AGT GENE VARIANTS ASSOCIATED WITH HYPERTENSION – A SHORT REVIEW

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Abstract

The present review provides an in-depth study of variants of the angiotensinogen (AGT) gene, which plays an important role in risk factors associated with cardiovascular disease and hypertension. The AGT gene is used in our body to regulate blood pressure and also ensure the balance of different fluids in the human body. This study aimed to identify common variants that play an important role in cardiovascular disease. This research also includes determining the impact that variants and their mutations may have on the development of essential hypertension. Kurdi, De Mello, and Booz (2005, p.1357-1367) stated that the renin-angiotensin-aldosterone system "RAAS"; is responsible for the cause of hypertension.

The results of this study focused on 9 SNPs formed in the AGT gene, the SNPs present in exon number 2 named rs699 and rs4762 and in the untranslated region, 5 SNPs named rs5046 were found, rs5049, rs11568020, rs5050 and rs5051.

Finally, the intron contains two SNPs named rs2148582 and rs3789679. She determined that the AGT gene helps us better understand the function and processes of different variants. Several studies have found an association between enhanced AGT gene variants that cause hypertension and plasma AGT. The following research covers various aspects of angiotensinogen AGT, its system, and its impact on various functions in our body.

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Introduction

Globally, cardiovascular disease (CVD) is the primary cause of death [1]. According to the 2013 Global Burden of Disease Study, cardiovascular disease (CVD) accounts for over 30% of all deaths globally.

Recent data from Europe, however, indicates that cancer may now be the main cause of mortality in some nations, surpassing CVD [1].

In the past ten years, England has seen an improvement in myocardial infarction (MI) survival.3.The quantity of medications prescribed to treat different CVD problems and the kinds of operations performed to treat MIs have also changed during the past ten years.

In Asia, cardiovascular disease (CVD) is the primary cause of death. Of the 18.6 million deaths globally from CVD in 2019, 58% happened in Asia [2]. Asia presents numerous problems in the prevention and treatment of CVD because it is the continent with the largest population and the greatest range of ethnicities, cultures, socioeconomic level, and health care systems.

In the Gulf Council countries, such as Saudi Arabia, where CVD is thought to be the cause of more than 45% of all deaths, it is also emerging as a significant health concern. The INTERHEART and INTERSTROKE investigations found that obesity, smoking, low physical activity, poor diet, diabetes, dyslipidemia, hypertension, and alcohol consumption were the most common risk factors for CVD [3].

Rapid urbanization in the Gulf countries has resulted in a drastic shift in lifestyle, with a rise in bad food and sedentary behavior. As a result, the Gulf population has high prevalence of chronic non-communicable illnesses and CVD risk factors [3].

Because it is regarded as a risk factor for cardiovascular disease (CVD), hypertension is the most prevalent and complicated human illness that significantly increases morbidity and death globally. Due to its deadly consequences, which include heart failure, stroke, and renal illness, it continues to be a serious health issue that requires significant financial outlays [4].

According to the WHO, hypertension expression, also referred to as high blood pressure, is a condition in which the blood vessels have a continuously elevated pressure. The blood cycle refers to the flow of blood via veins from the heart to every area of the body. The heart pumps blood into the vessels with each beat. Blood presses against the walls of blood vessels to create blood pressure. The cardiac pump has grown more complicated in response to elevated blood pressure.

Two forms of hypertension are distinguishable. The first is essential hypertension, a condition with high blood pressure and an unidentified cause. The second kind, termed as secondary hypertension, is brought on by recognized or direct causes. Primary risk factor cardiovascular disease, which includes aneurysm, heart attack, stroke, and heart failure, is the most common consequence of hypertension [5]. It is unknown what the actual, primary causes of elevated blood pressure are. Nonetheless, a variety of factors could be involved, including as being overweight, not exercising, smoking, being obese, being active, eating a diet high in salt, and heredity. From the research which is done in this field, it was found that a polymorphism mass localized in the *AGT* gene is present. These *AGT* founded were included nine SNPs rs4762 (exon 2), rs699 (exon 2), rs2148582 (intron), rs3789679 (intron), (rs5046 (5'UTR), rs11568020 (5'UTR), rs5051 (5'UTR), rs5050 (5'UTR), rs5049 (5'UTR). These *AGT* genes variants have a strong link with essential hypertension in several different populations [6].

The variants mentioned not only act as an epidemiological factor for cardiovascular disease (CAD), but it is also responsible for the demonstration in atherosclerosis severity. It shows us that the *AGT* gene has severe risk factors concerning these medical conditions [7].

Numerous investigations discovered polymorphisms in the RAAS gene, such as the single nucleotide polymorphism (SNP) M235T, the polymorphism that modifies the ACE by removal or insertion, and the single nucleotide polymorphism (SNP) A1166c in AGTR1. Everybody is at risk for hypertension or disorders related to hypertension in one way or another. According to a previous study, a particular kind of AGT genotype called the TT genotype is associated with a higher risk of lacunar infarction and a history of hypertension [8]. It was discovered that the AGTR1 genotype known as the CC genotype is connected with an increase in the left ventricular concentration index, and that A1166C plays a critical role in determining the presence of hypertension.

Renin-angiotensin-aldosterone system

The main endocrine system is the RAAS, which affects blood pressure control. The site where renin substances are secreted from the kidneys precisely within the juxtglomerular apparatus in response to glomerular substances with minimal salt intake or perfusion and are released in response to stimulation by the sympathetic nervous system [9]. Angiotensin I is formed by the conversion of the renin substrate (angiotensinogen) to renin. Angiotensin I is a physiologically inert substance

that is rapidly converted to angiotensin II in the lungs by angiotensin-converting enzyme (ACE).
Angiotensin II is an effective vasoconstrictor and therefore causes an increase in blood pressure. Furthermore, it stimulates the release of aldosterone from the glomerular zone of the adrenal glands, causing water retention and a further increase in blood pressure due to sodium [9](Figure 1).
Circulating RAAS is not a direct cause of hypertension in essential hypertension. In particular, many hypertensive patients have low renin and angiotensin II levels (mainly black people and older people), and drugs that block the renin-angiotensin system are not particularly effective [9]. There is further evidence that there is an essential noncirculating "local" paracrine or epicene renin angiotensin system that controls blood pressure. Local renin systems in the kidney, arterial tree, and heart have been reported. They may play an important role in regulating local blood flow [9].

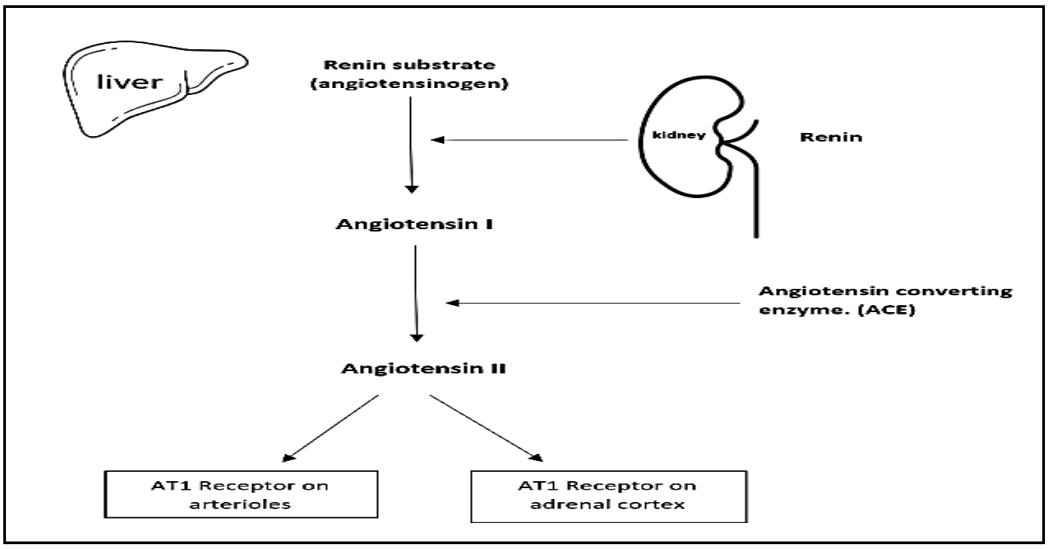


Figure 1: Renin-angiotensin system and effects on blood pressure and aldosterone release.

AGT gene:
The AGT cDNA was a 1,455 nucleotide long structure that coded for a 485 amino acid long protein [10].
As shown in (Figure 2), AGT consists of four introns and five exons distributed over 13 kb. The first exon, 37 bp, is part of five untranslated regions. The origin of the formation of active angiotensin peptide lies in the 10 N-terminal amino acids that are cleaved by renin, which then generates angiotensin I [11].
The exon at the second number contains the code for a single peptide of less than 24 or 33 residues. This also includes the remainder of the mature protein, the first 252 amino acids. The third exon encodes 90 amino acids and the fourth exon encodes 48 residues. The fifth exon consists of 62 amino acids and has a smaller coding sequence.
This is followed by a long 3-inch untranslated series containing two polyadenylation signals. It involves the creation of dual mRNA species of different lengths. The size difference is 200 nucleotides [10]. Studies using in situ hybridization have shown that the human AGT gene is located on chromosome 1q42 [7].

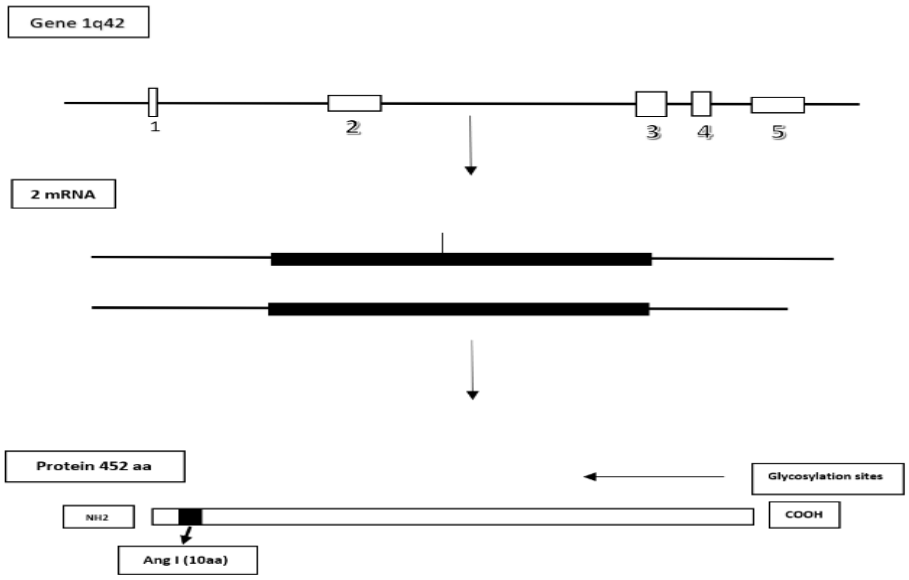


Figure 2: structure of AGT Gene, mRNA, and Protein.

Function of the AGT gene:

The function of AGT ensures the regulation of blood pressure. Variations in gene sequences play an important role in risk factors associated with cardiovascular diseases [12].

The etiology and associated risk factors for cardiovascular disease include evidence of hypertension and coronary heart disease (CHD) [13].

AGT variants such as rs699 (p.M268T or p.M235T) and rs4762 (p.M207T) appear to influence cardiovascular disease risk factors [14].

Characteristics of AGT Proteins:

The molecular weight of AGT is 55-65 kDa, and human AGT is a globular glycoprotein depending on its glycosylation status. It contains four putative glycosylation sites that could be the source of glycosylated chains.

However, the role of this glycosylation process in humans is unclear. Enzyme assays were typically measured for Ang(I) after complete hydrolysis of excess renin.

Direct immunoassays using monoclonal and polyclonal antibodies against AGT have also been developed to determine both the inactive C-terminal portion and the complete AGT, (Ang I) AGT.

In the liver, which primarily contains enzymes that can metabolize Ang I, this method does not accurately quantify AGT in tissues, creating problems in the interpretation of enzyme tests [15].

AGT variants associated with hypertension:

Various studies have reported associations between different phenotypes and blood pressure. Different phenotypic variations include plasma parameters.

However, this association is only partially assumed to be secondary or primary to the increase in blood pressure. The connections and relationships between them can only be revealed with the help of genetic research.

Related studies on AGT polymorphisms and hypertension:

Hypertension is a medical problem that can significantly reduce mortality and its association with various other diseases such as cardiovascular diseases [15]. It has been found to be a complex disorder resulting from multiple environmental factors [5].

A number of studies have also found that interactions between genes and numerous elements within the domain cause hypertension [8].

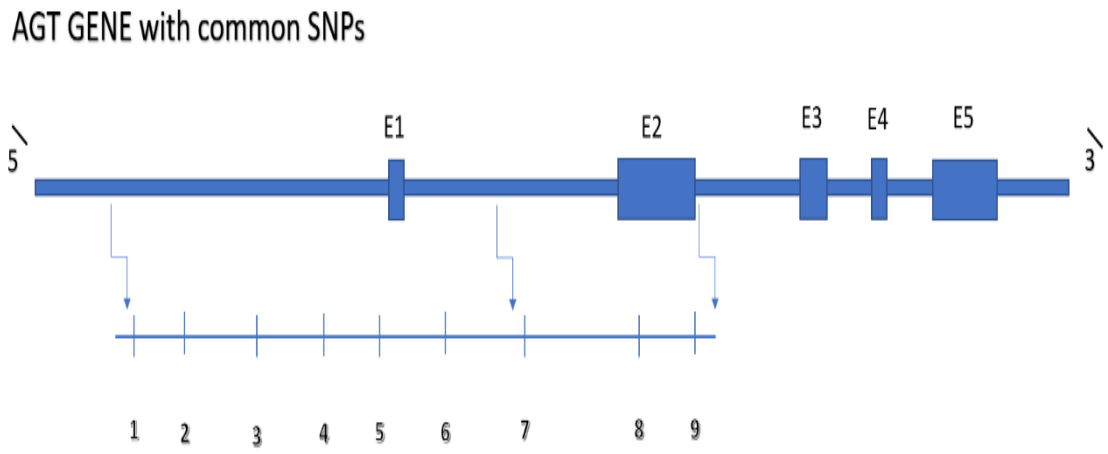
The RAS system is known to play an important role in regulating blood pressure and the causes of hypertension.

Therefore, AGT, angiotensinogen-modifying enzyme (ACE), and angiotensinogen II type 1 receptor (AGTR1) have been extensively studied to examine their association with hypertension [4].

Various studies have shown that RAAS genetic polymorphisms, such as single nucleotide polymorphism (SNP) (M235T), modification of ACE by polymorphism (either deletion or insertion), and A1166c single nucleotide polymorphism (SNP) in AGTR1. discovered. Everyone has some risk of hypertension-related diseases [4]. An older study found that a specific genotype of AGT, the TT genotype, was associated

with an increased risk of lacunar infarction (24) and history of hypertension [6].
It found that A1166C of AGTR1 plays an important role in detecting hypertension and found that the improvement of left ventricular concentration index was associated with the AGTR1 CC gene. They found that there is a correlation between type (called genotype) [16].

Statistical analysis:
This research paper describes a study focused on the AGT gene, specifically the 5'UTR, exon and intron regions of the AGT gene, which are regions of interest. Therefore, this study searched the Ensemble Genome Browser and the NCBI SNP database. This includes nine SNPs rs4762 (exon 2), rs699 (exon 2), rs2148582 (intron), rs3789679 (intron), rs5046 (5'UTR), rs5049 (5'UTR), rs11568020 (5' UTR), rs5051 (5'UTR), and rs5050 (5'UTR) were analyzed by statistical analysis and all results showing the association between AGT variants and hypertension were reviewed (Figure 3) [6].



	1	2	3	4	5	6	7	8	9
rs. No	rs5046	rs5049	rs11568020	rs5050	rs5051	rs2148582	rs3789679	rs4762	rs699
SNP LOCATION	-532	-217	-152	-20	-6	68	172	174;3389	235;4072
ALLELE	G>A	C>T	C>A C>T	T>C T>G	C>A C>G C>T	A>C A>G A>T	G>A G>T	G>A	A>G
Position	5'UTR	5'UTR	5'UTR	5'UTR	5'UTR	Intron	Intron	Exon 2	Exon 2

Figure 3: AGT with [6]common SNPs.

Number of study patients:
In the eastern Indian state of West Bengal, this study selected Bengali speaking ethnic groups in Kolkata city and surrounding areas and carried out a cross-sectional case consisting of 256 hypertensive patients and 158 controls conducted a controlled study [6].

Method Usage:
A review of this study shows that the researchers performed genotyping of the AGT gene for hypertension to confirm the association in the Indian population. To achieve this, specific SNPs analysis and analysis of AGT and gene region promoters were performed in 414 subjects (158 controls vs. 256 with hypertension) [6].

Subject characteristics:
In this study, descriptive statistics for indicator variables were generated according to disease. By comparison, researchers found that many factors, including blood pressure, mean age, low-density lipoprotein, uric acid, urea, blood urea nitrogen, chloride, glucose, and cholesterol, were

significantly higher in the normotensive group than in the hypertensive group. I found it to be low. Shown in Table 1 [6].

Table 1: The study group's clinical characteristics [6].

Variables	Hypertensive ($n = 256$)		Normotensive ($n = 158$)		*t*-test (*p*-value)
	Mean	SE	Mean	SE	
Glucose(mg/dl)	132.50	3.70	120.77	3.71	**0.035**
Age (YEAR)	56.45	0.51	53.03	0.41	**0.000**
SBP (mm of mercury)	161.38	1.08	105.37	0.61	**0.000**
DBP (mm of mercury)	91.98	0.74	75.51	0.67	**0.000**
Body Mass Index (BMI) (Kg/m^2)	24.22	0.28	23.45	0.31	**0.075**
Triglycerides (mg/dl)	162.83	5.08	153.38	5.81	0.233
Cholesterol (mg/dl)	177.82	2.70	167.19	2.75	**0.009**
LDL (mg/dl)	97.66	2.03	90.79	1.94	**0.022**
HDL (mg/dl)	47.71	1.07	45.73	1.40	0.259
Urea(mg/dl)	46.44	2.28	22.40	1.25	**0.000**
BUN (mg/dl)	21.69	1.06	10.46	0.58	**0.000**
Chloride (mmol/L)	110.10	0.84	103.92	0.76	**0.000**
Uric Acid (mg/dl)	6.10	0.10	5.48	0.11	**0.000**

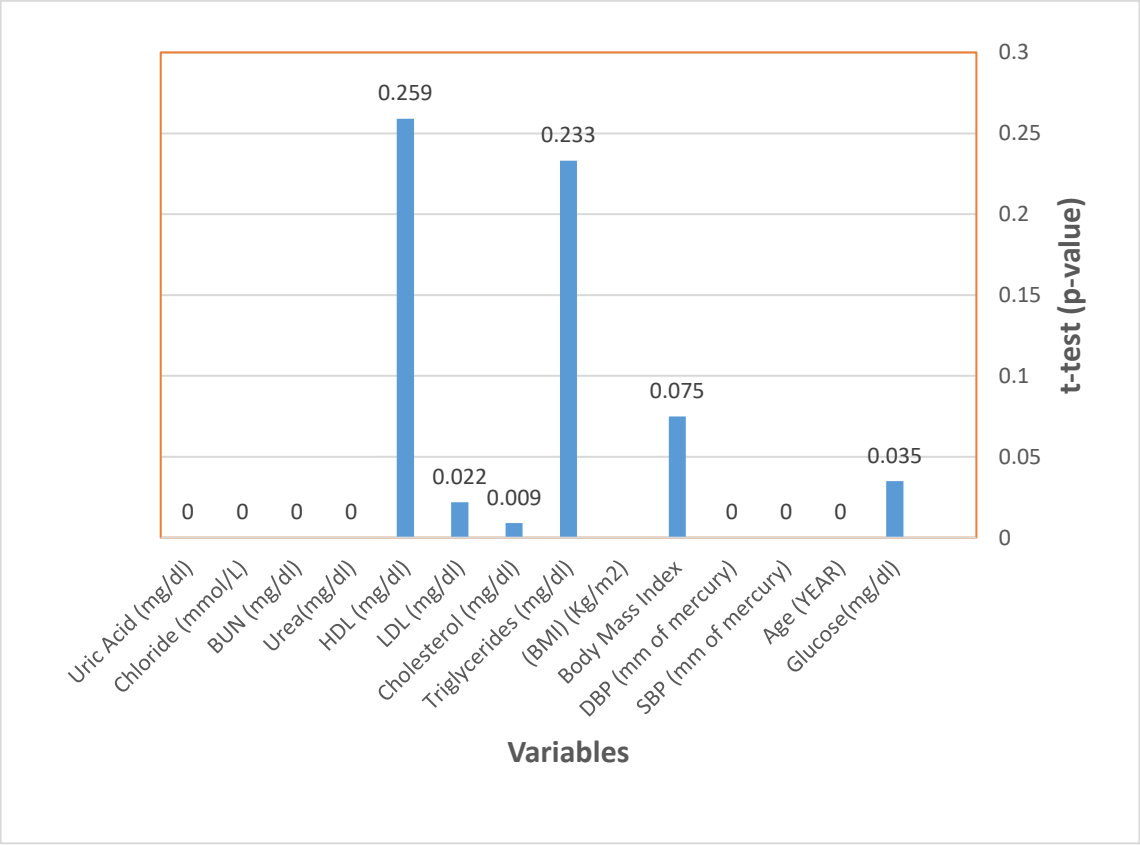


Figure 4: chart which appears the p. value of variables.

Discussion:

Genetic research aims to identify genes responsible for specific diseases, which are the main targets. These genetic results aim to focus on disease pathways to provide the best treatment and prevention. There are two types of diseases depending on the cause. The first is a disease with a relatively simple genetic basis. H.

A single gene disruption, gene detection method is sufficient to find the genes involved. However, problems have arisen in detecting multi-inherited diseases. The most common diseases such as stroke, heart disease, cancer, diabetes, and mental illness are influenced by complex genetic regulation. This means further research is needed to investigate the changes caused by these diseases.

Conclusion:

According to all the information, data, statistical analysis, and results of previous studies, there is an association between some mutations of the AGT gene and hypertension. Identification of genes associated with complex diseases is a more complex process and is very difficult to identify with certainty. Further research and search for AGT genes is needed to learn more about vast populations and large samples. It also requires the use of modern technologies such as next-generation sequencing (NGS) and whole exome sequencing (WES).

This study identified and evaluated the angiotensinogen (AGT) gene, which plays an important function in the epidemiology of essential hypertension and elevated blood pressure. Variants in the AGT gene, particularly 235T, have been widely studied and found to be associated with high concordance rates of the AGT gene.

This response increases plasma and tissue concentrations of the AGT gene. The risk of cardiovascular disease due to the AGT gene is 20-30%. Furthermore, it was found that increased tissue AGT leads to the regulation of blood pressure in the ANG II generation. AGT variants are usually influenced by various environmental factors and interactions between genes, such as the ACE gene. However, extensive research in this area is needed to gain a deeper understanding.

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