North Clin Istanb 2025;12(1):55–61
doi: 10.14744/nci.2023.84770

Original Article MEDICAL BIOCHEMISTRY

# Investigation of the effects of MTHFR gene variations and homocysteine levels in hypertensive patients

**Sibel Kuras,[1] Mahmud Esad Pence,[2] Esref Arac,[3] Ahmet Yildiz,[4] Bekir Erdogan,[5] Sadrettin Pence[6]**

[1]Department of Medical Biochemistry, University of Health Sciences, Hamidiye Faculty of Medicine, Istanbul, Turkiye
[2]Department of Medical Biochemistry, Istanbul Medipol University Faculty of Medicine, Istanbul, Turkiye
[3]Department of Internal Medicine, Dicle University Faculty of Medicine, Diyarbakir, Turkiye
[4]Department of Cardiology, Istanbul University Faculty of Medicine, Istanbul, Turkiye
[5]Department of Physiology, University of Health Sciences, Hamidiye Faculty of Medicine, Istanbul, Turkiye
[6]Department of Physiology, Istanbul Medeniyet University Faculty of Medicine, Istanbul, Turkiye

## ABSTRACT

**OBJECTIVE:** To investigate the effects of methylenetetrahydrofolate reductase (MTHFR) gene C677T/A1298C polymorphisms on serum homocysteine levels and hypertension.

**METHODS:** Venous blood samples were collected in EDTA tubes from patients and controls (80 hypertensive patients and 67 healthy controls) and genomic DNA was isolated. The polymorphisms of MTHFR C677T and A1298C were identified using the polymerase chain reaction (PCR) and restriction fragment length polymorphisms (RFLP) technique. The enzyme-linked immunosorbent assay (ELISA) method was used to determine serum homocysteine levels. ANOVA, Student's t-test, chi-square test and logistic regression analysis tests used in the evaluation of statistical analysis between patient and control groups were performed with SPSS 21.0 program.

**RESULTS:** A statistically significant difference was observed between the patient group, which were hypertension-diagnosed patients, and control group for C677T polymorphism ($p<0.001$), but not for the A1298C polymorphism ($p=0.058$). When serum homocysteine levels were compared between the patient and control groups, no significant difference was observed ($p=0.065$). A significant difference was observed between C677T allele frequency (TT + CT versus CC) and homocysteine levels in both groups ($p=0.027$), whereas no significant difference was observed between A1298C allele frequency (CC + AC versus AA) and homocysteine levels ($p=0.996$).

**CONCLUSION:** The MTHFR C677T polymorphism is more common in hypertensive patients. T allele frequencies (CT and TT genotypes) and TT genotypes might increase the risk of hypertension and homocysteine levels. Although the A1298C C allele frequency (AC and CC genotypes) might increase the risk of hypertension, CC genotype distributions and homocysteine levels show no statistical significance on hypertension. C677T polymorphism is associated with hypertension thus it may be used as a potential biomarker.

*Keywords: Gene polymorphism; homocysteine; hypertension; MTHFR.*

***Cite this article as:*** *Kuras S, Pence ME, Arac E, Yildiz A, Erdogan B, Pence S. Investigation of the effects of MTHFR gene variations and homocysteine levels in hypertensive patients. North Clin Istanb 2025;12(1):55–61.*

Hypertension is a common chronic disease and is an important modifiable risk factor for cardiovascular complications such as atherosclerosis. The prevalence of hypertension is increasing worldwide and it continues to increase similarly in Turkiye [1]. According to The Global Burden of Disease study, it has been shown that 1.28

*Received:* September 05, 2023 *Revised:* November 04, 2023 *Accepted:* December 04, 2023 *Online:* February 04, 2025

Correspondence: Sibel KURAS, MD. Saglik Bilimleri Universitesi, Hamidiye Tip Fakultesi, Tibbi Biyokimya Anabilim Dali, Istanbul, Turkiye.
Tel: +90 216 777 90 00 e-mail: sibel.kuras@gmail.com

Istanbul Provincial Directorate of Health - Available online at www.northclinist.com

billion people (20% of women and 24% of men) have hypertension worldwide. It has also been stated that 9.4 million people die each year due to hypertension [2, 3].

Homocysteine is an amino acid containing a thiol group (-SH) and derived from methionine and its homologue cysteine. Homocysteine amino acid is non-proteinogenic and occurs naturally in humans [4, 5]. The methyl group from 5-methyltetrahydrofolate or betaine, the active form of folate in the remethylation pathway, is taken up by homocysteine to be transformed to methionine. The transsulfuration process, in which homocysteine condenses with serine to generate cystathionine, is the mechanism by which homocysteine is irreversibly removed [6].

Although high levels of homocysteine are considered as a risk factor for atherosclerosis, its molecular basis has not been fully elucidated. However, hyperhomocysteinemia (HHcy), which is characterized by increased plasma/serum levels of homocysteine, is seen in endothelial dysfunction as the initial event for atherosclerosis [7, 8]. Although homocysteine levels are 5–10 μmol/L in healthy individuals, it can reach up to 500 μmol/L in individuals with HHcy [8]. HHcy has been associated with a variety of adult and pediatric pathologies [4]. HHcy is caused by genetic mutations and enzyme deficiencies of 5, 10- methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MS) and cystathionine β-synthase (CβS) [4, 9].

The gene encoding the MTHFR protein is localized in the short arm (1p36.3) of the 1st chromosome and encodes dimeric proteins. MTHFR catalyzes the irreversible reduction of 5, 10-methylenetetrahydrofolate (5, 10-MTHF) to 5-methyl THF, a circulating form of folate used in the remethylation of homocysteine to methionine [10]. The MTHFR enzyme is also involved in DNA methylation and nucleotide synthesis, which play a major role in processes such as gene regulation and cellular differentiation [11, 12].

C677T (C>T) and A1298C (A>C) polymorphisms are two of the most common polymorphisms seen in the MTHFR gene. The C677T polymorphism (rs1801133) results in the substitution of the amino acid valine for the amino acid alanine at the 222nd codon of the enzyme as a result of the replacement of cytosine at position 677 with thymine. This polymorphism causes the enzyme to become thermolabile, causing enzyme dysfunction and may affect homocysteine levels. Another polymorphism, the A1298C polymorphism (rs1801131), results in the replacement of adenine at position 1298 with cytosine, resulting in the replacement of glutamate with the amino acid alanine at the 429th codon of the enzyme [10, 13]. Although the A1298C polymorphism is not as effective as the C677T polymorphism, it causes a decrease in enzyme activity, but its effect on homocysteine levels is not clear [10, 13, 14].

**Highlight key points**

- MTHFR C677T polymorphism is more common hypertensive patients.
- MTHFR C677T polymorphism has more effect on homocysteine levels than A1298C polymorphism.
- Allele frequency distributions between patient and control groups were statistically significant for both C677T and A1298C polymorphisms.
- In the C677T polymorphism, the T allele is associated with HHcy, especially in the TT genotype.

Studies have shown that both C677T and A1298C co-heterozygotes are associated with a 50–60% decrease in MTHFR enzyme activity, while the C677T TT genotype is associated with a 35–70% decrease in MTHFR enzyme activity [14–16]. Clinical studies demonstrated a significant association between MTHFR polymorphism and various diseases, such as psychiatric disorders, neuronal developmental diseases, cancers as well as cardiovascular diseases [11]. Given this information, we looked at the influence of MTHFR polymorphisms (C677T and A1298C) and serum homocysteine levels on hypertension.

## MATERIALS AND METHODS

In the study, 80 participants with only hypertension [no other concomitant diseases (i.e., coronary artery disease, other atherosclerotic disorders)] followed by Istanbul University Cardiology Institute Cardiology Department, were included in the patient group. Patients with a blood pressure of 140/90 mm Hg or higher in ambulatory measurements were considered to have hypertension. In the control group, 67 healthy individuals without any signs of cardiovascular disease, hypertension, metabolic disorders (diabetes, kidney failure, liver failure, etc.) and lipid metabolism disorders were included. Informed consent forms about the research to be conducted had been read and signed by the volunteers who participated in the study. Ethical approval of the study was obtained from the

Istanbul University Faculty of Medicine Clinical Research Ethics Committee (date: 08.06.2015, number: 2015/1102). The Helsinki Declaration of Human Rights was followed.

Genomic DNAs were extracted using Blood DNA Isolation Kit (Jena Biosciences, Germany) from peripheral blood samples taken from healthy and hypertensive volunteers. Detecting variations of MTHFR gene C677T (rs1801133) and A1298C (rs1801131) were performed by the polymerase chain reaction (PCR) and restriction fragment length polymorphism method. Forward primer sequence 5′-TGAAGGAGAAGGTGTCTGCGGGA-3′ and reverse primer sequence R-5′-AGGACGGTGCGGTGAGAGTG-3′ were used for C677T polymorphism. Forward primer sequence 5′-ATGTGGGGGGAGGAGCTGAC-3′ and reverse primer sequence R-5′-GTCTCCCAACTTACCCTTCTCCC-3′ were used for A1298C polymorphism. A total of 25 µl PCR mix containing 10X reaction solution, 10 mM dNTP, 0.1 U Taq DNA polymerase, gene site-specific primers and 500 ng DNA samples were prepared for DNA amplification. Thermal cycler (C1000™; BioRad, CA, USA) was used for PCR amplifications with a total volume of 25 µl. HinfI (Fermentas) and MboII (Fermentas) enzymes were applied for digesting 198 bp (rs1801133) and 241 bp (rs1801131) PCR products, respectively. 3% agarose gel electrophoresis containing ethidium bromide was used to separate restriction fragments, and after electrophoresis, the gel was visualized under ultraviolet light. The 175 and 23 bp restriction fragments of C677T polymorphism were obtained for T allele. The 204 and 37 bp restriction fragments of A1298C polymorphism were obtained for C allele.

Peripheral blood samples taken into tubes with separator gel were centrifuged at 3000 rpm for 5 minutes and serums were separated. Serum homocysteine concentrations of the separated serum were measured with the "YH Biosearch Laboratory Homocysteine ELISA Kit" using the protocol in accordance with the kit.

### Statistical Analysis

Statistical analysis of the findings and data obtained was performed with SPSS 21.0 (IBM Corp., Armonk, NY, USA) programm. ANOVA, Student's t-test, chi-square test and logistic regression analysis were used to show comparative data between patient and control groups. The significance level was accepted as $p<0.05$.

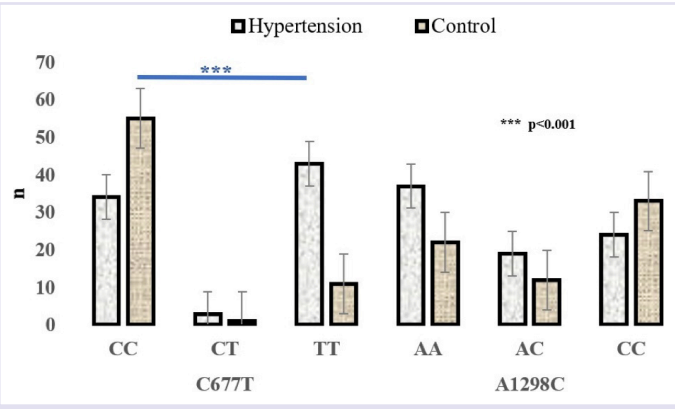


FIGURE 1. Genotype disributions between hypertension and control groups.

## RESULTS

In MTHFR C677T polymorphism, CC genotype is wild-type with only 198 bp, CT genotype is heterozygote with 198 and 175 bp, and TT genotype is homozygote mutant with 175 bp. In MTHFR A1298C polymorphism, AA genotype is wild-type with only 241 bp, AC genotype is heterozygote with 241 and 204 bp, and TT genotype is homozygote mutant with 204 bp.

The distribution of C677T and A1298C polymorphisms between patient and control groups were evaluated by chi-square test. When statistical significance was observed between C677T genotype distributions and groups ($p<0.001$), no statistical significance was observed between A1298C genotype distributions and groups ($p=0.058$). The most common genotype in the patient group was TT (79.60%), whereas the most common genotype in the control group was CC (61.80%) for C677T polymorphism. In A1298C polymorphism, the genotype distributions were similar between the patient and control groups (Fig. 1).

When the allele frequency distributions between the patient and control groups were evaluated, statistical significance was observed in both C677T and A1298C allele frequency distributions ($p<0.001$ and $p=0.005$, respectively) (Fig. 2).

According to Hardy-Weinberg analysis, when the observed and expected values for C677T and A1298C polymorphisms were compared, both were found to be statistically significant ($p<0.001$). Adjusted for sex, age and body mass index, C677T polymorphism T allele and A1298C C allele was statistically significant between patient and control groups ($p<0.001$ and $p=0.034$, respectively).

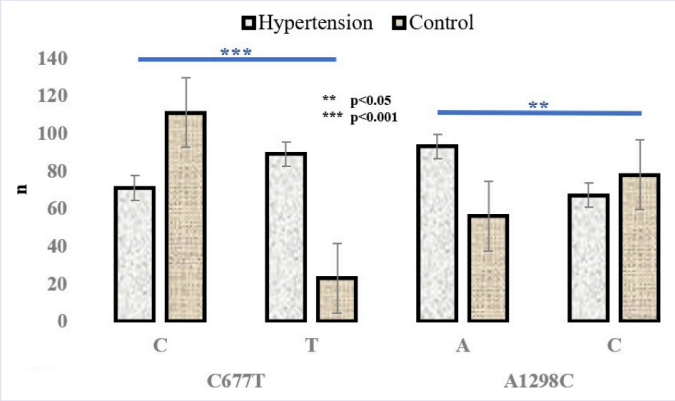


FIGURE 2. Allele frequencies of MTHFR polymorphisms between hypertension and control groups.

There was no statistically significant difference between serum homocysteine levels and groups (p=0.065). The fact that the p-value is very close to significance is closely related to the increased frequency of the T allele in the patient group. Serum homocysteine levels were 24.63±2.18 μmol/L in patient group and 19.41±1.76 μmol/L in control group. When compared with the homocysteine levels and genotype frequencies, statistical significance was between serum homocysteine levels and C677T (p=0.027), but no statistical significance was observed between serum homocysteine levels and A1298C (p=0.996). According to student t-test, when compared with the homocysteine levels and allele frequencies, statistical significance was between serum homocysteine levels and C677T (p=0.022), but no statistical significance was observed between serum homocysteine levels and A1298C (p=0.97).

## DISCUSSION

Hypertension is defined as systolic blood pressure (SBP) at least 130 mm Hg or diastolic BP (DBP) at least 80 mm Hg. Hypertension is associated with an increased risk for cardiovascular diseases and death [17]. Hypertension is a well-known modifiable risk factor for cardiovascular disease, with substantial morbidity and mortality rates [18]. Blood pressure-related deaths are increasing worldwide. It is thought that a number of factors, including aging, obesity, and insulin resistance, contribute to the development of hypertension [19]. Previous research has indicated that genetic factors associated with an elevated risk of HT account for about 60% of risk factors [20]. In the treatment of hypertension, lifestyle modifications such as weight loss, a healthy diet including low sodium and high potassium intake, physical activity and reduction/elimination of alcohol consumption are primarily applied. Antihypertensive medication is administered taking into account the blood pressure level and the high risk of atherosclerosis [17, 21]. Short and long-time consequences of hypertension are stroke, coronary artery disease, heart failure and cardiovascular death. Among the long-term complications of hypertension are hypertensive cardiomyopathy, valvular heart disease, heart failure with preserved ejection fraction, aortic syndromes, atrial fibrillation, peripheral artery disease, chronic renal disease, diabetes mellitus, dementias and erectile dysfunction [22].

Vascular damage resulting from persistently increased arterial pressure is a characteristic of hypertension and one of the first signs of target organ damage [23]. As an indicator of vascular health, arterial stiffness provides an additional independent predictive value for both hypertension-mediated organ damage and adverse cardiovascular outcomes [24].

MTHFR is one of the enzymes that has an important role in maintaining the balance between methionine and homocysteine to prevent cellular dysfunction [10]. The roles of the C677T and A1298C polymorphisms observed in the MTHFR gene, which encodes the MTHFR enzyme, have been investigated in various diseases, including cardiovascular disorders, rheumatoid arthritis, diabetes, psychiatric illnesses, and cancer [10, 11, 13, 23]. These polymorphisms in the MTHFR gene may affect the activity of the enzyme, which is the product of the gene, resulting in an increase in homocysteine levels. It is now known that the mutant allele 677C>T, which causes a decrease in the activity of the MTHFR enzyme, which plays an important role in homocysteine metabolism, is now the most common genetic cause of HHcy [25]. So the effect of C677T polymorphism on enzyme activity is greater than that of A1298C [10]. When there is a deregulation of the homocysteine metabolic pathway, intracellular homocysteine enters circulation and increases plasma/serum levels of homocysteine [26].

Although the correlation between hypertension and MTHFR C677T gene polymorphisms was not clear in previous studies, Xu et al. [20] showed that blood pressure levels were significantly higher in participants with C677T TT genotype compared to those with CC or CT genotypes. Homocysteine levels were also higher in individuals with TT genotype [20]. In our study, the hypertension group consisted only of people with a diagnosis of hypertension. In our study, both genotype distribu-

tions (TT genotype was higher in hypertension group) and allele frequency (T alleles were higher in hypertension group) of C677T polymorphism were statistically significant in only hypertension-diagnosed patients than controls. Considering the A1298C polymorphism, while genotype distributions were not statistically significant between groups, allele frequency (C alleles were higher in hypertension group) was statistically significant in patient group than control group. According to a study by Al Hageh et al. [25], patients with the T allele of the C677T polymorphism, especially TT genotype had greater homocysteine levels. In addition, homocysteine levels were higher in hypertensive patients with the TT genotype compared to CC carriers [25].

Alghasham et al. [27] showed that T allele (TT and CT genotypes) for C677T polymorphism and C allele (CC and AC genotypes) for A1298C polymorphism were statistically more significant in hypertension patients compared to the control group. However, due to the presence of obesity and diabetes in the hypertension group, it was observed that these allele frequencies were not significant in only hypertension patients [27]. Based on this, it may be considered that MTHFR polymorphisms may contribute to the presence of other comorbidities in addition to hypertension but may not have an effect on the occurrence of hypertension alone. In a meta-analysis conducted by Wu et al. [28], it was reported that C677T polymorphism may play a role in the development of hypertension, whereas A1298C polymorphism was not associated with hypertension risk, which supports the results of our study [28].

Although the results of the meta-analyses are controversial, different results have emerged in different population-based studies, including studies conducted in Turkiye. According to a meta-analysis by Meng et al. [29], A1298C polymorphism genotype distributions were not associated with hypertension, both in the general population and when grouped by ethnicity. However, when subgrouped by geographical location, a clear risk correlation was observed in the South Asian region. When C677T polymorphism genotype distributions were evaluated, it was found to be associated with hypertension in the overall population. When subgrouped according to ethnicity and geographical location, it was observed to increase the risk of hypertension to different degrees [29]. In another meta-analysis, the C677T polymorphism rather than the A1298C polymorphism was associated with hypertension, especially among East Asians and Caucasians [30].

Homocysteine is a risk factor for cardiovascular and cerebrovascular disease that has been linked to vascular dysfunction and increased venous thrombosis [24, 31]. The impact of HHcy, a predictor of cardiovascular disease, on hypertension is controversial. Some studies found low homocysteine levels in those with high blood pressure, while others found greater homocysteine levels in people with high blood pressure, which is consistent with our findings. Several mechanisms have been proposed to explain the relationship between hypertension and homocysteine, which may play an important role in the onset of hypertension. These can be explained as HHcy causing endothelial dysfunction due to autooxidation of homocysteine and homocysteine contributing to arterial stiffness by destroying elastin fibers and increasing collagen production [19]. Because it has been suggested that HHcy-induced oxidative stress, inflammation, endothelial dysfunction, smooth muscle cell proliferation and endoplasmic reticulum (ER) stress are key factors in the etiology of a number of illnesses, including atherosclerosis and stroke [32].

In a study conducted by Zhao et al. [19] in a group with an average follow-up of 6 years, each 1 μmol/l homocysteine increase in hypertensive patients was found to be statistically significant for all-cause and CVD mortality. In nonhypertensive individuals, the association of homocysteine with neither all-cause mortality nor CVD mortality was statistically significant [19]. It is thought that the administration of folic acid and B vitamins as homocysteine-lowering treatments may be effective for preventing atherosclerosis, CVD and neurodegenerative diseases [32]. Although there are epidemiological studies showing that homocysteine is associated with an increased risk of CVD, many homocysteine-lowering interventional trials have not been found to reduce the risk of CVD. Therefore, it is debatable whether homocysteine represents a biomarker or reversible causal risk factor for elevated CVD risk [18].

Zhang et al. [18] showed that HHcy is an independent risk factor and when accompanied by hypertension, it increases both the incidence of cardiovascular disease and all-cause mortality in Chinese elderly individuals with no cardiovascular history [18]. Although many studies, including the Framingham study, cannot identify HHcy as the culprit of hypertension, there are many studies showing that it is related. The Third National Health and Nutrition Examination Survey's NHANES III large observational trial demonstrated a link between HHcy and hypertension. The SHEP (Systolic Hypertension in the Elderly Program) study revealed similar results, demonstrating a connection between HHcy and high systolic blood pressure [25].

## Conclusion

In conclusion, we analyzed the link between homocysteine, one of the important risk factors for CVD, and hypertension, as well as the MTHFR gene C677T and A1298C polymorphisms, which may have a significant effect on serum/plasma homocysteine levels. We suggest that C677T polymorphism rather than A1298C can be evaluated as a potential biomarker for the risk of hypertension. In addition, C677T polymorphism has more effect on homocysteine levels and HHcy may contribute to the development of hypertension. Although there are many studies supporting our results, further studies with a larger sample size are needed because the results are still contradictory.

**Ethics Committee Approval:** The Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 08.06.2015, number: 2015/1102).

**Authorship Contributions:** Concept – SK; Design – SK, SP; Supervision – SP; Materials – EA, AY; Data collection and/or processing – SK, SP, MEP; Analysis and/or interpretation – SK, SP, BE; Literature review – SK, EA, MEP; Writing – SK, MEP; Critical review – SK, SP, MEP.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Use of AI for Writing Assistance:** Artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots or image generators, such as ChatGPT) were not used in the study.

**Financial Disclosure:** Istanbul University Scientific Research Coordination Unit (Project Number: 55929).

**Peer-review:** Externally peer-reviewed.

## REFERENCES

1. Pamukcu B. Profile of hypertension in Turkey: from prevalence to patient awareness and compliance with therapy, and a focus on reasons of increase in hypertension among youths. J Hum Hypertens 2022;36:437-44. [CrossRef]
2. Franco C, Sciatti E, Favero G, Bonomini F, Vizzardi E, Rezzani R. Essential hypertension and oxidative stress: novel future perspectives. Int J Mol Sci 2022;23:14489. [CrossRef]
3. WHO. Hypertension. Available at: https://www.who.int/news-room/fact-sheets/detail/hypertension. Accessed Sept 12, 2024.
4. Zaric BL, Obradovic M, Bajic V, Haidara MA, Jovanovic M, Isenovic ER. Homocysteine and hyperhomocysteinaemia. Curr Med Chem 2019;26:2948-61. [CrossRef]
5. Hermann A, Sitdikova G. Homocysteine: biochemistry, molecular biology and role in disease. Biomolecules 2021;11:737. [CrossRef]
6. Yuan S, Mason AM, Carter P, Burgess S, Larsson SC. Homocysteine, B vitamins, and cardiovascular disease: a Mendelian randomization study. BMC Med 2021;19:97. [CrossRef]
7. Esse R, Barroso M, Tavares de Almeida I, Castro R. The contribution of homocysteine metabolism disruption to endothelial dysfunction: state-of-the-art. Int J Mol Sci 2019;20:867. [CrossRef]
8. Hasan T, Arora R, Bansal AK, Bhattacharya R, Sharma GS, Singh LR. Disturbed homocysteine metabolism is associated with cancer. Exp Mol Med 2019;51:1-13. [CrossRef]
9. Moll S, Varga EA. Homocysteine and MTHFR mutations. Circulation 2015;132:e6-9. [CrossRef]
10. Raghubeer S, Matsha TE. Methylenetetrahydrofolate (MTHFR), the one-carbon cycle, and cardiovascular risks. Nutrients 2021;13:4562. [CrossRef]
11. Wan L, Li Y, Zhang Z, Sun Z, He Y, Li R. Methylenetetrahydrofolate reductase and psychiatric diseases. Transl Psychiatry 2018;8:242. [CrossRef]
12. Raoufi A, Rahimi Kelarijani B, Ahadi HR, Hassani Derakhshandeh B, Nooroollahzadeh Z, Hajifathali A. Association of MTHFR C677T and A1298C polymorphisms with susceptibility to chronic lymphocytic leukemia: a systematic review and meta-analysis. Iran J Public Health 2021;50:83-92. [CrossRef]
13. Petrone I, Bernardo PS, Dos Santos EC, Abdelhay E. MTHFR C677T and A1298C polymorphisms in breast cancer, gliomas and gastric cancer: a review. Genes (Basel) 2021;12:587. [CrossRef]
14. Li Y, Qiu S, Shi J, Guo Y, Li Z, Cheng Y, et al. Association between MTHFR C677T/A1298C and susceptibility to autism spectrum disorders: a meta-analysis. BMC Pediatr 2020;20:449. [CrossRef]
15. Pan X, Lu Y, Long Y, Yao D. Genetic polymorphisms of methylenetetrahydrofolate reductase (MTHFR) gene Ala222Val and susceptibility to ovary cancer: a systematic review and meta-analysis. Tumour Biol 2014;35:2133-9. [CrossRef]
16. Rai V. Association of methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism with autism: evidence of genetic susceptibility. Metab Brain Dis 2016;31:727-35. [CrossRef]
17. Carey RM, Moran AE, Whelton PK. Treatment of hypertension: a review. JAMA 2022;328:1849-61. [CrossRef]
18. Zhang ZY, Gu X, Tang Z, Guan SC, Liu HJ, Wu XG, et al. Homocysteine, hypertension, and risks of cardiovascular events and all-cause death in the Chinese elderly population: a prospective study. J Geriatr Cardiol 2021;18:796-808.
19. Zhao W, Gao F, Lv L, Chen X. The interaction of hypertension and homocysteine increases the risk of mortality among middle-aged and older population in the United States. J Hypertens 2022;40:254-63. [CrossRef]
20. Xu JR, Zhang XY, Zhao L, Han QH. Correlation between hypertension and high homocysteine levels caused by the MTHFR C677T gene polymorphisms. Asian J Surg 2022;45:1039-40. [CrossRef]
21. Di Palo KE, Barone NJ. Hypertension and heart failure: prevention, targets, and treatment. Cardiol Clin 2022;40:237-44. [CrossRef]
22. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. Hypertension 2020;75:285-92. [CrossRef]
23. Arida A, Nezos A, Papadaki I, Sfikakis PP, Mavragani CP. Osteoprotegerin and MTHFR gene variations in rheumatoid arthritis: association with disease susceptibility and markers of subclinical atherosclerosis. Sci Rep 2022;12:9534. [CrossRef]
24. Carnagarin R, Nolde JM, Ward NC, Lugo-Gavidia LM, Chan J, Robinson S, et al. Homocysteine predicts vascular target organ damage in hypertension and may serve as guidance for first-line antihypertensive therapy. J Clin Hypertens (Greenwich) 2021;23:1380-9. [CrossRef]
25. Al Hageh C, Alefishat E, Ghassibe-Sabbagh M, Platt DE, Hamdan H, Tcheroyan R, et al. Homocysteine levels, h-hypertension, and the MTHFR C677T genotypes: a complex interaction. Heliyon 2023;9:e16444. [CrossRef]
26. Azzini E, Ruggeri S, Polito A. Homocysteine: its possible emerging role in at-risk population groups. Int J Mol Sci 2020;21:1421. [CrossRef]

27. Alghasham A, Settin AA, Ali A, Dowaidar M, Ismail H. Association of MTHFR C677T and A1298C gene polymorphisms with hypertension. Int J Health Sci (Qassim) 2012;6:3-11. [CrossRef]
28. Wu YL, Hu CY, Lu SS, Gong FF, Feng F, Qian ZZ, et al. Association between methylenetetrahydrofolate reductase (MTHFR) C677T/A1298C polymorphisms and essential hypertension: a systematic review and meta-analysis. Metabolism 2014;63:1503-11. [CrossRef]
29. Meng H, Huang S, Yang Y, He X, Fei L, Xing Y. Association between MTHFR polymorphisms and the risk of essential hypertension: an updated meta-analysis. Front Genet 2021;12:698590. [CrossRef]
30. Yang B, Fan S, Zhi X, Li Y, Liu Y, Wang D, et al. Associations of MTHFR gene polymorphisms with hypertension and hypertension in pregnancy: a meta-analysis from 114 studies with 15411 cases and 21970 controls. PLoS One 2014;9:e87497. [CrossRef]
31. Fung MM, Salem RM, Lipkowitz MS, Bhatnagar V, Pandey B, Schork NJ, et al; AASK Study Investigators. Methylenetetrahydrofolate reductase (MTHFR) polymorphism A1298C (Glu429Ala) predicts decline in renal function over time in the African-American Study of Kidney Disease and Hypertension (AASK) Trial and Veterans Affairs Hypertension Cohort (VAHC). Nephrol Dial Transplant 2012;27:197-205. [CrossRef]
32. Moretti R, Caruso P. The controversial role of homocysteine in neurology: from labs to clinical practice. Int J Mol Sci 2019;20:231. [CrossRef]