Assessing effect of interaction between the FTO A/T polymorphism (rs9939609) and physical activity on obesity-related traits

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Abstract

Background: The first described obesity-susceptibility gene was the fat mass and obesity-associated (FTO) gene. However, knowledge about FTO’s potential modifying effect on changes in body weight achieved through a training program is still limited. We decided to study the association between the FTO A/T polymorphism (rs9939609) and obesity-related traits. Additionally, we investigated whether body mass and body composition, as well as metabolic variables observed in physically active participants, are modulated by the FTO polymorphism.

Methods: A group of 201 young Polish women were recruited for the study. The genotype distribution was examined in participants measured for selected changes before and after the completion of a 12-week training program.

Results: Our results confirm the association between the common FTO A/T polymorphism and increased BMI. Subjects with AA and AT genotypes had higher BMI during the entire study period compared with the TT genotype. Although parameters such as BMI, basal metabolism rate, tissue independence, fat mass percentage, fat mass, fat-free mass, total body water, high-density lipoprotein, and glucose changed significantly during the training program, none of the examined parameters changed significantly across the FTO genotypes (genotype × training interaction).

Conclusion: We confirm an association between the FTO A/T polymorphism and increased BMI; this polymorphism is therefore a candidate for influencing obesity and other disease-related phenotypes. Although the gene × physical activity interaction was not shown, we want to point out that promoting physical activity is an important approach to controlling the increasing obesity epidemic.

Keywords: Exercise; FTO gene; Gene × physical activity interaction; Obesity-related traits; Polish women; Sport genetics

1. Introduction

An excess of human body weight gain owing to an increase in adipose tissue is the consequence of an imbalance between energy consumption and energy expenditure. This imbalance can be influenced by both caloric intake and physical activity (PA), which may be dependent on behavioral, developmental, and/or environmental factors. Additionally, genetic factors play a fundamental role in the regulation of body weight. It has been shown that the heritability of body mass index (BMI) ranges from 40% to 70%. However, Li et al. revealed that living a physically active lifestyle is associated with a 40% reduction in genetic predisposition to obesity and emphasized the importance of exercise in prevention of excess body weight.

Since 2007, genome-wide association studies have identified numerous genetic loci that are obviously linked with obesity-related traits. The first described obesity-susceptibility gene, with the largest influence on increased BMI to date, was the fat mass and obesity-associated (FTO) gene. Recently, studies concerning the relationship between FTO and weight have been frequently replicated for BMI, obesity risk, body fat percentage, waist circumference, and other obesity traits. Subsequently, these associations are replicable across multiple ethnic populations as well as different age groups. A common FTO A/T polymorphism (rs9939609) is one of the most
frequently investigated genetic markers in the context of genetic conditioning for a predisposition to obesity.

The human FTO gene is located in chromosome region 16q12.2 and is expressed mainly in key brain regions, such as the hypothalamus, skeletal muscle, and adipose tissue. The product of the gene is a nuclear protein, 2-oxoglutarate Fe(II) dependent demethylase; however, little is known about the exact physiological function of the protein. The latest studies suggest that the enzyme is able to remove methyl groups from DNA and RNA nucleotides in vitro, with the highest affinity for single-stranded RNA molecules. It was hypothesized that the FTO gene can influence the activity of pathways controlling not only daily food intake but also nutrient preference.

The FTO polymorphism with T to A change is located in the first intron of the gene, which has been shown to be strongly associated with increased risk of excess body weight. The A allele, known as a risk allele, has been shown to be associated with increased energy intake, increased intake of dietary fat or protein, increased appetite and reduced satiety, poor eating habits, and loss of control over eating. As a consequence, it is related to a higher risk of excessive weight gain and obesity, increasing the risk by 20%–30%. Moreover, the TA heterozygous genotype has been shown to be a strong risk factor for metabolic syndrome in association with female gender and, together with total cholesterol, basal metabolic rate (BMR), and age, accounted for 21% of the risk for metabolic syndrome in white populations.

The FTO polymorphism does not influence PA level, yet several studies reported that its obesity-increasing effect may be suppressed in physically active individuals. Several studies have reported that the FTO effect on obesity-related traits is reduced by approximately 30% in physically active compared with sedentary adults. In other studies, the effect size of FTO variants is up to 80% lower in physically active individuals. However, not all studies have demonstrated this correlation between PA interaction.

Additionally, there are still many questions about its biological role, the association between FTO polymorphisms and obesity, and how the FTO risk alleles influence protein, and the interaction between the gene’s effect and PA.

The aim of the present study was to examine the association between the FTO A/T polymorphism (rs9939609) and obesity-related traits. Additionally, we decided to check whether body mass and body composition, as well as metabolic variables observed in physically active participants, are modulated by the FTO polymorphism. Therefore, we studied the allele and genotype distribution in a group of young Polish women measured for selected body mass and body composition as well as obesity-related metabolic traits before and after a 12-week training program to see whether there is an interaction between genotype and training.

2. Materials and methods

2.1. Ethics statement

All the procedures followed in the study were approved by the Ethics Committee of the Regional Medical Chamber in Szczecin, Poland (approval No. 09/KB/IV/2011), and were conducted ethically according to the principles of the World Medical Association Declaration of Helsinki and ethical standards in sport and exercise science research. Furthermore, the experimental procedures were conducted in accordance with the set of guiding principles for reporting the results of genetic association studies defined by the Strengthening the Reporting of Genetic Association studies statement. All participants were given a consent form and a written information sheet concerning the study, which provided all pertinent information (purpose, procedures, risks, and benefits of participation). The potential participant had time to read the information sheet and the consent form. After ensuring that the participant had understood the information, every participant gave written informed consent (signed consent form) to genotyping with the understanding that the testing was anonymous and that the obtained results would be confidential.

2.2. Participants

Two hundred and one white women aged 21 ± 1 years (mean ± SD, range 19–24 years) met the inclusion criteria and were included in the study. None of these individuals had engaged in regular PA in the previous 6 months. They had no history of any metabolic or cardiovascular diseases. Participants were nonsmokers and refrained from taking any medications or supplements known to affect metabolism. Prior to the start of the training phase, participants were asked to maintain a balanced diet of approximately 2000 kcal/day.

2.3. Physical exercise training protocol

The training stage was preceded by a week-long familiarization stage, when the examined women exercised 3 times/week for 30 min, at an intensity of about 50% of their maximum heart rate (HRmax). After the week-long familiarization stage, the proper training started. Each training unit consisted of a warm-up routine (10 min), the main aerobic routine (43 min), and a cool-down phase (stretching and breathing exercise for 7 min). The main aerobic routine was a combination of 2 alternating styles—low and high impact. Low-impact style is composed of movements with at least 1 foot on the floor at all times, whereas high-impact styles include running, hopping, and jumping with a variety of flight phases. Music of variable rhythm intensity (tempo) was incorporated into both styles. A 12-week program of low- and high-impact aerobics was divided as follows: (1) 3 weeks (9 training units), 60 min each, at about 50%–60% of HRmax, tempo 135–140 beats per minute (bpm); (2) 3 weeks (9 training units), 60 min each, at 60%–70% of HRmax, tempo 140–152 bpm; (3) 3 weeks (9 training units), 60 min each with an intensity of 65%–75% of HRmax, tempo 145–158 bpm; and (4) 3 weeks (9 training units), 60 min each with an intensity of 65%–80% of HRmax, tempo 145–160 bpm. All 36 training units were administered and supervised by the same instructor.

2.4. Body composition measurements

All participants were measured for selected body mass and body composition variables before and after the completion of a 12-week training period. Body mass and body composition
were assessed with the bioimpedance method (testing the body’s inherent resistance to an electrical current) using a Tanita TBF-300M electronic scale (Tanita, Arlington Heights, IL, USA). The device was plugged in and calibrated to account for the weight of clothing (0.2 kg). Afterward, data regarding age, body height, and sex of the subject were inserted. Then the subjects stood on the scale with their bare feet on the marked places. The device analyzes body composition based on differences in the ability of different body tissues to conduct electrical current (different resistance) owing to differing water content. Body mass and body composition measurements taken with the use of the Tanita electronic scale are as follows: total body mass (kg), fat-free mass (kg), fat mass (kg), fat mass percentage (%), BMI (kg/m²), tissue impedance (Ω), total body water (kg), and BMR (kJ or kcal).

2.5. Biochemical and hematological analyses

Fasting blood samples were obtained in the morning from the elbow vein. Blood samples from each participant were collected in 2 tubes. For biochemical analyses, a 4.9-mL S-Monovette tube with ethylenediaminetetraacetic acid (K3EDTA; 1.6 mg EDTA/mL blood) and separating gel (Sarstedt AG & Co., Nümbrecht, Germany) were used. For complete blood count, a 2.6-mL S-Monovette tube with K3EDTA (1.6 mg EDTA/mL blood) was used. Blood samples for biochemical analyses were centrifuged at 300 × g for 15 min at room temperature to receive blood plasma. Biochemical and hematological analyses were performed before the start of the aerobic fitness training program and repeated at the 12th week of the training program (after the 36th training unit). The analyses were performed immediately after the blood collection. Complete blood count, including measurement of white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemo- globin, mean corpuscular hemoglobin concentration, and total platelet level, was obtained using Sysmex K-4500 hematology analyzer (Sysmex, Kobe, Japan). All biochemical analyses were conducted using the A15 random access automatic biochemical analyzer for clinical chemistry and turbidimetry (Biosystems S. A., Barcelona, Spain). Blood plasma was used to determine lipid profile: triglycerides (Tg), cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) concentrations. Plasma Tg and cholesterol concentrations were determined using the diagnostic colorimetric enzymatic method according to the manufacturer’s protocol (Biomaxima S.A., Lublin, Poland). The manufacturer’s declared intra-assay coefficient of variation (CV) for the method was <2.5% and <1.5% for the Tg and cholesterol determinations, respectively. HDL plasma concentration was determined using human anti-β-lipoprotein antibody and the colorimetric enzymatic method according to the manufacturer’s protocol. The manufacturer’s declared intra-assay CV for the method was <1.5%. Plasma concentrations of LDL were determined using a direct method according to the manufacturer’s protocol (PZ Cormay S.A., Lomianki, Poland). The manufacturer’s declared intra-assay CV of the method was 4.97%. All analysis procedures were verified with the use of multiparametric control serum (BIOLABO S.A.S, Maizy, France) as well as control serum of normal-level (BioNormL) and high-level (BioPathL) lipid profiles (BioMaxima S.A.).

2.6. Genetic analyses

The buccal cells donated by the subjects were collected in Resuspension Solution (GenElute Mammalian Genomic DNA Miniprep Kit; Sigma-Aldrich, St. Louis, MO, USA) with the use of sterile foam-tipped applicators (Puritan Medical Products, Guilford, ME, USA). DNA was extracted from the buccal cells using a GenElute Mammalian Genomic DNA Miniprep Kit (Sigma-Aldrich) according to the manufacturer’s protocol. All samples were genotyped in duplicate using an allelic discrimination assay on a StepOne Real-Time Polymerase Chain Reaction instrument (Applied Biosystems, Waltham, MA, USA) as previously described.20

2.7. Statistical analyses

Allele frequencies were determined by gene counting. A χ² test was used to test the Hardy–Weinberg equilibrium. Normality was evaluated by means of the Kolmogorov-Smirnov test as well as visual inspection of the histograms. Because there were between-subject (FTO genotype) and within-subject factors (training status), the 2 × 2 mixed-design analysis of variance with repeated measures was used to test the influence of the FTO A/T polymorphism on training response. Two main effects (the genotype: TT vs. AA + AT, and training, before vs. after) and a genotype × training interaction were determined. The post hoc Fisher’s least significant difference test was used. The level of statistical significance was set at p < 0.05.

3. Results

The FTO genotypes were in Hardy-Weinberg equilibrium (p = 0.105). To examine the hypothesis that the FTO A/T polymorphism modulates training response, we conducted a mixed 2 × 2 analysis of variance with 1 between-subject factor (FTO genotype: TT vs. AA + AT) and 1 within-subject factor (before training vs. after training) (Table 1). Except for cholesterol, Tg, and LDL, all parameters altered significantly during training; however, these changes did not differ with respect to the FTO genotypes. Thus no genotype × training interactions were found. The main effects of genotype were demonstrated for BMI (F(1,199) = 4.1, p = 0.045) and for tissue impedance (F(1,199) = 7.9, p = 0.006) (Table 1). Specifically, the carrier status of 1 or 2 copies of the A allele was associated with higher BMI before (21.8 ± 2.3 vs. 21.1 ± 2.2, p = 0.038) but not after training (21.6 ± 2.3 vs. 20.9 ± 2.2, p = 0.055), compared with TT homozygotes. Conversely, the carriers of at least 1 A allele had lower tissue impedance, both before (543.2 ± 54.8 vs. 565.0 ± 69.5, p = 0.019) and after training (529.1 ± 49.9 vs. 556.9 ± 74.1, p = 0.003).

4. Discussion

Obesity is a complex heterogeneous abnormality that has a well-confirmed genetic basis but requires environmental influences, caloric intake, and PA to develop. Numerous studies
have showed the role of lifestyle, including exercise and dietary factors, in regulation of body weight. Nevertheless, the problem is in defining genes and polymorphisms related to obesity and describing by which mechanisms they exert their effect. Another important problem is the role of the gene variants in the characteristics and range of the body’s adaptive response to training. Currently, some studies have tried to answer these questions; however, they still represent only the first steps toward an understanding of the genetic factors that influence obesity-related traits and gene variants x PA interactions, so continuing research is necessary.

Our results confirm the association between the common FTO A/T polymorphism (rs9939609) and higher BMI; the polymorphism is thus a candidate for influencing obesity and other disease-related phenotypes. Subjects with AA and AT genotypes had higher BMI during the entire study period compared with the TT genotype. This result may be supported by many previous studies, which described this association in multiple populations including children, adolescents, and adult men and women. The authors showed that carrier status of 1 or 2 copies of the risk allele is linked with average increases in body mass of 1.2 kg and 3.0 kg, respectively. In addition, the BMI-increasing allele was associated with higher risk of type 2 diabetes, heart failure, coronary heart disease, hypertension, dyslipidemia, metabolic syndrome, and mortality. The latest studies suggest that the FTO gene contributes to weight gain mainly by influencing the activity of pathways controlling not only daily food intake but also nutrient preference, such as higher fatty acid intake. However, the underlying biological mechanism of FTO polymorphism that contributes to higher risk of overweight, obesity, and metabolic abnormalities is mostly unknown. It should be pointed out that elucidating the way in which the FTO variant affects obesity-related traits may help us understand the pathogenesis of obesity. Consequently, further in-depth research is needed to explore the mechanism by which FTO is associated with overweight and obesity.

Parameters such as body mass, BMI, BMR, tissue independence, fat mass, fat mass percentage, fat-free mass, total body water, and glucose changed significantly during the 12-week training program. We also observed a significant decrease in HDL cholesterol concentration, which can be explained by an increase in energy consumption and achieving an “energy expenditure threshold” during physical effort by participants. However, none of the examined parameters changed significantly across the FTO genotypes (genotype x training interaction). Furthermore, Freathy et al. tested the association between the FTO genotype and 10 metabolic traits using data from 17,037 white European individuals and established that the FTO A allele was linked with higher levels of fasting insulin, glucose, and Tg as well as lower HDL cholesterol. Kring et al. demonstrated that the FTO genotype is connected with insulin sensitivity and HDL cholesterol level in their study comparing 753 obese Danish men with a control group. In a study performed on a homogeneous population of 1000 morbidly obese young adults from southern Italy, Ligouri et al. indicated that the rs9939609 in the FTO gene was a strong risk factor for metabolic syndrome in the studied population; in particular the TA heterozygous genotype, together with total cholesterol, BMR, and age, accounted for 21.3% of metabolic syndrome phenotype. Additionally, we have revealed that the A allele is associated with tissue impedance. The carriers of at least 1 A allele had lower tissue impedance, both before and after training. There is a shortage of reports concerning this subject, and more experimental studies are required.

A large-scale meta-analysis of 45 studies showed that the FTO effect on obesity risk is approximately 30% less in physically active than in sedentary adults. Li et al.
genotyped 12 single-nucleotide polymorphisms in a population-based sample of 20,430 individuals from Europe and showed that living a physically active lifestyle is associated with a 40% reduction in the genetic predisposition to common obesity. In other studies, the effect size of the FTO variants was as much as 80% lower in physically active individuals.\textsuperscript{15,16} This observation emphasizes the significance of a physically active lifestyle in body weight regulation, showing that even those who are genetically predisposed benefit from being active. Little is known about what the biological mechanisms are behind the interaction between PA and the FTO effect, as well as whether this decrease in effect is noticed only with PA or also with other lifestyle factors. It has been suggested that eating habits and smoking might reduce the FTO effects on tendency toward obesity as well. The FTO polymorphisms in the first intron have been linked with methylation capability, such that some authors have suggested that this region might be sensitive to epigenetic effects.\textsuperscript{7,8,10}

Our study did not confirm the gene × PA interaction effects on somatics, glucose concentration, and lipid profile in young females. However, the finding that living a physically active lifestyle is associated with a reduction in obesity-related parameters is still an important observation for public health. Kilpelainen et al.\textsuperscript{12} found a geographic difference in the interaction of FTO and PA. In particular, the interaction was stronger in North American populations than in populations from Europe, which may explain our findings. Reasons for the observed geographic difference are unclear. Our results were in accordance with a few studies aimed at weight loss interventions.\textsuperscript{17–19} In studies performed on Swedish and Finnish participants, authors revealed that the A allele at rs9939609 was associated with higher BMI. However, they also found no evidence of an effect of interaction between the FTO polymorphism and PA on levels of BMI.\textsuperscript{17–19}

The present study has several limitations that should be mentioned. Results obtained during genetic association studies need to be interpreted with caution because they can be influenced by many factors. The failure to detect gene × PA interaction effects in our study may reflect the influence of population-specific characteristics such as high overall PA levels and relatively low weight in the studied population, a small sample size, or the effect of age.\textsuperscript{5} In addition, obesity is a polygenic trait; over 75 polymorphisms have been associated with an excess of body weight.\textsuperscript{8} The genetic marker analyzed independently is likely to make only a limited contribution to an “obesity phenotype”: it seems more likely that such status depends on the simultaneous presence of multiple such variants. It is also unclear whether and to what extent the effect is due to changes in DNA methylation, because in our study we did not directly measure the methylation status of the participants.

5. Conclusion

In summary, we confirm the effect of the A allele of the FTO A/T polymorphism (rs9939609) on higher BMI. Additionally, the A allele was associated with lower tissue impedance. Although selected body mass and body composition as well as obesity-related metabolic variables changed significantly during the 12-week training program, we found no evidence of an interaction between the FTO polymorphism and PA on levels of BMI. However, we want to point out that promoting PA, particularly in those who are genetically predisposed to obesity, is an important step toward controlling the current obesity epidemic. More experimental studies are needed to establish the FTO gene × PA interaction.

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Authors’ contributions

ALD carried out the genetic studies, conceived of the study, coordinated the study, and drafted the manuscript; ZJ carried out body composition measurements; AZ carried out the specialized physical training; AM participated in the genetic studies; KF helped draft the manuscript; and PC performed the statistical analysis. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

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