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The reversion of A23525T of polymorphism of FTO gene in persons with overweight in conditions of hypocaloric diet

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ABSTRACT

Objective: To study the association of A23525T polymorphism of the FTO gene with overweight/obesity and the possibility of reversion of single-nucleotide replacements rs9939609 in a hypocaloric diet.

Materials and methods: Polymorphisms of the FTO gene (A23525T, rs9939609) are typified by the SNP method (single nucleotide polymorphism) with allele-specific primers on the test systems of the NPF "Liteh".

The frequencies rs9939609 were studied in persons with overweight, I–III degree of obesity (n = 84) compared with the control group (n = 32). The reversion of polymorphic variants of genes under the influence of a hypocaloric diet has been analyzed. The experimental data are processed in SPSS Statistics 22.0.

Results: In the pilot study, unlike previously published studies, a reliable association of the genotype of the FTO gene with a violation of lipid metabolism (OR = 2.33, CI 95%) was shown not by A23525A, but by T23525T. A positive correlation was established between the mean force between the TT genotype and the weight of the participants in the experiment (r = + 0.625, p = 0.022), fat mass (r = + 0.610; p = 0.046), body mass index (BMI) (r = + 0.577; p = 0.039) and the circumference of the hips (r = + 0.636; p = 0.039). In 25 out of 84 participants (29.7%) after RTD, a partial or complete reversal (reversal) of nucleotides occurred in rs9939609: 40% of them were mutations transversion caused by the replacement of T→A nucleotides and the A23525T, T23525T transition of genotypes into the homozygous A23525A variant.

Conclusion: The TT genotype of the FTO gene is associated with obesity. The reversal of polymorphisms in the FTO gene under the influence of RDT is mainly associated with transversion of nucleotides (A→T) at the corresponding site (23525) of the intron mutation (rs9939609).

1. Introduction

Obesity is one of the global problems of the 21st century that threaten modern society. According to the 2016 World Health Organization (WHO) final report, in 2014, over 1.9 billion adults (over 18 years old) and 41 million children under the age of five suffered from overweight and obesity. Total for the period from 1980 to 2014. This figure has grown more than twice in the whole world (World health organization, 2013). From the point of view of clinical diagnosis, obesity is considered as a violation of lipid metabolism, caused by an energy imbalance between the amounts of consumed (food) and consumed energy (World health organization, 2013; Hindorff et al., 2009).

Overweight, according to WHO, is one of the main risk factors for the development of type 2 diabetes, endocrine disorders, cardiovascular, oncological and other non-communicable diseases (NCDs), the annual loss of which is about 36 million people (63% of cases). Prematurely (up to 50 years), more than 14 million die and, according to WHO experts, by 2030, NCDs that take the nature of pandemics will carry 52 million lives each year, if current trends continue. In Russia, about 40% of the able-bodied population, according to S.I. Kuzina, M.V. Karmanov (2016), have excessive body weight and obesity of varying degrees (World health organization, 2013; Kuzin and Karmanov, 2016).

The identification of cause-effect relationships in the development of obesity and socially significant diseases, taking into account the achievements of modern molecular biology, will promote health promotion and prevention of NCD, prevent depopulation processes in the world including Russia. However, the concept of the development of obesity under the influence of risk factors established by WHO, do not give an exhaustive idea of the trigger mechanisms of the emergence of pathologies and the role of heredity. According to modern data,

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mutations - SNP - single nucleotide polymorphism, which influence the regulation of the expression of the corresponding genes and the structure of synthesized protein products, can play an important role in the development of diseases with a prograde current (Puzyrev et al., 2007).

"Genome-wide linkage scans" (GWLS) and "Genome-wide association studies" (GWAS) international projects have identified approximately two thousand genetic loci associated with more than 300 different diseases, including 52 polymorphisms associated with obesity. One of the first markers of dyslipidemia in Europe residents is the "Fat mass and obesity-associated protein" (FTO) gene, which is expressed practically in all tissues of the body (brain, muscles, adipose tissue, adrenal glands, pancreas) (Frayling et al., 2007; Scuteri et al., 2007; Gulati et al., 2013; Wu et al., 2010; Hubacek et al., 2012).

Based on the generalized material in 2013, it was suggested that the FTO could play a key role in regulating metabolism and total fat mass through the hypothalamic-pituitary system, with a change in the expression level in the paraventricular, dorsomedial and ventromedial nuclei of the hypothalamus regulating food behavior, the energy balance organism, as well as in the arcuate nucleus, responsible for the formation of a sense of saturation (Gulati et al., 2013; Wu et al., 2010; Hubacek et al., 2012).

In the FTO gene, according to GWAS (2017), there are 139 mutations, but most of them are not of functional significance. The most promising polymorphism for clinical medicine is rs9939609 with the nucleotide substitution (SNP) of adenine (A) for thymine (T) at position 23525 of the first intron. The database "HuGE Literature Finder" (2010–2017) published 375 articles on the identification of the association A23525T polymorphism with various diseases, of which 280 are associated with obesity (Genome-wide association studies; HuGE Literature Finder).

According to the results of the complex population study "1000 Genomes Project" (Genome-wide association studies), the highest frequencies of the prognostically unfavorable A23525 allele were noted in peoples living in Europe and Africa, especially among Kenyan people (0.556) and Nigeria (0.519). In the regions of East and South Asia, as well as of America, rs9939609 is detected much less often - approximately 1.5 times. It is necessary to cancel that in all analyzed groups, regardless of geographical distance, the heterozygous genotype A23525T of the FTO gene is most common, due to which high frequencies of A23525 allele are formed. "The HuGE Literature Finder" provides numerous data confirming the association of rs9939609 polymorphism with dyslipidemia and elevated body mass index (BMI), depending on the population and geographical distribution of the population (HuGE Literature Finder).

In the works of Russian authors conducted in Russia, the association of the A23525 polymorphic variant of FTO with obesity and an increased body mass index was also confirmed (Zavyalova et al., 2011; Nasibulina et al., 2012; Korelskaya et al. 2014; Baturin et al., 2011, 2012, 2016, 2017).

Despite the revealed correlationships of rs9939609 with excess body weight and functional parameters, the effect of mutations of genes associated with obesity and, in particular, A23525 SNP FTO, on body weight correction by eating behavior modeling has not been investigated. In a number of foreign works, the results of the influence of the minor allele rs9939609 SNP on the process of weight reduction with changes in diet and physical activity were obtained. Since similar studies have not been carried out in Russia, the experimental confirmation of the effect of diet and exercise on the effectiveness of reducing BMI, depending on the carriage of allelic variants and genotypes rs9939609, will reveal molecular genetic mechanisms that affect predisposition to obesity.

2. Objective

Studying the association of A23525T polymorphism of the FTO gene with overweight/obesity and the possibility of reversion of single-nucleotide replacements rs9939609 in a hypocaloric diet.

2.1. Contingent of the surveyed persons

The control group is represented by unrelated donors (n = 32) aged 20–60 years old, without hereditary complications and clinical manifestations of chronic diseases, as confirmed by the database of the "Adyghe Republican Blood Transfusion Station". The second group comprised (n = 84) patients of the clinic "Health Center" Ltd. (Maikop, Republic of Adygeya, Russia), aged 21–63 years old with overweight (BMI), I–III degree of obesity and concomitant diseases diabetes mellitus type 2, arterial hypertension, chronic pancreatitis, etc.). Both groups examined were represented by residents of the North Caucasus region.

2.2. Methods of research

The complex examination included: measurement of anthropometric data, basic hemodynamic indices using computer oscillometry ("Globus", Russia) and standard biochemical parameters of blood (total cholesterol, high, low, triglyceride lipoproteins). The body mass index (BMI) was calculated by the method of Quetelet (IR = body weight to height ratio). Quantitative estimation of muscular, fat mass of the body throughout the whole cycle of RTD was carried out with the help of instruments "Tanita" (Japan) and DDFAO (France).

Weight adjustment, as a result of unloading and dietary therapy (RDT), was carried out within 19–21 days, including fasting with a mandatory daily intake of at least 1.5–2 L of water, walking with a constant increase in distance from 3 to 6 km. The complex of rehabilitation procedures included: cleansing enemas or hydrocolonotherapy (2–3 times a week); laser - and bioresonance therapy, massage, a warm shower (2–3 times a day), visiting an infrared sauna (once a week). Contact laser therapy with a projection on the spleen region (4.2 cm^2) was performed 2–3 times a week by an infrared laser with a wavelength of 0.85–0.89 μm with the help of the Milta device (ZAO "NPO Kosmicheskogo Instrument Engineering"). The courses of bioresonance therapy (6–8) were performed in a mode set by the EIS CE 0535 interstitial scanner (ESTECK System Complex, USA).

The genomic DNA of the examined individuals was isolated from whole blood leukocytes using the "DNA-express-blood" reagent (NPF "Litech" (Russia)). The purity of DNA samples was tested on a NanoDrop 2000c spectrophotometer (Termo Scientific, USA). Polymorphisms of the FTO gene (A23525T, rs9939609) in DNA samples of donors and patients are typified using commercial test systems of NPF "Liteh" (Russia) with electrophoretic detection of results on the basis of the "Immunogenetic Laboratory" of the Institute of Complex Problems of the Adyghe State University (Maikop, Russia). In order to verify the obtained data, DNA samples from rs9939609 were SNP-typed in the independent laboratory "Biology of Development and Organization of the Genome" (Rostov-on-Don, Russia) with the obligatory condition of observing identical experimental conditions.

The correspondence between the distribution of genotypes to the expected values at the Hardy-Weinberg equilibrium and the comparison of the frequencies of the allelic variants/genotypes of the FTO gene was carried out using $\chi 2$ (chi-square) for conjugation tables 2×2 with Iates correction for continuity and odds-ration or OR calculation, 95% confidence interval (95% CI). To calculate the correlation, Spearman's nonparametric method was used in SPSS Statistics 22.0.

The study was conducted in accordance with the principles of the Helsinki Declaration with written informed consent of all participants in the experiment.

3. Results

To determine the prognostic significance of the A23525T SNP of the FTO gene in the development of obesity, at the first stage of the study