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Gene Polymorphisms Associated with Atrial Fibrillation

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Abstract

Atrial fibrillation (AF), which causes severe health problems, is a multi-factor disorder and is increasing day by day. AF is known to be one of the most common cardiac arrhythmias in clinical practice. AF can also be described as a cardiac dysrhythmia that causes severe cardiovascular morbidity and mortality. AF is known as an independent risk factor for death and it occurs a significant risk of morbidity due to stroke. There are many diseases that contribute to the development of AF. Diseases such as aging, heart failure, heart valve disorders, myocardial infarction, hypertension and diabetes mellitus are important factors in the development of structural AF. It is a known fact that AF prevalence increases with age. The mechanism underlying of AF is not fully understood, but genetic factors play an important role in the pathogenesis of this disease. There have been many studies aimed at investigating the genetic basis of AF, especially in recent years. In these studies, many mutations and variants have emerged which are identified as genetic risk factors in the development of AF. Identification of gene polymorphisms that play a role in the development of AF will be an important guide in the development of new therapies for the treatment of this condition.

Keywords: AF, cardiac arrhythmia, gene polymorphism, related diseases, PCR

1. Introduction

AF, which has a significant morbidity and mortality rate, is a multifactorial disorder as one of the most common cardiac arrhythmias [1, 2]. This cardiac arrhythmia affects 1–2% of the general population. AF is an increasingly prevalent dysrhythmia and is associated with many cardiac risk factors. Disorders such as hypertensive, ischemic or structural heart diseases are important risk factors for AF [3].

The underlying mechanisms in the development of AF are still not fully understood, but a heterogeneous model plays an important role in the pathophysiology of this disease. This heterogeneous model is based on the interaction of multiple substrates and triggers [3].

There are many studies showing that genetic factors play an important role in the pathogenesis of AF. Monogenic mutations known to be associated with AF have been identified. A total of 25 gene mutations proven to be associated with AF have been identified. Genome-wide association studies (GWAS) have been conducted to investigate AF genetics, and these studies have shown that single nucleotide polymorphisms play a very important role in the development of AF. Several single nucleotide polymorphisms associated with AF predisposition have been identified in these GWAS studies [3].

AF is an electrical disease caused by defects in ionic currents, and a variety of studies have been undertaken to determine the genetic causes of these electrical illnesses. Studies conducted to investigate the hereditary predisposition of AF found that the development of AF in pups with AF detected in their parents was found. Even though disorders such as hypertension, myocardial infarction and diabetes mellitus, which are important risk factors for the development of AF, are regulated, they still have the risk of developing fourfold AF [3].

In many genetic studies, variants known to be associated with AF have emerged. These variants are formed as a result of abnormalities in genes encoding cardiac gap junctions, signaling molecules, ion channels and auxiliary subunits. In addition, gene polymorphisms may cause loss of function in genes that encode proteins contributing to cardiac depolarization or repolarization leading to AF's increased sensitivity, are also genetic risk factors that play an important role in the development of AF [3].

The purpose of this chapter is to give general information about AF and compiling the studies made with the aim of determining the gene polymorphisms that can play an important role in the development of AF.

2. Renin angiotensin aldosterone gene polymorphism

The renin angiotensin aldosterone system (RAAS) plays an important role in the regulation of humoral regulation. RAAS, which is also important in the regulation of blood pressure, cardiovascular homeostasis, fluid and electrolyte balance such as hypertension, heart failure and arrhythmia, plays an important role in the pathophysiology of various cardiovascular diseases. Renin, an acid protease synthesized by renal juxtaglomerular cells, is involved in circulation through the renal vein. A decrease in renal blood flow or a decrease in plasma sodium levels leads to an increase in renin secretion. Renin plays a key role in the production of angiotensin I in plasma or tissues. It is provided that renin is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensinogen (AGT), the original subtype of renin, is an important source of angiotensin II. Angiotensin II functions by binding to the angiotensin II receptor on fibroblasts. Angiotensin II plays an important role in enhancing the synthesis and secretion of collagen types I and III in the regulation of proliferation of fibroblasts. Angiotensin II induces aldosterone release, resulting in myocyte

necrosis and susceptible fibrosis. RAAS is functioning via angiotensin II. Angiotensin II is involved in the elevation of blood pressure in the systemic arterial and venous systems and in the increase of blood return to the heart. It increases the central sympathetic activity by increasing the oscillation from the sympathetic nerve endings. Thus, synthesis and release of aldosterone is regulated. RAAS, which plays a role in atrial remodeling and pathogenesis of AF, is an important regulator. There are not many studies aiming to investigate the relationship between RAAS gene polymorphisms and the risk of developing AF. In a study conducted by Tsai et al., it was determined that the polymorphisms occurring in RAAS genes increased the susceptibility to AF development as a result of association with environmental factors leading to elevated atrial pressures. RAAS gene polymorphisms include ACE insertion/deletion (I/D), AGT (G-217A, A-20C, G-7A, M235T and T174M) and ATR1 A1166C gene polymorphisms. In a study aiming to investigate the association of these polymorphisms with AF, in exon 2 of the AGT gene, the M235 allele, a significant relationship was found between haplotypes associated with the G-6 and G-217 alleles in the promoter region and AF development risk [4, 5].

2.1. ACE (I/D) gene polymorphism

The 21-kilobase pair (kbp) long ACE gene locates on chromosome 17q23. This gene consists of 26 exons and 25 introns. The ACE (I/D) gene polymorphism is characterized by I/D of 287 base pairs in the 16th intron of the ACE gene. The genotypes of ACE (I/D) gene polymorphism differ in terms of ACE plasma and tissue levels. The DD genotype of the ACE (I/D) gene polymorphism is associated with high cellular ACE activity, which leads to myocardial fibrosis, so myocardial fibrosis develops. There are studies showing that ACE (I/D) gene polymorphism is associated with the risk of developing AF. There is a positive relationship between DD genotype and ACE activity of ACE (I/D) gene polymorphism. As a result of this relationship, angiotensin II level increases and myocardial hypertrophy, arrhythmia can develop. In the study carried out by Zhang and colleagues found a significant association between DD genotype of the ACE (I/D) gene polymorphism and increased AF. In another study conducted by Topal et al., a significant relationship was found between the incidence of ACE Alu D and increased AF [2].

2.2. ACE 2350G/A (rs4343) gene polymorphism

One of the ACE gene polymorphisms from the AF associated genes is the ACE 2350G/A (rs4343) polymorphism, and this polymorphism has a significant effect on the plasma ACE concentration. The ACE 2350G/A (rs4343) gene polymorphism is a synonymous mutation that is accepted as silent. There is insufficient study to investigate the relationship between ACE 2350G/A (rs4343) gene polymorphism and the risk of developing AF. In a study conducted by Jiang et al. in a Chinese population, the A allele of ACE 2350G/A (rs4343) gene polymorphism has been associated with the risk of developing AF in patients with essential hypertension. ACE 2350G/A (rs4343) polymorphic locus do not effect expression directly of ACE mRNA or it has not functional variant. It is assumed that there may be link imbalance between this fragment and an unknown DNA fragment acting as a muffler. In order to be able to identify gene loci in this linkage disequilibrium, a large number of studies have to be performed [1].

2.3. Angiotensin II type 1 receptor and angiotensin-converting enzyme 2 gene polymorphisms

RAAS, which plays an important role in the pathophysiology of AF in the structural and electrical remodeling of the atrium, contains ACE/angiotensin II/AGTR1 and ACE2/angiotensin (1–7)/MAS axes. These axes regulate myocardial hypertrophy, fibrosis and remodeling. ACE/angiotensin II/AGTR1 and ACE2/angiotensin (1–7)/MAS axes have been found to play an important role in AF pathogenesis. Angiotensin II is the most vasoactive component of RAAS, and angiotensin II, which causes increased myocardial fibrosis and hypertrophy, may contribute to AF development. Angiotensin II, an important signaling molecule of RAAS, plays a role in cardiovascular effects via AGTR1. AGTR1, G-protein is a bound receptor and has been associated with some disorders such as heart failure, prehypertension and stroke. There are studies showing that in AF patients AGTR1 levels increase in the left atrium. In a study conducted with Chinese Han population, the roles of AGTR1 rs1492100, rs1492099, rs1492097 and rs3772616 gene polymorphisms in AF development were investigated. A significant correlation was found between rs1492099 gene polymorphism from these polymorphisms and the development of structural AF. The ACE2 gene shows the X chromosome. In a study conducted by Freg et al., ACE2 expression was found to be significantly reduced in patients with chronic AF. In contrast, it is observed that atrial tissue angiotensin II levels were also significantly elevated. In another study with Chinese Han population, the effects of AGTR1 and ACE2 gene polymorphisms development of structural AF were examined. It is thought that polymorphisms occurred in this gene may be genetic risk factors in the development of structural AF in the Chinese Han male population. Also, it has been shown that ACE2 and AGTR1 genes are associated in patients with structural AF [6].

2.4. Aldosterone synthase 344 C/T gene polymorphism

Aldosterone synthase (CYP11B2) is an enzyme that plays an important role in the synthesis of aldosterone. CYP11B2 is the mitochondrial P450 oxidase found in the adrenal cortex of the zona glomerulosa. Aldosterone plays an important role in regulation of ion motions and collagen expression, including myocardial remodeling. Delayed or reversed myocardial remodeling is achieved by the aldosterone inhibitor, thus can prevent AF. In a study by Goette et al., there was a positive relationship between elevation of AF and aldosterone levels. The CYP11B2 gene is 7 kilobases long and locates on chromosome 8q22. This gene consists of 9 exons and 8 introns. The CYP11B2-344 C/T gene polymorphism is characterized by a C/T substitution in the –344 position in the promoter region of the CYP11B2 gene. Several studies have been conducted to investigate the relationship between CYP11B2-344 C/T gene polymorphism and hypertension. In some studies, CYP11B2-344 C/T gene polymorphism has been identified as a genetic risk factor for hypertension and myocardial hypertrophy. However, a limited number of studies have been conducted to investigate the relationship between CYP11B2-344 C/T gene polymorphism and AF. In a study conducted by Lu et al., no significant relationship was found between CYP11B2-344 C/T gene polymorphism and AF development risk. In the study conducted by Shuxin Hou et al., there were no significant differences in CYP11B2-344 C/T gene polymorphism genotype distributions between AF patients and healthy control groups. The CYP11B2-344 C/T gene polymorphism has been

AGTR1 and ACE2	Forward primer 5'-3'	Reverse primer 3'-5'
rs1492100	TTCAATAACAGATTCCCAGAG	CCACCTCAACTTGCCTGTG
rs1492099	TTCAATAACAGATTCCCAGAG	CCACCTCAACTTGCCTGTG
rs1492097	TTCAATAACAGATTCCCAGAG	CCACCTCAACTTGCCTGTG
rs3772616	TGATAATTTATGTACTCCCTC	CAAAGCATAAGTGTCAACAGA
rs6632677	CTGACTTGTTCAGCAAGATGC	TAGGAGTCCAGGCACAGTTCAG

PCR, polymerase chain reaction; SNP, single nucleotide polymorphism; AGTR1, angiotensin II receptor 1; ACE2, angiotensin-converting enzyme 2; Amp, amplification.

Table 1. Primer sequences used in PCR for AGTR1 and ACE2.

GENES amp. size (bp)	Primer	Primer sequences
AGT M235T 163 bp	Forward	5'-CGTTTGTGCAGGGCCTGGCTCTC-3'
	Reverse	5'-AGGGTGCTGTCCACACTGGACCC-3'
ACE AluI/D 490 bp	Forward	5'-CTGGAGACCACTCCCATCCTTTCT-3'
	Reverse	5'-GATGTGGCCATCACATTCGTCAGAT-3'
CYP112B2-344C/T 537 bp	Forward	5'-CAGGAGGAGACCCCATGTGAC-3'
	Reverse	5'-CCTCCACCCTGTTCAGCC-3'

PCR, polymerase chain reaction; AGT, angiotensinogen; ACE (I/D), angiotensin-converting enzyme (insertion/deletion); CYP112B2, aldosterone synthase; Amp, amplification.

Table 2. Primer sequences used in PCR and amplification product size for AGT, ACE (I/D) and CYP112B2-344C/T.

found to be associated with an increase in C allele binding to steroidogenic transcription factor 1 and thus an increase in CYP112B2 activity. In a study conducted by Amir et al., CYP112B2-344 C/T gene polymorphism CC genotype was found to be an independent risk factor for AF in patients with heart failure. In a study in China Han population, conducted by Huang et al., found that CYP112B2-344 C/T gene polymorphism is not a genetic risk factor in the development of AF in patients with hypertensive heart disease. In a study performed by Zhang et al., the significant relationship is not also found between CYP112B2-344 C/T gene polymorphism and AF development [2]. It is presented primer sequences that used to determine AGTR1, ACE2, AGT, ACE (I/D) and CYP112B2-344C/T gene polymorphisms in **Tables 1** and **2**.

3. Nitric oxide synthase gene polymorphisms

The major products of cellular metabolism are reactive oxygen species (ROS) and reactive nitrogen products (RNS) and they have sources in the myocardium. Redox homeostasis is disturbed when oxidant species overcome the capacity to reduce of the cell. While excessive ROS results in oxidative stress; excessive RNS results in nitrosative stress. Potentially reactive species such as the mitochondrial electron transport chain, xanthine oxidase, NADPH oxidases and nitric oxide synthases (NOS) are present in the myocardium. There are three NOS isoforms: NOS1 (neuronal NOS = nNOS), NOS2 (inducible NOS = iNOS) and NOS3 (endothelial NOS = eNOS). These isoforms are named according to the first description of the tissues. It

Genes amp. size (bp)	Primer	Primer sequences
eNOS T-786 180 bp	Sense	5'-TGGAGAGTGCTGGTGTACCCCA-3'
	Antisense	5'-GCCTCCACCCACCCCTGTC-3'
eNOS G894T 200 bp	Sense	5'-AACCCCTCTGGCCCACTCCC-3'
	Antisense	5'-TCCATCCCACCCAGTCAA-3'
Intron 4a/4b 393 (4a) 420 (4b)	Sense	5'-AGGCCCTATGGTAGTGCCTTT-3'
	Antisense	5'-TCTCTTAGTGCTGTGGTCAC-3'

PCR, polymerase chain reaction; eNOS, endothelial nitric oxide synthase; Amp, amplification.

Table 3. Sequence of primers, size of the PCR products eNOS T-786C, G894T, Intron 4a/4b gene polymorphisms.

is known that enzymes that occur in NOS1 and NOS3 are expressed in the heart. NOS2 is expressed in inflammatory and pathological conditions such as hypertrophy or heart failure. While in cardiac myocytes, NOS1 and NOS3 were present in intracellular compartments, NOS2 is present in the cytosol of cardiac myocytes. NOS plays an important role in stimulating effects of NO on guanylate cyclase, or in arising and mediating effects of nitrosation of tyrosine, cysteine residues. NO, which a highly reactive radical, is spreadable and its life is very short. L-arginine is converted to citrulline by NO production and is a substrate for NOS. NOS2 is expressed in macrophages, neutrophils, endothelial cells, vascular smooth muscle cells and cardiomyocytes. The competitive inhibition of endogenous methylarginine regulates the substrate level in NOS isoforms. Oxidative stress plays an important role in AF pathogenesis. NOS enzymes can be decomposed and transferred from NO production to superoxide anion, strong free radicals and oxidation. Therefore, NOSs that are associated with oxidative stress are important in AF pathogenesis. In the case development of AF, left atrial endocardial NOS reduction occurs. Thus, a significant reduction in NO production occurs. Clinical cohorts were performed to investigate the relationship between AF development and eNOS gene polymorphisms. In a study with a Caucasian population that developed AF, it was determined that eNOS T-786C, G894T and 4a/4b gene polymorphisms did not have genetic risk factors in the development of AF. In another study, while CC genotype of eNOS T-786C polymorphism was found to be a genetic risk factor for homocysteine concentrations, there was no significant relationship between this polymorphism and the risk of developing AF. In another study conducted with heart failure and AF patients, 894TT genotype of G894T gene polymorphism was determined as a genetic risk factor in development of AF. In a study conducted by Giusti et al., eNOS T-786C gene polymorphism was found to be associated with a decrease in eNOS gene promoter activity. Furthermore, in the same study, this polymorphism was found to be an independent risk factor for plasma homocysteine concentrations [7–9]. It is presented primer sequences that used to determine eNOS T-786, G894T, Intron 4a/4b gene polymorphisms in **Table 3**.

4. Endothelin 2 A985G gene polymorphism

AF is an important complication of hypertrophic cardiomyopathy and is observed in approximately 20% of patients with hypertrophic cardiomyopathy. Hemodynamic changes following

Genes	Primer	Primer sequences
Endothelin 2 A985G gene	Forward	5'-ACAAACCAGGAGCAACCGTG-3'
	Reverse	5'-AGGGAATGAGGGTGCAAGAA-3'
	G allele-specific probe	5'-VIC-CCCTGGAGACTGGA-MGB-3'
	A allele-specific probe	5'-FAM-CCGGAGGCTGGAT-MGB-3'

PCR, polymerase chain reaction.

Table 4. Sequence of primers for endothelin 2 A985G gene polymorphism.

sympathetic or parasympathetic activation play an important role in AF triggering. In a study conducted by Thomson et al., hypertension was reported to induce triggering in developing of AF in patients with hypertrophic cardiomyopathy. Since myocardial hypertrophy is present in patients with hypertrophic cardiomyopathy, the left ventricular space is small in these patients. Thus, a decrease occurs in venous conversion and intravascular volume. As a result of this, in the patients with hypertrophic cardiomyopathy, low heart debit and various symptoms arise. Cheung et al. suggested that AF could be induced in the study they performed. Endothelin 2, which constricts the systemic vessels, protects venous return and prevents hypertension that may develop. Acute hypertension causes an increase in sympathetic nerve activity. Hypertension can occur in hypertrophic cardiomyopathy. A vasoconstrictor may show protective effect against AF in hypertrophic cardiomyopathy. Proximal AF is more common in hypertrophic cardiomyopathy than in other structural heart diseases. This monogenic disorder is a disorder affecting left ventricular hypertrophy in patients with hypertrophic cardiomyopathy. These disorders result from mutations in genes encoding the sarcomeric proteins. In a study conducted by Sharma et al., it has been shown that the endothelin 2 gene may be effective in the development of hypertension, and that this gene is expressed to in human atrial tissue. Endothelin 2 gene is localized on chromosome 1p34. It has been suggested that there is a significant relationship between hemodynamic changes and polymorphisms occurring in endothelin 2 gene in patients with essential hypertension. The functional role of endothelin 2 A985G gene polymorphism is not known precisely. mRNA stability is affected by variations in 3'-UTR. Thus, endothelin 2 transcription and translation may be affected in the endothelin 2 A985G gene polymorphism. Differences in A985 allele frequencies are observed in studies with different populations. Endothelin 2 A985G gene polymorphism plays a protective role for A985 allelic cardiovascular diseases, but this allele may trigger AF development in hypertrophic cardiomyopathic patients. In a study conducted by Nagai T et al., The endothelin 2 A985T allele has been shown to be a genetic risk factor for the development of AF in hypertrophic cardiomyopathic patients [10]. It is presented primer sequences that used to determine Endothelin 2 A985G gene polymorphism in **Table 4**.

5. Connexins gene polymorphisms

AF can also occur when there is or no structural heart disease. Most of the foci that cause AF are at the site where combine the cardiomyocytes and vascular smooth muscle cells are located near the pulmonary venules. Connexins (Cx) are gap junction proteins and play an important role in direct cell-cell interactions in the majority of the tissues of the body in electrical conduction in the heart. It is known that there are 20 different Cxs in humans, and each Cxs create channels with different

Genes	Primer	Primer sequences
Cx37 1019 C>T	Forward	5'-CTGGACCCACCCCCTCAGAATGGCCAAAGA-3'
	Reverse	5'-AGGAAGCCGTAGTGCCTGGTGG-3'
Cx40 G-44A	Forward	5'-CCCTCTTTTAAATCGTATCTGTGGC-3'
	Reverse	5'-GGTGGAGGGAAGAAGACTTTTAG-3'

PCR, polymerase chain reaction; Cx, connexin.

Table 5. Sequence of primers for the connexins.

characteristics and specific expression patterns. The polymorphisms occur in gap junction channels and in Cx proteins that play a role in action potential spread. Variants that occur in genes encoding variants that occur in genes encoding Cx40 and Cx37 that contribute to pulmonary vein-arrhythmogenic affect gene expression and function. Cx40 and Cx37 that contribute to pulmonary vein-arrhythmogenic affect gene expression and function. Variants that occur in genes encoding Cx40 and Cx37 that contribute to pulmonary vein-arrhythmia affect gene expression and function. The Cx40 gene is encoded by GJA5 and is expressed in endothelial cells, coronary vascular smooth muscle cells, atrial cardiomyocytes and cardiac conduction systems. In GJA5, the TATA box sequence also changes is the result of the single nucleotide polymorphism found in the promoter region. Cx40 gene modulates broad mRNA levels and is known to be associated with AF. In a previous study, Cx40-26G>A gene polymorphism-26G allele was identified as a genetic risk factor in patients with cardiomyopathy AF. In a study performed by Carballo et al., Cx40-26G>A gene polymorphism was found to affect protein expression levels in cardiomyocytes and this polymorphism was associated with structural AF. There are significant relationships between polymorphisms occurring in GJA5 in the Cx40 gene and susceptibility to AF. Somatic mutations in the Cx40 gene have also been associated with idiopathic AF. The Cx43 gene is also encoded by GJA1 and is expressed by ventricular, atrial cardiomyocytes, vascular smooth muscle cells, endothelial cells, monocytes and macrophages. Other genes and polymorphisms associated with polymorphisms in the CX43 gene have also been reported to be effective in the development of AF. The Cx37 gene is encoded by GJA4 and is found in endothelial cells, pulmonary and vascular smooth muscle cells, monocytes/macrophages and platelets. Polymorphisms occurring in GJA4 in the Cx37 gene are associated with atherosclerosis and coronary heart disease, and these polymorphisms have an effect on monocyte adhesion. Thus, they are important in the regulation of local inflammation. Systemic and local inflammation may play a role in the development of AF before or after surgery in some cases. The 1019 C>T gene polymorphism in the CX37 gene in GJA4 is characterized by proline/serine (P319S) substitution at position 319 in the cytoplasmic tail of the Cx37 gene. As a result, channel conductivity and permeability change. Cx37 1019 C>T gene polymorphism is also associated with platelet aggregation or monocyte adhesion. Due to the effect of this polymorphism on monocyte adhesion, sensitivity to non-structural AF may change [11–13]. It is presented primer sequences that used to determine Cx37 1019 C>T, Cx40 G-44A gene polymorphisms in **Table 5**.

6. Gamma-glutamyl carboxylase gene polymorphism

Warfarin, an oral anticoagulant, is used in the correction of various thromboembolic disorders such as prosthetic heart valves, deep vein thrombosis and pulmonary embolism.

Genes	Forward primer (5'-3')	Reverse primer (5'-3')
rs699664	AGTGGCCTCGGAAGCTGGT	ACACAGGAAACACTGGGCTGAG
rs2592551	GGACTTAGAAAGGAACGGATGA	CTTGAGAAAAGGCAAAGCAGAC

PCR, polymerase chain reaction; SNP, single nucleotide polymorphism; GGCX, gamma-glutamyl carboxylase.

Table 6. Primer sequences used in PCR for GGCX.

Thromboembolism or bleeding may develop as a result of inadequate or excessive intake of warfarin. Discomforts such as stroke and systemic thromboembolism can be reduced with anticoagulant treatments. Factors such as age, body size, environment, interacting drugs and gene polymorphisms are effective at warfarin dose requirements. Stable warfarin dose is affected by gene polymorphisms such as single nucleotide gene polymorphism. These polymorphisms play a role in the modulation of warfarin pharmacodynamics and pharmacokinetics. Gamma carbon carboxylation occurs on gamma glutamic acids. Gamma-glutamyl carboxylase (GGCX) found in the endoplasmic reticulum membrane oxidizes vitamin K-2,3 epoxide reduced vitamin K. Therefore, functional vitamin K-dependent clotting factors (II, VII, IX and X) are produced by this enzyme. GGCX catalyzes the biosynthesis of vitamin K-dependent clotting factors. Thus, this enzyme affects warfarin metabolism. Warfarin metabolism, one of the most frequently used anticoagulants in clinical therapy, is affected by the GGCX enzyme. GGCX is a gene that plays an important role in the individual differences of warfarin response. Warfarin is a common anticoagulant that a narrow therapeutic range. Genetic factors that play an important role in warfarin dose requirements include GGCX gene polymorphisms. GGCX gene that consisted of 15-exon is located on human chromosome 2p12. It has been reported that there is a relationship between polymorphisms occurring in the GGCX gene and warfarin dose variability. GGCX rs11676382, rs12714145, rs10654848 and rs699664 gene polymorphisms are the most common polymorphisms of the GGCX gene. GGCX rs11676382 (C>G) gene polymorphism found in intron 14 was found to be associated with low Warfarin dose requirements in the Caucasus. In intron 2, GGCX rs12714145 (3261G>A) gene polymorphism was found to have more warfarin dose requirements in Chinese patients with the AA genotype. In Caucasians and African Americans, there is a significant relationship between GGCX rs10654848 microsatellite (DNA repeats) gene polymorphism in intron 6 and high warfarin dose requirements. GGCX rs699664 gene polymorphism, characterized by a G/A base substitution at the 8th exon. This displacement results in the arginine/glutamine amino acid exchange at position 325. In Japanese and Chinese patients, a significant relationship was determined between this polymorphism and high warfarin dose requirements. In contrast, in Caucasians or African Americans, this gene polymorphism was found not to be associated with warfarin dose. In AF patients, it was determined that GGCX rs699664 gene polymorphism was significantly correlated with GA, AA genotypes and high warfarin dose requirements. Another polymorphism associated with warfarin dose in patients with AF is the GGCX rs2592551 gene polymorphism. The effect of GGCX rs2592551 gene polymorphism on the warfarin dose was investigated in a study conducted by Kamali et al. in a population living in the Xinjiang region (region of multiple ethnic communities of Khan, Uyghur, Kazakh, Hui, Kyrgyz, Mongol and Tajik). In this study, CT and TT genotypes of GGCX rs2592551 gene polymorphism were found to be associated with higher warfarin dose requirements than CC genotype in patients with AF [14, 15]. It is presented primer sequences that used to determine GGCX rs699664, rs2592551 gene polymorphisms in **Table 6**.

7. G-protein $\beta 3$ subunit C825T gene polymorphism

G-protein $\beta 3$ subunit C825T gene polymorphism plays an important role in the change of electrophysiological properties of human atrium. This polymorphism occurs in 10th exon of gene, which encodes the G-protein $\beta 3$ subunit. It has been determined by Siffert et al. that this polymorphism is a genetic risk factor in the development of hypertension. Increased human atrial internal rectifier regulatory potentials have been associated with the TT genotype of G-protein $\beta 3$ subunit C825T gene polymorphism. There is also a significant relationship between the TT genotype of the G-protein $\beta 3$ subunit C825T gene polymorphism and the increased internal rectifier flow and reduced acetylcholine stimulating potassium flux in the human atrium. In the European white population, 825 T allele of G-protein $\beta 3$ subunit C825T gene polymorphism was found to be significantly associated with various cardiovascular disorders such as increased obesity, hypertension, left ventricular hypertrophy and coronary artery disease. In a study performed by Schreieck et al., heterozygote T and homozygote T allele carriage were found to be low risk factors for AF development. G-protein $\beta 3$ subunit the TT and CT genotypes of the C825T gene polymorphism play an important role in atrial cellular electrophysiological changes. In a study conducted by Dobrev et al., it was determined that TT genotype of this polymorphism correlates with the downregulation of acetylcholine mRNA transcripts in human atrial myocytes. Although there is no relationship between G-protein $\beta 3$ subunit C825T gene polymorphism and any arrhythmia, in some studies this polymorphism has been associated with the risk of developing AF. In conclusion, gene polymorphisms encoding ion channels are very important in AF pathogenesis. Identification of these polymorphisms will elucidate the multigenic mechanism of AF predisposition [16]. It is presented primer sequences that used to determine G-protein $\beta 3$ subunit C825T gene polymorphism in **Table 7**.

Genes	Primer	Primer sequences
G-protein $\beta 3$ subunit C825T gene	Forward	5'-TTCTCCCACGAGAGCATCATCT-3'
	Reverse	5'-GTCGTCGTAGCCAGCGAATAGTA-3'
	Allele 825C probe	5'-CATCACGTCCGTGGCCTTCTCC-3'
	Allele 825T probe	5'-CATCACGTCTGTGGCCTTCTCCCT-3'

PCR, polymerase chain reaction.

Table 7. Sequence of primers for G-protein $\beta 3$ subunit C825T gene polymorphism.

8. Polymorphisms in the genes coding ion channels

8.1. KCNN3 rs13376333 gene polymorphism

Differences in populations due to myocardial membrane stability, conduction routes or genetic polymorphisms are important factors in predisposing to AF development. In recent association studies, gene polymorphisms found on chromosomes 4q25, 16q22 and 1q21 have been identified as genetic risk factors for AF development. Moreover, these genetic variants

are more important in the development of early onset AF. The relationship between these gene polymorphisms and the risk of developing AF has been explored in different populations. From these populations, in one Chinese and European origin considerable differences have been found in terms of these polymorphisms. rs2200733 on the 4q25 chromosome and rs106261 gene polymorphisms on the 16q22 chromosome have been observed quite often in the Chinese population in particular. However, the relationship between the rs7193343 gene polymorphism on the 16q22 chromosome and the risk of developing AF was not significant in the Chinese Han population. In a study conducted by Ellinor et al. with the European population, KCNN3 single nucleotide gene polymorphism, which is associated with AF in the new genetic locus, has been discovered in the potassium medium/small conductance calcium-activating channel. The KCNN3 gene encodes voltage-independent calcium and activated potassium channels. The KCNN3 rs13376333 gene polymorphism is located between the first and second exons of the KCNN3 gene. There are three subtypes of potassium channels as SK1, SK2 and SK3. Atrial myocytes are formed by the subunits of these channels to form heteromultimeric complexes. The expression of SK3 channels is similar to the expressions of SK1 and SK2 channels. There are studies showing that the relationship between these SK channels and AF is significant. However, more studies are needed to determine the role of SK3 channels in AF development. Studies were also conducted in the Asian population to investigate AF associations with KCNN3 gene polymorphisms, which are the ionic channel gene identified in AF GWAS. However, a large number of replication studies are needed to determine this relationship. In a study conducted by Chang et al., KCNN3 rs13376333 gene polymorphism in the Taiwanese population was found to be an important risk factor for the development of AF. Also Ellinor et al. showed that there is a significant association between AF and KCNN3 rs13376333 gene polymorphism. In a study conducted with Chinese Han population, KCNN3 rs13376333 gene polymorphism has not been identified as a genetic risk factor in the development of AF. In Taiwan and China populations, the T allele of KCNN3 rs13376333 gene polymorphism was observed at a significantly lower frequency [17].

8.2. SCN10A gene polymorphism

Voltage-gated sodium channels play an important role in impulse generation and conduction during the rising phase of action potential in excitable cells. There are sodium channel isoforms in the heart. These channels include voltage-gated sodium 1.1, voltage-gated sodium 1.3, voltage-gated sodium 1.5 (Nav1.5), voltage-gated sodium 1.6 and voltage-gated sodium 1.8 channels. The Nav1.5 encoded by SCN5A is responsible for the regulation of cardiac conduction. The Nav1.5 channel plays a very important role in cardiac impulse spread. As a result of the activation of sodium channels, the cardiac action potential is rapidly increasing. Each sodium channel consists of an α subunit and modulating β subunits. The α subunit of the Nav1.5 channel is encoded by the SCN5A gene. Each of the Nav1.5 α subunit consists of 4 homologous domains (DI-DIV) with 6 transmembrane alpha helices (S1-S6). The S1-S4 domains are repeatable and these domains constitute the voltage sensing areas of the channel. The functional pore and selectivity filter of the sodium channel consists of S5, S6 and S5-S6 loops. More than 300 mutations have been identified in the SCN5A gene. SCN5A mutations determined to be associated with Brugada Syndrome (BrS) lead to variable reductions in the sodium flow inward with channel transit changes. These channel passing changes delayed

activation, increased inactivation, slow recovery from inactivation, or impaired exchange of channel. As a result, decrease in expression occurs in the cell membrane. Consequently, these mechanisms cause loss of function in the cardiac sodium channel. The most common genotype found among BrS patients stems from mutations in the SCN5A gene. As a result of these mutations occurring in the gene, there is a loss of function in the cardiac sodium channel through different mechanisms. Depolarization or repolarization of cardiac action potential may be affected by due to reduced sodium current. Nevertheless, the underlying pathophysiological mechanism of the BrS phenotype is still being discussed [18]. BrS is defined as a disease characterized by sudden cardiac death characterized by a right bundle branch with an ST segment elevation in leads V1 and V2 in 1992. This syndrome was found to be associated with sudden cardiac death, especially in young men [19]. BrS, determined to be genetic, is a cardiac electrical disorder. BrS, an arrhythmogenic and autosomal dominant inherited cardiac syndrome, is characterized by typical electrocardiographic changes. In a study conducted in the Chinese population, localized in the domain II S4 segment of NaV1.5 α subunit protein, a new mutation, L812Q mutation, has been described. In this study, it was shown that this mutation improved the sodium channel inactivation process and disrupted the membrane expression of the canal in BrS patients [18]. In a Dutch population study, it was determined that SCN5A gene mutations, which cause loss of function in BrS patients, are associated with dilation and deterioration in contractile function of both ventricles [20]. In another study, SCN5A showed a high penetrance for BrS in a large family with the E1784K mutation. In addition, in the same study, overexpressing phenotypes of BrS were shown in E1784K and H558R carriers after the fourth decades of their lives [21]. There is an effect in the cardiac electrophysiological properties of sodium-gated voltage channel 1.8 via the effect intrinsic on cardiac ganglion neurons. In the isolated ventricular myocardium, it is known that the sodium-gated voltage 1.8 channel is not expressed. In isolated intrinsic cardiac ganglia, there are immunoelectrochemical studies indicating that significant amounts of sodium-gated voltage 1.8 channels are expressed. Facer et al. have shown that sodium-gated voltage 1.8 channel immunoreactive sensory nerves are present in human atrial myocardium. Voltage-gated sodium 1.8 channel is encoded by SCN10A and is a tetrodotoxin (TTX)-resistant sodium channel. This channel is expressed in dorsal root ganglia, cranial sensory ganglion sensory neurons. The SCN10A gene, which contains 27 exons, is localized on chromosome 3q22.2. The SCN10A gene has been shown to be associated with cardiac transmission. Because the SCN10A gene plays a role in increasing the PR interval and QRS duration in the electrocardiogram. Therefore, it was found that there is a relation between SCN10A and AF development. The SCN10A sodium-gated voltage 1.8 channel plays an important role in modulating the induction of AF. Verkerk et al. have demonstrated that the SCN10A sodium-gated voltage 1.8 channel is present in intrinsic cardiac neurons. In a study conducted by Chambers et al., a significant relationship was found between SCN10A rs6795970 gene polymorphism and PR interval. SCN10A rs6795970 (G>A) gene polymorphism is a missense mutation and causes an A1073V amino acid substitution in the sodium-gated voltage channel 1.8 IDII/III intracellular cycle. In a study conducted by Ritchie et al., the G allele of SCN10A rs6795970 gene polymorphism was found to be a genetic risk factor for the development of AF. In another study performed by Sabbari et al., G allele of SCN10A rs6795970 gene polymorphism was associated with increased risk of AF. A significant association was found between the SCN10A rs6800541 gene polymorphism and AF development in the study conducted by Pfeufer et al. [22, 23].

8.3. KCNE1 G38S gene polymorphism

KCNE1 widely known as a potassium ion channel encoding gene for humans and it is localized on chromosome 21q22.1–21q22.2 encoding the subunit of the potassium ion channel (IKs). KCNE1 plays an important role in atrial and ventricular repolarization. The KCNE1 gene was discovered by Murai et al. in 1989. Studies have shown that KV7.1, the α subunit of the IKS current, plays an important role in AF pathogenesis. The regulatory β subunits of the IKS current also bind to the KCNE1 gene. Biophysical properties of these β subunits of KV.71 can be altered by expression together. The β subunits of IKS contain 130 amino acids, which is called the Mink protein. Several single nucleotide gene polymorphisms have been identified in the KCNE1 gene. The most common of these polymorphisms is the KCNE1 G38S (rs1805127 G>A, G38S) polymorphism. The KCNE1 gene polymorphism is characterized by a glycine or serine amino acid substitution in the 38th position of the gene. As a result, stronger IKs flows occur. Various studies have been carried out to demonstrate that the KCNE1 gene and polymorphisms are highly effective in AF pathogenesis. In a study conducted by Lai et al., a significant association was found between the risk of developing AF in the Taiwanese population and the KCNE1 G38S gene polymorphism. Despite this conclusion in the Taiwanese population, it has been determined that this polymorphism is not a genetic risk factor in the development of AF in the Chinese population. Studies conducted with European and Uighur populations have also found that KCNE1 G38S polymorphism is a risk factor associated with AF. A total of 14 studies were conducted to investigate the relationship between KCNE1 G38S gene polymorphism and the risk of developing AF. In eight of these studies, a significant relationship was found between the risk of developing KCNE1 G38S gene polymorphism and AF. However, no significant relationship was determined in other six studies. In a meta-analysis study conducted by Jiang et al., to evaluate the relationship between KCNE1 G38S polymorphism and AF, it is concluded the KCNE1 G38S gene polymorphism increased AF risk. In a study carried out by Yadav et al., in the North Indian population, KCNE1 G38S gene polymorphism was found to be not a risk factor for postoperative AF development. In a study by Chen et al., it was found that the arrhythmia matrix is important

SNP rs	Forward primer (5'–3')	Reverse primer (5'–3')
KCNN3 rs13376333	TGAGAGCACCTGCAGACATC	GCAGCAAGAAGTGGGTCAAT
SCN10A-1 rs6795970	ATGACCCGAACTGACCTTCC	TGACGCTAAAATCCAGCCAGT
SCN10A-2 rs6795970	TGACAGAGGAGCAGAAGAAATACTACA	GTTGAGGCAGATGAGGACCA
KCNE1 rs1805127	GTGACGCCCTTTCTGACCAA	CCAGATGGTTTTCAACGACA
KCNE1 rs1892593	TGGGCTCTATTTTCAG	CCATTGGTCATTTTCC

PCR, polymerase chain reaction; SNP, single nucleotide polymorphism.

Table 8. Primer sequences used in PCR for polymorphisms in the genes coding ion channels.

at the onset or maintenance of AF. The arrhythmia matrix is formed by the interaction of proteins encoded by KCNE1 with other proteins. Therefore, the KCNE1 gene plays a very important role in regulating cardiac rhythm. Studies involving subgroup analyzes also found that the risk of developing AF in white populations with risk alleles was higher than in the Chinese population. The pathogenesis of AF is unknown. However, as a result of mutations in the genes encoding the ion channel, AF can develop due to a decrease in IKs. Environmental factors and genetic factors play a role in the pathogenesis of AF. It has been determined that different polymorphisms in genes encoding ion channels other than the KCNE1 G38S gene polymorphism may also be important risk factors for AF development [24, 25]. It is presented primer sequences that used to determine polymorphisms in the genes coding ion channels in **Table 8**.

9. RPL3L and MYZAP gene polymorphisms

A polygenic process involving transcription factors, cardiac ion channels, myocardial and cytoskeletal proteins plays an important role in AF pathogenesis. Based on the entire genome sequence, GWAS has shown that three low-frequency coding variants are effective in the development of AF. The myosin sarcomeric genes MYH6 and MYL4, the cytoskeletal gene PLEC, are these variants. MYH6, MYL4 and PLEC genes also encode cardiomyocyte structural components such as MYZAP. Ribosome activity can be specifically regulated in the cell via changes in the ribozyme protein composition. The eukaryotic ribosome consists of 4 different ribosomal RNAs and about 80 ribosomal proteins. This ribosome plays an important role in translating the messenger mRNA into a protein. Ribosomal proteins or genes encoding ribosome biogenesis factors may result in mutations leading to ribosomopathy, a hereditary disease. It is known that RPL3L-containing ribosomes may cause translational activity changes. Among RPL3L missense mutations, a negative regulator of muscle growth, p.Ala75Val and p.Gly12Arg mutations are important. Apart from these mutations, the RPL3L c.1167+1G>A mutation is involved in the impairment of the interaction of RPL3L with endoplasmic reticulum. As a result of these mutations, the risk of developing AF is increasing. Human Myozap mRNA is expressed primarily in the heart. Myozap regulates serum response factor signaling in the nucleus. This is why it plays an important role in cardiac signal transduction. Mutations in intercalated disk genes result in cardiomyopathies and sudden cardiac deaths that are a significant risk for AF. AF variants are defined in the genes coding for components of intercalated discs and in the vicinity of these genes. Seeger et al. found the MYZAP gene in the components of intercalated discs. Intercalated discs are a cell-cell contact structure that provides mechanical, electrical and chemical communication between cardiomyocytes. The risk of AF is also increasing as a result of MYZAP p.Gln254Pro gene polymorphism. In a previous study, there was a significant relationship between four low-frequency coding variants in the RPL3L and MYZAP genes and the risk of developing AF. The missense variant in MYZAP was identified as a genetic risk factor in the development of AF [26].

10. Gene polymorphisms and C-reactive protein levels related to inflammation

Several studies have been carried out to investigate the relationship between inflammation and AF. These studies have led to the conclusion that inflammation may cause AF or play an important

role in the onset and maintenance of AF. Myocarditis, pericardiotomy and C-reactive protein (CRP) levels were associated with AF, a dysrhythmia, in studies conducted. However, in some other studies, it has been determined that there is a relationship between AF and the induction of inflammatory response. Previous studies have suggested that AF may be due to inflammatory processes and there is a significant relationship between the CRP levels and the risk of developing AF in these studies. A study performed by Lo et al. found a significant relationship between high basal CRP levels and increased postoperative AF risk. Non-Willebrand factor expression, which is effective in tissue factor, fibrinogen, factor VIII and prothrombic state, is induced by the IL-6 gene, which plays an important role in inflammation. Another study by Gaudino et al. found that -174 G/C polymorphism, a polymorphism in the promoter region of the interleukin-6 (IL-6) gene, was a significant effect on the inflammatory response and was associated with the risk of postoperative AF development. Also Marcus et al., in their study showed a significant relationship between increased IL-6 levels and the risk of developing AF. There is also a study showing that patients with high CRP levels have higher AF risk than patients with normal CRP levels [27].

11. Gene polymorphisms on chromosome 4q25

There are four unique nucleotide polymorphisms on the 4q25 chromosomal region, rs2200733, rs2220427, rs2634073 and rs10033464, and in studies conducted in European and Chinese populations, a significant relationship was found between these polymorphisms and the risk of developing AF. There are no known biological roles of these single nucleotide polymorphisms. These polymorphisms near to the homeobox transcription factor 2 (PITX2) gene and potentially alter the function of this factor. PITX2 is involved in the cardiac pathogenesis of ischemic and pulmonary venous access pathways. rs2200733 and rs13143308 that among the polymorphisms found on the 4q25 chromosome have also been identified as genetic risk factors for AF development. There are also several epidemiological cohorts recently showing a significant association between rs2200733, rs10033464 single nucleotide polymorphisms located in the 4q25 chromosome and AF development. In a recent study, rs2200733 polymorphism was found to be a genetic risk factor for AF development, proliferation and recurrence [28].

12. PRRX1 rs3903239 gene polymorphism

PRRX1 (paired-related HomeBox 1) is a gene encoding homeobox transcription factor that is expressed high in the developing heart. As a result of GWAS, the molecular mechanisms related to AF have been tried to be elucidated. In a recent meta-GWAS, significant correlations were found between the risk of developing rs3903239 polymorphism and AF on the 1q24 chromosome of the PRRX1 gene. In another study conducted with the Greek population, the role of the genetic interaction between PRRX1 rs3903239 and PITX2 rs2200733 gene polymorphisms in the development of AF was investigated and no significant interaction could be detected between these polymorphisms in AF patients. In addition, there was no significant difference in terms of PRRX1 rs3903239 allele frequencies and genotypes between AF patients and healthy controls in the same study. In another study conducted with the Chinese population, PRRX1 rs3903239 gene polymorphism was not detected as a significant genetic risk factor for AF [29].

13. β -fibrinogene 455G/A gene polymorphism

Various studies have been conducted to investigate the relationship between β -fibrinogen 455G/A polymorphism and ischemic stroke in different populations. In a study conducted by Kessler et al., the AA genotype of the β -fibrinogen 455G/A polymorphism was more observed in patients with major vascular infarction. In a study conducted by Nishiuma et al., in a Japanese population, A allele of β -fibrinogen 455G/A polymorphism was identified as an independent risk factor for hypertensive patients. In a study conducted by Martiskainen et al., a significant association was found between the A-allele and the lacunar infarction susceptibility in the β -fibrinogen 455G/A polymorphism. In a study conducted by Zhang et al., in the Chinese population, β -fibrinogen 455G/A polymorphism was found to be a genetic risk factor in the development of ischemic stroke. There are some meta-analysis studies showing that β -fibrinogen 455G/A polymorphism is associated with ischemic stroke in Chinese or Asian populations. A number of studies have been conducted to determine the association between this polymorphism and ischemic stroke, but no study has shown genetic effects in the pathogenesis of cardioembolic stroke in AF patients. The role of β -fibrinogen 455G/A polymorphism in cardioembolic stroke pathology is unclear. Promoter elements play an important role in regulating gene transcription. Transcription factor binding sites and transcription initiation rates can be varied by a promoter variant. β -fibrinogen 455G/A polymorphism has an important stimulatory effect on the rate of basal and induced transcription rate of the β -fibrinogen gene. There is a significant association between A allele of this polymorphism and increased promoter activity. β -Fibrinogen 455G/A polymorphism is one of the genetic polymorphisms associated with an increase in plasma fibrinogen. The increase in fibrinogen levels of individuals with A allele is greater than the increase in fibrinogen levels of individuals with G allele. Therefore, A allele of β -fibrinogen 455G/A polymorphism was found to be associated with higher fibrinogen level. Platelet aggregation, fibrinogen, an important determinant of blood viscosity, is a component that plays a role in the coagulation cascade. As a result of elevated fibrinogen levels, thrombosis progresses and coagulation increases. In animal studies, fibrinogen applications have been shown to increase thrombosis and embolic status at increasing doses. In addition, it is known that fibrinogen has been implicated in triggering various inflammatory processes. As a basic component of inflammation, fibrinogen can cause impairment of thrombus plaque and is effective in the development of ischemic stroke. As a result of all these events, hemorheological disorders occur. As a result of all these events, hemorheological disorders occur. Other polymorphisms that occur in the fibrinogen gene may also cause high fibrinogen concentrations such as β -fibrinogen 455G/A polymorphism β -fibrinogen 455G/A polymorphism has also been proven to be ineffective in the development of thrombotic events. In a study carried out by Xiaofeng Hu et al., in Chinese AF patients, proved that there is a relationship between increased risk of cardioembolic stroke and β -fibrinogen 455G/A polymorphism [30].

14. MTHFR (C677T and A1298C) and MTR A2756G gene polymorphisms

Hyperhomocysteinemia plays an important role in the pathogenesis of nonvalvular AF. Hyperhomocysteinemia develops as a result of polymorphisms occurring in genes encoding

Genes	Forward primer (5'-3')	Reverse primer (5'-3')
MTHFR C677T	biotinTGAAGGAGAAGGTGTCTGCGGGA	CCACTCCAGCATCACTCACT
MTHFR A1298C	biotinCAAGGAGGAGCTGCTGAAGA	CTTGAGAAAAGGCAAAGCAGAC
MTR A2756G	CATGGAAGAATATGAAGATATTAGAC	biotinGAACTAGAAGACAGAAATTCTCTA

PCR, polymerase chain reaction; SNP, single nucleotide polymorphism; MTHFR, methylenetetrahydrofolate reductase; MTR, methionine synthase reductase.

Table 9. Primer sequences used in PCR for MTHFR C677T and A1298C, MTR A2756G.

homocysteine metabolism. These polymorphisms are thought to be effective in the development of nonvalvular AF, which is the most common arrhythmia in clinical practice. Homocysteine is a highly reactive, sulfur-containing amino acid that occurs as a product of the essential amino acid methionine. Gene polymorphisms known to be associated with homocysteine occur in genes encoding enzymes that play a role in the metabolism of homocysteine. Of these polymorphisms, MTHFR C677T and A1298C gene polymorphisms are associated with a decrease in MTHFR enzyme activity. In addition to these polymorphisms, there is also the MTR A2756G gene polymorphism. Homocysteine plays an important role in the pathogenesis of AF and there are studies showing that there is a significant relationship between increased homocysteine levels and AF. In some studies, there was a significant relationship between MTHFR C677T gene polymorphism and increased plasma homocysteine levels in patients with low folate levels. There are few studies related to MTHFR A1298C and MTR A2756G polymorphisms. In a study conducted by Betti Guisti et al., there was a significant relationship between plasma total homocysteine levels and MTHFR C677T gene polymorphism genotype distributions in patients with nonvalvular AF. Furthermore, no significant relationship was observed between plasma total homocysteine levels and MTHFR 1298AA and MTR 2756GG genotypes in nonvalvular AF patients. Given the combined genotype distributions, it is known that the MTHFR C677T and A1298C gene polymorphisms are related to each other [31]. It is presented primer sequences that used to determine MTHFR (C677T and A1298C) and MTR A2756G gene polymorphisms in **Table 9**.

15. Conclusion

Different results have been obtained in gene polymorphism studies to explain the pathogenesis of AF in which environmental and genetic factors play a role together. Differences in the results of these studies may result from different selection criteria for patients and control groups. Moreover, the findings obtained from these studies are different from each other because they are carried out with different races and populations. Identification of genes associated with AF and polymorphisms that occur in these genes will allow us to have information about the underlying mechanisms of the disease in susceptibility to this disease. Identification of candidate genes that play a role in genetic susceptibility to AF will be mentor to the prevention of this disease and the development of new therapies for disease. In order to be able to explain the pathogenesis of AF and to develop appropriate therapies for this disease, comprehensive studies should be conducted with different populations and with a large number of patients and control groups.

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Conflict of interest

We declare that there is no conflict of interest with any financial organization regarding the material discussed in the chapter.

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