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Analysis of paraoxonase-1 (PON1) gene polymorphisms in vitiligo

Vitiligo'da paroksinaz-1 (PON1) gen polimorfizminin araştırılması

Abstract: Objective: Vitiligo is a chronic autoimmune depigmentation disease, which is characterized by loss of function of the melanocytes in epidermis. Recent studies suggest that oxidant/antioxidant status plays important role in the pathogenesis of vitiligo. We aimed to investigate possible associations between vitiligo and PON1 M / L55 and PON Q192R gene polymorphisms in the Turkish community.

Methods: The 57 patients with vitiligo and 69 healthy controls were enrolled into the study. Genotyping was performed to identify PON1 M / L55 and PON Q192R gene polymorphism. Genotype and allele frequencies were compared between patients with vitiligo and healthy control group.

Results: In patients (p=0.0061) and healthy controls (p=0.550), there was no significant statistical difference between L55M and Q192R polymorphisms of the PON1 gene. However, when L55M polymorphism was compared to MM homozygous genotype and LL+LM genotypes, it was notably higher in controls than in patients, which seems to be protective against the disease (p=0.034, OR:0. 3, 95% CU: 0.08-0.93). Although, there was no not a statistical difference in allele frequencies of Q192R polymorphism between patients and controls (p=0.242), the M allele of L55M polymorphism was significantly higher in controls than in patients with vitiligo, which means that it might be protective against vitiligo (p=0.009, OR: 0.48, 95% CI: 0.27–0.84).

Conclusion: Even though there were no differences between patients and controls, this is the first study that investigated the possible associations between the PON1 M/L55 and PON Q192R gene polymorphisms within the Turkish population.

Keywords: Vitiligo, PON1 m/L55 gene, PON Q192R gene polymorphism

Özet: Amaç: Vitiligo epidermisde melanositlerin fonksiyon kaybı ile karakterize kronik otoimmün bir depigmentasyon hastalığıdır. Son çalışmalar oksidan / antioksidan durumum vitiligo patogenezinde önemli bir rol oynadığını ileri sürmektedir. Bu çalışmada, Türk toplumunda vitiligo ile PON1 M/L55 ve PON Q192R gen polimorfizmlerinin olası ilişkisini araştırmayı amaçladık.

Metod: Çalışmaya vitiligolu 57 hasta ve 69 sağlıklı kontrol alındı. Genotipleme PON1 M / L55 ve PON Q192R gen polimorfizmlerinin belirlenmesi amacıyla yapılmıştır. Genotip ve allel frekansları vitiligo ve sağlıklı kontrol grubunda olan hastalar arasında karşılaştırıldı.

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Bulgular: Hastalarda (p=0,061) ve kontroller (p=0,550) arasında PON1 geninin L55M ve Q192R polimorfizmlerinde istatistiksel olarak anlamlı bir farklılık yoktu. Ancak L55M polimorfizmi, MM homozigot genotipi, LL+LM genotipleri ile karşılaştırıldığında hastalara göre kontrollerde, anlamlı olarak daha yüksek bulundu ve bu hastalığa karşı koruyucu olduğu görüldü (p=0,034, OR: 0,3, %95 CI: 0,08-0,93). Hastalar ve kontrol arasında Q192R polimorfizminin alel frekanslarında istatistiksel olarak anlamlı bir fark yoktu (p=0,242). Ancak L55M polimorfizminin M alellinin kontrollerde hastalara göre istatistiksel olarak anlamlı derecede yüksek olduğu ve ayrıca bu alellin hastalığa karşı koruyucu olduğu gösterildi (p=0,009, OR:0,48, %95 CI: 0,27–0,87).

Sonuç: Hasta ve kontrol grubu arasında anlamlı bir fark olmamasına rağmen bu çalışma Türk popülasyonunda vitiligo ile PON1 M/L55 ve PON Q192R gen polimorfizmi arasındaki olası ilişkiyi araştıran ilk çalışmadır.

Anahtar Kelimeler: Vitiligo, PON1 M/L55 gen, PON Q192R gen, polimorfizm

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Introduction

Vitiligo, which may be acquired or hereditary, is a progressive disease that is characterized by depigmentation of the skin color as a result of progressive loss of function of melanocytes. It is also common all around the world and can be seen at any age group. Demarcated, generally symmetric, sometimes unilateral and generally dermatomal, milky white macules in varying size and localizations are the clinical characteristics of the disease. These traits have been equally encountered in both genders. Its incidence rate is 0.1–4% that varies according to the ethnical groups and geographical distributions [1,2].

Although the etiopathogenesis of vitiligo is not yet fully understood, the autoimmune, auto cytotoxic, neural, and biochemical-based hypothesizes are considered [3]. Genetic predisposition and triggering factors have roles in the emergence of the disease [4]. Furthermore, recent studies have shown that reactive oxygen radicals (ROS) play role in the pathogenesis of vitiligo [5–14]. The increased ROS has damaging effects on DNA, membrane lipids, and cell proteins. Skin, the largest human organ, is a potential target for oxidative damage due to being continually exposed to physical and chemical stimulants [15]. There are many antioxidant systems in the biologic systems to prevent ROS production and its oxidative damage [16]. Paraoxanase, being an ester hydrolase calcium dependent glycoprotein compound that has arylesterase and paraoxanase activity, is a part of antioxidant defense mechanism. Its primary function is to protect the lipoproteins from oxidation and takes role on hydrolysis of oxidized phospholipids and lipid peroxides [17].

There are three members of paraoxanase family: PON1, PON2, and PON3. Amongst the members of the paraoxanase family, PON1 is the first discovered and the most researched enzyme. Today, PON1 gene shows two common codon polymorphisms: the M/L55 polymorphism that switched methionine and leucine in the 55th codon and Q/R 192 polymorphism that switched glutamine and arginine in the 192th codon [18]. Many researches have shown the relationships between those polymorphisms and certain diseases. In the literature, there are no studies that show the possible relation between PON1 M/L55 and PON Q192R gene polymorphisms and vitiligo. That being said, in our study, we aim to analyze the possible connection between vitiligo and these polymorphisms in Turkish population and the effects of these gene polymorphisms in the etiopathogenesis of vitiligo.

Materials and Methods

Subjects

The study group consisted of 57 unrelated patients with vitiligo (25 male and 32 female; mean age: 38.61±14.767 standard deviation [SD] years), and 69 (20 male and 49 female; mean age: 27.48±10.154 SD years) unrelated healthy controls. Vitiligo patients were recruited consecutively and prospectively from those whom were treated and followed up in the Dermatology Department of Gaziosmanpasa University Research Hospital, Tokat, Turkey. The diagnosis of vitiligo was confirmed by clinically. The control group included healthy individuals who had normal physical and routine examination, and no chronic diseases. Exclusion criteria for both groups included inflammatory diseases accompanying to infectious diseases, autoimmune disorders, neoplastic diseases, immune-suppressive patients, liver and kidney diseases, diabetes mellitus and familial hypercholesterolemia as well as a chronic disease presence. Moreover, the patients with vitiligo who had photo-chemotherapy and who were on systemic medication for the last three months and has topical drugs for the last one month were also excluded.

The clinical and demographical features including age, gender, onset period of the disease and type of the disease were recorded. All participants, patients and healthy controls, were of Turkish origin, from the inner Central Black Sea region of Turkey. The study protocol was approved by the Local Ethics Committee of Gaziosmanpasa University, Faculty of Medicine and written informed consent was obtained from the study participants.

Genotyping

Genomic DNA was extracted from peripheral leukocytes from EDTA-anticoagulated blood using the High Pure Polymerase Chain Reaction Template Preparation Kit (Roche Molecular Biochemicals, Mannheim, Germany) according to the manufacturer's instructions. To identify PON1 L55M and Q192R single-nucleotide polymorphisms (SNPs), genotyping was performed using commercially synthesized primers and fluorescently labeled probes (Metabion, Mar- tinsried, Germany) and the LightCycler 480 II Real- Time Polymerase Chain Reaction System (Roche Diagnostics). The genotyping method was based on methods developed previously for genotyping both PON1 55 and 192 polymorphisms using LightCycler real-time polymerase chain reaction technology, which relies on fluorescence resonance energy transfer [19]. Target fragments of the human PON1 gene were amplified with specific primers. To detect the PON1 L55M polymorphism, 10 pmol of the forward primer 5'-CCTGCAATAATATGAAACAACCTG-3' and the reverse primer 5'-CTAGAACACAGAAAAGTGA- AAGAAAAC-3' and 3 pmol of the sensor probe 5'-CTCTGAAGACATGGAGATACTGCC-fluorescein-3' and the anchor probe 5'-LC Red 640-ATGGACTGGCTTTCATTAGCTCTGTGAGT-3' were added to genomic DNA. To detect the PON1 Q192R poly- morphism, we also used 10 pmol of the forward primer 5'-TATTGTTGCTGTGGGACCTGAG-3' and the reverse primer 5'-CCTTCTGCCACCAC TCGAAC-3'and 3 pmol of the sensor probe 5'-CCCCTACTTACAATCCTGGGAGAT fluores-cein-3' and the anchor probe 5'-LC Red 705- ATTTGGGTTTAGCGTGGTCGTATGTTG-3'. Melting curves were transformed to melting peaks by plotting the negative derivative of the fluorescence signal versus the temperature. The genotypes were identified by creating a melting curve with specific melting points.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Released 2011) and Open EpiInfo software package version 3.01 (www.openepi.com). The Chi-square (χ^2) test was used to evaluate the Hardy-Weinberg equilibrium (HWE) for the distribution of the genotypes of the patients and the controls. The relationships between *PON1*gene Q192R and L55M polymorphisms and the clinical and demographical characteristics of patients were analyzed by using χ^2 test or analysis of variance (ANOVA) statistics. χ^2 test and Fisher's exact test were used to compare categorical variables. Odds ratio (OR) and 95% confidence interval (CI) were used for the assessment of risk factors. All p values were 2-tailed and p values less than 0.05 were considered as significant.

Results

Clinical and demographical characteristics of vitiligo patients (gender, age, duration of disease, age at disease onset, family history of vitiligo and type of the disease) stratified according to PON1gene polymorphisms were shown in Table 1. Any association were not found between clinical and demographical characteristics of vitiligo patients and the PON1gene Q192R and L55M polymorphisms (p>0.05) (Table 1).

Allelic and genotypic distributions of the PON1 gene Q192R and L55M polymorphisms were shown in Table 2. Genotype frequencies didn't show any significant differences between patients and controls according to PON-1gene Q192R and L55M polymorphisms (p>0.05) (Table 2). However when we compared MM genotype with LL+LM genotypes for the L55M polymorphism, a significant difference was observed between patients and controls (p=0.034, OR: 0.30, 95% Cl: 0.08-0.93). And statistical power analysis was calculated as 56%. MM genotype was significantly higher in control group, which showed a protective effect of this genotype against vitiligo. The allele frequencies of L55M polymorphism also showed a statistically significant difference between patients and controls (p=0.009, OR: 0.48, 95% Cl:0.27-0.84). M allele was significantly higher in control group than patient group. And statistical power analysis was calculated as 73%. A significant association with vitiligo was not observed for the allele frequencies of Q192R polymorphism (Table 2).

We also examined the risk associated with inheriting the combined genotypes for the two polymorphisms (Table 3). Only the homozygosity for MM at L 55 M and homozygosity for QQ at Q192R polymorphisms encoded a significant p value of 0.034. Thus, individuals who were MM homozygous and QQ homozygous have a lower risk of developing vitiligo. The observed and expected

Table 1: Clinical and demographical characteristics of vitiligo patients stratified according to *PON1* gene Q192R and L55M polymorphisms.

Characteristics	Total n=57	Q192R				L55M			
		QQ n=22	QR n=23	RR n=12	P value	LL n=36	LM n=17	MM n=4	P value
Gender, male/female, n (%)	25/32 (43.9/56.1)	8/14 (36.4/63.6)	12/11 (52.2/47.8)	5/7 (41.7/58.3)	0.557	17/19 (47.2/52.8)	7/10 (47.2/52.8)	1/3 (25.0/75.0)	0.673
Age (years)	38.61±14.767	38.18±14.438	36.09±15.638	44.25±13.219	0.300	39.97±12.903	37.18±18.335	32.50±15.864	0.571
Duration of disease (years)	5.88±6.703	7.00±6.272	3.96±5.304	7.50±9.180	0.203	5.44±6.704	6.35±7.271	7.75±4.924	0.767
Age at disease onset					0.408				0.065
≤20	20 (35.1)	10 (50.0)	7 (35.0)	3 (15.0)		9 (45.0)	8 (40.0)	3 (15.0)	
>20	37 (64.9)	12 (32.4)	16 (43.2)	9 (24.3)		27 (73.0)	9 (24.3)	1 (2.7)	
Family history of vitiligo, n (%)					0.720				0.658
Yes	8 (14.0)	4 (50.0)	3 (37.5)	1 (12.5)		5 (62.5)	3 (37.5)	0	
No	49 (86.0)	18 (36.7)	20 (40.8)	11 (22.4)		31 (63.3)	14 (28.6)	4 (8.2)	
Klinical class					0.530				0.145
Local	32 (56.1)	11 (34.4)	13 (40.6)	8 (25.0)		23 (71.9)	8 (25.0)	1 (3.1)	
Common	22 (38.6)	9 (40.9)	10 (45.5)	3 (13.6)		11 (50.0)	9 (40.9)	2 (9.1)	
Universal	3 (5.3)	2 (66.7)	0	1 (33.3)		2 (66.7)	0	1 (33.3)	

Data were analyzed by χ^2 test or Fisher's exact test. Mean plus standard deviation values are presented for age and age at disease onset. *PON1*: Paraoxonase 1.

frequencies of PON1 gene L55M polymorphism were in Hardy-Weinberg equilibrium in patient group but not in control group. However, the observed and expected frequencies of PON1 gene Q192R polymorphism were in Hardy-Weinberg equilibrium in both groups.

Discussion

This research is the first to define the link between vitiligo and PON1 55 M/L polymorphism. In this study, there was no significant statistical difference between vitiligo patients and controls regarding the frequencies of PON1 M/L 55 and PON Q192R gene polymorphisms in the Turkish population. Between the clinical types of vitiligo and demographic features and PON1 M/L55 and Q192R gene polymorphisms was not found statistically different. However, in terms of PON1 M/L55 polymorphism, MM homozygous genotype compared to sum of LL+LM genotypes is higher in the vitiligo patients than in controls. The results show that the PON1 55M allele frequencies and MM homozygous genotypes might be protective against vitiligo.

Vitiligo is a common, polygenic and multifactorial disease that can be found worldwide and in patients of all ages. Even though its pathogenesis is not yet fully understood, Oxidant/Antioxidant imbalance has taken the center of attention in studies made within the past couple of years. Especially when vitiligo is in an active phase, the ROS and H_2O_2 levels in blood and tissue are found to be higher [3]. In a study made by Arican et al., the levels of superoxide dismutase and glutathione peroxidase amongst the antioxidant enzymes was higher and has shown an oxidant/antioxidant imbalance in patients with vitiligo [12]. In another study by Akoglu et al., the total oxidant status was high and the total antioxidant status was low in vitiligo patients [13].

PON1 is a very important ester hydrolase as part of antioxidant defense system; it protects lipoproteins from oxidation. The exact role of PON1 in the human body is not yet fully known. Nevertheless, it is known that it is an antioxidant enzyme that has links with high-density lipoprotein (HDL), the decreased activity of enzyme is also linked with dyslipidemia, diabetes mellitus, hypertension, older age, low HDL and increased oxidative stress [20–22]. PON1 protects lipoproteins from oxidation and hydrolases H_2O_2 that is a reactive oxygen metabolite was generated during oxidative stress [23]. In recent studies, the PON1 enzyme levels has found low in the skin diseases such as vitiligo, Behcet's disease, psoriasis, recurrent aphthous stomatitis and rosacea and has been suggested that

Table 2: Genotype and allele frequencies of PON1 gene Q192R and L55M polymorphisms in patient and control groups.

Polymorphism	Patients n=57 (%)	Controls n=69 (%)	p	OR (CI 95%)
PON1 Q192R				
Genotypes				
QQ	22 (38.6)	33 (47.8)	0.550	
QR	23 (40.4)	25 (36.2)		
RR	12 (21.1)	11 (15.9)		
QQ: QR+RR	22 (38.6): 35 (61.4)	33 (47.8): 36 (52.2)	0.300	1.45 (0.71–2.99)
QQ+QR: RR	45 (78.9): 12 (21.1)	58 (84.1): 11 (15.9)	0.460	1.40 (0.56–3.55)
Alleles				
Q	67 (58.8)	91 (65.9)	0.242	1.36 (0.81–2.27)
R	47 (41.2)	47 (34.1)		
PON1 L55M				
Genotypes				
LL	36 (63.2)	32 (46.4)	0.061	
LM	17 (29.8)	23 (33.3)		
MM	4 (7.0)	14 (20.3)		
LL: LM+MM	36 (63.2): 21 (36.8)	32 (46.4): 37 (53.6)	0.060	0.51 (0.24–1.04)
LL+LM: MM	53 (93.0): 4 (7.0)	55 (79.7): 14 (20.3)	0.034	0.30 (0.08–0.93)
Alleles				
L	89 (78.1)	87 (63.0)	0.009	0.48 (0.27–0.84)
M	25 (21.9)	51 (36.0)		

Data were analyzed by χ^2 test. *PON1*: Paraoxonase 1. The results that are statistically significant are typed in bold.

its levels take an important role in the etiopathogenesis of these diseases [24–28].

PON1 gene that responsible for the PON1 enzyme has two important polymorphisms: the 55L/M polymorphism that there is methionine (Met-M) instead of leucin(Leu-L) in the 55th position and 192q/R polymorphisms that there is arginine (Arg-R) amino acid instead of glutamine in 192th position. The amino acid changes in two positions of PON1 gene affects the serum levels of PON1 enzyme. In 192 Q/R polymorphism, people with Gln allele compared to people with Arg allele have lower PON1 enzyme activity [21,27]. As for the 55 L/M polymorphism, MM homozygous individuals have lower PON1 activity against paraoxonase compared to LL homozygotes. In some studies it was shown that PON 55 L/M polymorphism was connected to psoriasis, hyperlipidemia, rheumatoid arthritis and coronary artery diseases [29–33].

In their 2012 study, Asefi et al have found increased M / M genotype and PON1 55M allele frequency among psoriasis patients. Moreover, they claim that PON1 55M allele can be a risk factor for psoriasis [30]. In our study however, when compared to controls, PON1 55M allele frequencies and MM homozygote genotype was lower among vitiligo patients. According to this result, we think that PON1 55M allele frequency and MM homozygote genotype are phytoprotective.

Table 3: Comparative analysis of combined genotypes of patients and controls.

	Patient (n=57)		Control (n=69)		p
Genotypes	n	%	n	%	
L55M – Q192R					
LL-QQ	11	19.3	7	10.1	0.144
LL-QR	13	22.8	14	20.3	0.732
LL-RR	12	21.1	11	15.9	0.460
LM-QQ	7	12.3	12	17.4	0.425
LM-QR	10	17.5	11	15.9	0.810
MM-QQ	4	7.0	14	20.3	0.034

Data were analyzed by χ^2 test. The results that are statistically significant are typed in bold.

In recent studies, PON1 enzyme levels were observed to be lower in vitiligo patients and it has been argued that PON1 enzyme levels can have a role in the progression of vitiligo [23,34]. As far as we know, there are no studies present investigating the relationship between PON1 gene polymorphism and vitiligo. Genetic studies are very important for determining etiopathogenesis of vitiligo and developing effective treatment options.

At the end, no relationships were found between vitiligo and PON 192 Q/R gene polymorphism among Turkish population in this study. Furthermore, there were no statistically significant relationships between PON1 55 M gene polymorphism, MM homozygote genotype, and vitiligo. Although these results may suggest in the etiology of vitiligo, oxidative stress, antioxidant system and lack of PON 55 L/M gene MM homozygote genotype can be a risk factor, a study with a larger sample group will give better results. Moreover, we believe that larger sample size with various populations would give more accurate results with the relationships between early diagnoses of the disease, the variation among populations with vitiligo gene polymorphism, and development of vitiligo treatment.

Conflict of Interest: The authors have no conflict of interest.

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