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Correlation Between *GSH-Px Pro198Leu, CAT-262C/T, MnSOD Ala16Val* Gene Polymorphisms and Allergic Rhinitis

Pınar Kundi[1], Nazım Bozan[2], Mehmet Berkoz[3], Hakan Çankaya[4]

[1]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Otolaryngology, İstanbul, Turkey
[2]Van Yüzüncü Yıl University Faculty of Medicine, Department of Otolaryngology, Van, Turkey
[3]Van Yüzüncü Yıl University Faculty of Medicine, Department of Biochemistry, Van, Turkey
[4]VM Medical Park Mersin Hospital, Clinic of Otolaryngology, Mersin, Turkey

ABSTRACT

Introduction: In this study, we investigated the etiopathogenesis of allergic rhinitis by analyzing the polymorphisms including *GPx-1 Pro198Leu, CAT-262 C/T,* and *MnSOD Ala16Val*.

Methods: The diagnosis of allergic rhinitis was diagnosed by clinical history, examination, serum total immunoglobulin E levels and skin prick test. Five mL of peripheral blood from patients and individuals constituting the control group was taken into EDTA tubes. DNA isolation from whole blood samples was performed according to the Poncz method.

Results: Because of this study; for the Pro198Leu polymorphism of the GPX1; was concluded with 95% confidence that the presence of the Leu allele increased the susceptibility to allergic rhinitis 1.092 times. However, this increase was not found to be statistically significant. For the -262 C/T polymorphism of the *CAT* gene; was concluded with 95% confidence that the presence of the T-allele increased the susceptibility to allergic rhinitis 27,064 times. This increase was found to be statistically significant. For Ala16Val polymorphism of the *Mn-SOD* gene; was concluded with 95% confidence that the presence of the Ala allele increased the susceptibility to allergic rhinitis 25,791 times. This increase was found to be statistically significant.

Conclusion: A significant relationship was found between allergic rhinitis and the genotypes and the frequencies of alleles in the polymorphisms of the *MnSOD* and *CAT* genes. However, no significant relationship was found between allergic rhinitis and the polymorphisms of the *GPx-1* gene.

Keywords: Allergic rhinitis, *MnSOD, GPx-1, CAT,* polymorphism

Introduction

Allergic rhinitis is an inflammatory disease of the nasal mucosa characterized by nasal congestion, runny nose, nasal itching, frequent sneezing and conjunctival irritation, and it occurs due to an immunoglobulin E (IgE)-dependent type-1 hypersensitivity reaction (1-3). Allergic rhinitis typically begins in early childhood. An increase in symptoms is observed in the 20s, 30s, and 40s (4). It affects 10-40% of the entire population. Prospective studies have shown that its prevalence has been increasing (5). The dominant mechanism in the pathophysiology of allergic rhinitis is the IgE-dependent type-1 hypersensitivity reaction. Allergens in contact with the respiratory mucosa are taken in by antigen presenting cells (APC) in the nasal mucosa and broken down by proteolytic enzymes into peptides of 4-7 amino acids length. The broken down peptides are then expressed by MHC Class II molecules on the surface of APCs and presented to CD4+ (T-helper) lymphocytes. In people with atopic diathesis, CD4+ (T-helper) MCH II forms the Th2 cell because of the interaction between CD 28-B7. This Th2 cell then not only allows the Th2 cells in its own colon to proliferate, but also begins secreting its own characteristic cytokines such as interleukin-3 (IL-3), IL-4, IL-5, IL-13, and granulocyte macrophage colony-stimulating factor (GM-CSF) (6,7). IL-4 and IL-13 stimulate B-lymphocytes in circulation and cause their transformation into plasma cells. These plasma cells secrete allergen-specific IgE to which they are sensitized. These specific IgE antibodies bind to high affinity IgE receptors on circulating basophils and mast cells in tissues. IgE-bound mast cells that increase because of continuous allergen exposure pass into the epithelium and are degranulated by recognizing mucosal allergens (8). The products of this degranulation are Ready to Act mediators such as histamine, tryptase, chymase, quinogenase, heparin and other enzymes. Additionally, mast cells secrete new inflammatory mediators such as PGD_2, tumor necrosis factor-alpha, sulfidopeptidyl leukotrienes LTC_4, LTD_4, and LTE_4. These mediators lead to increased permeability and mucosal edema. These events occur within 1-2 minutes of allergen exposure and are called early phase allergic response (6). Late phase reactions occur because of infiltration with mast cells, basophils, neutrophils, eosinophils and mononuclear cells

Address for Correspondence: Pınar Kundi MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Otolaryngology, İstanbul, Turkey
Phone: +90 530 738 87 44 **E-mail:** pinarkundi@gmail.com **ORCID ID:** orcid.org/0000-0001-7590-634X

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2-4 hours after allergen exposure. The cells that play an important role in the late phase reaction are eosinophils. Cytokines and chemokines released from activated eosinophils cause tissue damage on the one hand, and increase inflammation via autocrine and paracrine pathways on the other hand (9). Th2 cells release IL-3, IL-4, IL-5, and other cytokines that facilitate IgE production, eosinophil chemoattraction, and eosinophil delivery, resulting in more eosinophils in the environment. Cysteinyl leukotrienes, eosinophilic cationic protein, major basic protein which are proinflammatory mediators released from eosinophils, cause epithelial damage and a late phase response occurs via GM-CSF (10). As a response to this situation, we encounter thickening of the nasal mucosa (hypertrophy), increased resistance to nasal flow and ultimately nasal obstruction in the clinic.

Cytokines released from eosinophils play a fundamental role in the generation of free oxygen radicals (FOR) in late phase reactions. Oxidative stress is thought to play an effective role in maintaining and increasing inflammation after this stage (1,11). Therefore, this suggests that free radicals may be effective in the pathophysiology of allergic rhinitis. Overproduction of free radicals and/or inability to neutralize them by antioxidant systems causes the oxidant/antioxidant balance in the cell to deteriorate and lead to "oxidative stress". Antioxidant systems play a critical role in maintaining this balance and preventing oxidative damage (12,13). In this study, we hypothesized that glutathione peroxidase (GSH-Px), catalase (CAT) and cytochrome oxidase enzymes, which are part of the antioxidant defense system in our body, may be effective in this mechanism, and investigated the relationship between gene polymorphisms of these enzymes.

Methods

In this study, the relationship between allergic rhinitis and *GPX1 Pro198Leu*, *CAT-262C/T,* and *Mn-SOD Ala16Val* gene polymorphisms was investigated. For this purpose, the control group of our study consisted of 236 healthy individuals, while the patient group consisted of 214 individuals diagnosed with allergic rhinitis. Five mL of peripheral blood from both the patients diagnosed with allergic rhinitis and the individuals in the control group were collected in EDTA tubes and stored at + 4 °C until the study day. Additionally, a patient follow-up form was created to determine the laboratory and clinical data of patients with allergic rhinitis, and these forms were completed in accordance with the outpatient clinic and service files of the patients. Each sample amplified by PCR was cut using *ApaI*, *SmaI* and *BsaWI* enzymes to determine the Pro → Leu change at position 198 of the *GPX1* gene, C → T change at position -262 of *CAT* gene and Ala → Val change at position 16 of the *Mn-SOD* gene. *GPX1 Pro198Leu*, *CAT -262 C/T,* and *Mn-SOD Ala16Val* polymorphisms of 450 individuals, including 236 healthy volunteers in the control group and 214 patients diagnosed with allergic rhinitis, were examined.

The study was approved by the Ethics Committee of Van Yüzüncü Yıl University Clinical Research Ethics Committee (approval number: 10, date: 27.10.2015).

Statistical Analysis

The SPSS 21 (SPP Inc., Chicago. IL., USA) program was used for statistical analysis of the data. Frequencies and percentage values were calculated for all parameters. The difference between the frequency of the allergic rhinitis patients and control groups was analyzed with the chi-square test. The cut off of p-value was determined as 0.05 in 95% confidence interval.

Results

Because of this study; for the Pro198Leu polymorphism of the *GPX1* gene, the total number of Pro alleles in the control group was 392, the allele frequency was 83.05%, the total Leu allele number was 80, and the allele frequency was found to be 16.95%. In the allergic rhinitis group, the total number of Pro alleles was 350, the allele frequency was 81.78%, the total Leu allele number was 78, and the allele frequency was found to be 18.22%. There was no significant difference between allergic rhinitis and control groups (p=0.62) (Table 1). For the -262 C/T polymorphism of the *CAT* gene; in the control group, the total number of C alleles was 412, the allele frequency was 87.29%, the total T allele number was 60, and the allele frequency was 12.71%. In the allergic rhinitis group, the total number of C alleles was 307, the allele frequency was 71.73%, the total T allele number was 121, and the allele frequency was 28.27%. This difference was found to be statistically significant between the allergic rhinitis and control groups (p<0.05) (Table 2). For Ala16Val polymorphism of the *Mn-SOD* gene; in the control group, the total number of Val alleles was 358, the allele frequency was 75.85%, the total Ala allele number was 114, and the allele frequency was found to be 24.15%. In the allergic rhinitis group, the total number of Val alleles was 235, the allele frequency was 54.91%, the total Ala allele number was 193, and the allele frequency was 45.09%. This difference was found to be statistically significant between the allergic rhinitis and control groups (p<0.05) (Table 3).

Discussion

The etiopathogenesis of allergic diseases have not been fully elucidated. For this reason, this study we conducted to elucidate the etiopathogenesis of allergic rhinitis is of great importance. Eosinophils are the cells that play a major role in late phase reactions in the pathophysiology of

Table 1. GPX1 Pro198Leu polymorphism allele frequency in allergic rhinitis patients and control groups

Alleles	Allergic rhinitis patient (n=428), n (%)	Control (n=472), n (%)	p-value
Pro	350 (81.78%)	392 (3.05%)	p=0.62
Leu	78 (18.22%)	80 (16.95%)	

n: Number of alleles. Allele frequencies of this polymorphism was evaluated by chi-square analysis

Table 2. CAT-262 C/T polymorphism allele frequency in allergic rhinitis patient and control groups

Alleles	Allergic rhinitis patient (n=428), n (%)	Control group, (n=472) n (%)	p-value
C	307 (71.73%)	412 (87.29%)	p<0.0001
T	121 (28.27%)	60 (12.71%)	

n: Number of alleles. Allele frequencies of this polymorphism was evaluated by chi-square analysis.

Table 3. Mn-SOD Ala16Val polymorphism allele frequency in patients with allergic rhinitis and control groups

Alleles	Allergic rhinitis patient (n=428), n (%)	Control group (n=472), n (%)	p-value
Val	235 (54.91%)	358 (75.85%)	p<0.0001
Ala	193 (45.09%)	114 (24.15%)	

n: number of alleles. Allele frequencies of this polymorphism was evaluated by chi-square analysis

allergic rhinitis. Cytokines released from eosinophils play a fundamental role in the production of FORs. Additionally, immunological or non-immunological stimulation of basophils, eosinophils and mast cells increased in the nasal mucosa results in the production of FORs such as superoxide anion, hydrogen peroxide (H_2O_2), or hydroxyl radicals. Oxidative stress is thought to play an effective role in maintaining and increasing inflammation after this stage. Based on this information, we investigated gene polymorphisms in GSH-Px, CAT and MnSOD, which serve as antioxidant enzymes in our body, to investigate the effect of FORs in the etiopathogenesis of allergic rhinitis. In the literature, GSH-Px, CAT and superoxide dismutase (SOD) gene polymorphisms decrease the normal activity of these enzymes. As a result, free radicals accumulate in our body and the oxidant/antioxidant balance in the cell is disrupted, which results in oxidative stress. FOR play a role in the etiopathogenesis of many diseases, and *GSH-Px, CAT* and *SOD* gene polymorphisms increase susceptibility to many other chronic diseases. No other study investigating these gene polymorphisms in allergic rhinitis has been found in the literature. However, some studies have shown that FORs may be effective in the etiopathogenesis of allergic rhinitis. A disruption in the oxidant/antioxidant balance in favor of oxidants directly causes damage to the upper and lower airway epithelial cells. The most important mechanism in the formation of tissue damage due to FOR is the peroxidation of lipids in the cell membrane. The increase in lipid peroxidation can be used as an indicator of tissue damage caused by free radicals. One of the lipid peroxidation degradation products is malondialdehyde (MDA) (14). This molecule causes the formation of superoxide anion and H_2O_2 by reducing oxygen, and these products damage cells and tissues. In a previous study, Akbay (15) compared the MDA level in allergic rhinitis patients with a control group. In this study, the patient group was between the ages of 4-63, the control group was between the ages of 5-56, 13 of the patients were male and 27 were female, and the control group consisted of 20 male and 20 female subjects. In this study, a statistically significant increase in MDA levels was detected in the patient group compared with the control group. Additionally, the same study found that the antioxidant enzymes myeloperoxidase and CAT levels were low in patients with allergic rhinitis. The author concluded that this strengthens the view that oxidants play a role in the pathogenesis of allergic rhinitis. In the same study, a statistically significant decrease was observed in vitamin A and E levels in patients with allergic rhinitis compared with the control group, but the author did not provide treatment and evaluate the results (15). Emin et al. (16) measured the total serum IgE levels and eosinophil count, total antioxidant status and its relation with oxidative stress in children with allergic rhinitis. This study included 106 patients and 70 controls. When the patient and control groups were compared, no significant difference was found in terms of age, gender and body mass index. However, there was a significant increase in serum total IgE and eosinophil counts in the patient group compared with the control group. Furthermore, it was shown that there was a significant increase in plasma oxidative stress level and a significant decrease in the antioxidant defense system in the patients (16). These studies show that oxidative stress mechanism plays an important role in allergic rhinitis. CAT is a critical endogenous antioxidant enzyme that detoxifies H_2O_2 into water and oxygen, thus protecting the body from the damaging effects of reactive oxygen species. The *CAT* gene is located on the 11p13 chromosome and contains 12 introns and 13 exons. There are different regions of polymorphism in the *CAT* gene. In *CAT-262 C/T* gene polymorphisms, T allele diversity was associated with lower enzyme activity compared to the C allele (17). This in turn increases the level of SOR in the body. Hu et al. (18) conducted a study to determine whether the *CAT-262 C/T* gene polymorphism increases the risk of prostate cancer. Based on the results, they found that *CAT -262 C/T* gene polymorphism significantly increased the risk of prostate cancer (18). In this study, we found that *CAT-262 C/T* gene polymorphism significantly increased susceptibility to allergic rhinitis. Zarafshan et al. (19) investigated the *CAT-262 C/T* gene polymorphism in women with endometriosis. By definition, endometriosis is the presence of the endometrial gland and stroma outside the uterine cavity. Recent studies have shown that this disease may be associated with oxidative stress. Based on the results of this study, the frequency of CAT-262 C/T CC/CT/TT genotypes in patients with endometriosis was 67.5%, 32.5%, and 0%, respectively, while it was 12%, 68%, and 20% in the healthy control group. In other words, a statistically significant difference was found in the genotype and allele distribution of *CAT-262 C/T* gene polymorphism in endometriosis compared with the control group. It was found that *CAT-262 C/T* gene polymorphism increases susceptibility to endometriosis (19). Wang et al. (20) investigated the relationship between survival and risk and *CAT-262 C/T* gene polymorphism in patients with cancer. Based on the results, they found a significant relationship between cancer risk and *CAT-262 C/T* gene polymorphism. In their subgroup analysis, they found that it especially increased the risk of prostate cancer. In the survival analysis, they showed that there was no significant relationship between *CAT-262 C/T* gene polymorphism and survival in patients with prostate cancer. The results of this study showed that the *CAT-262 C/T* gene polymorphism can be used as a marker for some specific types of cancer with geographic localization, but cannot be used as a good prognostic factor for survival in cancer patients (20). In this study, while the frequency of CAT-262 C/T CC/CT/TT genotypes in allergic rhinitis patients was 63.08%, 17.29% and 19.63%, respectively, the frequency was 82.63%, 9.32%, and 8.05% in the control group, respectively. Based on these results, we found a statistically significant relationship between allergic rhinitis and *CAT-262 C/T* gene polymorphism genotypes. This shows that as it plays a role in the etiopathogenesis of many other diseases, *CAT-262 C/T* gene polymorphism is also significant in allergic rhinitis and antioxidants can be used for treatment. GSH-Px is an endogenous enzyme that acts as an antioxidant in our body. There are at least 4 different GPX isoenzymes in mammals. *GSH-Px1* gene is located on chromosome 3p21.3 (21). GSH-Px 1 can metabolize organic peroxides including cholesterol and long chain fatty acid peroxides and H_2O_2.

Many studies have investigated *GSH-Px1 Pro198Leu* gene polymorphisms. Sousa et al. (22) investigated the relationship between chronic hepatitis C and *CAT* and *GSH-Px1* gene polymorphisms. Four hundred forty-five patients with chronic hepatitis C were included in this study. In this group, 139 patients had mild liver fibrosis (F0-F1), 200 patients had moderate liver fibrosis (F2-F4), and 106 patients had hepatocellular carcinoma (HCC). Because of this study, CT + TT genotypes and frequency of the T allele in the *CAT* gene was higher in patients with HCC compared to other patient groups (moderate and mild liver fibrosis). However, this value was not statistically significant. In terms of *GPx1 Pro198Leu* gene polymorphism, the frequency of pro/pro genotype and pro allele were found to be lower in patients with mild liver fibrosis compared with patients in other groups (HCC and moderate liver fibrosis). When the distribution of CT + TT genotypes in the *CAT* gene and pro/pro genotypes in *GSH-Px1* gene were evaluated together, a strong relationship was found with liver fibrosis grading and HCC (22). In this study, when the genotype frequency in the *GSH-Px1* gene of allergic rhinitis was compared with reference to the control group using multiple regression model, it was concluded with 95% confidence that Pro/Leu and Leu/Leu genotypes increased the susceptibility to allergic rhinitis by 0.9948 and 12,914 times, respectively. However, this increase was not statistically significant. When the genotype frequency of the *CAT* gene was compared using a multiple regression model, it was concluded with 95% confidence that the CT and TT genotypes increased susceptibility to allergic rhinitis by 3,044 and 3,193 times, respectively. This increase was found to be statistically significant. SOD catalyzes the superoxide radical to H_2O_2 and molecular oxygen. There are 3 forms of the SOD enzyme. SOD2, MnSOD is located in the mitochondria and this gene contains five exons and is located on chromosome 6q25 (23). Seçkin et al. (24) investigated the relationship between vitiligo disease and *Mn-SOD* and *GSH-Px1* gene polymorphisms in their study. *Mn-SOD Ala-9Val* and *GSH-Px 1 Pro-198Leu* gene polymorphisms were evaluated. Fifty-seven patients (32 female, 25 male) and 69 controls (40 female, 29 male) were included in this study. The frequencies of *Mn-SOD Ala-9Val* gene polymorphisms (Ala/Ala, Ala/Val, and Val/Val genotypes) in vitiligo patients were 19.3%, 49.1%, and 31.6%, respectively. In the control group, the frequency was 17.4%, 47.8%, and 34.8%, respectively. Additionally, the frequencies of Pro/Pro, Pro/Leu, and Leu/Leu genotypes of *GSH-Px1 Pro-198Leu* gene polymorphism in vitiligo patients were 38.6%, 49.1%, and 12.3%, respectively, whereas the frequency was 42.0%, 39.1%, and 18.8% in the control group, respectively. Based on these results, the authors could not find a significant difference between susceptibility to vitiligo disease with respect to *GSH-Px1 Pro-198Leu* and *Mn-SOD Ala-9Val* gene polymorphisms (24). In this study, we investigated whether there is a relationship between allergic rhinitis and *GSH-Px1 Pro198Leu* and *Mn-SOD Ala16Val* gene polymorphisms. Based on our results, Pro/Leu and Leu/Leu genotypes of *GSH-Px 1 Pro198Leu* polymorphism increased the susceptibility to allergic rhinitis by 0.9948 and 12,914 times, respectively, but this increase was not statistically significant. Val/Ala and Ala/Ala genotypes of Mn-SOD Ala16Val polymorphism increased the susceptibility to allergic rhinitis by 3.1048 and 2.9707 times, respectively, and this increase was statistically significant.

Study Limitations

The most important limitation of the study was that the patient group was small and none of the patients had a previous history of asthma or other allergic diseases.

Conclusion

The accumulation of FORs plays an effective role in the etiopathogenesis of many diseases. The number of studies on the etiopathogenesis of allergic rhinitis are limited in the literature. Therefore, to shed more light on the etiopathogenesis of allergic rhinitis, we examined gene polymorphisms in *GSH-Px, CAT* and MnSOD enzymes, which are known to act as antioxidants in our body. Based on the results of this study, although there was a statistically significant difference between allele frequencies and genoty-pes of *CAT-262 C/T* and *Mn-SOD Ala16Val* polymorphisms with respect to allergic rhinitis, no statistically significant difference was found between *GSH-Px 1 Pro198Leu* gene polymorphisms. In this study, we provided new treatment options by further illuminating the etiopathogenesis of allergic rhinitis. The results of this study indicate that antioxidant therapy may also be an option for treating allergic rhinitis.

Ethics Committee Approval: The study was approved by the Ethics Committee of Van Yüzüncü Yıl University Clinical Research Ethics Committee (approval number: 10, date: 27.10.2015).

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