk factors in existing pathways.
**Keywords:** Children, epigenetic, hypertension, polymorphism

**Corresponding author:** Özgür Özdemir Şimşek ozgur_ozdemir_07@hotmail.com **Received:** January 4, 2022 **Accepted:** March 12, 2022
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## INTRODUCTION

The prevalence of high blood pressure (BP) and hypertension (HT) in children and adolescents has increased in the last decade. This trend is most likely associated with increases in primary HT associated with increased obesity rates in children. It plays an important role in the development of lifestyle and genetic primary HT.[1] Hypertension is a multifactorial disease in which no single etiology or pathophysiological mechanism is responsible because there are many factors that determine BP and interact with each other. Genetics, renin-angiotensin system (RAS), sympathetic nervous system, kidney sodium retention, conditions that increase cardiac output, vascular hypertrophy, endothelium-based factors, vasoconstrictor agents, excessive production of vasodilator agents, obesity and insulin resistance, sodium-rich potassium-poor diet, and lifestyle choices are among these multiple factors.[2] 30%-50% of childhood HT is inherited. It is a polygenic disease with gene-gene and gene-environment interactions. Many more heterogeneous problems in the more common polygenic form can be found in the same patient.[3] If one of the parents is hypertensive, the risk of developing HT in their children is increased by 2 times.[4] Generally, there

are changes related to RAS genetic structure in the etiology of primary HT. Another important point is that polymorphisms in HT etiology are more common than mutations. In this study, it was aimed to determine the effect of renin, aldosterone synthetase, angiotensin genes, and lipid metabolism gene polymorphisms in primary HT etiology with multifactorial inheritance.

## METHODS

This study was planned as a case-control study involving patients with primary HT and healthy children. The study was designed in accordance with the WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. Approval was obtained from the ethics committee (Date: April 27, 2016, Protocol no: 16-3.1/15).

### Definition of Research Groups and Evaluated Parameters

The case group consisted of 50 patients (Group 1) who were followed up between November 2015 and April 2016, with the diagnosis of primary HT by the Department of Pediatrics, Pediatric Nephrology, Pediatric Endocrinology, and Pediatric Cardiology departments faculty of medicine. The control group was composed of 50 healthy children (Group 2) without chronic disease. Patients included in the study were patients with primary HT. Patients with secondary HT were excluded. Exclusion criteria were endocrine causes (hyperthyroidism, Cushing's syndrome, hyperaldosteronism, pheochromocytoma, adrenal hyperplasia, etc.), cardiovascular causes, renovascular diseases, and patients who refused to participate in the study. For the control group, patients without chronic disease and no drug use were included, while the family and child's unwillingness to participate in the study was defined as the exclusion criterion. Age, gender, height, weight, BMI, presence of HT in the family, HT stage, drug use, BP at the time of diagnosis, pre- and post-treatment BP, total cholesterol, triglyceride, HDL, LDL, fasting blood sugar, target organ involvement, and ACE, renin, angiotensin, aldosterone, FABP2, and ApoB100 gene polymorphism were evaluated for each group. About 50 healthy and 50 primary HT patients included in the study were seen during outpatient follow-up. Blood pressures were done with aneroid BP measuring devices. Values of BP at 95 p and above according to age, height, and gender were accepted as HT. The patients were classified according to the HT stages defined in the fourth report determined by the National Health and Nutrition Examination Survey group; the term prehypertensive is defined as that the BP is between 90 and 95 p, the Stage 1 hypertensive BP is 5 mmHg more than the 95-99 percentile, and the Stage 2 hypertensive BP is 5 mmHg more than the 99th percentile. Weight/length square (kg/m$^2$) formulation was used for body mass index (BMI). Patients with a BMI percentile above 95 p according to gender were considered obese. Post-fasting triglyceride, cholesterol, HDL, LDL, and fasting blood sugar levels were studied in all cases. Patients over 99 p by age were considered hyperlipidemic. Microalbumin level, optic fundus evaluation, and echocardiography results in 24-hour urine were evaluated for kidney evaluation from the file follow-ups available for patients for target organ damage. In echocardiography, all measurements were made in accordance with the rules of the American ECO Association using 2-dimensional M-mode ECO. Evaluations were made based on left ventricular end-diastolic thickness, interventricular septal thickness, and posterior wall thicknesses.



### Molecular Analyses

**DNA Isolation:** Genomic DNA was obtained by taking 200 µL of 2 cc blood obtained from patients with ethylenediaminetetraacetic acid (EDTA) tubes. Invitrogen Purelink Genomic Blood DNA Purification DNA isolation mini kit was used for this method. DNA extraction procedures were done according to the kit prospectus.

**DNA Control:** 2 µL (100 ng) of DNA solution was subjected to electrophoresis treatment in 1% agarose gel. To measure DNA purity, 260/280 nm wavelength was measured in NanoDrop Spectrophotometer. DNA molecules, whose control was completed, were stored at +40°C to begin DNA sequence analysis. The products of the patients successfully processed in PCR were placed on the ABI 3130XL Genetic Analyzer automated DNA sequencing device and the nucleotide sequence was read according to the peaks.

### Statistical Evaluation

Data were analyzed by using the Statistical Package for Social Sciences Version 15.0 (SPSS, Chicago, Ill, USA). The descriptive presentation of the research results was made according to the case and control groups. In the descriptive analysis, the suitability of variables taken as quantitative measurement data was checked for normal distribution. If the data are not suitable for normal distribution, logarithmic transformation was applied, and normal distribution control was performed again. Data not showing normal distribution in all cases were shown with median (minimum-maximum) values. If it is suitable for normal distribution, it was indicated by mean and SD. Number and percentage distributions were checked in frequency distributions. For the comparison of independent groups in analytical

## MAIN POINTS

- When the patient and control groups were compared, only Apo B100 genotype distributions were found to be different in terms of ACE, renin, angiotensin, aldosterone, FABP2, ApoB100 gene polymorphisms ($P < .001$).
- Recent studies show that ApoB100 gene polymorphism is responsible for increased postprandial lipemic response and is a risk factor for the development of metabolic syndrome. However, there is no study in the literature related to hypertension (HT) etiology.
- When this study conducted in regard to genetics of primary HT was evaluated, ACE, renin, angiotensin, aldosterone, FABP2, and ApoB100 gene polymorphisms were not identified as risk factors in existing pathways.

evaluation, averages for parametric continuous data were performed using the *t*-test, and nonparametric comparisons were done with the Mann–Whitney *U*-test. The frequency difference of categorical variables in the case and control groups was analyzed by independent groups using the Chi-square test and McNemar Chi-square test in the dependent condition before the treatment. Post-treatment BP measurements were compared with paired *t*-test in parametric condition and Wilcoxon test in nonparametric condition. In the multivariate examination where the obesity variable of each gene was corrected, the logistic regression analysis was performed. It was checked whether the genotype allele frequencies of each group were in the Hardy–Weinberg equilibrium. In all comparisons, $P < .05$ was accepted as the limit of significance.

## RESULTS



A total of 50 patients (Group 1) and 50 healthy controls (Group 2) were included in the study. The median age of the patients was 12.5 (3-18) years, and the mean age of the control group was 11 (6-15) years. In terms of age distribution, the patient and control groups were not similar ($P = .040$). Fifty-six percent of the patient group is male and 44% is female; 62% of the control group were boys and 38% were girls. Their distribution by gender was similar ($P = .542$; Chi-square). When the distribution of anthropometric properties of patients and controls was examined, the mean weight and BMI of the patients were significantly higher than the controls ($P < .001$), and the height averages were found to be statistically similar ($P = .058$) (Table 1). When the family history was evaluated, the presence of HT in the family of the patient group was found to be significantly different than the control group ($P < .001$). When HDL, LDL, triglyceride, total cholesterol, and fasting blood glucose values were analyzed, HDL mean of Group 1 was found statistically significantly lower than the control group ($P < .001$), and LDL, triglyceride, total cholesterol, and fasting blood glucose levels were similar in the case and control group. When the cardiac pulse, systolic and diastolic BP values were compared, the systolic and diastolic BP values of Group 1 were significantly higher than that of Group 2 ($P < .001$) The distribution of the cardiac pulse rates was similar in both groups ($P = .228$). When the distribution of 39 patients receiving treatment in Group 1 according to the antihypertensive drug groups used was examined, it was found that the most common ACE inhibitors (84.6%) were treated with 17.9% ARB and 12.8% Ca channel blockers. In addition, 6 patients received double combined therapy. Pre-treatment and post-treatment BP values are evaluated. A significant reduction in both systolic and diastolic BP was observed, when the target organ involvement was evaluated, the presence of target organ involvement was observed in 8 patients (16%). While only 7 of these 8 patients had cardiac involvement; 1 had both cardiac and kidney involvement (Table 2). ACE, renin, angiotensin, aldosterone, FABP2, and ApoB100 gene polymorphisms of both groups are shown in Table 3. In terms of both groups, only Apo B100 genotype distributions were found different ($P < .001$). However, there was no statistical conclusion about which of the homozygous genes is at risk for HT. Frequency distributions of gene (ACE, Renin, angiotensin, aldosterone, FABP2, and APO100) polymorphisms were similar in the groups with a BP percentile

**Table 1.** Demographic and Anthropometric Properties of Patients

| | Group 1 | Group 2 | *P* |
|---|---|---|---|
| Gender | | | |
| Female n (%) | 22 (%44) | 19 (%38) | .542 |
| Male n (%) | 28 (%56) | 31 (%62) | |
| Median age-year (min-max) | 12.5(3-18) | 11(6-15) | **.004** |
| Mean weight (kg) ± SD | 72.6 ± 26.9 | 43.9 ± 11.9 | **<.001** |
| Mean height (cm) ± SD | 156.5 ± 21.0 | 149.9 ± 12.5 | .058 |
| Mean BMI ± SD | 28.6 ± 6.0 | 19.2 ± 2.3 | **<.001** |

**Table 2.** Biochemical Results of Groups, End Organ Involvement, BP Values Before and After Treatment

| | Group 1 | | Group 2 | *P* |
|---|---|---|---|---|
| **Biochemical results** | | | | |
| HDL (mean ± SD) | 47.7 ± 13.9 | | 58.32 ± 9.1 | **<.001** |
| LDL (mean ± SD) | 92.9 ± 28.9 | | 91.4 ± 11.8 | .745 |
| Total cholesterol (mean ± SD) | 154.7 ± 34.3 | | 150.8 ± 23.8 | .510 |
| Trigliseride median (min–max) | 100.5 ± 11.9 | | 101.3 ± 66.2 | .933 |
| Blood glukoce (mean ± SD) | 87.4 ± 7.3 | | 85.5 ± 7.0 | .184 |
| Cardiac pulse [median (min–max)] | 80.5 (69-128) | | 85 (71-101) | .229 |
| Sistolic BP (mean ± SD) | 137.7 ± 10.0 | | 109.6 ± 6.0 | **<.001** |
| Diastolic BP (mean ± SD) | 79.9 ± 9.3 | | 69.4 ± 4.1 | **<.001** |
| **BP values before and after treatment** | **BT** (N = 39) | **AT** (N = 39) | | ***P*** |
| Sistolic BP (mean ± SD) | 138.8 ± 10.1 | 114.1 ± 8.3 | | **.001** |
| Diastolic BP median (min–max) | 82 (63-94) | 71 (51-82) | | **<.001** |
| Grade of BP (n = 100) | | | | |
| Normotensive [n(%)] | 0 (0) | 35 (89.7) | | |
| Prehypertensive [n(%)] | 0 (0) | 4 (10.3) | | **<.001** |
| Grade I [n(%)] | 3 (7.7) | 0 (0) | | |
| Grade II [n(%)] | 36 (92.3) | 0 (0) | | |
| End organ involvement | 8 (16%) | | | |

**Table 3.** ACE, Renin, Angiotensin, Aldosterone, FABP2, and ApoB100 Gene Polymorphisms of the Cases

| | Group 1 n (%) | Group 2 n (%) | *P* |
|---|---|---|---|
| ACE gene polymorphism | | | |
| DD | 20 (40%) | 19 (38%) | .314 |
| ID | 19 (38%) | 25 (50%) | |
| II | 11 (22%) | 6 (12%) | |
| Renin gene polymorphism | | | |
| DD | 20 (40%) | 15 (30%) | .448 |
| ID | 26 (52%) | 28 (56%) | |
| II | 4 (8%) | 7 (14%) | |
| Angiotensin gene polymorphism | | | |
| MM | 11 (22%) | 13 (26%) | .890 |
| MT | 28 (56%) | 27 (54%) | |
| TT | 11 (22%) | 10 (20%) | |
| Aldosterone gene polymorphism (344T/C) | | | |
| CC | 7 (14%) | 13 (26%) | .295 |
| TC | 31 (62%) | 25 (50%) | |
| TT | 12 (24%) | 12 (24%) | |
| FABP2 gene polymorphism | | | |
| AA | 7 (14%) | 3 (6%) | .597 |
| AG | 26 (52%) | 22 (44%) | |
| GG | 20 (40%) | 25 (50%) | |
| ApoB100 gene polymorphism | | | |
| AA | 2 (4%) | 0 (0%) | **<.001** |
| AG | 13 (26%) | 0 (0%) | |
| GG | 35 (70%) | 50 (100%) | |

value at the time of diagnosis at both 95 p and 99 p and below. In this study, the distribution of the gene polymorphisms examined was tested for the compatibility of both groups separately to the Hardy–Weinberg equation, and both groups were found to be suitable for the Hardy–Weinberg equation in terms of genotype phenotype and the population was in balance in terms of these genotype brakes (all *P* values > .05). The combined effects of obesity and genetic changes were evaluated using the logistic regression model. In 6 different models created for each gene, it was found that changes in BMI did not affect genotype changes (Table 4). When Group 1 was classified as BP percentile and above and without 99 p and above, 6 separate logistic regression model analyses of the BMI and all gene polymorphisms examined in our study showed that the gene polymorphisms and BMI did not affect the presence of BP over 99 p (Table 5).

## DISCUSSION

This study is planned to examine some of the genetic changes that may take place in the etiology of childhood primary HT. In the meantime, other parameters (such as BMI) that may affect genetic results were evaluated. Regarding the prevalence of childhood HT, regional variations are associated with many factors such as ethnic groups, dietary habits, environmental factors, and differences in measurement methods and age groups.[5] Primary HT is common in the postpubertal period. In this study, it is supported in accordance with the literature that primary HT occurs especially at postpubertal age. In a study conducted in our country, HT prevalence in obese children admitted to the hospital was reported as 31.8% in adolescents and 15% before adolescents.[5] Although there are studies that childhood HT is not related to gender, new results have been reported that HT is more common in boys in different countries and ethnic groups. In 949 patients performed by Wühl et al.[6] it was found that the mean of the BP showed a continuously high level of trend in men, which was attributed to the incomplete formation of sex steroids. Yoon et al.[7] in a study conducted by Michigan with 4296 adolescent primary HT cases, a 2:1 ratio of male cases prevailed. In this study, this rate was determined as M/F: 1.2/1 and was not found appropriate in the literature. However, this study was not a prevalence study performed in the community. In recent years, due to the increase in obesity, negative changes in nutritional habits, consumption of foods containing high calories, fat, and salt, decreased physical activity, sleep disorders, and increased stress factor increased HT prevalence in adolescents. Especially in obese children, the rate has increased up to 11%-30%.[8, 9] In a study with 25 000 school children aged 5-16, it was shown that preHT and HT prevalence increased significantly in overweight and obese children.[10] In this study, the patients' BMI was found to be significantly higher and compatible with the literature compared to the control group. One of the most important factors in primary HT pathogenesis is hereditary transition.[11] Having a history of HT in the parents is an important indicator for the risk of developing primary HT in children before the age of 18.[12] In our study, 40% of the patients had a family history of HT and were consistent with the literature. Although genetic transition is of great importance, HT is a multifactorial hereditary disease. Obesity is known to create a tendency to dyslipidemia alone. In metabolic syndrome, lipid metabolism is impaired. There is hypertriglyceridemia and low HDL-cholesterol levels.[13] In this study, when both groups were compared under the heading of metabolic syndrome accompanying obesity, HDL levels were significantly lower in the patient group. In the literature, triglyceride elevation was observed in the patient group. In our study, triglyceride levels were not different between the patient and control groups. These values do not partially support the existing literature. As BP severity increased, LDL cholesterol increased, but there was no statistically significant difference between the patient group and the healthy group in terms of LDL and total cholesterol levels. When the distribution of ACE, renin, angiotensin, aldosterone, FABP2, and ApoB100

**Table 4.** LR Models in Which the BMI is Controlled for 6 Genes in Patient Control Separation

| | | *P* | OR | 95%CI OR | $R^2$ |
|---|---|---|---|---|---|
| Model 1 | BMI percentile (continuously variable) | **.000** | **1.102** | **1.055-1.151** | 0.554 |
| | ACE[**II-11/6**; (DD-20/19 ve ID-19/25)] | .522 | 1.608 | 0.375-6.883 | |
| | $\beta_0$ constant | .000 | 0.000 | | |
| Model 2 | BMI percentile | **.000** | **1.104** | **1.056-1.153** | 0.551 |
| | AGT[**TT-../..**; (MM-./. ve TM-../..)] | .918 | 0.936 | 0.269-3.254 | |
| | $\beta_0$ constant | .000 | 0.000 | | |
| Model 3 | BMI percentile | **.000** | **1.104** | **1.057-1.153** | 0.550 |
| | CYP11B2[**TT-../..**; (CC-./. ve TC-../..)] | .931 | 1.057 | 0.304-674 | |
| | $\beta_0$ constant | .000 | 0.000 | | |
| Model 4 | BMI percentile | **.000** | **1.102** | **1.055-1.151** | 0.557 |
| | APOB100[**AA-../..**; (GG-./. ve AG-../..)] | .999 | 0.000 | 0.000-. | |
| | $\beta_0$ constant | 1.000 | 103874.7 | | |
| Model 5 | BMI percentile | **.000** | **1.104** | **1.057-1.154** | 0.552 |
| | FABP2[**AA-../..**; (GG-./. ve AG-../..)] | .747 | 0.725 | 0.103-5.119 | |
| | $\beta_0$ constant | .000 | 0.000 | | |
| Model 6 | BMI percentile | **.000** | **1.103** | **1.056-1.151** | 0.558 |
| | RENIN[**DD-../..**; (II-./. ve ID-../..)] | .356 | 1.718 | 0.545-5.422 | |
| | $\beta_0$ constant | .000 | 0.000 | | |

ACE, II: risk genotype n/n (DD ve ID): reference genotypes; AGT, TT: risk genotype n/n (MM ve MT): reference genotypes; CYP11B2, TT: risk genotype n/n(CC ve TC): reference genotypes; APOB100, AA: risk genotype n/n (AG ve GG): reference genotypes; FABP2, AA: risk genotype n/n (AG ve GG): reference genotypes; RENIN, DD: risk genotype n/n (II ve ID): reference genotypes, LR: Logistic regression.

**Table 5.** Blood Pressure for Group 1 Percentile 99 and LR Models in 6 Group Separations in Which BMI is Controlled for 6 Genes

| | | *P* | OR | 95% CI OR | $R^2$ |
|---|---|---|---|---|---|
| Model 1 | BMI percentile (continuously variable) | **.549** | **1.014** | **0.968-1.063** | 0.011 |
| | ACE[**II-.../..**;(DD-../.. ve ID-../…)] | .926 | 1.086 | 0.191-6.180 | |
| | $\beta_0$ constant | .991 | 1.025 | | |
| Model 2 | BMI percentile | **.560** | **1.014** | **0.968-1.063** | 0.024 |
| | AGT[**TT-../..**; (MM-./. ve TM-../..)] | .519 | 0.597 | 0.125-2.859 | |
| | $\beta_0$ constant | .927 | 1.231 | | |
| Model 3 | BMI percentile | **.467** | **1.018** | **0.970-1.070** | 0.019 |
| | CYP11B2[**TT-../..**; (CC-./. ve TC-../..)] | .629 | 1.564 | 0.256-9.561 | |
| | $\beta_0$ constant | .863 | 0.658 | | |
| Model 4 | BMI percentile | **.578** | **1.013** | **0.967-1.062** | 0.038 |
| | APOB100[**AA-../..**; (GG-./. ve AG-../..)] | .999 | 392201874.3 | 0- | |
| | $\beta_0$ constant | .966 | 1.101 | | |
| Model 5 | BMI percentile | **.625** | **1.012** | **0.965-1.060** | 0.065 |
| | FABP2[**AA-../..**; (GG-./. ve AG-../..)] | .999 | 416908662.7 | 0- | |
| | $\beta_0$ constant | .993 | 1.209 | | |
| Model 6 | BMI percentile | **.535** | **1.015** | **0.969-1.063** | 0.011 |
| | RENIN[**DD-../..**; (II-./. ve ID-../..)] | .971 | 0.974 | 0.235-4.040 | |
| | $\beta_0$ constant | .994 | 1.016 | | |

ACE, II: risk genotype n/n (DD ve ID): reference genotypes; AGT, MM: risk genotype n/n (TT ve MT): reference genotypes; CYP11B2, TT: risk genotype n/n(CC ve TC): reference genotypes; APOB100, AA: risk genotype n/n (AG ve GG): reference genotypes; FABP2, AA: risk genotype n/n (AG ve GG): reference genotypes; RENIN, DD: risk genotype n/n (II ve ID): reference genotypes, LR: Logistic regression.

polymorphism distribution difference (with 1 homozygous dominant, 1 homozygous recessive, and heterozygous grouping) was examined in the patient and control groups, no statistically significant difference was found. Insertion in the ACE gene reduces ACE expression thus, DD homozygotes have 65% ACE and II homozygotes have 31% more ACE than II homozygotes.[14] Studies have reported that there is a relationship between ACE I/D polymorphism and the development of many pathological conditions such as coronary heart disease, ventricular hypertrophy, myocardial infarction, restenosis after coronary angioplasty, cardiomyopathy, and sudden cardiac death.[15-18] There are studies that reported that plasma ACE activity is higher in the ACE D allele compared to the ACE I allele.[17] In a study conducted in the Turkish population, it was concluded that DD genotype is a predisposing factor in serious HT patients with positive family history and ACE I/D polymorphism may affect HT development as one of the independent factors.[19] Besides studies reporting that there is a relationship between ACE genotype and diastolic BP in men; there are also studies reporting no relationship.[20] When the M235T polymorphism in the AGT gene was examined in a study conducted by Say et al[21] on the Malaysians in 2005, it was observed that the frequency of TT in patients with HT increased significantly compared to the control group. In a study conducted on Czechs by Vasku et al[22] in 2002, frequencies of M235T polymorphisms in HT and healthy candidates were examined, but no significant difference was observed. Many studies investigating the relationship between 344T/C polymorphism and BP have obtained contradictory results. While some of the studies mention a significant relationship between high BP and the C allele, other studies have associated the T allele with high BP. In a few studies, it was reported that there was no significant relationship between BP and 344T/C polymorphism.[23-25]

In a study conducted by Abbas et al to elucidate polygenic etiology, FABP2 gene polymorphism was investigated in 138 primary HT patients; it was observed that there was a risk factor in the development of HT in patients.[26] Studies have shown the relationship between insulin resistance, hypertriglyceri demia, increased risk of BMI, and metabolic syndrome and FABP2 gene polymorphism. In the study conducted by Gomez et al[27] no significant relationship was found in terms of FABP2 and cardiovascular risk. Recent studies show that ApoB100 gene polymorphism is responsible for increased postprandial lipemic response and is a risk factor for the development of the metabolic syndrome.[28] However, there is no study in the literature related to HT etiology. To examine the relationship of these 6 genotype changes with their severity at the time of diagnosis, genotype frequencies were compared in 2 different groups, the ones with BP percentiles over 99 and over 95 at the time of diagnosis, but no difference was found. In the literature, no study investigating the effect of genetic polymorphisms, which are the subject of the study, on the severity and stage of the disease at the time of HT diagnosis has been found. In this study, this relationship was examined and contributed to the literature. In the study of FABP2 conducted in Argentina, allele frequencies were calculated directly and the population was found to be in balance.[27] Although the 6 gene changes we examined in our study in univariate analyses were not identified as a risk for HT in these children, they were examined in the multivariate analysis model (logistic regression analysis) in changes in the presence of obesity. Genotype changes were not identified as a risk in 6 different models we created in 6 genes, BMI was found as an important risk. By measuring the BP 3 times, Fuiano et al[29] conducted a study on 1563 school children aged between 3 and 16 and found obesity in 23% of boys and 31.2% of girls whose BP was over the 95th percentile. This height was higher and statistically significant compared to children with normal BP. In the same study, obesity was reported as a risk factor for HT.[29] Mohan et al[30] found that the frequency of HT in 2467 school children aged between 11 and 17 in the Ludhiana region of India was statistically significantly higher in obese children. In obesity, it is known to be associated with some of these genes and is thought to be indirectly involved in HT etiology. A limitation to be said about the study is that Task Force 4 criteria, which are still used during the study, have been used.



In conclusion, when this study conducted in regard to genetics of primary HT was evaluated, ACE, renin, angiotensin, aldosterone, FABP2, and ApoB100 gene polymorphisms were not identified as risk factors in existing pathways.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee of Ege University (Date: April 27, 2016, Decision No: 70198063-050.06.04-193).

**Informed Consent:** Informed consent was obtained from all individual participants included in the study.

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**Author Contributions:** Concept – ÖÖŞ; Design – ÖÖŞ; Supervision – ÖÖŞ.; Funding – ÖÖŞ; Materials – AB; Data Collection and/or Processing – AB; Analysis and/or Interpretation – AB; Literature Review – AK; Writing – ÖÖŞ; Critical Review –AK.

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