ORIGINAL STUDY

Изучение ассоциаций полиморфных маркеров генов факторов некроза опухоли и их рецепторов *rs1800629 TNFα, rs909253 Ltα, rs767455 TNFR1, rs1061624 TNFR2* с формированием сахарного диабета 2 типа

© М.И. Чурносов, О.Н. Белоусова, С.С. Сиротина

ФГБАОУ ВО «Белгородский государственный национальный исследовательский университет», Белгород

Одной из наиболее продуктивных современных технологий геномных исследований сахарного диабета 2 типа (СД2) является анализ ассоциаций полиморфных маркеров генов-кандидатов с развитием заболевания.

***Цель**. Изучение ассоциации полиморфных генетических маркеров факторов некроза опухоли и их рецепторов (rs1800629 TNFα, rs909253 Ltα, rs767455 TNFR1, rs1061624 TNFR2) с формированием СД2 среди населения Центрального Черноземья РФ.*

***Материалы и методы**. Проведен анализ результатов наблюдений 544 человек из русских жителей Центрального Черноземья России: 236 пациентов с установленным диагнозом СД2 (диагноз установлен на основании стандартных диагностических критериев) и 308 человек контрольной группы. Анализ всех локусов осуществлялся методом ПЦР синтеза ДНК, с использованием TaqMan зондов. Статистический анализ распределения частот генотипов проводили с использованием таблиц сопряженности и критерия χ^2, $p \leq 0,05$.*

***Результаты**. Анализ методом «случай-контроль» показал, что генотип GG rs909253Ltα является фактором риска развития СД2 (OR=2,36, p=0,01). Установлено, что индивидуумы с генотипом AA rs767455 TNFR1 отличаются ранним возрастом манифестации СД2 по сравнению с больными, имеющими генетические варианты AG и GG (p=0,01).*

***Заключение**. В результате проведенного исследования впервые продемонстрирована вовлеченность полиморфных маркеров генов факторов некроза опухоли и их рецепторов в формирование СД2 у русских жителей Центрального Черноземья России.*

***Ключевые слова:** сахарный диабет 2 типа; генетический полиморфизм; гены факторов некроза опухоли и их рецепторов*

Study of the associations between polymorphic markers *rs1800629 TNFα, rs909253 Ltα, rs767455 TNFR1, rs1061624 TNFR2* and the development of type 2 diabetes

© Mikhail I. Churnosov, Oksana N. Belousova, Svetlana S. Sirotina

Belgorod National Research University, Belgorod, Russia

***Aim.** To study the association between polymorphic genetic markers, tumor necrosis factors and their receptors (rs 1800629 TNFα, rs 909253 Ltα, rs 767455 TNFR1, rs 1061624 TNFR2) and the development of type 2 diabetes (T2D) among the population of the Central Black Earth Region of Russia.*

Materials and methods. The results obtained from 544 patients, of which 236 were already diagnosed with T2D and 308 were healthy control individuals, were analysed. All the loci were analysed by DNA synthesis using PCR TaqMan probes. The statistical analysis of the frequency distribution of genotypes was performed using contingency tables and the χ^2 test, with $p \leq 0.05$.

Results. A case-control analysis showed that genotype GG rs 909253Ltα was a risk factor for T2D (OR = 2.36, p = 0.01). Also, individuals with genotype AA rs 767455TNFR1 had significantly earlier age of T2D manifestation than that of patients with genetic variants AG and GG (p = 0.01).

Conclusion. This study demonstrated the involvement of polymorphic markers of tumor necrosis factors and their receptors in the development of T2D among the residents of the Central Black Earth Region of Russia.

***Keywords:** type 2 diabetes; genetic polymorphism; genes of the tumor necrosis factors and their receptors*

Type 2 diabetes mellitus (DM2) is the most common endocrine disease and is one of the most acute medical and social problems because it leads to early disability and an increase in mortality among the population due to the development of various complications [1]. Currently, more than 415 million people aged be-

Received: 19.04.2016. Accepted: 06.06.2017.

Сахарный диабет. 2017;20(3):166-171 doi: 10.14341/2072-0351-5845 Diabetes Mellitus. 2017;20(3):166-171

tween 20 and 79 years worldwide suffer from DM, and 90% of these cases are DM2. Correspondingly, in Russia, more than 4 million people have DM, of which 3.7 million have DM2 [2]. In terms of the incidence of disability and mortality, DM ranks third after cardiovascular diseases and cancer. Meanwhile, epidemiological studies conducted by the Federal State Budgetary Institution Endocrinology Research Center of the Ministry of Health of the Russian Federation from 2002 to 2010 showed that the true number of patients with DM in Russia is approximately 3–4 times greater than that officially registered and reaches 9–10 million people, which is approximately 7% of the population [3].

DM2 is often referred to as a multifactorial disease. According to the literature, the role of genetic factors in the development of DM2 amounts for 15%–50% [4]. Recent research has shown that cytokines that contribute to the development of insulin resistance play an important role in the development of DM2, with tumour necrosis factors (TNFs) being one of the key mediators of its development [5]. TNFs [TNFα and lymphotoxin-α (Ltα)] have a wide range of biological effects (such as immunomodulatory, cytotoxic and proinflammatory effects; stimulation of lipolysis; activation of the haemostasis system and induction of apoptosis) which may influence the development and progression of DM2 [6].

It is known that hyperproduction of TNFα leads to a decrease in the sensitivity to the action of insulin and consequently, a change in the metabolism of glucose in the adipose and muscle tissues and the liver. It has also been established that in the presence of obesity and insulin resistance, TNFα is synthesised in large quantities in the adipose and muscle tissue and exhibits both para- and autocrine properties [7]. Ltα is a chemoattractant for neutrophils, stimulates the formation of peroxide ions, enhances phagocytosis and adhesion to the endothelium, stimulates fibroblast activity, induces the production of stress hormones and affects glucose metabolism [8]. TNFs (TNFα and Ltα) implement their biological effects through specific type 1 and 2 receptors (TNFR1 and TNFR2, respectively). TNFR1 is responsible for acute inflammatory responses and is expressed by most cell types. TNFR2 is mainly involved in the implementation of metabolic effects of TNFs, namely, regulating adipose tissue and carbohydrate metabolism. Thus, TNFs can influence the development and progression of DM2 through their receptors.

From the molecular and genetic points of view, DM2 is studied quite actively both abroad and in the Russian Federation [9]. However, results of studies investigating the relationship of candidate genes of TNFs and their receptors with the development of DM2 are ambiguous in different populations. For example, it was demonstrated that allele *A rs1800629 TNFα* is a risk factor for DM2 development in Iranian [odds ratio (OR) = 2.34] [10], Indian (OR = 3.21) [11] and Brazilian (OR = 1.82) [12] populations. However, among the populations of Croatia and Hungary, this association could not be confirmed [13]. In contrast, in the Mexican population, it was found that the risk factor for DM2 development is the genotype *GG rs1800629 TNFα* (OR = 3.64) [14].

The role of polymorphic genetic markers of TNFs and their receptors in DM2 in our country has not been sufficiently studied, which necessitates conducting these studies in various populations of the Russian Federation.

AIM

The aim of this study was to investigate the association of polymorphic markers of TNFs and their receptors (*rs1800629 TNFα*, *rs909253 Ltα*, *rs767455 TNFR1,* and *rs1061624 TNFR2*) with the development of DM2 among the population of the Central Black Soil Region of the Russian Federation.

MATERIALS AND METHODS

The results of observations of 544 people were analysed: 236 patients with an established diagnosis of DM2 and 308 patients in the control group. Patients with DM2 and those in the control group included individuals of Russian nationality who were natives of the Central Black Soil Region of Russia and were not related. Diagnosis of DM2 was established after a detailed clinical and laboratory examination of patients in the

Table 1

Demographic and clinical characteristics of the study groups

Index	Patients (N = 236)	Control (N = 308)	p
Gender (m/f)	64/172	82/226	>0.05
Age, years	57.85±6.11	60.20±6.28	>0.05
Age of onset, years	48.2±0.48	-	-
Duration of diabetes, years	9.7±0.37	-	-
Body mass index, kg/m^2	29.7±4.8	27.3±5.5	>0.05
Glycated haemoglobin, %	8.77± 0.13	-	-
Fasting plasma glucose, mmol/l	9.6±1.7	5.6±1.1	<0.05
Plasma glucose level 2 h after a meal, mmol/l	-	6.8±0.8	-
Basal insulin level, μU/ml	14.8±9.1	10.2±4.9	<0.05
Insulin level 2 h after a meal, μU/l	-	46.5±21.7	-
Specific weight of patients with hereditary burden on DM2, n, %	103		

Note: x is the mean, SD is the standard quadratic deviation

Table 2

Conditions of amplification, sequences of primers and fluorescent probes

Gene	Polymorphous marker	Sequence of primers and probes, 5′-3′	Annealing temperature (°C)
TNFα	*G/A rs1800629*	*GAAATGGAGGCAATAGGTTTTGAG GGCCACTGACTGATTTGTGTGTAG FAM-CCGTCCTCATGCC- RTQ1 ROX-CCGTCCCCATGCC - RTQ1*	52
Ltα	*A/G rs909253*	*CAGTCTCATTGTCTCTGTCACACATT ACAGAGAGAGACAGGAAGGGAACAFAM:CCATGGTTCCTCTC-RTQ1 ROX:CTGCCATGATTCC-RTQ1*	50
TNFR1	*A/G rs767455*	*AGCCCACTCTTCCCTTTGTC CCACCGTGCCTGACCTG FAM: CTGCTGCCACTGGT-RTQ1 ROX: CTGCTGCCGCTGGT-BHQ2*	62
TNFR2	*A/G rs1061624*	*TGACCTGCAGGCCAAGAG CCATGGCAGCAGAGGCTTT FAM: CACAACCCGCTGCC - RTQ1 ROX: CCACAACTCGCTGCC - BHQ2*	59

Department of Endocrinology of the Belgorod regional clinical hospital of St. Joasaph based on the criteria of the WHO Expert Committee (1999) and the Fede'ral Target Program 'Diabetes Mellitus' (2002). The control group included age- and sex-matched individuals without DM2. All patients signed the informed consent form prior to inclusion in the study.

The groups studied were comparable in terms of their basic biological parameters including gender, age and body mass index (Table 1).

Venous blood (8–9 ml) taken from the basilic vein of the proband was used for molecular and genetic studies. Isolation of genomic DNA from the peripheral blood was performed by phenol-chloroform extraction using a standard protocol.

Analysis of all loci (*rs1800629 TNFα*, *rs909253 Ltα*, *rs767455 TNFR1*, and *rs1061624 TNFR2*) was performed by polymerase chain reaction (PCR) on isolated DNA. PCR was performed on an IQ5 thermocycler (Bio-Rad, Hercules, CA, USA), with *Thermus aquaticus* DNA polymerase (Silex-M, Moscow, Russia) and oligonucleotide primers and probes synthesised by Sintol (Moscow, Russia) (Table 2). Genotyping was performed by the method of discrimination of alleles using TaqMan probes. Designations of polymorphic markers are given in accordance with the dbSNP database.

Construction of the database and statistical calculations were performed using the program STATISTICA 6.0. Determination of phenotypic and gene frequencies was conducted by standard methods. To assess the compliance of the observed distribution to the expected one, the χ^2 criterion was used based on the Hardy–Weinberg equilibrium.

Statistical analysis of the distribution of the frequency of genotypes was performed using contingency tables and the Yates corrected chi-square test (χ^2) for continuity and OR with 95% confidence interval. In a comparative analysis of qualitative indicators characterising patients with DM2 and those in the control group, the nonparametric Mann–Whitney test was used [15].

Ethics statement

The study protocol was approved by the ethics committee of Belgorod State University (Belousova O.N., Department of Medical and Biological Disciplines), protocol No. 3, 14/05/2009.

RESULTS AND DISCUSSION

Investigation of the genotype frequencies of genetic markers studied showed that for all the loci examined in patients in the control group and in patients with DM2, the empirical distribution of the genotypes corresponds to the theoretically expected distribution by Hardy–Weinberg equilibrium ($p > 0.05$). Similarly, the observed heterozygosity (H_0) did not differ from the expected heterozygosity (H_E) ($p > 0.05$).

The case-control analysis (patients with DM2–healthy individuals) revealed the presence of a statistically significant association of the polymorphic marker *rs909253 Ltα* with the development of DM2. The *GG* genotype significantly increased the risk of DM2 development (OR = 2.36, $p = 0.01$) (Table 3).

Note: H_0 and H_E are the observed and expected heterozygosity, respectively.

Data obtained in the current study correspond to the literature on the biological significance of Ltα in the body. Ltα has pronounced proinflammatory, cytotoxic and immunomodulatory actions, and these mechanisms play important roles in the etiopathogenesis of DM2 [16]. It should be emphasised that the genotype *GG rs909253 Ltα* controls the increased production of Ltα. Therefore, in individuals with this genotype, we can also expect more pronounced etiopathogenetic effects of Ltα [17]. Notably, to the best of our knowledge, this is the first study to establish the importance of the locus *rs909253* of Ltα in DM2 among the Russian population.

No significant differences in the frequencies of alleles and genotypes were revealed in the other genetic polymorphisms investigated ($p > 0.05$).

When analysing the age of DM2 onset, it was established that individuals with genotype *AA rs767455 TNFR1* have an earlier age of DM2 onset ($x \pm S_D = 47.01 \pm 0.92$ years)

Table 3

Distribution of polymorphic markers of genes of tumour necrosis factors and their receptors in patients with DM2 and in those in the control group

Loci	Alleles, genotypes	Patients with DM2 (N = 236) (%)	Control group (N = 308) (%)	OR (95% CI)	χ^2; p
*rs909253 Lt*α	*A*	341 (72.25)	473 (77.04)	0.77 (0.58-1.03)	χ^2=3.01; p=0.08
	G	131 (27.75)	141 (22.96)	1.29 (0.97-1.74)	χ^2=3.01; p=0.08
	AA	129 (54.66)	180 (58.63)	0.85 (0.59-1.81)	χ^2=0.70; p=0.40
	AG	83 (35.16)	113 (36.80)	0.93 (0.64-1.34)	χ^2=0.09; p=0.76
	GG	24 (10.18)	14 (4.57)	2.36 (1.14-4.95)	χ^2=5.61; p=0.01
	$H_0(H_E)$. PHWE	0.35 (0.40). >0.05	0.36 (0.35). >0.05		
*rs1800629 TNF*α	*G*	405 (85.81)	539 (88.94)	0.75 (0.91-1.94)	χ^2=2.12; p=0.14
	A	67 (14.19)	67 (11.06)	1.33 (0.51-1.09)	χ^2=2.12; p=0.14
	GG	176 (74.57)	242 (79.87)	0.73 (0.48-1.13)	χ^2=1.84; p=0.17
	AG	53 (22.45)	55 (18.15)	1.30 (0.83-2.05)	χ^2=1.27; p=0.25
	AA	7 (2.98)	6 (1.98)	1.51 (0.45-5.15)	χ^2=0.20; p=0.64
	$H_0(H_E)$. PHWE	0.22 (0.24). >0.05	0.18 (0.19).>0.05		
rs767455 TNFR1	*G*	237 (50.42)	318 (51.62)	0.94 (0.73-1.21)	χ^2=0.16; p=0.68
	A	235 (49.58)	298 (48.38)	1.05 (0.82-1.35)	χ^2=0.16; p=0.68
	GG	66 (27.96)	76 (24.68)	1.18 (0.79-1.77)	χ^2=0.58; p=0.44
	AG	106 (44.91)	166 (53.89)	0.69 (0.48-0.99)	χ^2=3.95; p=0.04
	AA	64 (27.13)	66 (21.43)	1.36 (0.90-2.06)	χ^2=2.07; p=0.15
	H0(HE). PHWE	0.44 (0.50) >0.05	0.53 (0.49) >0.05		
rs1061624 TNFR2	*G*	272 (57.63)	341 (55.74)	1.07 (0.83-1.37)	χ^2=0.25; p=0.61
	A	200 (42.37)	269 (44.26)	0.93 (0.72-1.19)	χ^2=0.25; p=0.61
	GG	81 (34.32)	101 (33.12)	1.05 (0.72-1.53)	χ^2=0.04; p=0.83
	AG	110 (46.61)	138 (45.24)	1.05 (0.74-1.50)	χ^2=0.05; p=0.81
	AA	45 (19.07)	66 (21.64)	0.85 (0.54-1.33)	χ^2=0.39; p=0.53
	$H_0(H_E)$. PHWE	0.46(0.48) >0.05	0.43(0.49). >0.05		

Note: H_0 and H_E are the observed and expected heterozygosity, respectively

compared with patients with the genetic variants *AG* and *GG rs767455 TNFR1* ($x \pm S_D$ = 48.99 ± 0.72 years, p = 0.01) (Table 4).

Data obtained indicate a significant effect of *rs767455 TNFR1* on the age of DM2 onset. According to the literature [18], *TNFR1* mediates the functions of multiple types of action of TNFs, thereby participating in the implementation of a wide range of biological processes in the body (mitogenesis in adipocyte, apoptosis, stimulation of leptin secretion, regulation of mitochondrial functions, participation in the regulation of the metabolism of carbohydrates and fats, induction of insulin resistance in the adipose tissue and muscles and suppression of insulin secretion by β-cells of pancreatic islets) that are important in the etiopathogenesis of DM2 [19]. According to the literature, the genotype *AA rs767455 TNFR1* is associated with an increase in the expression of the receptor of TNF 1pe [20], which may cause an early age of DM2 onset.

CONCLUSION

The importance of polymorphic markers of Ltα (*rs909253 Lt*α) and TNFR1 (*rs767455 TNFR1)* in the development of DM2 in Russian residents of the Central Black Earth Region should be noted. The genotype *GG rs909253 Lt*α is a risk factor for the development of DM2 (OR = 2.36), whereas individuals with the genotype *AA rs767455 TNFR1* have an earlier age of DM2onset than

Table 4

Demographic and clinical characteristics of patients with DM2, depending on the genotypes of the locus *rs767455 TNFR1*

Indices	Genotype on locus *rs767455 TNFR1*		p
	AA (n=64)	AG и GG(n=175)	
Age, years	56.93±0.79	58.53±0.76	0.06
Age of onset, years	47.01±0.92	48.99±0.72	0.01
Duration of diabetes, years	9.92±0.67	9.60±0.59	0.06
Body mass index, kg/m^2	31.71±0.68	33.19±0.49	0.06
Glycated haemoglobin, %	9.12±0.25	8.65±0.22	0.06

Note: x is the mean, S_D is the standard quadratic deviation

patients with the genetic variants *AG* and *GG rs767455 TNFR1* ($p = 0.01$). To the best of our knowledge, this is the first time this has been demonstrated in this population.

ADDITIONAL INFORMATION

Financing of the research

The research was funded by the Presidential Scholarship.

Conflicts of interest

The authors declare no obvious and potential conflicts of interest related to the publication of this article.

Authors' contributions

Churnosov M.I.: concept and design of the study, writing the text; Belousova O.N.: collection and processing of the material, writing the text and Sirotina S.S.: analysis of the data obtained, writing the text.

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Информация об авторах [Authors Info]

Сиротина Светлана Сергеевна, к.б.н. [**Svetlana S. Sirotina**, PhD in Biology]; адрес: Россия, 308015, Белгород, улица Победы, д. 85 [address: 85 Pobedy street, Belgorod, 308015 Russian Federation]; ORCID: http://orcid.org/0000-0002-4163-7863; eLibrary SPIN: 4242-8166; e-mail: sirotina@bsu.edu.ru

Чурносов Михаил Иванович, д.м.н., профессор [Michail I. Churnosov, MD, PhD, Professor]; ORCID: http://orcid.org/0000-0002-9319-7185; eLibrary SPIN: 7407-9649; e-mail: churnosov@bsu.edu.ru. Белоусова Оксана Николаевна, к.м.н. [Oksana N. Belousova, MD, PhD]; ORCID: http://orcid.org/0000-0003-0588-14363; eLibrary SPIN: 2272-2670; e-mail: belousova@bsu.edu.ru.

Цитировать:

Чурносов М.И., Белоусова О.Н., Сиротина С.С. Изучение ассоциаций полиморфных маркеров генов факторов некроза опухоли и их рецепторов *rs1800629 TNFα, rs909253 Ltα, rs767455 TNFR1, rs1061624 TNFR2* с формированием сахарного диабета 2 типа // Сахарный диабет. — 2017. — Т. 20. — № 3. — С. 166-171. doi: 10.14341/2072-0351-5845

To cite this article:

Churnosov MI, Belousova ON, Sirotina SS. Study of the associations between polymorphic markers *rs1800629 TNFα, rs909253 Ltα, rs767455 TNFR1, rs1061624 TNFR2* and the development of type 2 diabetes. *Diabetes mellitus.* 2017;20(3):166-171. doi: 10.14341/2072-0351-5845