Glutathione S-Transferase Enzyme Gene Polymorphisms and Cardiovascular Diseases

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Özet

Anahtar Kelimeler
Kardiyovasküler Hastalıklar; Glutatyon S-Transferaz; Gen Polimorfizmisi

Abstract
Cardiovascular diseases still ranks in first place among causes of death around the world. Environmental and genetic factors both play roles in the pathogenesis of cardiovascular diseases. One of the genetic changes that are claimed to contribute to the occurrence of cardiovascular diseases is the glutathione S-transferase (GST) family that has been intensely examined recently. GST gene polymorphisms, which are among antioxidant system enzymes, have a relationship with each of the factors that are considered among the risk factors for cardiovascular diseases. Consequently, it can be said that the polymorphisms of GST genes are effective both in the risk factors of cardiovascular diseases and directly in cardiovascular diseases.

Keywords
Cardiovascular Diseases; Glutathione S-Transferase; Gene Polymorphisms
Introduction
Cardiovascular diseases still rank in first place among the causes of death around the world [1]. Environmental and genetic factors play roles in the pathogenesis of cardiovascular diseases [2]. One of the genetic changes that is claimed to contribute to the occurrence of cardiovascular diseases is the Glutathione S-Transferase (GST) family which has been intensely examined recently. The GST family consists of many genes, and 5 of them have been defined in humans. The polymorphisms in M, t, and p classes of GSTs were assessed in many diseases, and their relations were explained. GST was frequently examined in diseases in which environmental xenobiotics are thought to have an impact, especially cancer, cardiologic diseases, and dermatologic diseases. [3-5].

Many risk factors that play a role in the pathogenesis of cardiovascular diseases were defined, but the failure to carefully take these known risk factors under control to improve the outcome of the disease or to prevent its advancement shows that these risk factors are not the only ones responsible for the high incidence of cardiovascular diseases. Among the risk factors for cardiovascular diseases are genetics, age, family history, hypertension, hypercholesterolemia, low HDL-cholesterol, diabetes, obesity, stress, low physical activity, menopause, consumption of cigarettes and alcohol, and xenobiotic exposure [2, 6-9]. It is indicated that GST genes are the genes that are responsible for the formation of hypercholesterolemia, hypertension, cigarette, alcohol, xenobiotics, and cardiovascular diseases. It is known that many different pathways are effective in the pathomechanism of hypertension. Firstly, the defects in the genes that are responsible for ensuring electrolyte balance [10-14], the defects that play a role in vascular structure and function [15], and the defects in the genes that are related to oxidative stress may affect hypertension. As it is known, GSTs detoxify certain compounds that are of endogenous and exogenous origin. Especially the GSTM class among GST enzymes is responsible for the detoxification of free radicals. M-class genes are protective against oxidative stress, and it was indicated that decreasing GSTM1 expression is related to hypertension [16-18]. GST enzymes protect cell types of different origins, such as smooth muscle cells and endothelial cells, against oxidative damage [19-21]. Different studies have examined the different existence of GST M1 and T1 genes with hypertension. In the study carried out by Marinho et al., it has been indicated that GSTT1 deletion may be a protective factor for hypertension. No significant difference has been found between GSTM1 genotype frequency and hypertension. However, the frequency of GST M1/T1 null genotype is significantly low in the group with hypertension compared to the control group (78% against 19%). In the study, it has been also observed that individuals with GST M1/T1 non-null genotype are the candidates for hypertension disease, and it is a protective mutation for the development of cardiovascular disease [22].

In the study carried out by Saadat et al., the effect of GST T1 and M1 gene polymorphisms has been examined in the regulation of blood pressure of the individuals who are exposed to natural source gases containing sulfur compounds. In the study where it is observed that blood pressures vary in different genotypic combinations, systolic blood pressure decreased significantly in GSTM1 null and GSTT1 positive individuals, and diastolic blood pressure increased significantly in GSTM1 positive and GSTT1 null individuals. The results have made us think that the polymorphism changes of GSTs play a physiological role in the regulation of blood pressure in individuals who are exposed to natural gases that contain sulfur [23]. Another study showing the relationship between hypertension and GST has been carried out by Capoluongo et al. This study shows that individuals with GSTM1-null genotype are in the significantly high-risk group in terms of hypertension. Because there was no difference in the study between the individuals in the case group and the control group in terms of smoking (no difference of detoxification of polycyclic aromatic hydrocarbons) or in the state of consuming alcohol and kidney functions (similar urea, creatine values), this excludes those factors from being the reasons for hypertension. In the study, it is indicated that the main cause of the effect on blood pressure is the antioxidant effect of GSTs [24].

The levels of cholesterol and triglyceride, being another important factor in the occurrence of cardiovascular diseases, and the connection between GST enzyme gene polymorphisms and enzyme levels have been indicated in the literature [25-26]. In a study carried out by Gannage-Yared et al., glutathione and Glutathione S-Transferase were measured spectrophotometrically, and it was observed that the blood cholesterol levels of the amount of leukocyte and Glutathione S-Transferase enzyme increase significantly by gender and body mass index [25]. In the study carried out by Maciel et al., it has been expressed that there is a difference between GST polymorphism and triglyceride and HDL-cholesterol [26]. 1577 individuals from the general population and 871 individuals to whom coronary angiography was applied were taken as two different study groups. In the study, it was found that the ratio of triglyceride (TG), HDL-cholesterol, and triglyceride/HDL is significantly related to GSTM1,T1 null genotype (double deleted genotype) in the general population. These results were confirmed with a second population to which coronary angiography was applied, independently from the first study group. Furthermore, it was also shown that types of coronary artery disease are also associated with GST genotype. The relevant study shows that the existence of GSTM1, T1 genes null deletion is associated with hypertriglyceridemia and low HDL-cholesterol level. In the light of these findings, it was thought that there may be a connection between lipid metabolism and GSY balance, and it was explained as follows: that GSTs have Peroxisome Proliferator-Activated Receptor (PPAR) preventing effect may be associated with reverse cholesterol transport system. PPARs are defined as a group of nuclear proteins in the field of Molecular Biology. It has been found that PPARs act as transcription factors regulating gene expression. Their main roles have been determined in the regulation of cell differentiation and development, carbohydrate, protein and lipid metabolism, and also tumour formation. Retinoid X Receptor (RXR) becomes dimerized with PPAR and starts the transcription by connecting to a suitable part of the target gene on DNA. 15-Deoxy-Δ[12,14] is among the final products of prostaglandin J2 (15-d-PGJ2), prostaglandin D2 metabolism, and its biological effect is to mediate PPAR-γ. In the studies, it has been observed that the cytotoxicity of 15-d-PGJ2 and the activation of PPAR-γ-dependent transcription decrease. This decrease happens with the Glutathione conjugates of 15-d-PGJ2 and 15-d-PGJ2-SG (oxidized form) and the expressions of MRP ensuring its transportation outside the cell. GSTs that catalyze glutathione conjugates have no effect on 15-d-PGJ2 cytotoxicity alone or in combination with MRP1. Nevertheless, PPARγ that is 15-d-PGJ2-dependent activator inhibits PPARγ-responsible target gene. The level of this inhibi-
tion is in direct proportion to the level of GST expression. The prevention of PPAR activation leads to the increase in TG level, and it is expected that HDL-cholesterol level decreases with reverse cholesterol transport system [27]. As also indicated in the study in question, the fact that GSTs do not have both alleles (null deletion) is associated with hypertriglyceridemia and low level of HDL-cholesterol. It is possible that this connection affects the risk of coronary artery disease. Diabetes, which is regarded as another risk factor in the occurrence of cardiovascular diseases, has been associated with GST. In a study carried out in the Chinese population by Wang et al., whether there is a connection between GSTM1, T1 and quinone oxidoreductase 1 (NQO1) gene polymorphisms and type 2 diabetes has been assessed, and it has been found that T2 diabetes risk has statistically significantly decreased 0.49 times when compared to GSTT1 positive individuals. Starting from here, it has been put forward that the GSTT1 gene may be a candidate gene in the development of T2 in the Chinese population [28]. Also, in a study carried out in India, it is indicated that different combinations of GST gene polymorphisms affect T2 diabetes risk [29].

Connections between GSTM1 and T1 gene polymorphisms and the possibility of coronary artery disease have been defined in previous studies [9, 30–32].

**Conclusion**

There is a constant free radical formation in the organism as a result of the effect of oxygen in metabolic pathways, and the exposure to radiation, drugs, and harmful chemical substances. These free radicals create oxidative stress. Antioxidant system enzymes ensure the protection of the balance in the organism and the maintenance of life by deactivating these free radicals. Oxidative damage, which is formed as a result of the increase in oxidative stress and the insufficiency of the antioxidant system against this situation, exists in the formation of more than 100 diseases, including cardiovascular diseases. Free radicals deteriorate cell structure by damaging lipids, proteins, and nucleic acids because of their reactive structure. The organism has many proteins that bind enzymes such as Superoxide dismutase (SOD), Glutathione Peroxidase (GSH-Px), Glutathione S-Transferase (GST), Catalase (CAT), Glutathione Reductase, vitamins, and metal ions that act as an antioxidant system component in the organism and deactivate free radicals [33]. GST gene polymorphisms, which are among antioxidant system enzymes, have a relationship with each of the factors that are considered to be risk factors for cardiovascular diseases. Consequently, it can be said that the polymorphisms of GST genes are effective both in the risk factors of cardiovascular diseases and directly in cardiovascular diseases.

**Competing interests**

The authors declare that they have no competing interests.

**References**


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