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Chapter

Genetic Polymorphisms that Playing Role in Development of Hypertrophic Cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is a complex heart disease with various physiopathological, morphological, functional, and clinical features. In this disease, HCM is known to be an autosomal genetic disease in more than half of the cases. Mutations in sarcomeric genes are thought to play an important role in the pathogenesis of the disease. Modifying genes and environmental factors also together affect the phenotypic expression and severity of HCM. The phenotypic expression of HCM is determined by causal sarcomeric gene mutations and the regulatory genetic basis of genes. HCM, a multi-factorial disease, involves the effects of many environmental gene modifiers and the sarcomeric/cytoskeletal genes. The single nucleotide polymorphisms occurring in the human genome differ in terms of susceptibility to disease in various populations. Therefore, the determination of genetic polymorphisms involved in the development of HCM disease is very important for the diagnosis of the disease.

Keywords: hypertrophic cardiomyopathy, gene polymorphisms, LVH, PCR

1. Introduction

HCM is a complex cardiac disease with major clinical heterogeneity and diagnostic and prognostic effects specific to each mutation. At the same time, this disease has different physiopathological, morphological, functional, and clinical features. HCM, with left ventricular hypertrophy (LVH), is a primary cardiac disorder and occurs when there is no cardiac or systemic disease. Throughout life, it is known that it has a clinical course ranging from symptomatic patients to heart failure symptoms and sudden deaths. It is an autosomal dominant genetic disease in more than half of cases, but it still does not have a fully defined etiology [1]. Modifying genes and environmental factors play an important role in the pathogenesis of HCM. Phenotypic expression and the formation of cardiovascular events are affected by means of these factors [2]. The cardiac β-myosin heavy chain (MYHC) gene, cardiac troponin T (cTnT) gene, α-tropomyosin gene, myosin-binding protein C (MYBP-C) gene, cardiac troponin I gene, and regulatory and essential myosin light chain genes are found among genes encoding the proteins of sarcomere [1]. These genes encoding sarcomeric proteins are localized on different chromosomes. It is known that the first gene identified from these genes is the βMYHC gene encoding the major contractile protein. In HCM patients, due to

defects in sarcomeric proteins, mutations such as MYBP-C, α-tropomyosin, cTnT, ventricular myosin essential and regulatory light chains, cardiac troponin I, and cardiac α-actin and titin have been described. This disease, known to be caused by the defects in sarcomeric proteins, is called sarcomere disease [3]. In addition to mutations in sarcomeric and non-sarcomeric genes, many other gene mutations also lead to metabolic disorders with similar phenotypes in HCM [4]. So far, more than 1400 mutations have been identified in many genes, and the most important genes of these mutations have been identified to encode the protein components of cardiac sarcomere that perform contractile, structural, and regulatory functions [5]. The purpose of this chapter, in addition to giving general information about HCM, is to summarize the studies that investigated the relationship between gene polymorphisms that play a role in the development of HCM and the risk of developing HCM.

2. Hypertrophic cardiomyopathy

HCM, a cardiac disease, is characterized by marked hypertrophy and genetic variability. It is known as a disease characterized by LVH which may cause primary or systemic hypertrophy when there is no other disease [6]. LVH, known as a physiological adaptation to increased workload of the heart, usually develops in clinical conditions such as hypertension, valvular disease, and myocardial infarction. In some patients, cardiac hypertrophy develops when there are no clinical conditions causing cardiac overload. This condition is considered to be the basic form of LVH, and it is thought that this form, which is frequently familial, is caused by mutations in sarcomeric genes. This form of the most common hereditary heart disease is defined as HCM [7]. HCM is one of the leading causes of sudden deaths in young people and athletes. One person in 500 people worldwide is affected by this disease [6]. HCM is a common heterogeneous disease with high morbidity and mortality in the elderly, and it is characterized by enlarged heart, abnormally thickened left ventricular walls, and reduced chamber capacity [8]. Histologically, in this disease, characterized by left ventricular thickness resulting from cardiomyocyte hypertrophy, cardiomyocytes lose their cleavage ability in the first week after birth. Thus, cardiomyocyte hypertrophy is effective instead of cardiomyocyte proliferation in postnatal growth of the heart. Postpartum cardiac growth is a physiological response of myocardium to stress signals as well as its role in cardiomyocyte hypertrophy. It is known that the response of cardiomyocytes to stress signals is characterized by reactivation of fetal gene program [4]. This disease is thought to be caused by contractile proteins encoding genes that cause contractile dysfunction and then hypertrophy. Familial HCM, defined as an autosomal dominant disorder, is usually disseminated by incomplete penetrance due to heterozygous pathogenic gene mutations [8]. HCM is a genetically transmitted, cardiovascular disease with heterogeneous clinical features. Sudden cardiac death in HCM occurs as a frequent complication of 2–3% per year. HCM can be seen form of autosomal dominant feature as a familial disorder; on the other, it can also occur as a sporadic disease that may develop due to novo mutations. These familial and sporadic forms represent different parts of the same spectrum. According to phenotypic models, HCM phenotypes, asymmetric septal hypertrophy (ASH), apical hypertrophy (AH), diffuse hypertrophy (DH), and left ventricular free wall hypertrophy (FH) are classified as. The etiology of the disease is multifactorial, and the majority of cases occur due to secondary mutations in sarcomere myofilament genes. The sarcomere myofilament genes are genes that contribute to heterogeneity in the phenotype of the disease. HCM has a

wide familial variability ranging from severe symptomatic individuals to asymptomatic individuals [4]. Cardiac phenotype and variability in clinical course not only depend on pathogenic genes but also depend on environmental factors [3]. Important information can be obtained in terms of prognosis and treatment of the disease through the identification of these environmental and genetic factors [4].

3. Genetic polymorphisms

3.1 Sarcomeric gene polymorphisms

3.1.1 βMYHC versus MYBP-C gene polymorphisms

Mutations in cardiac β-myosin encoded by the MYH7 gene and myosin-binding protein C sarcomere proteins encoded by MYBC3 gene have been associated with the development of HCM disease. Mutations in these genes are responsible for 50–70% of HCM's genetic cases. β-myosin is a large protein containing 1935 amino acids and is localized on chromosome 14 (14q11) in human. During muscle contraction 2q13 interacts with the thin filament, and this gene consists of 40 exons. The MYBP-C gene is also localized on chromosome 11 (11p.11.2), and 14 mutations have been identified in this gene so far. It has been reported that four of these mutations to be caused by nucleotide changes and eight of which by truncated mutations. The most important feature of these mutations is moderate hypertrophy and low penetration until a certain period of life. About 40 mutations have been identified in β-MYHC that may cause disease, and it is known that most of these mutations occur as a result of the translocation of DNA nucleotides. Displacement in nucleotides also causes amino acid changes in the protein sequence. This change is particularly observed in the familial form of HCM. Among these 40 mutations, there are mutations with high, medium, and low sudden death risks. Arg403Gln, Arg453Cys, and Arg719Gln mutations are known to be malignant. Arg403Gln-related phenotypes were observed in many families, and it is determined that these phenotypes were associated with high penetrance, high incidence of sudden death, and severe hypertrophy. Glu930Lys and Arg249Gln polymorphisms were associated with the middle risk of sudden death. However, Leu908Val, Gly256Glu, Val606Met, and Fhe513Cys polymorphisms have been reported to be associated with benign prognostic and normal survival. Myosin, a hexameric protein, consists of two heavy and two light chains. Light chains contain two light chains as the regulatory light chain (RLC) and the basic light chain (ELC). The myosin heavy chain is also divided into three parts as the lower part 1 (S1), the lower part 2 (S2), and the light meromyosin (LMM). Regulatory and essential myosin light chains were first found in 1996. The regulatory MYL2 gene is localized on chromosome 12 (12q23-q24.3). The essential gene is localized on chromosome 3 (3p) [1]. A large number of mutations have been identified in most S1 and S2 regions, which are associated with HCM in the MYH7 gene. The frequency of these mutations is variable and is known to be associated with marked hypertrophy. MYH7 and MYBPC3 genes are responsible for about 70% of genotyped HCM cases. Mutations in the MYH7 gene are missense mutations and localized at the head of globular myosin. The MYH7 gene is also known to be associated with dilated cardiomyopathy, and a large number of mutations have been identified in the rod region of the gene. There are many studies that demonstrate a relationship between mutations in the MYH7 gene and the family history of HCM. Studies to investigate MYH7 mutations have generally been limited by the analysis of regions encoding the head and neck domains of βMYHC. However, it is

determined that mutations in the tail region of the protein may be related to the risk of developing HCM. Mutations in the MYH7 gene are known as a cause of HCM, and sudden death was significantly higher in the family history and in patients with severe left ventricular hypertrophy. In a previous study, four new mutations are identified. In some of these mutations, the relationship between genotype and phenotype is constant. There are significant differences between phenotypes in other mutations [9]. In a study conducted with the Venezuelan population, no missense mutation identified in the MYH7 gene was found. In the same study, the frequency of mutation of MYH7 gene in adult HCM patients was found to be low. In another study performed by Ronkaratti et al., in the Italian population, it is found that the frequency of mutations determined in the MYH7 gene was found to be very low. Many factors, such as modifying genes, epigenetic factors, microRNAs, posttranslational protein modifications, and environmental factors, may affect the clinical course of HCM disease [1, 10]. Genetic studies are required to understand the clinical and prognostic heterogeneity of HCM. The obtained information of clinical and morphological characteristics of different mutation carriers is important in terms of clinical decision-making in their genetic studies [9].

3.1.2 Cardiac troponin T gene polymorphisms

The cardiac troponin T gene is localized on chromosome 1 (1q3), and so far eight mutations have been identified in this gene. The most important feature of these mutations is that they cause hypertrophy and high incidence of sudden death in younger patients under 30 years of age [1].

3.1.3 Alpha tropomyosin gene polymorphisms

Alpha tropomyosin gene is localized on chromosome 15 (15q2), and two mutations of this gene have been observed to date. It is observed in a low proportion of HCM cases and is known to be associated with normal survival [1].

3.2 TLR4 gene polymorphisms

Studies have shown that the immune system and multiple proinflammatory factors play an important role in the pathogenesis of HCM. Toll-like receptor 4 (TLR4), a member of the pattern recognition receptors, plays an important role as mediation in inflammatory response. TLR4 consists of three exons involved in immunoregulation and is localized in region 9q32-q33. It acts by suppressing T lymphocyte proliferation and regulating macrophage function. The lack of TLR4, which is known to play an important role in the development of cardiovascular diseases, has been reported to be associated with doxorubicin-induced cardiomyopathy in mice. A significant relationship between abnormal expression or genetic polymorphisms and cardiovascular remodeling, which is considered to be an important risk factor for metabolic syndrome, has been found. TLR4, which can trigger protein kinase signaling and innate immune response active with mitogen, leads to activation of proinflammatory cytokines and Chemokines. Common polymorphisms in the TLR4 gene are the rs4986791 and rs4986790 polymorphisms. In addition to these polymorphisms, new polymorphisms have been identified in the promoter region and in the 3′ untranslated region (3′-UTR) of TLR4. Even if the polymorphisms occurring in the promoter region do not alter the gene's coding sequence, the initiation of gene transcription is affected when these gene polymorphisms lead to pathogenicity. Cohort studies aimed at determining the relationship between cardiovascular diseases and TLR4 gene polymorphisms were performed, and inconsistent results were

obtained in these studies. In a study by Lindstrom et al., TLR4 gene polymorphisms were associated with decreased risk of prostate cancer. In another study by Castano et al., TLR4 was found to be associated with increased gastric cancer risk in the 3′-UTR region. In a study by Kiechl et al., it was concluded that TLR4 gene polymorphisms were associated with heart diseases such as atherogenesis. No large number of studies have been carried out to determine whether TLR4 gene polymorphisms are genetic risk factors for HCM. In a study conducted with the Han-China population, TLR4 gene polymorphisms were found to be genetic risk factors in the development of HCM. In this study, it was determined that rs11536865 and rs10983755 gene polymorphisms in the promoter region of the TLR4 gene are important risk factors for HCM development. In this study, the potential relationships of TLR4 gene polymorphisms with the sensitivity and prognosis of HCM have been revealed. It is determined that it is associated with decreased plasma TLR4 levels of the GG genotypes of −728G > C polymorphism and GG genotypes of −2081G > A polymorphism in HCM patients. However, the C allele of the −728G > C polymorphism and the A-allele of −2081G > A polymorphism were found to be related to the highest plasma TLR4 levels. Inflammation and innate immunity are also contributed to the development of cardiomyopathy. Accordingly, it is believed that TLR4 gene polymorphisms affect the progression of natural immunity or inflammation, thus altering the expression level of TLR4, which is involved in the development of HCM. When studies with larger populations are performed, different results are likely to occur [8]. Primer sequences for −728G > C and −2081G > A gene polymorphisms are presented in **Table 1**.

3.3 HOPX gene polymorphisms

Homeodomain only protein x (HOPX) is a homeodomain protein that regulates the serum response factor (SRF)-dependent gene expression. In addition, HOPX is thought to play a role as tumor suppressor gene in some tissues, and expression is silenced in human carcinomas such as choriocarcinoma, lung cancer, head and neck squamous carcinoma, and esophageal cancer during cardiac hypertrophy, SRF activity, which controls the transcription of genes, including cellular immediate-early genes, and cell skeletal and contractile proteins, is controlled by cofactors such as myocardium and compressors such as HOPX. The expression of the HOPX gene encoding a homeodomain protein is under the control of the two promoter regions. One of these promoters is regulated by the cardiac-specific transcription factor Nkx2–5. The HOPX gene plays a role as SRF antagonist, and it is effective in prenatal cardiomyocyte proliferation and postnatal cardiomyocyte hypertrophy. This antagonistic effect performed through by the take of histone deacetylase. In addition, HOPX is thought to play a role as tumor suppressor gene in some tissues, and expression is silenced in human carcinomas such as choriocarcinoma, lung cancer, head and neck squamous carcinoma, and esophageal cancer. HOPX has a role coactivator on SRF activity. Through this, it plays an active role in cardiac hypertrophy. HOPX gene expression is known to be downregulated in kalp insufficiency, but

SNPs	Forward primer (5′–3′)	Reverse primer (5′–3′)
−728G > C	5′-TGATAGACCCCACAACTCCT-3′	5′-TGATTTCCCCC- CATAGGATG-3′
−2081G > A	5′-TACCACCACTGTTCGCTCAG-3′	5′-GGTTATGAGGGACATTGGAT-3′
PCR, polymerase chain reaction; SNP, single nucleotide polymorphism.		

Table 1.
Primer sequences used in PCR for TLR4 gene polymorphisms.

the association between gene polymorphisms in the HOPX gene and heart disease such as heart failure or HCM has not been well established. HOPX protein is not a component of sarcomere and plays a role as a modifying gene. In a study investigating the relationship between HOPX gene polymorphism and SRF-dependent gene expression, it was determined that the expression decreased in heart muscles of mutant mice. Sequence variations in the HOPX gene in particular in the regulatory region have been shown to be associated with HCM. The relationship between HOPX and syncope in HCM is classified in two ways as dependent on SRF and independent on SRF. The HOPX gene plays a modifying role in HCM pathogenesis through SRF-dependent genes, and it is thought that the modifying effect may be more pronounced in patients with mutations in target genes. In a previous study performed in HCM patients, no mutation was detected in the coding sequence of the HOPX gene, but two noncoding polymorphisms associated with syncope were detected. In these polymorphisms, it is determined that homozygous states are protective against syncope and heterozygote cases are a genetic risk factor for syncope. The epigenetic status and genetic variations of the HOPX gene are important as modifying factors in HCM [4]. Primer sequences for HOPXe1, HOPXe2, and HOPXe3 gene polymorphisms are presented in **Table 2**.

3.4 PRKHC gene polymorphisms

The PRKCH gene is a susceptibility gene that plays an important role in atherosclerotic diseases such as cerebral infarction and is associated with the development and progression of atherosclerosis in humans. This gene encodes protein kinase C (PKC), and PKC is activated by diacylglycerol which calcium and secondary messenger. Protein kinase C (PKC) functions as an important signal transduction pathway in the development of cardiac hypertrophy, and studies performed with cell culture and animal models explain this function. It is serine-threonine kinase which is effective in regulating various important cellular functions including proliferation, differentiation, and apoptosis. Members of the PKC family which phosphorylate a wide variety of protein targets are associated with several signalization pathways. There are studies showing that PKC activation is important in the pathology of cardiovascular diseases. The PRKCH gene is located in the ATP-binding region of PKCη in exon 9. PKCη, expressed in the skin and heart tissues, is effective by the way of contributing to cellular processes such as proliferation, differentiation, secretion, and apoptosis. PKCη also plays an important role in immune functions such as regulation of TLR2 responses in macrophages, T-cell proliferation, and homeostasis. The 1425G/A (Val374Ie) polymorphism in the PRKCH gene localized on 14q22-q23 in human increases the kinase activity. In a study conducted by Centurione et al., PKCη has been reported to regulate hypertrophic and apoptotic events, NF-Kb signaling system, and intrinsic mitochondrial apoptotic pathway in rat neonatal heart. In a study conducted with a Chinese population, the PRKCH 1425G/A gene polymorphism was found to be a genetic risk factor in the development of hypertrophic obstructive cardiomyopathy (HOCM). In studies conducted with Chinese and

SNPs	Forward primer (5′–3′)	Reverse primer (5′–3′)
HOPXe1	5′-AACGTGCTATCAGCAGCCTG-3′	5′-GACGAACAGGACCGCCCAGC-3′
HOPXe2	5′-CGACCGCCTTCCTTCGCTGC-3′	5′-CCTTCATGGAGTGAAGCTGTC-3′
HOPXe3	5′-CTTGTGCCACAGAGGCTACC-3′	5′-CCTTCATGGAGTGAAGCTGTC-3′

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

Table 2.
Primer sequences used in PCR for HOPX gene polymorphisms.

SNPs	Common primer (5′–3′)	Allele-specific primer (A) Allele-specific primer (G)
PRKCH 1425G/A	5′-GCAGAATCACGTCCTTC TTCAG-3′	5′-CATAGGTGATGCTTGCAAGAA-3′
		5′-CATAGGTGATGC TTGCAAGAG-3′

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

Table 3.
Primer sequences used in PCR for PRKCH gene polymorphism.

Japanese populations, PRKCH 1425G/A gene polymorphism was found to be associated with increased ischemic stroke and the risk of cerebral hemorrhage. More studies should be performed related to molecular mechanisms to determine the relationship between the risk of developing PRKCH and HOCM [5]. Primer sequences for PRKCH 1425G/A gene polymorphisms are presented in **Table 3**.

3.5 SCN10A gene polymorphisms

The SCN10A gene encodes NaV1.8, a neuronal sodium channel isoform. NaV1.8 is an alpha subunit of sodium channels with voltage door. NaV1.8 localized in the peripheral nervous system is associated with chronic and neuropathic pain. With rapid and sustained stimulation, long-term action potential is observed and excitability is maintained. SCN10A identified in the human heart was found to be associated with changes in cardiac and atrioventricular conduction. Significant relationships were found between the PR interval, QRS duration, and SCN10A gene polymorphisms in recent genome-wide association studies. Starting from this, it is concluded that NaV1.8 plays an important role in cardiac electrophysiology. In a study by Chambers et al., rs6795970 gene polymorphism has been shown to result in the amino acid exchange A1073V in the IDII/III intracellular cycle of NaV1.8. In another study, it was determined that the A-allele of the rs6795970 gene polymorphism occurring in the SCN10A gene may be related to the cardiac conduction abnormalities observed in HCM patients. In addition, significant correlations were found between the A-allele of the rs6795970 gene polymorphism and the increase in the risk of first-degree heart block, bundle brunch block, and bifascicular heart block [2].

3.6 HSP 70 gene polymorphisms

Heat shock protein 70 (HSP 70) is localized on 6p21.3 and is located in the class III region of the major histocompatibility complex (MHC). This gene is expressed in response to heat shock and stress stimulators such as oxidative free radicals and toxic metal ions. Some of the HSPs play an important role in controlling protein folding, translocation, or degradation and are structurally expressed in non-stressed cells. There are three gene modifiers such as HSP 70-1, HSP 70-2, and HSP 70-Hom. HSP 70-1 and HSP 70-2 are those that encode an identical protein of the heat-inducible HSP 70. HSP 70-Hom is expressed at structurally low levels; it encodes a protein non-inducible with heat. There are studies showing that the overexpression of heat shock proteins has a cardioprotective role and that genetic variants of HSP 70 may reduce the ability of cells to protect against ischemia. The genetic polymorphisms in the HSP 70 gene have been found to play an important role in various diseases such as Parkinson's disease, schizophrenia, breast carcinoma, ischemic stroke, and coronary artery disease. The relationship between HSP 70 specific genotypes and hypertrophic cardiomyopathy has not been reported so far. In a previous study, the modifying role of HSP 70 has been described. In the study, it was found that HSP plays a regulatory role in HCM-related inflammatory

responses and hemodynamic compensatory mechanisms. HSP genes are genes that encode a family of structurally produced proteins in the fulfillment of basic functions, which increase expression in response to various metabolic stimuli. One of the most important tasks of these genes is to facilitate the synthesis and folding of proteins within the cells. In addition HSP genes play an important role in protein binding, secretion, protein degradation, and in the regulation of protein kinases via transcription factors. Polymorphisms in the expression of HSP genes are controlled by a number of transcription factors, and these factors are called heat shock factors (HSF). As a result of the increase and accumulation of HSPs, the protection of the stressed cell is increased; thus the cell survival is maintained. Overexpression of HSP 70 elicits its cardioprotective property. As a result of the polymorphisms occurring in the HSP 70 gene, the synthesis of HSP 70 protein can be changed [11].

3.6.1 HSP 70-1 (+190G/C) polymorphism

The HSP 70-1 (+190G/C) polymorphism is a silent polymorphism of the initial domain translated in the 5′-UTR region of the gene. It has been reported to be a significant relationship between this polymorphism and various diseases such as Parkinson's disease, high-altitude illness, and diabetes mellitus. HSP 70 is known as a significant stress protein whose production is increased under stress [11].

3.6.2 HSP 70-2 (+1267A/G) polymorphism

The HSP 70-2 (1267A/G) polymorphism is a polymorphism located in the coding region of the gene. HSP 70-2 changes the expression of mRNA, and the relationship between this expression and the +1267A/G polymorphism is shown in several studies. In a study, G allele of HSP 70-2 (1267A/G) polymorphism was found to be an important risk factor in the development of HCM. In a study by Pociot et al., it was determined that the differences between individuals in HSP 70 expression may be related to different regulatory mechanisms than transcriptional regulation. In addition, the HSP 70 polymorphic region affects expression and enzyme activity of the synonymous gene polymorphism. As a result of changing the timing of co-translational folding, the secondary structure of mRNA, stability, substrate, or inhibitor binding sites of the brain vary. In a study, there was no change in the secondary structures of the A and G alleles of HSP 70-2 mRNA [11].

3.6.3 HSP 70-Hom (+2437C/T) polymorphism

The HSP 70-Hom (+ 2437C/T) polymorphism is characterized by the Met493Thr missense translocation, which affects the substrate specificity and chaperone activity of HSP 70-Hom. In a study conducted with a Mexican population, a significant relationship was found between the +2437 T allele and spondyloarthropathies of HSP 70-Hom (+ 2437C/T) gene polymorphism. It is known that nucleotide changes in the coding region may influence the peptide binding kinetics and the affinity of ATPase activity with HSP 70 proteins. Furthermore, as a result of the nucleotide changes that occur in the side regions, the inducibility, expression grade, and stability of mRNA can be affected. Overexpression of HSP 70 is a preservative against the damaging effects of ischemia. In consequence of excessive expression, the release of the creatine kinase of the heart, recovery of high-energy phosphate depots, and correction of metabolic acidosis are performed. Protective effects of HSP include protein folding, abnormal protein degradation, inhibition of apoptosis, preservation of the cell skeleton, and improved NO synthesis. Apoptosis, a programmed cell death involving the release of cytochrome c, is an important consequence of

SNPs	Forward primer (5′–3′)	Reverse primer (5′–3′)
HSP 70-1 +190G/C	5′-CGCCATGGAGACCAACACCC-3′	5′-GCGGTTCCCTGCTCTCTGTC-3′
HSP 70-2 −1267A/G	5′-CATCGACTTCTACACGTCCA-3′	5′-CAAAGTCCTTGAGTCCCAAC-3′
HSP 70-hom −2437T/C	5′-GTCCCTGGGGCTGGAGACG-3′	5′-GATGATAGGGTTACACATCTGCT-3′

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

Table 4.
Primer sequences used in PCR for HSP 70 gene polymorphisms.

hypertrophy decompensation. HSP 70 expression and activation of procaspase 9, leading to cardiac hypertrophy, can inhibit caspase-mediated apoptosis activity. Hence, the expression of HSP proteins is affected by HSP 70 genes and polymorphisms in these genes. Thus, the ability to inhibit apoptosis resulting in HCM due to cardiac hypertrophy may be affected. In a previous study, the C allele of the HSP 70-1 gene polymorphism and the G allele of the HSP 70-2 gene polymorphism were found to be associated with increased risk of HCM [11]. Primer sequences for HSP-70-1 +190G/C, HSP-70-2 −1267A/G, and HSP-70-hom −2437T/C gene polymorphisms are presented in **Table 4**.

3.7 RAAS gene polymorphisms

The renin-angiotensin-aldosterone system (RAAS) can cause ventricular hypertrophy through circulating angiotensin. RAAS plays an important role in cell proliferation, regulation, and the partial expression of heart hypertrophy, thereby developing LVH [3]. It is also known to play a regulatory role in cardiac function, blood pressure, and electrolyte homeostasis in the body. Angiotensinogen (AGT), renin, angiotensin-converting enzyme (ACE), and angiotensin II receptors of RAAS are found in the heart, and these components function more independently than circulating RAAS [7]. Angiotensin I is converted to angiotensin II through ACE, and angiotensin II is linked to type 1 receptor angiotensin II (AGTR1). Angiotensin II has an important role in supporting cell growth and hypertrophy. In addition, angiotensin II is converted to aldosterone by aldosterone synthase (CYP11B2), and aldosterone supports cardiac fibrosis. Aldosterone plays an important mediator role in HCM, among sarcomeric mutations and cardiac phenotypes [12]. RAAS activation or receptor function may increase as a result of genetic polymorphisms in genes encoding RAAS. In some studies, a significant relationship was found between RAAS gene polymorphisms and increased hypertrophic response against HCM. In some studies, RAAS gene polymorphisms have been found to be genetic risk factors in the development of LVH, but there are studies that have not confirmed this. Childhood HCM is an early onset HCM and it shows a rapid progress. Furthermore, a growing heart shows more dependence on RAAS than the adult heart. Therefore, it is thought that the growing heart may be more sensitive to RAAS gene polymorphisms. Although studies have shown that there is a relationship between RAAS and HCM, in some studies with different populations, the role of RAAS in the change of HCM phenotype is not well-known [7]. It is thought that modifier genes that regulate RAAS may alter the responses to drug therapies and hence may be effective in the prognosis of HCM patients. RAAS, which is known to be associated with hypertrophy in familial HCM, has been shown to be more effective in sporadic HCM. Early diagnosis of genetic risk factors such as RAAS gene polymorphisms in terms of risk classification and development

of new strategies for interventions to individual according to this classification are very important [13].

3.7.1 ACE gene polymorphisms

ACE increases the synthesis of angiotensin II by inducing cell proliferation, migration, and hypertrophy. Angiotensin II develops the proinflammatory cytokines and matrix metalloproteinases. Therefore, overexpression of angiotensin II is thought to play an important role in cardiomyopathy. ACE, which converts angiotensin I to angiotensin II, functions as a growth factor for cardiac myocytes. It has been reported to induce the cardiac hypertrophy independent of hemodynamic and neurohumoral effects. The ACE gene is localized on chromosome 17 (17q23.3) in the human genome. The gene, which is 21 kilobase in length, consists of 26 exons. The ACE insertion/deletion (I/D) gene polymorphism corresponds to a repetitive sequence of 287 base pairs (Alu) in intron 16. DD genotype of ACE (I/D) gene polymorphism was found to be associated with increased ACE and angiotensin II levels. This causes increased hypertrophy and fibrosis. Phenotypic expression of HCM is also affected as a result of increase of angiotensin II levels. Previous studies have shown a significant relationship between ACE (I/D) gene polymorphisms and plasma angiotensin II levels. ACE (I/D) gene polymorphism has been shown to modulate the phenotype in HCM patients. In studies conducted with different populations, contradictory results were found in terms of the relationship between ACE (I/D) gene polymorphisms and the risk of developing HCM. In a study performed in Japanese population by Yamada et al., no significant relationship was found between ACE (I/D) gene polymorphism and HCM. In a study by Perkins et al., it was determined that the DD genotype of the ACE (I/D) gene polymorphism was important in the phenotypic expression of HCM and the ACE tissue levels were higher in patients with DD genotype. In another study carried out by Schunkert et al., a significant association was found between D allele of the ACE (I/D) gene polymorphism and increased LVH in HCM patients. In a study conducted by Rai et al., in the Indian population, ACE (I/D) gene polymorphism was found to be a genetic risk factor for HCM and dilated cardiomyopathy. In a meta-analysis study, D allele of ACE (I/D) gene polymorphism has been reported to be associated with increased risk of HCM. In patients with HCM that carry the DD genotype of the ACE (I/D) gene polymorphism, higher serum ACE levels, increased risk of sudden death, and higher severity of hypertrophy are observed than other genotypes. Angiotensin II, which shows trophic effects on the heart, also plays an important role in the development of myocardial hypertrophy. The AGTR1 antagonist has an important role in reducing myocardial hypertrophy, so it may be an important treatment option to prevent the sudden cardiac death in patients with HCM. It is thought that obtaining different results in the studies is due to differences in research design, environmental backgrounds, genetic structure, or sample selection criteria in studies. Further genome-wide relationship studies are needed to determine the relationship between the ACE gene and HCM [3, 7].

3.7.2 AGTR1 and AGTR2 gene polymorphisms

LVH is known to be variable in patients with HCM. Angiotensin II plays an important role in the change of LVH. AGTR1 A1166C and angiotensin II type 2 receptor (AGTR2). As a result of A3123C gene polymorphisms, phenotypic expression of hypertrophy in HCM is affected. The AGTR1 gene is localized on

chromosome 3q21. AGTR1 A1166C gene polymorphism is characterized by adenine (A)/cytosine (C) base translocation at position 1166 of the gene. Different results have been obtained in studies attempting to explain the relationship between these gene polymorphisms and HCM development [12].

3.7.3 CYP11B2 gene polymorphisms

It has been determined that aldosterone, which can be produced locally in the heart, is associated with sarcomeric mutations and cardiac phenotype. The CYP11B2 −344C/T gene polymorphism is characterized by C/T base displacement at the −344 position of the CYP11B2 gene localized on the 8q22 chromosome. The CYP11B2 gene polymorphism was found to be associated with left ventricular mass in human essential hypertension. In a previous study, aldosterone was found to modify the phenotypic expression of the mutated gene in HCM. A significant relationship between CYP11B2 genotype and cardiac hypertrophy has been shown in HCM. It has also been reported that the T allele of the CYP11B2 gene polymorphism in patients with essential hypertension has been identified as a genetic risk factor for left ventricular mass. In another study, a significant association was found between the CYP11B2 −344C/T gene polymorphism CC genotype and cardiac hypertrophy among healthy controls [14]. Several previous studies have reported that the T allele of the CYP11B2 gene polymorphism is associated with increased plasma aldosterone levels. Therefore, it is thought to be a significant relationship between T allele of this gene polymorphism and cardiac hypertrophy [12].

3.7.4 AGT gene polymorphisms

AGT released into the circulation is a glycoprotein produced by hepatocytes containing 485 amino acids. It is known that AGT is converted into angiotensin I by the renin enzyme. The rate in angiotensin production plays a role in the regulation of AGT concentration and angiotensin II production. In addition, AGT plays an important role in essential hypertension, renal tubular dysgenesis, non-familial structural atrial fibrillation, and in LVH via strong myotrophic effect. The AGT gene is known to regulate the expression of AGT. AGT M235T gene polymorphism is characterized by methionine/threonine base displacement in chromosome 1q42 of the AGT gene [14]. In studies conducted to investigate the relationship between AGT M235T gene polymorphism and HCM, controversial results were found. Although in some studies significant relationships were determined, in some studies were not found. In a study conducted with the Japanese population by Kawaguchi et al., it was determined that TT genotype and T allele of the AGT M235T gene polymorphism were genetic risk factors for HCM. However, in the same study, no significant relationship was found between TT genotype and T allele of this gene polymorphism and familial form of HCM. A higher T allele frequency was found in patients with sporadic HCM. The TT genotype of the AGT M235T gene polymorphism is thought to be a genetic marker for LVH. It was also found to be significant relationship between this polymorphism and other cardiovascular diseases such as myocardial infarction, coronary atherosclerosis, and hypertension. In another study conducted with the South Indian population, the relationship between T704C gene polymorphism and HCM in exon 2 of the AGT gene was investigated. In this study, T allele of AGT T704C gene polymorphism was found to be associated with sporadic HCM. However, it was concluded that this allele is not a genetic risk factor for familial HCM. In conclusion, the T allele of the AGT

SNPs	Forward primer (5′–3′)	Reverse primer (5′–3′)
ACE (I/D)	5′-CTGGAGAGCCACTCCCATCCTTTCT-3′	5′-GACGTGGCCATCACATTCGTCAGAT-3′
AGTR1 A1166C	5′-GAAGCCTGCACCATGTTTTGA-3′	5′-GGCTTTGCTTTGTCTTGTTG-3′
CYP11B2 −344C/T	5′-CAGGAGGAGACCCCATGTGAC-3′	5′-CCTCCACCCTGTTCAGCCC-3′
AGT M235T	5′-CAGGGTGCTGTCCACACTGGACCCC-3′	5′-CCGTTTGTGCAGGGCCTGGCTCTCT-3′
AGT T704C	5′-CAGGGTGCTGTCCACACTGGACCCC-3′	5′-CCGTTTGTGCAGGGCCTGGCTCTCT-3′

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

Table 5.
Primer sequences used in PCR for RAAS gene polymorphisms.

T704C gene polymorphism has been reported to be associated with the development of sporadic HCM. A larger scale of cohort studies should be performed to confirm the relationship between T alleles and HCM development of these gene polymorphisms [3]. Primer sequences for RAAS gene polymorphisms are presented in **Table 5** [15, 16].

4. Conclusions

It is known that genetic and environmental factors play a role in the pathogenesis of HCM. Numerous studies have been conducted to investigate gene polymorphisms playing the role in HCM development. The differences in the results of these studies are thought to be stemmed from different race and population characteristics and different selection criteria of patient and control groups in the study. The identification of genes and the polymorphisms occurring in these genes that are effective in the development of HCM will enable us to have knowledge about disease-related mechanisms in HCM susceptibility and to develop new drug and treatment strategies in the prevention of HCM. Different results can be obtained in studies with different and larger populations.

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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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