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ORIGINAL ARTICLE

Investigation of Insulin-Like Growth Factor 2 mRNA Binding Protein 2 Gene Polymorphisms in Type 2 Diabetes Patients

Tip 2 Diyabet Hastalarında İnsülin Benzeri Büyüme Faktörü 2 mRNA Bağlayıcı Protein 2 Gen Polimorfizmlerinin Araştırılması

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ABSTRACT

Background/Aim: Genome-Wide Association Studies (GWAS) have reported that polymorphisms (rs1470579 and rsS4402960) in Insulin Like Growth Factor 2 mRNA Binding Protein 2 (IGF2BP2) gene partially increase the risk of Type 2 Diabetes (T2D). The aim of this study was to investigate the association of IGF2BP2 variants rs4402960 and rs1470579 with T2D in Turkish population.
Material and Methods: For IGF2BP2 rs1470579 and rs4402960 SNPs (Single Nucleotide Polymorhism), genotyping of 200 individuals (100 healthy individuals and 100 T2D patients) was performed by RT-PCR method (Applied Biosystems). Relationships of genotypes and alleles frequency of IGF2BP2 polymorphisms and T2D were examined by "Chi-square" or "Likelihood ratio" tests.
Results: When evaluated in terms of genotype and allele distributions; for IGF2BP2 rs1470579 (A/C), an association was found between T2D patients and healthy individuals (p= 0.0123) and individuals with AC genotype in the patient group were more than healthy individuals. For IGF2BP2 rs4402960 (G/T), there was no difference in genotype distribution between T2D patients and control group (p= 0.8205).
Conclusion: Our study showed that IGF2BP2 gene rs1470579 polymorphism was associated with T2D in the Turkish population (p<0.05). Furthermore, this is the first study to analyze the relation between IGF2BP2 gene polymorphisms and T2D in the Turkish population.

Keywords: IGF2BP2, T2D, Polymorphism

ÖZ

Amaç: Genom çapında ilişkilendirme çalışmaları (GWAS) İnsülin Benzeri Büyüme Faktörü 2 mRNA Bağlayıcı Protein 2 (IGF2BP2) genindeki rs1470579 ve rs4402960 polimorfizmlerinin Tip 2 diyabet (T2D) riskini kısmen arttırdığını bildirmiştir. Bu çalışmanın amacı, Türk toplumunda rs4402960 ve rs1470579 IGF2BP2 varyantlarının T2D ile olan ilişkilerini araştırmaktır.
Gereç ve Yöntem: IGF2BP2 rs1470579 ve rs4402960 SNP'leri (Single Nucleotide Polymorhism) için 100 sağlıklı birey 100 T2D hastası olmak üzere 200 bireyin genotipleme çalışması RT-PCR yöntemiyle gerçekleştirildi (Applied Biosystems). IGF2BP2 polimorfizmlerinin genotip ve allel sıklığı ile T2D arasındaki ilişkiler "Ki-kare" veya "Olabilirlik oranı" testleri ile incelenmiştir.
Bulgular: Genotip ve allel dağılımları açısından değerlendirildiğinde; IGF2BP2 rs1470579 (A/C) için T2D hasta ile sağlıklı bireyler arasında ilişki bulunmuş olup (p= 0.0123) hasta grubunda AC genotipine sahip olan bireyler sağlıklı bireylerden daha fazladır. IGF2BP2 rs4402960 (G/T) için ise, T2D hastaları ve kontrol grubu arasında genotip dağılımı açısından bir fark yoktur (p= 0.8205).
Sonuçlar: Çalışmamız, IGF2BP2 geni rs1470579 polimorfizminin Türk toplumunda T2D ile ilişkili olduğunu göstermiştir (p< 0.05). Ayrıca bu çalışma, Türk toplumunda IGF2BP2 gen polimorfizmleri ile T2D arasında yapılan ilk çalışmadır.

Anahtar Kelimeler: IGF2BP2, T2D, Polimorfizm

Introduction

Type 2 Diabetes accounts for about 95% of the diabetic population, although prevalence varies in different populations (1). Today, T2D, a chronic metabolic disorder with increasing cardiovascular morbidity and mortality, is recognized as one of the growing epidemics worldwide (2). Also, the addition of environmental factors and genetic components has led to an increase in the prevalence of the disease (3). Many factors such as high plasma glucose levels resulting from the combination of insulin resistance and deficiency, the course of blood sugar level, changes in lipid metabolism and platelet dysfunction lead to complications in T2D (4,5).

Genome-wide association and linkage-based studies have defined a large number of SNPs associated with T2D (6). The genes involved in glucose transport, blood glucose homeostasis, beta cell function, insulin secretion, and pancreatic developmental pathways are considered to be excellent candidates in T2D ethology (7-10). The IGF2BP2 gene has been implicated in pancreatic β-cell dysfunction, decreased insulin secretion and activation leading to the development of T2D (10-13).

The IGF2BP2 gene modulates the translation of IGF2 by binding to the 5'-untranslated region of IGF2 mRNA (11-13). The IGF2BP2 gene is located in the q27.2 region of chromosome 3 and has important functions in RNA trafficking, stability and translation (13,14). IGF2BP2 plays a role in pancreatic development and stimulation of insulin secretion by binding to IGF-2, an important growth

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and insulin signalling molecule (12,13). Also, other polymorphisms found in the promoter regions of the IGF2BP2 gene have been associated with adipocyte and insulin resistance. Thus, it has been stated that this gene can change the functions of pancreatic and adipose tissues by affecting the expression of IGF2 and other proteins (13).

Studies have shown that IGF2BP2 variants are associated with impaired beta cell function rather than fasting blood glucose level or decreased insulin sensitivity. One of these, IGF2BP2 gene rs1470579 and rs4402960 SNPs have been found to be associated with the development of T2D in many populations (7-10). Therefore, the aim of our study was to investigate the association of IGF2BP2 variants with T2D in the Turkish population.

Material and Methods

Subjects

The study included 100 patients diagnosed with T2D and 100 healthy controls at Mersin University, Faculty of Medicine, Department of Endocrinology and Metabolic Diseases. The individuals participating in the study were included in the study by approving the informed consent form. Our study was approved and accepted by the Local Ethics Committee of Mersin University Faculty of Medicine (Ethics approval no.: 2012/370).

Genotyping of Polymorphisms in IGF2BP2: DNA Isolation and Analysis

DNA isolation from peripheral blood was performed by kit method. Genomic DNA was isolated from leukocytes using a high purity template preparation kit (Roche, Switzerland) following the manufacturer's protocol. Genotype analysis of IGF2BP2 gene polymorphisms was performed by RT-PCR using the Light Cycler DNA Master Hybridization probes kit. Primer and probe sequences are given in Table 2.

The Assays on Demand SNP genotyping kit was used for RT-PCR (Applied Biosystems, USA). SNP amplification experiments were performed according to the protocol. In brief, 50 µl of reaction solution containing 43 µl PCR grade water, 1 µl (10 pmol/ µl), of each PCR primers,1 µl qPCR pre mix (Taq DNA polimeraz, 10X reaction buffer, dye (xylene cyanole), stabilizer (sorbitol), tween 20, dNTP) and 5 µl of DNA.

Statistical Analysis

Relationships of genotypes and alleles frequency of IGF2BP2 polymorphisms and T2D were examined by "Chi-square" or "Likelihood ratio" tests. "Hardy-Weinberg" balances of the patient and healthy groups were checked in terms of genotypes. Descriptive statistics are presented as frequency and percentage for categorical variables while continuous variables are presented as mean ± standard deviation.

According to the results of our study, odds ratios (OR) and 95% confidence intervals (CI) were calculated to express the risk of T2D in terms of genotype distributions. Variables were considered significant when p-values were less than 0.05, and statistical analysis was performed using SPSS version 11.5 software.

Results

In this study, 100 patients (male= 59, female= 41, mean age: 54.24 ± 16.52) and 100 controls (male= 56, female= 44, mean age: 51.32 ± 14.82) were studied (Table 1). The polymorphisms of the IGF2BP2 gene (rs1470579 and rs4402960) were determined by the RT-PCR according to the Q-PCR Premix system produced by Bioneer.

When the results were analyzed as percentages in terms of allele frequency, the genotype frequencies of AA, AC and CC genotypes for the rs1470579 SNP in T2D patients and healthy groups were found as 73%, 19% and 8% in controls and 54%, 33% and 13% in T2D patient groups. There was a significant difference in the genotype frequency of IGF2BP2 rs1470579 (A/C) polymorphism between the control group and T2D patients (p= 0.0123; OR; 2.348 (1.21-4.57)) (Table 3). Individuals with AC genotype in the T2D patient group were higher than those with AC genotype in the healthy control group.

When we analyzed the genotype frequencies of T2D patients and control group individuals for rs4402960 polymorphism, the percentages of GG, GT and TT genotypes were 48%, 13% and 39% respectively in controls, while they were 51%, 10% and 39% in T2D patient groups. On the other hand, no difference was found between T2D and control groups in terms of genotype distribution for IGF2BP2 rs4402960 (G /T) gene polymorphisms (p= 0.8205). For TT and GG+GT genotype distribution, no relation was found between T2D patients and control group (p= 0.8847) (Table 4).

Table 1: The number of T2D patient and control groups according to mean age and gender

	Patients	Controls	P value
Number	100	100	
Age(years)	54, 24 ± 16, 52	51,32 ± 14,82	0.189
Female (%)	41	44	0.775
Male (%)	59	56	

Table 2: The sequence of Primers for *IGF2BP2* gene (rs1470579 and rs4402960)

Gene/SNP	Sequences	
IGF2BP2 rs1470579 (A/C)	F	5'- TCCAAACAGCTATCATCATT -3'
	R	5'- ATGAGTGAGAGGGAAAAGTC-3'
IGF2BP2 rs4402960 (G/T)	F	5'- CTGGGGAGCAGTAA -3'
	R	5'- TTGACCATTCCTTATCT -3'

Table 3: Analysis of *IGF2BP2* rs1470579 SNP genotype and allele frequency in control and T2D patients

GENOTYPE IGF2BP2 (rs1470579)	CONTROL N (%)	T2D PATIENTS N (%)	P value	OR (95%CI)
AA	73 (73%)	54 (54%)		Reference range
AC	19 (19%)	33 (33%)	0,0123	2.348 (1.21-4.57)
CC	8 (8%)	13 (13%)		1.196 (0.85-5.67)
ALLELE				
A	165(82.5%)	141(70.5%)	**0.0651**	0.718 (0.68-4.35)
C	35(17.5%)	59 (29.5%)		

Table 4: Analysis of *IGF2BP2* rs4402960 SNP genotype and allele frequency in control and T2D patients

GENOTYPE IGF2BP2 (rs4402960)	CONTROL N (%)	T2D PATIENTS N (%)	P value	OR (95%CI)
GG	48 (48%)	51 (51%)		Referans
GT	13 (13%)	10 (10%)	0.8205	0.724 (0.29-1.80)
TT	39 (39%)	39 (39%)		0.941 (0.52-1.70)
ALLELE				
G	109 (54.5%)	112 (56%)	**0.8847**	1.000 (0.56-1.76)
T	91(45.5%)	88 (44%)		

Discussion

Type 2 diabetes is a metabolic disease manifested by impaired insulin secretion and insulin resistance, in which environmental and genetic factors play a combined role in the development of the disease (14-15).

IGF2BP2 is involved in many biological processes by interacting with miRNAs, mRNAs and long non-coding RNAs to regulate various signalling pathways (16-17). IGF2BP2 gene has been recognized to be linked with reduced secretion of insulin and B cell function (18). Genome-Wide Association Studies (GWAS) have shown that IGF2BP2 gene polymorphisms are also associated with pancreatic β-cell function and hyperglycaemia, and SNPs in the second intron of this gene are critical in the occurrence of T2D (13).

The rs1470579 and rs4402960 in this study are located in intron 2 region of IGF2BP2. SNPs in this intron are thought to affect gene function through possible mechanisms by alternative splicing, protein interaction of IGF2BP2, miRNAs or antisense mRNA transcription, regulation of large noncoding transcription factors. Many genes located near IGF2BP2 are metabolic regulators involved in insulin metabolism (11-14). SNPs may also be directly associated with miRNAs, non-coding transcripts and close variants affecting antisense mRNAs transcribed in intron 2 (11).

IGF2BP2 is widely expressed during the perinatal period and in many adult tissues such as intestine, bone marrow muscle, kidney, lung and brain. In these organs, differences in IGF2BP2 expression may affect feeding behaviour and glucose metabolism, which may influence physical activity or obesity risk and thus the lifetime occurrence of T2D (13). These two polymorphisms (rs4402960 and rs1470579), which are associated with obesity, have also been reported to be involved in low fasting insulin levels and impaired β-cell function (16).

In our study, T2D was significantly related with rs1470579 (A/C) polymorphism between patient and healthy groups (p = 0.0123; OR; 2.348 (1.21-4.57)). Individuals with AC genotype were 2,348 times more likely to be ill than the control group. According to this result, it was determined that having AC genotype increases the risk of T2D in the Turkish population. However, it is not significantly associated with the rs4402960 (G/T) polymorphism (p= 0,8205). When evaluated in terms of TT and GG+GT genotype distribution, no relation was found between T2D patients and healthy individuals (p= 0.8847).

Our results showed the frequency of different genotypes of SNPs in different populations. These polymorphisms have been shown to be associated with T2D in some populations such as Chinese Han Japanese, Moroccan Czech Greek-Cypriot German Icelandic Asian Israeli, Lebanese and Indian Tunisian Arabs (16). In addition, the wild C allele has been reported to be the protective allele against T2D for IGF2BP2 rs4402960 polymorphism in the Chinese Han population (19). A meta-analysis of nearly 176,000 people investigating the association between the IGF2BP2 gene (rs4402960, rs1470579) and T2D found that these SNPs increased the risk of T2D, but that this increase differed between ethnic populations (20).

In our results, we found that the genotype frequencies of rs4402960 polymorphism did not differ between T2D patients and healthy individuals. Grarup et al. (21) conducted a similar study in the Danish population and found no association between IGF2BP2 gene polymorphism and T2D. In this sense, it overlaps with our study. Groenewoud et al. (7) investigated the expression of IGF2BP2 gene SNPs in Dutch and German populations and reported that these SNPs negatively affect insulin secretion in the early stages of diabetes. Moreover, it has been reported that IGF2BP2 polymorphisms may differ in metabolic diseases even in the same ethnic groups. For example, Zhang et al. (22) examined IGF2BP2 gene polymorphisms in 4531 T2D cases and 3807 controls in a large-scale case-control study. They found that IGF2BP2 SNPs had strong relation with T2D in the Chinese Han population (rs1470579 p= 1.80×10 (-7), OR= 1.22, rs4402960 p= 7.46×10 (-9), OR = 1.26). However, this association has not been detected in many GWAS studies in the Chinese Han population (Li et al reported p= 6.5×10−2 for rs4402960, Tsai et al reported p= 0.22, Cui et al reported p= 0.31, Shu et al reported p= 2.4×10−3) (23-26).

Rao et al. (27) found significant correlation between T2D and IGF2BP2 polymorphisms in Asian populations. They conducted a study with 461 T2D patients and 434 healthy individuals on Asians. They found that individuals with the TT genotype at rs4402960 had a higher risk of T2D than carriers of the G allele (TG + GG) (AOR) = 1.962, p = 0.031), and individuals with the CC genotype at rs1470579 were reported to have a higher risk of developing T2D than individuals with the A allele (CA + AA) (AOR = 2.014, p = 0.021).

The IGF2BP2 protein is involved in the metabolic processes of IGF2 and disturbances in these processes can lead to the development of metabolic diseases such as obesity and T2D (14). Considering the results of our study, we found that rs1470579 IGF2BP2 gene polymorphism may be a risk for susceptibility to T2D. This suggests a strong role for IGF2BP2 in susceptibility to T2D. In addition, recent studies have reported that IGF2BP2 dysfunction is implicated in the development and progression of multiple metabolic diseases and cancers, which differ between ethnic populations.

Conclusion

This study was conducted to investigate the association of IGF2BP2 rs4402960 and rs1470579 SNPs with T2D and to determine the genetic predisposition in Turkish population. We showed that IGF2BP2 rs1470579 polymorphism is associated with T2D. This result suggests that people with this heterozygous mutant allele (AC) are at higher risk of developing T2D. Considering that environmental/lifestyle changes may change the risk of T2D, to include these possible factors in the study and to increase the sample size will contribute to further studies.

Information obtained as a result of the study

• We determined the genetic susceptibility of IGF2BP2 on T2D under different genetic variants of IGF2BP2 gene rs4402960 and rs1470579 and investigated the association with T2D in Turkish population.

• We have shown that this IGF2BP2 rs1470579 polymorphism is associated with T2D in the Turkish population. This result suggests that individuals carrying this heterozygous mutant allele (AC) are at greater risk of developing T2D.

• Our study was not adjusted for any covariates such as gender, smoking, alcohol intake. A more comprehensive analysis should be performed by increasing the sample size, replicating this study in different ethnicities and considering interactions between risk factors.

• Clarification of the pathogenesis of T2D is necessary to identify individuals at risk of the disease and to effectively treat patients by elucidating genome-drug interactions.

• Recent meta-analyses and SNP studies will provide an understanding of the genetic factors that play an active role in the development and progression of multifactorial diseases.

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Conflict of Interest

No conflicts of interests were disclosed by the authors.

Abbreviations

T2D: Type 2 diabetes

IGF2BP2: Insulin-like Growth Factor 2 mRNA Binding Protein 2 Gene

SNP: Single Nucleotid Polymorphism

PCR: Polymerase Chain Reaction

GWAS: Genome-Wide Association Studies

BMI: Body Mass Index

OR: Odds ratio

AOR: Adjusted Odd Ratio

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