

Body mass index change in females after short-time life style intervention is not dependent on the *FTO* polymorphisms

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Short title: *FTO* and intervention in obese females

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Abstract

Variants within the *FTO* gene are important determinants of body mass index (BMI), but, their role in determination of BMI changes after combined dietary/physical activity intervention is unclear. We have analyzed 107 unrelated overweight non-diabetic Czech females (BMI over 27.5 kg/m², age 49.2 ± 12.3 years). *FTO* variants rs17817449 (first intron) and rs17818902 (third intron) were genotyped. The life style modification program (ten weeks) consisted of an age matched reduction of energy intake and exercise program (aerobic exercise 4 times a week, 60 min each). The mean BMI before intervention was 32.8 ± 4.2 kg/m² and the mean achieved weight loss was 4.8 ± 3.5 kg (5.3 ± 35%, max. -15.5 kg, min. +2.0 kg, p < 0.01). No significant association between BMI decrease and *FTO* variants was found. Also waist to hip ratio, body composition (body fat, water, active tissue), lipid parameters (total, LDL and HDL cholesterol, triglycerides) glucose and hsCRP changes were independent on *FTO* variants. *FTO* variants rs17817449 and rs17818902 are not associated with BMI changes after combined short time dietary/physical activity intervention in overweight females.

Key Words Intervention, diet, exercise, *FTO*, polymorphism, lipid, glycaemia

Obesity is a serious health problem worldwide and is associated with increased mortality and morbidity. In combination with unfavorable genetic background, abundant energy intake and low physical activity are major causes of obesity on a population level, but, for example, sleeping habits, non-exercise activity thermogenesis and more stable inside room temperatures could also contribute to the recent increase of obesity prevalence (Hubacek 2009, Adamkova *et al.* 2009).

Independent genome wide association studies detected variants in the first (rs17817449) (Frayling *et al.* 2007, Scuteri *et al.* 2007) and third (rs17818902) (Tonjes *et al.* 2010) intron of the *FTO* (“fat mass and obesity associated”) gene to be (independently) responsible for the BMI determination. The exact function of *FTO* is unknown so far and the mechanism and the protein has no known similarity to other proteins that could help to predict its function. How *FTO* gene could affect BMI is not clear – possible role in determination of the energy intake or energy expenditure were suggested, but the achieved results are inconsistent (Cecil *et al.* 2008, Haupt *et al.* 2009, Liu *et al.* 2010, Hasselbalch *et al.* 2010).

The decrease of the BMI could be in most individuals achieved through restriction of energy intake and enhanced physical activity (both exercise and non-exercise). Nevertheless, the individual responses to lifestyle modification vary (Hainer *et al.* 2008) and it is clear, that it is partially genetically determined.

We have investigated the influence of *FTO* rs17817449 and rs17818902 variants on a response to a life style changes in 107 overweight (BMI over 27.5 kg/m², age 49.2 ± 12.3 years), but healthy (without diabetes, thyroid gland disease, any other endocrine disorders, autoimmune diseases, any chronic inflammation, or neoplastic disease) Czech Caucasian females.

The ten weeks life style modification program consisted of equilibrium to the

recommended dietary energy intake for the appropriate age and controlled physical activity (for more details see Suchanek et al. 2008, Suchanek et al., 2009).

Dietary intervention was aimed at lowering energy intake (to recommended values), together with decrease in animal fat intake and increase of fruits and vegetables intake. Volunteers participated 3 times weekly in a supervised 1-hour training session at a fitness center, and 3 more sessions per week (cycling, jogging, or brisk walking) were recommended (at least one session was performed by all individual). All these activities included an aerobic exercise component - the participants were supervised (and advised) to sustain heart rate of 115 to 145 beats (according to age) per minute within 60 minutes of exercise.

The probands have their anthropometrical parameters and blood pressure determined at baseline, after each 2 weeks of intervention and on the end of the study.

Body weight (measured with electronic weight), height (measured with a stadiometer), waist and hip circumferences, were measured by trained staff according the standard protocols. The waist-to-hip ratio (WHR) and BMI were calculated from obtained measurements.

DNA was isolated from frozen EDTA blood by standard method (Miller et al. 1988). *FTO* variants were analyzed by PCR and restriction analysis. Briefly oligonucleotides 5` GGT GAA GAG GAG GAG ATT GTG TAA CTG G and 5` GAA GCC CTG AGA AGT TTA GAG TAA ATT GGG with restriction enzyme AlwNI were used for the genotyping of rs17817449 variant (Hubacek et al. 2008, Hubacek et al. 2009) and oligonucleotides 5` ATC ATT CTG AAA ACA GAT CTG ACT GG and 5` ATG GGT TTA TGA ACC ATA GGA AAG AAT CGA G with restriction enzyme Bsal were used for the genotyping of rs17818902 variant.

The ethics committee of the Institute approved the study and all participants signed their informed consent. ANOVA for repeated measures was used in order to evaluate the statistical significance of the differences between before and after study tests. Because of the multiple testing, P value less than 0.01 was considered to be significant. All data are presented as means \pm SD.

There was no evidence for deviation of genotype frequencies from Hardy–Weinberg equilibrium. In comparison to the general populations (Hubacek et al. 2008, Dlouha et al. 2010) between obese females were nonsignificantly more carriers of the obesity associated GG genotypes (22.4% vs. 18.8%, for rs17817449 and 5.8% vs. 4.5% for rs17818902).

All subjects completed the follow-up during eight weeks, with the mean weight loss of 4.8 ± 3.5 kg ($5.3 \pm 3.5\%$), with minimum “loss” of +2 kg, and maximum loss of -15.5 kg).

No significant association between BMI changes and *FTO* rs17817449 and rs17818902 genotypes was found (Figure 1).

FTO gene variants had also no influence on waist, hip, body weight, waist to hip ratio, body composition (body fat, water, active tissue), lipid parameters (total, LDL and HDL cholesterol, triglycerides) glucose and hsCRP values development through the intervention (data not shown in details).

After ten weeks of lifestyle modification, consisting of at least 4 units of exercise per week and changing of dietary habits, we have observed significant decrease in BMI and body weight in all females. Further, our results confirmed a large interindividual variability in response to the applied lifestyle modification. Most importantly the difference between the maximal and minimal body weight change was 17.5 kg, As the exercise training was three times a week performed under

supervision at fitness centre, we suppose, that the differences likely reflect the different genetic predisposition than failure in the adherence to the dietary regimen and physical activity program.

So far, just interventions in children (Rendo et al. 2009), leads to the significant decrease of BMI, which was modulated by the *FTO* genotype and carriers of the obesity related genotype profit more from the intervention. In contrast, some another recent studies on differently defined individuals [children and adults (Müller et al. 2008) and diabetic patients (Lappalainen et al. 2009), the exact protocols used there for the duration and style of intervention differ from our study] also failed to report significant effect of the *FTO* variant on intervention dependent BMI changes. All these studies have analyzed first intron *FTO* variants (rs17817449 is in almost complete linkage disequilibrium with all of them) only.

Our study have at first time analyzed the role of *FTO* rs17818902 variation in third intron on life style modification associated changes on anthropometric and biochemical parameters in females, however, also with negative results.

In conclusion, in overweight healthy females, *FTO* gene variants in first (rs17817449) and third (rs17818902) intron have no effect on BMI, body composition and lipid parameters development over time of short lifestyle intervention. Most likely, despite the important role in obesity development per se, *FTO* variants have no effect on life style induced profitable changes in anthropometric and biochemical parameters.

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Figure 1

BMI decrease according the *FTO* genotypes (A for rs17817449 and B for rs1788902).

(In the figure just means are given, SD were, according the weeks of intervention ± 3.9 ; ± 3.8 ; ± 3.7 ; ± 3.7 ; ± 3.7 ; ± 3.7 ; for TT and ± 4.6 ; ± 4.5 ; ± 4.5 ; ± 4.3 ; ± 4.4 ; ± 4.3 ; for G allele carriers of the rs1788902 SNP and for rs17817449 than for TT ± 3.2 ; ± 3.0 ; ± 2.9 ; ± 2.9 ; ± 3.1 ; ± 3.0 ; for TG ± 3.8 ; ± 3.8 ; ± 3.6 ; ± 3.7 ; ± 3.7 ; ± 3.8 ; and finally for GG ± 5.3 ; ± 5.2 ; ± 5.1 ; ± 4.9 ; ± 5.0 ; ± 4.7).

Figure 1A

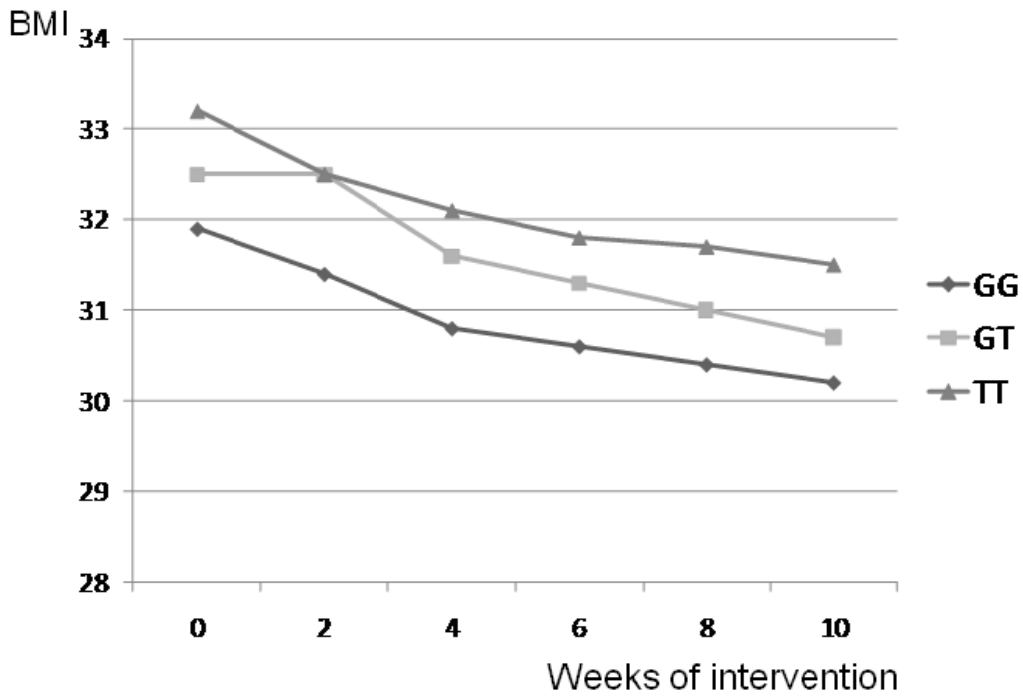


Figure 1B

