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Polymorphic Genetic Markers of Obesity and Their Associations with Clinical and Metabolic Indicators.

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ABSTRACT

The article summarizes the results of many years of work to identify molecular genetic markers associated with predisposition to obesity in young people. It was shown that the detection of the carriage of the combination of the allele A of the polymorphic marker rs8050136 of the FTO gene and the allele A of the polymorphic marker rs7172432 of the C2CD4A gene justifies the inclusion of patients in the high-risk group with the necessity of carrying out preventive measures for the prevention of obesity in this population category.

Key words: genes, obesity, molecular-genetic markers

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INTRODUCTION

Obesity is a serious medico-social and economic problem of modern society. The urgency of obesity is determined by its high prevalence and high risk of developing concomitant pathology. At present, it is well known that the deep metabolic abnormalities that occur with obesity naturally lead to the development of cardiovascular pathology, type 2 diabetes, joint diseases, infertility, fatty hepatosis, hyperuricemia, malignant neoplasms, diseases accompanied by hypoxia (apnea, asthma), and other diseases [2,7].

However, to date, obesity is often diagnosed late, there are no groups at risk for obesity. The predictors of the disease, which determine predisposition to the development of obesity in the future, are not sufficiently studied. In connection with this, the study of markers for the prediction of obesity is of particular relevance. Thanks to the development of biological sciences over the past decade, it has been proven that the identification of genetic risk is important for developing a differentiated approach to the prevention and treatment of obesity and associated diseases [3,5,7].

However, up to the present time, methodological approaches to the use of genomic and postgenomic technologies in obese patients have not been adequately studied. Numerous studies are under way to identify "candidate genes," whose structural changes can be considered as possible factors determining a predisposition to the development of dyslipidemia and obesity [1,4,6].

But, despite significant success in identifying factors regulating energy metabolism in obese patients, a number of questions concerning the diagnostic significance of proteomic and metabolic biomarkers in various polymorphic variants of genetic markers of obesity in obese patients remain insufficiently studied. In this regard, the improvement of diagnostic methods and approaches to the development of personalized prevention programs, the use of which is ineffective without the data of genomic and postgenomic studies, becomes especially topical [1,8].

MATERIALS AND METHODS

In the study, with voluntary informed consent, 192 unrelated female subjects (n = 110) and male (n = 82) sex were included. The control group is represented by 96 conditionally healthy individuals. All participants underwent a general clinical examination with evaluation of complaints, a history of the disease, heredity and objective clinical examination data. The body weight was evaluated using the body mass index, the type of distribution of fatty tissue was determined according to the index of the ratio of the waist to the hips according to the recommendations of the WHO (1997). To assess the state of carbohydrate metabolism, an oral glucose tolerance test was used to study basal and stimulated glucose concentrations (Glucose, Biosystems), immunoreactive insulin (DRG Insulin ELISA EIA-2935) and C-peptide (Beringwerke-AG). Additionally, cholesterol ("Bio-systems") and triglycerides ("Biocon") were investigated.

Genotyping of DNA samples of 192 participants was carried out using the BeadChip GoldenGate Illumina protocol using a synthesized DNA biochip containing 96 single nucleotide polymorphisms associated with obesity rs8050136, rs11642841 and rs1558902 (FTO), rs2867125 (TMEM18), rs571312 (MC4R), rs10938397 (GNPDA).

Statistical analysis of the data was carried out using the application software STATISTICA 6.0, SPSS 13.0. Quantitative indicators, subject to a normal distribution, are presented as the mean and standard deviation. In a distribution different from normal, the quantitative indicators are presented in the form of a median and interquartile range (Me (25%, 75%)). When comparing the mean values of two independent samples that obey a normal distribution, Student's statistical test was used. A comparison of two independent samples with a nonparametric distribution was performed using the Kolmogorov-Smirnov test and the Mann-Whitney U test. To determine the relationship between qualitative and / or quantitative indicators, the Spearman correlation coefficient was used. The analysis of qualitative indicators is carried out by the method of calculating absolute and relative frequencies with the construction of conjugacy tables. The reliability of the frequency differences in the traits studied was estimated using the $\chi 2$ criterion, for non-parametric Fisher's exact tests, for small samples. Differences were considered significant at $p < 0.05$.

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RESULTS OF THE RESEARCH AND THEIR DISCUSSION

As a result of the survey, it was found that all participants in the main group (100%) had an excess of body weight or obesity (mean BMI> 25 ± 5.8 kg), of which the first degree of obesity was registered in 32.3% of patients, 62.9% and the third - in 14.8% of patients. To determine the distribution of fat tissue in the subjects, the parameters RT, OB, and also the index OT / OB were analyzed. It was found that in the main group, 100% of men and 100% of women had an increase in waist circumference compared to the control group, where these values were 10.41% and 14.4%, respectively ($\chi 2 = 36.5$, $p < 0.001$ and $\chi 2 = 71.1$, $p < 0.01$). The study noted that the ratio of OT / OB more than 0.85 in women and more than 0.95 in men was found in 88.54% of cases in the main group, with the abdominal type of obesity more often recorded among women than among men.

In addition, 56.6% of patients had hereditary obesity, mainly on the maternal line (33.1%). The study of the hereditary history of the patients of the main group showed that over half of all mothers (42.8% of the fathers of the examined children) had overweight (BMI from 25 to 29 kg / m2) or obesity of various degrees (BMI from 30 kg / m2 and more). In families, 66 patients (34.3%), and the mother and father were overweight. Weighed down by heredity on the part of relatives of the second generation (grandparents both on the paternal and maternal line) had 67 patients (34.9%) of the main group, 59 of whom (30.7%) were obese or overweight The weight of the body also affected the parents. Thus, 128 patients (66.6%) of the main group had adverse heredity for overweight or obesity, while in the control group it was weighed only by 8 people (8.4%, $p < 0.001$) by relatives I generation. In addition, it was found that 72.3% of patients in the main group had hereditary agonist complications, 48.6% had early coronary artery disease, and 42.0% had disorders and carbohydrate metabolism. At the same time, 24.1% of the children of the main group among the native I and / or II generations had a combined pathology in the form of obesity, carbohydrate disorders and AH. The more significant the heredity was burdened by the number of these components, the greater was the excess body weight in the examined patients ($p < 0.05$). Among the representatives of the control group, 17.4% ($p < 0.001$) had an unfavorable heredity in obesity; 19,6% ($p < 0,01$) - according to AG; 17,4% ($p < 0,01$) - according to the IHD; 8,6% ($p < 0,001$) - with carbohydrate disorders. Based on the results of an assessment of the history of the disease in the patients of the main group, a direct relationship ($r = 0.47$, $p < 0.01$) between age and obesity was established and the inverse correlation between obesity and age of overweight ($r = -0.35$; $p = 0.04$). The established interrelation, most likely, specifies an essential role of time factor in the course of realization of hereditary predisposition to formation of adiposity in the conditions of the environment conducive to it.

Comparative characteristics of hormone-metabolic parameters revealed that among obese patients, in contrast to the control group, higher values of the HOMA-IR index, glycemic index, C-peptide, and IRI, which is compensatory in nature and aimed at maintaining euglycemia. The comparative analysis found that obese patients had higher rates ($p < 0.001$) of both basal and stimulated glucose levels 5.6 [4.9; 7.1] and 7.11 [5.6; 13.3] mmol / L than in the control group: 5.95 [4.69; 5.35] and 5.0 [4.5; 5.79] mmol / L, respectively.

In the study of associations of studied polymorphic genetic markers with obesity, the subjects of the main group (n = 96) were compared with patients of normal body weight from the control group (n = 71). In the study of associations with IR, the subjects were divided into a subgroup of patients with CD2 and MI (n = 65) and a subgroup of patients without disturbances in carbohydrate metabolism (n = 81). As a result, the links of the polymorphic markers rs8050136 and rs11642841 (FTO), rs7172432 (C2CD4A) and rs571312 (MC4R), rs16928751 (ADIPOR2), rs7593730 (PBMS1-ITGB6) with the IR were established. Comparison of patients with excess body weight and obesity and participants in the control group with normal body weight revealed associations of polymorphic markers rs8050136, rs11642841 and rs1558902 (FTO), rs2241766 (ADIPOQ), rs243021 (BCL11A) with obesity. In addition, during the study of the studied genetic markers, associations with obesity of the polymorphic marker rs1558902 of the FTO gene associated with fat and obesity, the polymorphic marker rs2241766 of the visceral adipose tissue adiponectin gene ADI-POQ and the polymorphic marker rs243021 of the BCL11A B cell lymphoma gene have been identified.

Relationships with an increased risk of obesity of the allele A (OR = 1.61 [1.03-2.52], p = 0.04) of the polymorphic marker rs1558902 of the FTO gene and the T allele (OR = 2.07 [1.04- 4.14], p = 0.04) of the polymorphic marker rs2241766 of the ADIPOQ gene.

Also, the association with reduced obesity risks of the allele T (OR = 0.62 [0.40-0.97], p = 0.04) rs1558902 of the FTO gene, the G allele (OR = 0.48 [0.24-0.96]; p = 0.04) rs2241766 of the ADIPOQ gene. For

the first time, associations with obesity of the polymorphic marker rs243021 of the BCL11A gene were established. The odds ratio calculation revealed that the allele A (OR = 1.66 [1.07-2.56], p = 0.02) and the AA genotype (OR = 2.50 [1.07-5.84], p = 0.03) of the polymorphic marker rs243021 of the BCL11A gene are associated with an increased risk of obesity, and the C allele of the polymorphic marker rs243021 of the BCL11A gene with a decrease in risk (OR = 0.6 [0.39-0.93], p = 0.02).

CONCLUSIONS

Thus, in the Russian population of the Voronezh Oblast, the allele A (OR = 1.82, p = 0.005) of the marker rs8050136 of the FTO gene, the allele A (OR = 1.87, p = 0.007) of the marker rs11642841 of the FTO gene, allele A (OR = 1.64; p = 0.04) of the marker rs1558902 of the FTO gene, allele T (OR = 2.05; p = 0.04) of the marker rs2241766 of the ADIPOQ gene, allele A (OR = 1.64; p = 0.02) and the genotype AA (OR = 2.24, p = 0.03) of the BCL11A gene, and alleles C (OR = 0.51, p = 0.005) and the SS genotype (OR = 0.33; p = 0.009) of marker rs8050136 of FTO gene, allele C (OR = 0.54, p = 0.007) and genotype CC (OR = 0.44, p = 0.008) of marker rs11642841 of FTO gene, allele T (OR = 0.64; p = 0.04) of the marker rs1558902 of the FTO gene, the G allele (OR = 0.46, p = 0.04) of the marker rs2241766 of the ADI gene POQ, allele G (OR = 0.62, p = 0.02) of marker rs243021 of the BCL11A gene.

The identification of the carriage of the risky combination of allele A of the polymorphic marker rs8050136 of the FTO gene and the allele A of the polymorphic marker rs7172432 of the C2CD4A gene justifies the inclusion of patients in the high-risk group and the need for preventive measures to prevent obesity in this population category.

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