Biomedical Research 2017; 28 (8): 3619-3622 *ISSN 0970-938X*
www.biomedres.info

IGF2BP2 gene polymorphism in patients with psoriasis.

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Abstract

Psoriasis is a chronic inflammatory disease with genetic transmission, the etiology of which has not been completely clarified yet. Insulin-like Growth Factor Binding Protein 2 (*IGF2BP2*) plays a role in growth, development, cellular differentiation, and cellular metabolism, and *IGF2BP2* gene exists on the 3rd chromosome. In the present study, we aimed to investigate the *rs1470579* and *rs4402960* gene polymorphisms of *IGF2BP2* in patients with psoriasis, which were confirmed to be related with insulin resistance. The study was conducted with a total of 100 patients diagnosed with psoriasis who were between the ages of 18 to 60 years and 100 healthy volunteers as controls. Blood samples of the participants were isolated and Deoxyribonucleic Acid (DNA) samples were obtained and analysed using y the real-time Polymerase Chain Reaction (PCR) method with TaqMan probes for *rs1470579* and *rs4402960* polymorphisms. There was no statistically significant difference in the genotype and allele distributions of the *rs1470579* and *rs4402960* regions of *IGF2BP2* between the groups (p>0.05). However, there was a statistically significant difference in triglyceride and Low-Density Lipoprotein (LDL) levels between the groups (p<0.001). *rs1470579* and *rs4402960* gene polymorphisms of *IGF2BP2*, which are considered to play a role in the course of type 2 diabetes mellitus, were not determined to be risk factors for the pathogenesis of psoriasis.

Keywords: Psoriasis, *IGF2BP2*, polymorphism, Real time PCR.

Accepted on January 7, 2017

Introduction

Psoriasis is a chronic inflammatory dermatosis which affects 2 to 3% of the overall population [1]. The etiology of psoriasis has not been fully understood; however, the disease has genetic and autoimmune components [2,3]. It is considered that genetic predisposition plays a role in psoriasis, as genetic risk factors have been determined in the related studies [4]. Recently, it has been shown that chronic inflammation associated with psoriasis leads to atherogenesis and peripheral insulin resistance, and, thereby, development of hypertension and type 2 diabetes mellitus in these patients [5,6].

System of the Insulin-like Growth Factor system (IGF) consists of different groups such as *IGF-1*, *IGF-2*, IGF-binding proteins (IGFBP) and IGF Receptors (IGFR) [7,8]. *IGF-2* gene is known to play a role in growth, development, cellular differentiation, and cellular metabolism [9]. Insulin-like growth factor binding protein 2 (*IGF2BP2*) is a member of the mRNA binding protein family, which has functions related with the RNA localization, stability and translation [10]. *IGF2BP2* regulates the translation of *IGF2*, by binding to the 5' UTR region of the *IGF2 mRNA* [11]. Studies have demonstrated that carriers of the *IGF2BP2* gene *rs1470579* and *rs4402960* mutations have the risk of type 2 diabetes mellitus, and it has been demonstrated that the level of insulin secretion shows variability in patients with type 2 diabetes who have different *IGF2BP2* genotypes [12].

It has been shown psoriasis is associated with systemic disease such as diabetes mellitus, metabolic syndrome, and hypertension in many studies. The genetic basis of this relation for psoriasis isn't well established yet. Recently, multiple genes that predispose to psoriasis have searched in association studies.

Demonstration of these mutations leading to variabilities in cellular metabolism has encouraged us to investigate whether the *IGF2BP2* gene *rs1470579* and *rs4402960* polymorphisms play a role in the development of psoriasis.

Materials and Methods

Patients

The present study was approved by the local Ethics Committee, which is the Presidential of Non-interventional Researches Ethical Committee, T.R. Fırat University (dated 18.11.2014, No: 02). The study included a total of 200 participants, of whom 100 were patients between the ages 18 to 60 years who were diagnosed with psoriasis at the Dermatology Clinic, Hospital of School of Medicine, Fırat University, and 100 were healthy controls. An informed consent was obtained from each individual. Values of duration of disease, Body Mass Index (BMI), the measure of waist circumference, Body Surface Area (BSA), Dermatology Life Quality Index (DLQI), and Psoriasis Area and Severity Index (PASI) were evaluated and recorded for all patients.

Exclusion criteria for the study participants included the followings: age<18 years, systemic diseases (diabetes, hypothyroidism or hyperthyroidism), pregnancy, malignancy, and systemic drug or alcohol abuse. Evaluations of age, sex, height, weight, and waist circumference were recorded for all participants. Body Mass Index (BMI=weight (kg)/height^2 (m^2)) was calculated and obesity was determined according to the World Health Organization (WHO) classification as follows: normal range (18.5-24.9 kg/m^2), Grade 1 overweight (25.0-29.9 kg/m^2), Grade 2 overweight (30.0-39.9 kg/m^2), and Grade 3 overweight (≥ 40.0 kg/m^2), and a BMI of>30 was accepted as obesity [13]. Severity of psoriasis was assessed according to the Psoriasis Area and Severity Index (PASI), and percent Body Surface Area (BSA) involvement was evaluated [14]. Quality of life was evaluated by calculating the score in the Dermatology Life Quality Index (DLQI), which has been tested for validity and reliability in Turkish by Oztürkcan et al. [15]. In addition, Glucose (mg/dl), Triglycerides (mg/dl), LDL-cholesterol (mg/dl), HDL-cholesterol (mg/dl), Total cholesterol (mg/dl) and Insulin (µIU/ml) were measured in both control and patients as biochemical parameters.

Blood samples (2cc) of study participants were withdrawn into Ethylenediaminetetraacetic acid (EDTA) tubes, and DNA was isolated in the Molecular Biology and Genetics Laboratory, using the DNA isolation kit (PureLink™ genomic DNA kits). Micro-volume spectrophotometer was used to measure the purities and quantities of DNAs isolated from the blood samples of patients. Ready-to-use master mix was used for Quantitative Polymerase Chain Reaction (QPCR) amplification, while real-time polymerase chain reaction device was used for the analysis (BIONEER brand, ExiCycler96 Model QPCR). Samples of patient DNAs were stored at -20°C until analysis. Later, the primers of related mutation regions were then designed and polymorphisms were analysed by real time PCR, using proper protocols. Single Point Mutation (SNP) was screened in the patients and control subjects with proper primer sets and probes, by reproducing the target sequences.

Statistical analysis

Statistical analysis was performed using the SPSS version 22 (SPSS Inc., Chicago, IL, USA) software. Gene frequencies of each allele were determined, and equilibrium control of the study population was determined by the Hardy-Weinberg equilibrium test and Chi-square test. The frequency of each genotype was expressed in percent (%). A p value of<0.05 was considered statistically significant.

Results

The present study included 100 patients with psoriasis in total of whom 44 were women and 56 were male. Of the total 100 healthy control subjects, 60 were females and 40 were males. The mean ages of the patients with psoriasis and control group were 40.59 ± 12.81 years and 36.93 ± 10.69 years, respectively, indicating a non-statistically significant difference (p>0.05). The clinical and demographic characteristics of the patients are shown in Table 2.

Table 1. *Primer sequences used for the IGF2BP2 gene regions.*

A-T alteration	
rs1470579(A) P1	CATACGAGTT [A] ATCCTGCCT
rs1470579(T) P2	CATACGAGTT [T] ATCCTGCCT
G-T alteration	
rs4402960(G)-P1	ACAGTAGATT [G] AAGATACTGATT
rs4402960(T)-P2	ACAGTAGATT [T] AAGATACTGATT

Table 2. *Clinical and demographic characteristics of patient and control groups.*

	Psoriasis vulgaris	Control	P
N	100	100	
Sex (M/F)	44/56	60/40	p>0.05
Age* (year)	40.59 ± 12.81	36.93 ± 10.69	p>0.05
BMI* (kg/m^2)	23.04 ± 2.03	23.76 ± 3.99	p>0.05
Waist circumference* (cm)	86.95 ± 9.47	85.46 ± 10.25	p>0.05
Duration of disease (years)	10.57 ± 8.68		
BSA (%)	20.64 ± 16.73		
PASI	9.19 ± 10.24		
DLQI	7.22 ± 3.79		

BMI: Body Mass Index; BSA: Body Surface Area; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index.

Patients and control groups have been evaluated through the *IGF2BP2* Gene polymorphism. Difference at genotype and allelic distribution at *IGF2BP2 rs1470579* and *rs4402960* gene polymorphism were not statistically significant (p>0.005). The

distributions of the *rs1470579* and *rs4402960* genotypes and alleles in patients and controls have been summarised in Table 3. An average Triglycerides (mg/dl) value was 129.75; an average LDL-cholesterol (mg/dl) value was 118.02, and these results were statistically significant ($p<0.005$). But there was no significant links among the other parameters. The biochemistry values of the patient and control groups are listed in Table 4.

Table 3. *Distributions of the rs1470579 and rs4402960 genotypes and alleles in the patient and control groups.*

Gene	Genotype allele	Patient (n=100)	Control (n=100)	X^2	P
rs1470579	AA	77 (0.770)	74 (0.740)	0.678	0.712
	AT	12 (0.120)	16 (0.160)		
	TT	11 (0.110)	10 (0.100)		
	A	165 (0.825)	158 (0.790)	0.788	0.374
	T	35 (0.175)	42 (0.210)		
Gene	**Genotype allele**	**Patient (n=100)**	**Control (n=100)**	**X^2**	**P**
rs4402960	GG	60 (0.600)	70 (0.700)	2.678	0.262
	GT	18 (0.180)	11 (0.110)		
	TT	22 (0.220)	19 (0.190)		
	G	142 (0.710)	159 (0.795)	3.879	0.048
	T	58 (0.290)	41 (0.205)		

Table 4. *Biochemistry results of patient and control groups.*

Variable	*Psoriasis vulgaris*	Control	p
Glucose* (mg/dl)	89.25 ± 15.99	90.98 ± 12.58	p>0.05
Triglycerides* (mg/dl)	129.75 ± 63.49	94.76 ± 39.104	p<0.001
LDL-cholesterol* (mg/dl)	118.02 ± 37.08	69.90 ± 29.30	p<0.001
HDL-cholesterol* (mg/dl)	46.52 ± 11.33	47.53 ± 7.60	p>0.05
Total cholesterol* (mg/dl)	191.43 ± 151.07	163.04 ± 29.37	p>0.05
Insulin* (µIU/ml)	5.55 ± 4.87	6.16 ± 3.89	p>0.05

LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein.

Discussion

Psoriasis is a chronic inflammatory disease mediated via T lymphocytes which appears as a response to an unknown antigenic stimulus and which may be triggered by various factors like infections, drugs and injuries in individuals having genetically predisposition. Increased epidermal proliferation, T lymphocytes and inflammatory mediators are included in the pathogenesis [16]. It is estimated in 1% to 2% of whites and 0.4% to 0.7% of the Asians and Africans. Also, it has been reported in 35% to 73% in monozygotic twins and 12% to 20% in dizygotic twins. The frequency of psoriasis varies with races and family cases have been reported, which support the view that the disease is related with genetic factors [17]. The first genetic investigation related to the patients with psoriasis had been conducted with *HLA-Cw6*, which is one of the alleles of Human Leukocyte Antigen (HLA) class 1 of the Major Histocompatibility Complex (MHC) family located on the short arm of the sixth chromosome [18]. This gene exists in the Psoriasis Susceptibility Region-1 (PSORS-1), which is located on 6p21.3 [19]. Determination of single nucleotide polymorphisms in the IL-2B and IL-23 receptors has proven that the genes for IL-2B and IL-23 receptors are related with the risk of development of psoriasis [20]. On the other hand, nuclear factor kappa B (NF-KB) pathway plays a major role in the pathogenesis of psoriasis, which is the proliferation and differentiation of keratinocytes, and response to stress. Genes for the TNF-α-Induced Protein 3 (TNFAIP3), TNFAIP3 Interacting Protein 1 (TNIPI), v-rel Reticuloendotheliosis viral oncogene homolog (REL) and Tyrosine Kinase 2 (TYK2) also contribute to the pathogenesis of psoriasis by modulating the NF-ƙB pathway [21].

Genes related with epidermal proliferation are located on the first chromosome (1q21.3), and about 45 genes are included in this group. Genes coding the proteins related with barrier function of the skin and keratinization, such as loricrin, involucrin, proline-rich proteins, late cornified envelope proteins (LCE 1, 2, 3C, 3B), filaggrin, trichohyalin, hornerin, comulin, psoriasin (S100A7) and calgranulin (S100A8, S100A9) are also included in the pathogenesis of psoriasis [22,23].

In the study of Batalla et al. [24] conducted among the Hispanic population, the genes for IL-17 pathway were found to be related with the risk for psoriasis or severity of disease. However, Feng et al. [25] showed that the *CARD14* gene was not related with psoriasis in the Chinese population. In another study, Wu et al. [26] reported that the *MTHFR C677T* polymorphism did not have a qualitative effect on psoriasis; however, it might represent quantitative severity of the disease.

Several suggestions related to the main causes of psoriasis and the course and regulation of this disease have been attempted to be developed in studies on various genes. Recent studies have demonstrated that chronic inflammation associated with psoriasis leads to atherogenesis and peripheral insulin resistance, and thus results in hypertension and type 2 diabetes in these patients [5,6]. In the literature review, a genetic research investigating *IGF2BP2* gene in the patients with psoriasis was unable to be found. Studies have demonstrated that mutations of the *IGF2BP2* gene carry the risk for the type 2 diabetes, and levels of insulin secretion vary in the patients with type 2 diabetes having different *IGF2BP2* genotypes [12].

In the present study, frequencies of the alleles of *rs1470579* and *rs4402960* regions on the *IGF2BP2* gene did not show statistically significant differences between the groups. However, there was a statistically significant difference in the triglyceride and LDL levels between patient and control group. In conclusion, *rs1470579* and *rs4402960* gene polymorphisms of *IGF2BP2*, which are considered to play a role in the course of type 2 diabetes mellitus, were not determined to be risk

factors for the pathogenesis of psoriasis. However, further large scale studies are required to establish a definite conclusion and our study would serve as a pioneer for the further studies.

Acknowledgement

We thank the Fırat University, Scientific Research Projects Unit (FUSRP, Project number: TF.14.74) for their contributions to this study. This study has been presented in the National Medical Biology and Genetics Congress held at Fethiye/Mugla from 27-30 October 2015, numbered PS-0735.

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