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Lack of an association between *FTO* polymorphism and changes in obesity-related traits in response to an aerobic training program

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F Literature Search
G Funds Collection

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abstract

Background: The first described obesity-susceptibility gene, with the largest influence on increased BMI to date, was the fat mass and obesity-associated (*FTO*) gene. However, the role of *FTO*'s potential modifying effect on changes in obesity-related parameters achieved through a training program is still unclear.

The aim of the present study was to examine whether *FTO* A/T polymorphism (rs9939609) influences the effects of a training program.

Material and methods: Accordingly, we studied the allele and genotype distribution in a group of 55 male participants measured for selected body mass and composition, as well as biochemical parameters before and after the realization of a 10-week aerobic training program.

Results: The body mass (F1,52 = 12.4, p = 0.0009, 61.04 ± 6.55 vs 60.49 ± 6.48), body mass index (BMI; F1,52 = 7.8, p = 0.007, 21.91 ± 2.43 vs 21.74 ± 2.35), basal metabolic rate (BMR; F1,52 = 14.7, p = 0.0003, 1452 ± 67 vs 1447 ± 67), fat mass percentage (FM%; F1,52 = 12.6, p = 0.0008, 24.73 ± 4.83 vs 23.91 ± 4.81), fat mass (FM; F1,52 = 19.5, p = 0.00005, 15.37 ± 4.51 vs 14.69 ± 4.52), and high-density lipoprotein level (HDL; F1,52 = 5.7, p = 0.020, 60.85 ± 12.08 vs 58.12 ± 12.81) changed significantly during regular physical activity (PA). However, we did not observe any main effects of genotype as well as the genotype x training interactions.

Conclusions: In conclusion, our data did not show the effect of the A allele of the *FTO* polymorphism (rs9939609) on higher obesity risk and the association between PA and the polymorphism on the chosen variabilities. However, more experiments are needed to establish this complicated association between the *FTO* gene, obesity, and PA in differential study populations.

Key words: *FTO* gene, sport genetics, physical activity, body composition.

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INTRODUCTION

The number of people with obesity is increasing globally across all age groups, and it has become an important public health problem [1]. It is well established that individual susceptibility to an excess of body weight gain is the consequence of an imbalance between energy consumption and energy expenditure. This disproportion can be influenced by both caloric intake and physical activity (PA), which may be dependent on developmental, behavioral, and environmental factors [2, 3]. Additionally, genetic components play a significant role in the development of obesity, since there are genes involved in regulation of energy expenditure, appetite, lipid and carbohydrate metabolism, adipogenesis, thermogenesis, and cell differentiation [4, 5]. The reported heritability of obesity ranges from 31% to even 90% [6].

Currently, genome-wide association studies (GWASs) have shown single nucleotide polymorphisms (SNPs) in various genes, including the fat mass and obesity-associated gene (FTO), that are strongly associated with the development of obesity [7, 8]. The FTO gene is located in chromosome region 16q12.2 [7] and its product is a 2-oxoglutarate (2-OG) Fe (II) dependent demethylase [8]. This nuclear enzyme is able to remove methyl groups from DNA and RNA nucleotides in vitro with the main affinity for single stranded RNA molecules [9, 10]. The FTO gene expression is associated with control of daily food intake, nutrient preference, and energy balance [9].

The FTO polymorphism with T to A change (rs9939609) is one of the most often investigated genetic variants in the context of genetic conditioning for a predisposition to obesity. This SNP is located in the first intron of the gene, which is linked to a 20–30% higher risk of an excess of body weight gain. It has been shown that the carrier status of the risk (A) allele is related to increases in body mass of an average of 1.2 to 3.0 kg [7].

With numerous studies which have confirmed that the FTO genetic variants effect on weight gain, it is of growing interest whether these genetic effects on obesity are modified by lifestyle factors such as PA. Some studies have shown that the FTO effect on obesity-related traits is attenuated by an average of 30–80% in physically active individuals compared to sedentary individuals [9, 11, 12, 13, 14, 15]. However, some studies have not observed an association between PA and FTO polymorphisms on obesity [16, 17, 18, 19].

The aim of the present study was to examine whether the FTO A/T polymorphism (rs9939609) influences the effects of a training program. Accordingly, we studied the allele and genotype distribution in male participants measured for selected body mass and composition, as well as biochemical parameters before and after the realization of a 10-week aerobic training program.

MATERIAL AND METHOD

ethics statement

The procedures followed in the study were conducted ethically according to the principles of the World Medical Association Declaration of Helsinki and ethical standards in sport and exercise science research.

participants

55 Polish Caucasian men aged 24 ± 1 years (range 20–28) were included in the study. None of these individuals had engaged in regular physical activity in the previous 6 months.

body composition measurements

Before and after the completion of a 10-week training period, all participants were measured for selected body mass and body composition variables, which were assessed using the bioimpedance method (Tanita electronic scales).

biomechanical and hematological analyses

Fasting blood samples were obtained in the morning from the elbow vein before the start of an aerobic fitness training program and repeated at the 12th week of this training program. The examined parameters were as follows: total cholesterol (TC), triglycerides (TGL), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and glucose.

training phase

The training stage was preceded by a week-long familiarization stage, when the examined men exercised 3 times a week for 40 minutes at an intensity of about 50% of their maximum heart rate (HR_{max}). After the week-long familiarization stage, the proper training started. Each training unit consisted of a warm-up routine (10 minutes), the main aerobic routine (40 minutes), and stretching and breathing exercises (10 minutes).

genetic analyses

DNA was extracted from the buccal cells using Extractme Genomic DNA (Blirt, Poland) according to the manufacturer's protocol. All samples were genotyped in duplicate using an allelic discrimination assay on a CFX Connect Real-Time System (Bio-Rad, Germany) instrument with TaqMan® probes. To discriminate FTO rs9939609 alleles, TaqMan® Pre-Designed SNP Genotyping Assays were used (Applied Biosystems, USA) (assay ID: C_30090620_10), including primers and fluorescently labelled (FAM and VIC) MGBTM probes to detect alleles.

statistical analyses

Allele frequencies were determined by gene counting. A chi-square test was used to test the Hardy-Weinberg equilibrium. To test the influence of the FTO A/T polymorphism on training response, the 2×2 mixed-design ANOVA test was used. Additionally, the Kolmogorov-Smirnov test was used to check for data normality. The level of statistical significance was set at $p < 0.05$.

RESULTS

The FTO genotype counts (AA: 16 [29%], AT: 26 [47%], TT: 13 [24%]) were consistent with Hardy-Weinberg expectations (AA: 15.3, AT: 27.4, TT: 12.3, $\chi^2 = 0.15$, $p = 0.699$). The results of factorial ANOVA with repeated measures are summarized in Table 1. The body mass ($F_{1,52} = 12.4$, $p = 0.0009$, 61.04 ± 6.55 vs 60.49 ± 6.48), body mass index (BMI; $F_{1,52} = 7.8$, $p = 0.007$, 21.91 ± 2.43 vs 21.74 ± 2.35), basal metabolic rate (BMR; $F_{1,52} = 14.7$, $p = 0.0003$, 1452 ± 67 vs 1447 ± 67), fat mass percentage (FM%; $F_{1,52} = 12.6$, $p = 0.0008$, 24.73 ± 4.83 vs 23.91 ± 4.81), fat mass (FM; $F_{1,52} = 19.5$, $p = 0.00005$, 15.37 ± 4.51 vs 14.69 ± 4.52), and high-density lipoprotein level (HDL; $F_{1,52} = 5.7$, $p = 0.020$, 60.85 ± 12.08 vs 58.12 ± 12.81) significantly changed during training. However, we

did not observe any main effects of the genotype as well as the genotype x training interactions (Table 1).

Table 1. Training adaptation with respect to the FTO A/T polymorphism (rs9939609) (ANOVA with repeated measures)

Parameter	AA (n=16)		AT (n=26)		TT (n=13)		Genotype	Training	Genotype x training
	before training	after training	before training	after training	before training	after training			
Body mass (kg)	61.78±5.64	61.18±5.12	61.60±7.15	61.07±7.23	59.00±6.39	58.49±6.44	0.445	0.0009	0.972
BMI (kg x m ⁻²)	22.43±2.60	22.26±2.45	21.96±2.43	21.74±2.35	21.16±1.78	21.09±1.69	0.398	0.007	0.568
BMR (kcal)	1460±59	1454±54	1460±70	1454±72	1429±70	1423±72	0.373	0.0003	0.983
FM% (%)	24.61±3.91	23.72±4.14	25.20±5.04	24.45±4.93	23.91±5.65	23.08±5.55	0.712	0.0008	0.967
FM (kg)	15.36±3.61	14.53±3.49	15.85±4.96	15.24±5.08	14.42±4.75	13.81±4.63	0.651	0.00005	0.797
FFM (kg)	46.23±2.40	46.54±2.65	45.85±2.64	45.82±2.60	44.61±2.29	44.68±2.42	0.172	0.440	0.614
TBW (kg)	33.86±1.77	34.01±1.95	33.22±2.82	33.49±1.90	33.43±3.32	32.72±1.76	0.528	0.717	0.310
TC (mg/dL)	172±20	174±25	171±26	170±26	182±22	188±40	0.205	0.455	0.753
TGL (mg/dL)	93±28	97±65	86±25	81±21	95±30	96±29	0.305	0.958	0.784
HDL (mg/dL)	59±12	57±13	61±12	60±12	63±13	56±15	0.870	0.020	0.166
LDL (mg/dL)	94±22	97±18	93±22	94±23	100±20	113±35	0.187	0.059	0.313
Glucose (mg/dL)	72±9	71±9	72±9	73±10	75±7	69±8	0.836	0.055	0.080

Mean±standard deviation; p values (ANOVA) for main effects (genotype and training) and genotype x training interaction; bold p values - statistically significant differences (p < 0.05); BMI - body mass index; BMR - basal metabolic rate; FM% - fat mass percentage; FM - fat mass; FFM - fat free mass; TBW - total body water; TC - total cholesterol; TGL - triglycerides; HDL - high-density lipoprotein; LDL - low-density lipoprotein

DISCUSSION

Our main findings are that the common FTO A/T polymorphism (rs9939609) was not associated with significant changes of body mass and composition, as well as biochemical parameters in young Caucasian males. We did not show an association between PA and the FTO A/T polymorphism on the chosen variabilities either.

The described results are inconsistent with most of the previous studies, which described the association between risk (A) allele and higher body mass parameters in female and male representing multiple populations, different age, and health conditions [7, 8, 19]. Frayling et al. revealed that the carrier status of 1 or 2 copies of the A allele is linked with increases in body mass of an average of 1.2 to 3.0 kg, respectively [7].

As previously mentioned, the energy imbalance influenced by both PA and food intake contributes to the obesity epidemic and may interact with genetic effects to modify the risk for excess of body weight gain [2]. A growing number of studies have currently demonstrated whether there are associations between the lifestyle factors and FTO polymorphisms on obesity risk. Physical inactivity was linked to an increased risk of FTO genetic predisposition to obesity while physically active individuals showed a lower risk for obesity. These studies indicate that the A allele is an unfavorable factor for achieving the desired training-induced body mass measurement changes [9, 11, 12, 13, 14, 15]. The above described findings were confirmed by a large-scale meta-analysis of 45 studies involving 218,166 adults and 19,268 children that showed that the FTO effect on obesity risk is approximately 30% smaller in physically active than in sedentary people, at least among adults [12]. Li et al. genotyped 12 SNPs, including FTO polymorphism, in a population of 20,430 European participants and also revealed that PA is associated with a 40% reduction in the genetic predisposition to obesity [11].

On the other hand, many studies have not shown the association between PA and FTO polymorphisms on obesity-related traits [16, 17, 18, 19, 20]. The meta-

analysis of 8 studies involving 9,563 adults showed that carriage of the FTO A allele does not influence changes in adiposity measures in response to weight loss intervention, compared with a control group [20]. Likewise, the present study did not show an association between PA and the FTO A/T polymorphism on the body mass and composition, as well as biochemical parameters in young Caucasian males. These findings are consistent with a previous Polish study involving 201 young Caucasian females. Leońska-Duniec et al. did not show the gene \times PA interaction, but revealed an association between the FTO A/T polymorphism and increased BMI [19]. Similarly, in studies performed on Swedish and Finnish individuals, authors revealed that the A allele was linked to higher BMI, but they found no interaction between the FTO polymorphism and PA on BMI levels [16, 17, 18].

Kilpeläinen et al. described a geographic difference in the association between FTO and PA on obesity-related traits. In particular, the interaction was stronger in North America populations than in European populations which may explain inconsistent findings obtained by scientists from various parts of world. Unfortunately, reasons for the observed geographical difference are unclear [12]. It has also been indicated that smoking and eating habits may reduce the FTO effects on the obesity risk. The first intron of the FTO gene has been associated with methylation capability, so some researchers have suggested that this region may be sensitive to epigenetic effects [9].

The underlying biological mechanism for how the FTO polymorphisms contributes to higher risk of overweight and obesity remains mostly unclear. There is some evidence suggesting that SNPs within intron 1 and 2 may modify the function of adipocytes from substrate storage to fuel utilization through increased thermogenesis. The noncoding variants may affect the thermogenic capacity of cells, and consequently result in differences in human body mass. Claussnitzer et al. described an enhancer region in the adipocytes' FTO gene that has control over homeobox regulatory genes (IRX3 and IRX5). They demonstrated cell-autonomous effects of IRX3 and IRX5 by means of their genetic knockdown to restore thermogenesis in fat cells from individuals at high genetic risk for obesity. In contrast, overexpression of the proteins in adipose tissue from people without the genetic risk resulted in reduced thermogenesis and mitochondrial function [21]. Many authors have tried to explain the association between the FTO polymorphisms and PA, but there is no strong evidence on whether this may be due to complicated interactions between multiple genes that may control PA or dietary intake or to gene-environment interplay [22, 23].

CONCLUSIONS

In conclusion, our data did not confirm the effect of the risk (A) allele of the FTO A/T polymorphism (rs9939609) on higher body mass and composition, as well as biochemical parameters in young Caucasian males. Similarly, we did not find an association between PA and the FTO A/T polymorphism on the chosen variabilities. However, we want to point out that promoting PA, particularly in genetically predisposed individuals, is a key step towards controlling the obesity epidemic. More experiments are needed to establish this complicated association between FTO gene, obesity, and PA in differential study populations.

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