

# PREVENTION OF CARDIOVASCULAR DISEASE: A NUTRIGENETIC APPROACH

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## ABSTRACT

Cardiovascular diseases are the leading cause of death worldwide. Besides genetic factors, environmental factors also contribute to their etiology. Nutrigenetics provides the opportunity to prevent or reduce the incidence of many diseases. In this review article, we investigated the incidence of cardiovascular diseases in relation to nutrigenetics, genotype-specificity, personalized conditions, nutrition, genetic polymorphisms, and environmental factors. We concluded that the genes encoding miRNA, APOB, PCSK-9, SORT1, cytokines, and IFN- $\gamma$  are strongly associated with development and progression of cardiovascular diseases. Through nutrigenetic testing, we can determine the risk factors, identify preventative strategies, and improve the quality of life through personalized nutrition.

**Keywords:** Cardiovascular disease, nutrigenetics, genotype, diet

## INTRODUCTION

Nutrigenetics is a branch of genetics that analyzes the relationship between genetic polymorphisms of individuals and their response to a diet (1). Previous research has suggested that nutrigenetics may be associated with many conditions such as obesity, cardiovascular disease (CVD), and hypertension (1). Nutrigenetics can improve the quality of life for many people and allow us to develop preventative measures for metabolic diseases through analyzing their genomes and providing a personalized diet based on their genetic composition (1).

The human genome consists of almost 3 billion base pairs encoding 30,000 genes and 100,000 proteins (2). Although 99.9% of the genome is identical in humans, about 1,500 base pairs contain polymorphisms (2). Previous genetic studies have identified genetic variants related to obesity and concluded that in addition to environmental and lifestyle

factors, genetic factors strongly correlate with CVD, cancer, diabetes, and osteoporosis (2).

Molecular genetics and pharmacogenetics play an important role in the diagnosis, treatment, and prevention of CVDs (3). Genetic testing is used to determine genetic transmission of and familial predisposition to diseases such as hypertrophic cardiomyopathy and familial hypercholesterolemia (4, 5). Nutrigenetics aims to provide another preventative approach through dietary changes based on one's genome (1).

## NUTRIGENETICS IN DISEASE

Nutrigenetic studies have provided insights into many diseases from obesity to bone disease to CVD (1, 6). Genetic factors play a crucial role in obesity and these genetic variants have been useful in the development of nutrition plans in obesity treatment (7). Similarly, 50-80% of bone diseases are associated with genetic polymorphisms. For instance, vitamin D receptor



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polymorphisms are important in mineral density, calcium, and vitamin D supplementation, while vitamin B and K polymorphisms are not as critically associated (6). Genes related to sodium metabolism have shown that the amount of salt in the diet is associated with hypertension (8).

### Cardiovascular Diseases

Cardiovascular diseases are the leading cause of mortality and disability worldwide but can be preventable through lifestyle and dietary changes (9). Genes interact with nutrients to influence cardiovascular regeneration or repair (10). Polymorphisms in certain genes can predispose individuals to myocardial infarction (MI) and stroke, as well as hypertension, diabetes, and inflammation (11). The genetic risk factors of CVDs are not yet fully determined (12, 13). However, it has been observed that individuals with the E4 allele in the *apolipoprotein E* gene have higher levels of low-density lipoprotein (LDL) in fat intake when compared to other individuals (14). Obesity, sedentary lifestyle, and hyperinsulinemia may also contribute to the risk of CVDs (11).

### Hypertension

Hypertension is one of the most prevalent risk factors for CVDs and its treatment has been shown to reduce the incidence of CVDs (15). In particular, the Framingham Heart Study showed a clear relationship between hypertension and the risk of CVDs (15). Its prevalence increases with increasing age such that prevalence is 7.3% in adults aged 18-39 years, 32.2% in adults aged 40-59 years, and 64.9% in adults aged 60 years and over (16).

There are many mechanisms by which hypertension causes atherosclerosis. An increase in blood pressure can cause an increase in vascular stress (14). Especially in areas of non-laminar flow, there is evidence that increased radial forces cause changes in the endothelial layer that make it more susceptible to movement of LDL into the subendothelium as well as making it easier for monocyte attachment (17). Another contributing mechanism is increased oxidative stress. In hypertension, nicotinamide adenine dinucleotide phosphate-oxidase, xanthine oxidase, and cyclo-oxygenase enzyme systems are activated, and the detoxifying enzyme superoxide dismutase is decreased, resulting in increased availability of superoxide anions, which reduces the availability of nitric oxide and generates pro-inflammatory radicals (18).

### Smoking

A 2005 INTERHEART study examined the risk factors for heart disease, such as smoking and second-hand smoke, as a prospective case-control study in 52 different countries (19). The INTERHEART study showed that the risk of acute MI increased approximately threefold in smokers and was directly proportional to the number of cigarettes smoked (19).

Smoking increases the risk for atherosclerosis and CVDs through inhibition of nitric oxide production (20). Decreased nitric oxide production impairs vasoconstriction and vasodilation due to endothelial dysfunction and causes LDL oxidation, which is an important factor in the development of atherosclerosis (20). Endothelial damage induces adhesion of monocytes and increases the recruitment and migration of monocytes into the subendothelial space, which further advances atherosclerosis (20). In addition to its role in the development of atherosclerotic plaque, it has been shown that smoking increases fibrinogen levels, which increases thrombosis and therefore may cause subsequent clot formation in the ruptured plaque, which causes acute MI (20).

### Obesity

Thirty nine percent of the world's adult population was overweight and 13% were obese in 2016 (21). Obesity may play a role in the formation and progression of adiposity and other metabolic diseases by affecting energy balance and body weight regulation (21).

There is evidence that obesity triggers atherosclerosis (22). Obesity is an inflammatory disease because adipose tissue is a source of proinflammatory adipokines such as tumor necrosis factor alpha, interleukins, monocyte chemoattractant protein-1, resistin, and leptin. These adipokines have effects such as stimulating vascular reactivity, stimulating inflammation, and even coagulation (22). Therefore, obesity is both a risk factor and a risk marker for CVDs, and its increase over the past 20 years makes it an important target for intervention (11).

Having a sedentary lifestyle increases the risk of CVDs (23, 24). One study considered that decreasing lipoprotein lipase activity during sitting resulted in less catabolism of triglycerides and increased plasma triglyceride levels (23). A sedentary lifestyle also decreases endothelial nitric oxide expression caused by low blood flow in the limbs with prolonged sitting (24).

## ROLE OF GENETICS

### Role of MicroRNAs in CVDs

MicroRNAs (miRNAs) are part of the non-coding RNA family, which are associated with gene expression and intercellular communication (25). They play a key role in pathogenicity in many diseases such as MI, inflammation, hypertrophy, and atherosclerosis (26). miRNAs in the cardiovascular system control the functions of muscle cells and vascular endothelial cells, and abnormal expressions of these miRNAs are associated with cardiac dysfunction (27-29).

Previous studies demonstrated that miRNA expression in damaged tissues in patients with CVDs is irregular (27, 30).

In an experiment in mice, severe developmental defects in the heart and blood vessels demonstrated the importance of miRNAs in heart biology through tissue-specific erasure of genes such as Droscha, DGCR8, Argonaute RISC Catalytic Component 2, or Dicer, which are essential for miRNA biogenesis (23). miRNAs became the new biomarker for the diagnosis of CVDs (31).

#### Use of Molecular Genetics in the Diagnosis of CVDs

Genetic tests are used to determine the underlying causes of CVDs (32). To better interpret genetic test results in terms of CVD risk, the patient should be evaluated comprehensively (33). Hereditary features of CVDs are of varying degrees. Although most CVD-associated polymorphisms are polygenic, they can also be monogenic. When monogenic CVD markers are not recognized and treated accordingly, they can lead to serious illness, disability, and even death. Familial hypercholesterolemia is a widespread monogenic disease caused by mutations in the LDL receptor, *apolipoprotein B (APOB)*, and *proprotein convertase subtilisin/kexin type 9* genes with a frequency of 1/200 (32). Another common familial CVD caused by mutations in approximately 11 genes that encode sarcomere proteins is hypertrophic cardiomyopathy (32).

Our knowledge of CVD risk factors and the genetic background of many non-infectious diseases has increased through Genome-wide Association Studies (GWAS). GWAS identified that the single nucleotide polymorphisms (SNPs) that are associated strongest with CVDs are located in the p21.3 region of chromosome 9 in humans (32, 34). Another gene identified by GWAS is Sortilin (*SORT1*) (32). The most important signals indicating the risk of LDL cholesterol causing CVDs are the *SORT1* gene, which also plays a role in determining plasma cholesterol levels, and the *CELSR2/PSRC1/SORT1* gene set (32). Although research on *SORT1* supported its impact on plasma cholesterol levels and identified it as a risk factor in creating MI, its effects are quite complex and still controversial (35).

There is also a complex relationship between dietary habits and gene expression. Studies show that SNPs in nutrigenetics are associated with plasma lipid rates of nutrients consumed. The relationship of homocysteine with folate intake is thought to be a risk factor for MI and stroke (32). Also, it has been determined that homocysteine concentration is high and methylenetetrahydrofolate reductase polymorphism is more pervasive in regions with low folate intake (36).

#### Association of Extracellular Vesicles with CVDs

Membranous structures that carry bioactive substances, such as macronutrients, messenger RNA, and miRNA, are called

extracellular vesicles (EVs). Key sources of these vesicles in the heart are endothelial cells, cardiomyocytes, macrophages, and fibroblasts (37). EVs have an important role in the signaling and function of their target organs. Moreover, EV molecules are helpful for transferrin's protective role in cardiomyocytes (38). EVs enriched with miRNA-30a are released from cardiomyocytes in response to hypoxia-inducible factor1 $\alpha$  to protect the myocardium from damage during hypoxia (39). EVs produced in cardiomyocytes express exclusive cellular markers such as flotillin-1 and caveolin 3, as well as sarcomeric and mitochondrial proteins such as myomyosin, cardiac-type myosin binding protein C, and tropomyosin (40).

EVs release their cargo to target cells by budding from the plasma membranes (41). With the stimulation of the calcium-dependent mechanism in the plasma membrane, substances inside the EV are poured into the extracellular area (42). Calcium ion affects enzymes such as gelsolin and calpain, which are involved in the disintegration of the cytoskeleton and cause an easy release of microvesicles (37).

Hsa-miRNA-208a was identified as one of the specific miRNAs carried by EVs which increased in blood after MI (43). This research suggested that miRNAs could be useful in the diagnosis of MI and circulating RNAs could be useful biomarkers in the diagnosis of CVDs (43). EVs also protect the heart against MI and arrhythmias (37). Due to the aforementioned features of EVs, they have been proposed to be used as a new diagnostic tool in preventing CVDs (35).

#### The Effect of the Calcium-Calmodulin Mechanism on CVDs

Intracellular calcium, which plays a key role as a second messenger in heart contraction, and the accompanying calmodulin (CaM) protein are major signaling mechanisms (44). With each heartbeat, calcium is released and then taken back into the cell, and CaM plays a role in the excitation-contraction mechanism (44, 45). CaM is a highly preserved protein that can interact with about 300 different proteins other than calcium (46). CaM binds four calcium molecules and is involved in the regulation of calcium channels (45). CaM is also important in regulating cellular events such as infection, cell death, cell growth, and immunity (44).

Calmodulin-related genes are present in chromosomes 2, 14, and 19 and encode isoforms of CaM which differ at a single nucleotide level (44). To understand the genetics of MI predisposition, it is necessary to identify the polymorphisms formed in the CaM mechanism (44). These polymorphisms have been associated with serious diseases of the heart such as ventricular fibrillation, catecholaminergic polymorphic ventricular tachycardia, and diseases with different pathologies such as osteoarthritis and adolescent idiopathic scoliosis (44, 47-49).

It has been reported that polymorphism 34T>A in chromosome 19 affecting the CALM3 transcript is more common in patients with familial hypertrophic cardiomyopathy (FHC) and may therefore be a gene that affects FHC (50). As we learn more about the transcriptional mechanism of the excitation-contraction mechanisms in the heart, we can conclude that genetic factors contribute to the predisposition of individuals to disease CVDs (44).

#### Role of Cytokines in the Formation of Atherosclerosis

As aforementioned, atherosclerosis is an inflammatory disorder that has a role in the formation of CVDs (10). The atherosclerotic plaque formation causes the vascular lumen to narrow, while the rupture of this plaque causes the vascular lumen to become blocked completely through thrombus formation (51). Such vascular obstruction can lead to MI (10). The severity of atherosclerosis was found to be related to cytokine genes in studies conducted with patients recovering from MI (52, 53). Cytokines regulate the expression of inflammatory molecules that can cause atherosclerotic plaque rupture, so it has been recommended to use inflammatory cytokine levels to track the clinical course of CVDs (54).

Interferon-gamma (IFN- $\gamma$ ), a proinflammatory cytokine, is secreted from macrophages and is associated with the formation of atherosclerosis. IFN- $\gamma$  stimulates the production of chemokines and cytotoxic molecules from macrophages, and its expression increases in atherosclerosis (10, 55). In the early stages, IFN- $\gamma$  supports the development of atherosclerosis by stimulating the secretion of adhesion molecules from the endothelium. In the late stages, IFN- $\gamma$  works to separate atherosclerotic plaques by speeding up apoptosis and extracellular degeneration of macrophages (10, 56).

Countless SNPs have been found in the *IFN- $\gamma$*  gene localized at 12q24 (10). One example is the IFN- $\gamma$  +874 T/A (rs2430561) polymorphism, which affects the formation and development of atherosclerotic plaques, and can therefore be used as a biomarker candidate for early MI detection (10).

## TARGETED THERAPIES

### Preventative Medicine and Genetics

Health is defined as a state of complete physical, mental, and social well-being (57). Preventive medicine interventions are medical evaluations that reduce the risk of disease and provide early detection and treatment (57). Through genetic diagnostic tests and nutrigenetics, risk factors that may induce diseases can be identified, and preventative measures can be taken with nutrition and lifestyle changes (58). The goals of nutrigenetics include effective individual dietary

strategies to improve quality of life, prevent diseases, and promote wellness (59).

### Individualized Nutrition

Both genetic and environmental factors contribute to development of CVDs, and nutrition has special importance in CVDs. Nutritional interventions that are personalized according to the individual's genetic background may present a new diet-based approach to treat CVDs and improve health outcomes (1). Studies have shown that genetics can be used to identify individuals who are most likely to lose weight, but these findings should be further investigated before wide use (60).

Historically, nutrition interventions were focused on the relationship between nutrient deficiencies and disease but with new studies, there is a potential to improve chronic metabolic disorders through nutrition (61-64). Through nutrigenetics, it is possible to understand the effects of dietary response and nutritional elements on gene expression based on genetic variations (65). However, despite recent advances in nutrigenetics, there are not enough studies about personalized nutrition. Moreover, the cost of genetic testing poses a great challenge to the widespread use of personalized nutrition (63).

### Nutrigenetics in Controlling Inflammation and Cardiovascular Risk Factors

Inflammation underlies a wide spectrum of diseases from CVDs to psychiatric disorders (66). There is evidence that genetic variation can predispose one to increased inflammation and can increase the likelihood of disease development through interactions with environmental factors such as diet (67). The Mediterranean diet is suggested for reducing inflammation and reversing inflammatory diseases (68).

### Nutrigenetics and the Response to the Mediterranean Diet

As the world population ages, the prevalence of CVDs is also increasing (69). Along with medical treatment, lifestyle changes are also very important in the treatment process (70, 71). Research shows that a diet rich in plant sterols is important in maintaining good health (72).

Previous studies have shown that the Mediterranean diet protects the heart and overall health (73). The traditional Mediterranean diet is characterized by a large consumption of fruits and vegetables, unrefined grains, nuts, fish, legumes, olive oil, moderate consumption of wine, preferably with main meals, and low intake of dairy products and meat (74). The protective effects of the Mediterranean diet are revealed by dietary fiber, unsaturated fatty acids, antioxidants, and bioactive components (75). To get the best results from the Mediterranean diet; cultural, genetic, and socioeconomic factors should be considered (74).

## Nutrigenetics Challenges

For nutrigenetics to be useful as a public health tool, there is a great need to use statistical and bioinformatics tools to examine the combined effects of multiple gene variants on health outcomes (76). While personalized nutrition based on genetics has great potential, there are many challenges in translating scientific advances into successful strategies for managing dietary intake and dietary health outcomes. These challenges include translating research results into practice, public perception and the likelihood of acceptance, issues of privacy and ethics, commercialization, and the level of evidence needed to enable a beneficial transition from traditional approaches (77).

## CONCLUSION

In this review, we explored preventative approaches to CVDs through nutrigenetics. Many genetic variants related to obesity and CVDs have been previously described. In our review, we concluded that genes encoding miRNA, APOB, PCSK-9, SORT1, cytokines, and IFN- $\gamma$  are strongly associated with CVDs the development and progression of CVDs. Mutations in these genes can cause serious morbidity and mortality. Therefore, genetic testing should be widely implemented, and familial predispositions should be considered when assessing an individual's health plan. With the help of nutrigenetics, we can determine the risk factors, identify preventative strategies, and improve the quality of life through personalized nutrition.

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