

The role of the rs1421085 polymorphism in the pathogenesis of obesity

Rola polimorfizmu rs1421085 w patogenezie otyłości

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Słowa kluczowe: FTO, polimorfizm, otyłość, wskaźnik masy ciała.

Abstract

Introduction: Genome-wide association study (GWAS) has revealed the relationship between polymorphisms in the FTO gene and the risk of obesity. Based on the literature data, the authors selected the rs1421085 polymorphism of the FTO gene associated with an increased risk of obesity. Data on the Polish population are scarce.

Aim of the research: Analysis of the relationship between the rs1421085 FTO gene polymorphism and the risk of obesity among participants of the PONS study (Polish Norwegian Study).

Material and methods: The verification covered data from 200 Polish residents who participated in the PONS study. Peripheral blood lymphocyte DNA was isolated from the available blood samples using the Genomic Micro AX Blood Gravity Kit (A&A Biotechnology). The quality and quantity of DNA obtained were checked using a NanoDrop One/OneC (Thermo Scientific) spectrophotometer. A commercial set of primers and probes and the TaqMan™ Genotyping Master Mix (Thermo Scientific) using the QuantStudio 5 Real-Time PCR System device (Thermo Scientific) according to the manufacturer's protocol were used for genotyping the rs1421085 FTO gene.

Results: People with obesity had statistically significantly higher systolic blood pressure ($p < 0.001$), higher triglyceride concentration ($p < 0.001$), and lower total cholesterol ($p < 0.01$). In the serum of obese people statistically significantly higher glucose levels were found compared to the control group ($p < 0.001$). The genotype distribution for the rs1421085 FTO gene polymorphism in the entire study group was 29.5% for TT homozygotes, 45% for CT heterozygotes, 25.5% for CC homozygotes.

Conclusions: The rs1421085 polymorphism of the FTO gene does not show a statistically significant association with the occurrence of obesity in the Polish population. The lack of association between the rs1421085 polymorphism of the FTO gene and obesity may result from the small size of the examined group. Analyses of a larger group of respondents are necessary.

Streszczenie

Wprowadzenie: Całogenomowe badania asocjacji (GWAS) umożliwiły wykrycie związku pomiędzy polimorfizmami w genie FTO a ryzykiem wystąpienia otyłości. Na podstawie danych z piśmiennictwa autorzy pracy wytypowali polimorfizm rs1421085 genu FTO związany ze zwiększonym ryzykiem wystąpienia otyłości. Dane dotyczące populacji polskiej są nieliczne.

Cel pracy: Analiza zależności pomiędzy polimorfizmem rs1421085 genu FTO a ryzykiem wystąpienia otyłości wśród uczestników badania PONS (*Polish Norwegian Study*).

Materiał i metody: Weryfikacją objęto dane 200 mieszkańców Polski, uczestników badania PONS. Z udostępnionych próbek krwi wyizolowano DNA z limfocytów krwi obwodowej z zastosowaniem zestawu Genomic Micro AX Blood Gravity (A&A Biotechnology), jakość i ilość uzyskanego DNA sprawdzono za pomocą spektrofotometru NanoDrop One/OneC (Thermo Scientific). Do genotypowania polimorfizmu rs1421085 genu FTO zastosowano komercyjny zestaw starterów i sondy oraz TaqMan™ Genotyping Master Mix (Thermo Scientific) w wykorzystaniu urządzenia QuantStudio 5 Real-Time PCR System (Thermo Scientific) zgodnie z protokołem producenta.

Wyniki: Osoby z otyłością miały istotnie statystycznie wyższe ciśnienie skurczowe krwi ($p < 0,001$), wyższe stężenie trójglicerydów ($p < 0,001$), niższe stężenie cholesterolu całkowitego ($p < 0,01$). W surowicy osób otyłych stwierdzono istotnie statystycznie wyższe stężenia glukozy w stosunku do osób z grupy kontrolnej ($p < 0,001$). Rozkład genotypów dla polimorfizmu rs1421085 genu FTO w całej grupie badawczej wynosił odpowiednio: 29,5% – homozygoty TT, 45% – heterozygoty CT, 25,5% – homozygoty CC.

Wnioski: Polimorfizm rs1421085 genu FTO nie wykazuje znamiennej statystycznie zależności z występowaniem otyłości w populacji Polski. Brak korelacji pomiędzy polimorfizmem rs1421085 genu FTO a otyłością może wynikać z niewielkiej liczebności badanej grupy. Konieczne są analizy większej grupy osób.

Introduction

Obesity is a rapidly growing social problem affecting an increasing number of adults as well as children and adolescents. The occurrence of obesity is associated with a higher risk of developing, among other diseases, diabetes, cardiovascular disease or cancer. In the pathogenesis of this disease, the role of genetic factors is suggested, including polymorphisms of genes coding for leptin, adiponectin, FTO and TCF7L2 [1–5].

In 2007, due to genome-wide association study (GWAS), the association of polymorphisms in the FTO gene with the risk of obesity was detected [6]. The FTO gene occupies 400 bp on chromosome 16 at position q12.2 and consists of 9 exons.

Scientific studies indicate that the FTO gene has the greatest impact on the occurrence of obesity in polygenic predisposition to this disease [7, 8]. It is believed that polymorphisms in the FTO are much more associated with food consumption than with energy expenditure [8–10].

On the basis of literature data, the authors selected for genotyping an FTO gene polymorphism associated with an increased risk of obesity (rs1421085) [11, 12]. Data on the Polish population are scarce [12].

The aim of the research is to look for a significant correlation between the presence of the rs1421085 polymorphism of the FTO gene and the occurrence of overweight or obesity. The frequency of TT, CT and CC genotypes in a group of 100 obese people will be assessed compared to people with normal body weight (body mass index – BMI, etc.). The presence of CT and CC genotypes is associated with an increased risk of obesity, 1.3× and 1.7×, respectively [13]. According to data collected in the 100Genomes project, the frequency of genotypes is as follows: TT: 0.360 (181) CC: 0.225 (113) CT: 0.416 (209) [14].

The obtained results will allow us to deepen the understanding of the etiopathogenesis of such socially significant diseases as overweight and obesity, and will significantly affect the standards of clinical prac-

tice, allowing for more effective prevention of diabetes and obesity.

Aim of the research

Analysis of the relationship between the FTO rs1421085 gene polymorphism (NC_000016.10: g.53767042T> C) and the risk of obesity among participants of the PONS (*Polish Norwegian Study*).

Material and methods

In accordance with the right of access to PONS data, this study only used information about participants who had a permanent registration address in the city of Kielce. The verification covered data from 4.799 (33.7% of men) study participants aged 45–64. The purpose of the PONS project, i.e. “Establishment of infrastructure for population health research in Poland”, was the collection of data on the population to assess the determinants of health and the main causes of morbidity and mortality in Poland. The study protocol included the Health Status Questionnaire, medical examination, basic anthropometric measurements, and blood and urine sampling. The PONS study was conducted in 2010–2011, and the analysis of blood samples in 2019.

Verification of data

In the research, using the random number calculator from the whole group ($n = 4.799$), 98 participants were selected who were the test group, who, according to the World Health Organization (WHO) recommendation, had BMI indicating the presence of obesity ($BMI \geq 30 \text{ kg/m}^2$). In order to minimize the selection of bias between the study and control groups, the propensity score matching method (PSM) was used. A control group of 102 people with normal BMI ($18.5 \text{ kg/m}^2 \leq BMI < 25.0 \text{ kg/m}^2$) was fitted to the study group with similarity in the distribution of variables: age, sex, marital status, education, professional activity and smoking status. In the above group, there were no

obesity or other chronic metabolic and endocrine diseases that could predispose to overweight and obesity.

Anthropometric measurements

Body weight was measured with the Tanita S.C.-240 MA body composition analyzer with an accuracy of 0.1 kg. Body height was measured using the Seca height measure (with accuracy of 0.1 cm). Body mass index was calculated as the ratio of body weight (in kg) divided by the square of body height (in meters). The natural waist indentation or navel was a marker for measuring waist circumference (WC). Hip circumference was measured at the widest part of the hips. Waist to hip ratio (WHR) was calculated as the quotient of waist circumference and hip circumference. Systolic and diastolic blood pressure were measured using Omron (M3 Intellisense model) and calculated as the arithmetic mean of two consecutive readings taken by medical personnel.

Laboratory measurements

Total cholesterol (TC) was obtained by the cholesterol oxidase and cholesterol esterase method. High density lipoprotein concentration (HDL-C) was obtained by the direct method with TOOS and surfactant. Triglyceride concentration (TG) was determined by means of the phosphoglyceride oxidase-peroxidase method. Fasting blood glucose was determined by the enzymatic method with hexokinase. Laboratory tests were carried out with CB 350i Wiener Lab. Low density lipoprotein level (LDL-C) were estimated using the Friedewald equation for TG levels below 400 mg/dl.

Genotyping methods

From the available blood samples DNA was isolated from peripheral blood lymphocytes to perform genotyping using Genomic Blood AX Micro Gravity (A & A Biotechnology). The quality and quantity of DNA obtained was checked using a NanoDrop One/OneC spectrophotometer (Thermo Scientific). The polymorphism change study was performed using a commercial probe and primer kit for the FTO rs 1421085 gene (Thermo Scientific) and the TaqMan™ Genotyping Master Mix (Thermo Scientific) using a QuantStudio 5 RealTime PCR System (Thermo Scientific) according to the manufacturer's protocol.

Health Status Questionnaire

Self-reported socio-demographic and lifestyle-related information was based on the Health Status Questionnaire. The variables were classified as: marital status (single/in a relationship), education (lower level/upper level), professional activity (professional inactive/professional active), smoking status (never smoking/current smoking) and comorbidities (no/yes). The basic characteristics of the test and control groups are presented in Table 1.

Statistical analysis

The basic characteristics of the variables studied were presented in the form of means \pm standard deviations as well as numbers and percentages. The significance of the differences in the studied variables in the study and control groups was examined by the independent *t* test (continuous variables) or chi-square test (categorized variables). *P*-values < 0.05 were considered to be statistically significant. All statistical analyses were pursued in R version 3.5.3.

Results

The study group consisted of 200 people, including 154 (76.87%) women and 46 (23.13%) men. A hundred and forty-four respondents declared being in a relationship, 173 have a university degree, 85 work professionally. In an interview 122 patients declared smoking. Twenty-one (21.35%) subjects had diabetes, 80 (89.15%) subjects had hypertension, 18 (18.33%) had coronary heart disease, and 21 (21.35%) had circulatory failure. People with obesity had statistically significantly higher systolic blood pressure ($p < 0.001$), higher triglyceride concentration ($p < 0.001$), and lower total cholesterol ($p < 0.01$). In the serum of obese people statistically significantly higher glucose levels were found compared to the control group ($p < 0.001$). Obese people were also characterized by a higher incidence of diabetes, hypertension, coronary heart disease and circulatory failure. The results of anthropometric and biochemical tests are summarized in Table 1.

Genotype distribution for the rs1421085 FTO gene polymorphism

The genotype distribution for the rs1421085 FTO gene polymorphism in the entire study group was 29.5% for TT homozygotes, 45% for CT heterozygotes, and 25.5% for CC homozygotes. There were no statistically significant differences between the occurrence of a given polymorphism and the presence of obesity in the studied group of women and men (Table 2).

The distribution of alleles in the above study complies with Hardy Weinberg's law. The frequency of the dominant allele (T) is 7.96% higher in the control group compared to the study group.

Discussion

The research results among patients with an abnormal BMI showed significantly higher incidence of higher blood pressure, higher triglycerides, glucose and lower total cholesterol. Hypertension, diabetes, circulatory failure and ischemic heart disease were also more commonly reported.

Results similar to those mentioned above were also obtained by Woźny *et al.* [12]. People with over-

Table 1. Basic characteristics of studied groups

Parameter	Study group (n = 98)	Control group (n = 102)	P-value
Age [years]	57.27±4.72	57.08±3.73	> 0.05
Sex/female, n (%)	69 (70.41)	85 (83.33)	> 0.05
Marital status/in a relationship, n (%)	69 (70.41)	75 (73.53)	> 0.05
Education/upper level, n (%)	79 (80.61)	94 (92.16)	> 0.05
Professional active, n (%)	38 (38.78)	46 (45.10)	> 0.05
Smoking, n (%)	62 (63.27)	60 (58.82)	> 0.05
Height [cm]	162.17 ±8.72	163.13 ±7.79	> 0.05
Weight [kg]	106.77 ±12.99	60.02 ±5.93	< 0.001
BMI [kg/m ²]	40.53 ±3.12	22.50 ±0.30	< 0.001
WC [cm]	115.88 ±10.40	76.99 ±6.89	< 0.001
SBP [mm Hg]	150.49 ±21.07	129.75 ±17.44	< 0.001
DBP [mm Hg]	86.59 ±12.11	77.02 ±9.51	< 0.001
FBG [mg/dl]	112.93 ±26.84	90.80 ±9.80	< 0.001
TC [mg/dl]	198.46 ±34.76	222.03 ±36.08	< 0.001
HDL-C [mg/dl]	51.63 ±12.59	67.83 ±13.81	< 0.001
LDL-C [mg/dl]	117.41 ±29.75	135.99 ±30.44	< 0.001
TG [mg/dl]	150.54 ±78.33	91.02 ±42.16	< 0.001
Diabetes mellitus	19 (19.39)	2 (1.96)	< 0.001
Hypertension	72 (73.47)	8 (7.84)	< 0.001
Stroke	2 (2.04)	No	Nc
Ischemic heart disease	17 (17.35)	1 (0.98)	< 0.001
Circulatory failure	19 (19.39)	2 (1.96)	< 0.001
Asthma	8 (8.16)	3 (2.94)	> 0.05
COPD	4 (4.08)	1 (0.98)	> 0.05
Cancer	7 (7.14)	No	Nc

Data are presented as mean ± standard deviation unless stated otherwise. BMI – body mass index, WC – waist circumference, SBP – systolic blood pressure, DBP – diastolic blood pressure, FBG – fasting blood glucose, TC – total cholesterol, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, TG – triglyceride, COPD – chronic obstructive pulmonary disease, no – not observed, nc – not calculated.

Table 2. Distribution of genotypes in studied groups by sex

Variable	Females		Males		All	
	Study group	Control group	Study group	Control group	Study group	Control group
TT	21 (30.43)	24 (28.24)	7 (24.14)	7 (41.18)	28 (47.46)	31 (52.54)
CT	29 (42.03)	40 (47.06)	15 (51.72)	6 (35.29)	44 (48.89)	46 (51.11)
CC	19 (27.54)	21 (24.71)	7 (24.14)	4 (23.53)	26 (50.98)	25 (49.02)
P-value	NS		NS		NS	

NS – not significant.

weight and obesity have certain metabolic disorders compared to people without obesity. Among the metabolic disorders in the group of obesity, the authors mention a significantly higher incidence of hypertension and diabetes, higher systolic and diastolic blood pressure, and higher fasting glucose [12]. Diabetes occurs in people who are overweight and obese much more often than in the general population, and its incidence increases with the degree of obesity. The occurrence of diabetes and other types of carbohydrate metabolism disorders in obesity is caused by many pathophysiological factors. Undoubtedly, insulin resistance associated with obesity is the most important factor. When considering the occurrence of diabetes in obesity, the type of obesity should be taken into account. The development of diabetes is particularly favored by the so-called polymetabolic syndrome, especially abdominal android obesity. A larger amount of abdominal fat accelerates the development of diabetes due to the greater generation of insulin resistance and overproduction of fatty acids (lipotoxicity). However, these relationships are not linear and are also associated with the degree of overall overweight [5].

The involvement of environmental and genetic factors in the pathogenesis of obesity is suggested. Identification of mutations or polymorphisms in genes may contribute to understanding the etiology of the disease. In the search for these genetic changes, the so-called GWA study has been a very useful tool in recent years. It is a project that aims to identify genetic differences that shape variability in disease susceptibility. It is based on a comparison of polymorphic changes in people belonging to the study and control group. Detection of statistically significant differences allows one to determine the polymorphic relationship with a given disease. In GWA studies, single nucleotide polymorphisms (SNPs) are analyzed [15].

The HapMap Project also brings a lot of relevant information regarding polymorphic changes and related diseases. The goal of this international project is to identify and determine the incidence and correlation of gene variants that shape variability in disease incidence. The HapMap Project bases its research on population groups from parts of Africa, Europe and Asia. Projects such as the Genome-Wide Association and the HapMap Project offer the chance to significantly speed up genetic testing and to learn about the genetic aspects of many diseases. Recent discoveries related to the FTO gene as the one responsible for obesity are very promising. The genome-wide association study showed a link between the simultaneous occurrence of polymorphisms such as the rs1421085 FTO gene and rs17782313 MC4R gene and obesity. Research results from 4,700 Finnish residents and more than 3,000 French people have shown that carriers of three or four risk alleles (the FTO gene and MC4R) are three times more susceptible to developing obesity, espe-

cially during childhood. A simultaneous carrier of the FTO and MC4R gene risk allele has significantly increased risk of obesity and type 2 diabetes. It was also found that low physical activity deepens the effect of rs1421085 polymorphism on the development of obesity. Physically inactive carriers of the risk allele of the FTO gene had a higher BMI value, while active carriers had comparable BMI to non-carriers. It was also investigated whether there is a relationship between other FTO gene polymorphisms – rs1421085 and rs17817449 – and the occurrence of obesity and biochemical features associated with it. Among surveyed 900 overweight residents (mean BMI value = 27.6 kg/m²) from Quebec, it was found that there is a relationship between the polymorphisms studied and BMI, body weight and waist circumference, as well as insulin sensitivity and leptin concentration [15].

Albuquerque *et al.* also found significant associations between rs1421085 polymorphism and body weight, BMI, waist circumference and hip circumference in Portuguese children [16].

Kopelman *et al.* reported that obesity-related quantitative features such as body weight, waist circumference, and fat mass were significantly increased in A allele carriers [17].

Cha *et al.* reported that the rs1421085 C allele was significantly associated with increased BMI [18]. Douglas *et al.*, in turn, reported that FTO polymorphisms are associated with a change in the feeling of satiety and may play a role in regulation of food intake [19].

The authors of the study examined the relationship between rs1421085 polymorphism and obesity in the Polish population. Despite the confirmed literature data, there was no significant relationship between FTO gene polymorphisms and obesity in the study group.

Also, Solak *et al.* did not find a significant relationship when comparing rs9939609 genotypes (TT, TA, AA) and rs1421085 genotypes (TT, TC, CC) in terms of anthropometric measurements and body composition results [20]. Ohashi *et al.* reported that Oceanic populations showed no significant association between FTO polymorphisms, including rs1421085 and BMI, as opposed to European populations [21]. In addition, they suggested that population frequencies in Oceanic populations were similar to those of southwestern and eastern Asia. The Anatolian peninsula (Turkey) served as a junction connecting the Middle East, Europe and Central Asia, and thus was subject to large population movements [21].

The authors of the study did not find any relationship between FTO polymorphisms and obesity in the study group. According to the discussion, the research on this topic is divergent. The reason for the discrepancy may be due to regional differences, a limited study group, lifestyle or age. However, the results of our own research, similarly to other authors, clearly

show that the risk of developing cardiovascular complications in obese people is much higher than those maintaining a normal body weight [22, 23]. It is therefore important to consider what to do to prevent overweight and obesity developing.

Conclusions

The rs1421085 polymorphism of the FTO gene does not show a statistically significant association with the occurrence of obesity in the Polish population. The lack of association between the rs1421085 polymorphism of the FTO gene and obesity may result from the small size of the examined group. Analyses of a larger group of respondents are necessary.

Conflict of interest

The authors declare no conflict of interest.

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