Effects of the *FTO* Gene on Lifestyle Intervention Studies in Children

Tara Rendo · Adriana Moleres · Amelia Marti del Moral

Department of Nutrition, Food Science, Physiology and Toxicology, University of Navarra, Pamplona, Spain

Key Words

Obesity · *FTO* · Lifestyle intervention · Children · Adults

Summary

The effects of *FTO* on body weight, body composition, and the risk of developing overweight and obesity in children, adolescents, and adults are analyzed in this review. Most trials have been conducted on the rs9939609 SNP of the *FTO* gene. The minor A-allele frequency ranged from 0.38 to 0.49 in different European populations. Briefly, it has been reported that overweight-obesity risk per A-allele ranged from 1.76 to 1.35, whereas z-score for BMI has a wider variation from 0.05 to 0.5 kg/m² in European children and adolescents. As for other adiposity indexes, a waist circumference increase from 0.60 to 0.95 cm per A-allele was found together with an increase in fat mass from 0.68 to 1.78 kg in European children and adolescents. In regard to food intake, AA carrier subjects were reported to have reduced satiety responsiveness scores and a higher total energy and fat intake. However, it is not clear whether energy expenditure did modify the role of the rs9939609 *FTO* gene variant in adiposity. Furthermore, few reports examined the influence of *FTO* gene variants using intervention studies. Overall, it seems that the A-allele (rs9939609 *FTO*) is associated with higher body weight gain. However, further studies into *FTO* gene variants in children and adults are needed.

Introduction

Obesity is a chronic disease characterized by the accumulation of excessive body fat which is maintained over time, and derived from an imbalance between energy intake and energy expenditure [1].

According to the World Health Organization (WHO), approximately 1.6 billion adults (age 15+) were overweight, and at least 400 million adults across the world in 2005 were obese [2]. Being the projections for 2015, approximately 2.3 billion adults will be overweight, and more than 700 million will be obese. The prevalence of obesity in developed countries is generally higher among females than among males [3]. Moreover, the prevalence of obesity has been increasing at an alarming rate worldwide during recent decades [4].

The development of obesity is largely due to the environmental and social changes that have taken place in recent decades. These include several factors such as increased calorie intake, a sedentary lifestyle, and psychosocial causes. In summary, obesity is the result not only of several environmental risk factors but also of genetic predisposition [5].

Genome-wide association is one of the latest gene finding strategies. For the last two decades, candidate gene and genome-wide linkage studies have been the commonest approaches used in the search for genes and genetic variants linked to several diseases and traits [6]. Genome-wide association is a hypothesis-free approach requiring the screening of the whole genome with the aim of identifying new, unanticipated genetic variants associated with a given disease/trait. It entails simple association between hundreds of thousands of genetic variants, generally single nucleotide polymorphisms (SNPs), and a trait or disease of interest. Hence, recent advances in genome-wide association mapping hold tremendous potential that contribute to the identification of human obesity genes and provide deeper insight into the genetic effects on obesity development [7, 8]. Twin and adoption studies have demonstrated that genetic factors play an important role in individuals within a population that are most likely to develop obesity in response to a particular environment [9].

A genome-wide search for type 2 diabetes mellitus (T2DM) susceptibility genes identified a common variant in the *FTO*

(fat mass and obesity associated) gene that predisposes to diabetes through an effect on BMI [10]. This gene has been convincingly associated with the risk of obesity in children and adults [5, 10–13].

Role of *FTO* in the Genetics of Obesity

While it is clear that environmental factors play a significant role in the development of obesity, research carried out in recent decades has also clearly documented a genetic contribution to obesity-related phenotypes [14, 15]. Indeed, it is estimated that 40–70% of the variation in obesity-related phenotypes is inherited [16]. Moreover, more than 100 genes have been involved in the determination of body weight [17].

The *FTO* gene is composed of nine exons that span more than 400 kb on chromosome 16. Several SNPs were initially identified by Frayling et al. [10], Scuteri et al. [5], and Dina et al. [11]. They are located in the first intron of the gene, a region where the sequence is strongly maintained across species [13].

It is known that *FTO* is a member of the non-heme dioxygenase superfamily, that it encodes a 2-oxoglutarate-dependent nucleic acid demethylase, and that it is located in the nucleus [18, 19]. Studies in rodents have demonstrated that *FTO* mRNA is not only abundant in the brain, particularly in the hypothalamic nucleus that regulates energy balance, but also in several peripheral tissues [18, 20]. Furthermore, it has been shown that *FTO* mRNA in the arcuate nucleus is up-regulated by feeding and down-regulated by fasting in mice [18, 21]. However, opposite expression patterns have been observed in rats [20].

In 1999 Peters et al. [22] described a mouse (called *Ft* due to the phenotype of ‘fused toes’) with a major deletion (1.6 Mbp) in a genomic region covering the *Fto* gene as well as other 5 genes. The authors considered *Fto* as a candidate gene involved in physiological processes such as programmed cell death or craniofacial development [22, 23]. Besides, two mouse model studies have shown that the inactivation of the *Fto* gene protects from the development of obesity [24, 25]. Based on these findings, it has been suggested that the inhibition of *Fto* activity may be a possible target for the treatment of morbid obesity.

Recently, studies in humans have shown that *FTO* is essential for the normal development of the central nervous and cardiovascular system and have found that a mutation results in a severe polymalformation syndrome [26].

Variations in the *FTO* gene strongly contribute to the development of early onset obesity [27, 28]. The A-allele of the variant rs9939609 is associated with a 31% increase in the risk of developing obesity [10], revealing that in fact rs9939609 is associated with an increased risk for both T2DM and obesity [10]. However, after adjustment for BMI, the association of the at-risk A-allele with T2DM vanished, indicating that

the impact of *FTO* on T2DM is mainly due to the association of *FTO* with BMI [10]. The T allele (rs9939609) is protective against overeating by promoting responsiveness to internal signals of satiety [29].

Other polymorphisms of *FTO* (rs1421085 and c.896+223A>G, among others) were also examined in relation to a higher risk of developing obesity (table 1) [11, 30, 31]. Obese individuals with the GG genotype (variant c.896+223A>G) had significantly increased fasting serum insulin levels and the degree of insulin resistance. Both of these factors remained statistically significant after adjusting for BMI SDS [31, 32]. The fact that *FTO* is associated not only with BMI but also with hip circumference and weight is consistent with previous analyses of heritability [33].

The importance of *FTO* as an obesity susceptibility gene was highlighted by a genome-wide association study that compared 487 extremely obese young individuals and 442 healthy lean controls [27]. It was found that each *FTO* risk allele increases the BMI by ~0.10–0.13 z-score units, which is equivalent to ~0.40–0.66 kg/m² in BMI or ~1.3–2.1 kg in body weight for a person 1.80 m tall [5, 10, 34].

In spite of the fact that variations in *FTO* contribute to early obesity onset, the mechanisms that underlie this effect are not clear. Some studies have focused on how *FTO* polymorphisms may act in human subjects tilting energy balance, either by increasing energy intake or decreasing energy expenditure. Some observational and interventional studies have been carried out especially during the last 2 years.

Observational Studies

Recent studies have shown that SNPs in the *FTO* gene predispose to childhood obesity [35]. The influence of *FTO* on body composition and the risk to develop overweight and obesity is already observed in childhood and persists into adolescence [10, 11]. Most trials have been conducted on the rs9939609 SNP of the *FTO* gene. The minor A-allele frequency ranged from 0.38 to 0.49 in different European populations.

Briefly, it has been reported that overweight-obesity risk per A-allele ranged from 1.76 to 1.35, whereas the z-score for BMI has a wider variation from 0.05–0.5 kg/m² in European children and adolescents (table 1).

Frayling et al. [10] demonstrated an association of *FTO* with BMI among both white European children and adults. The association was observed from children aged 7 years upward and reflects a specific increase in fat mass. Interestingly, 16% of AA carriers weighed 3 kg more and had 1.67-fold higher obesity risk than non-carriers.

Jacobsson et al. [35] reported that the A-allele of the *FTO* gene (rs9939609) predisposed to obesity in girls – but not in boys – in 962 children and adolescents. The A-allele was associated with an increase in BMI, BMI z-score, and glucose levels. After stratification by gender, these associations were

Table 1. Studies on *FTO* gene polymorphisms in children and adolescents

Children and adolescents	<i>FTO</i> : rs9939609 variant		Reference
	A-allele effect in adiposity or energy intake	main effect	
7,477 UK children from the ALSPAC cohort (7–11 years) and 4,320 children from the NFBC1966 cohort (14 years)	BMI z-score increase per A-allele: 0.08 kg/m ² ; $p = 3 \times 10^{-5}$ (7 years) 0.12 kg/m ² ; $p = 7 \times 10^{-9}$ (11 years) 0.05kg/m ² ; $p = 0.04$ (14 years)	obesity risk per A-allele: 1.35; $p = 6 \times 10^{-4}$ (11 years) 1.36; 95% CI (1.17–1.57) (14 years)	Frayling et al., 2007 [10]
450 severely obese Swedish children (232/218 w/m, 12 years) and 512 normal weight controls (268/244 w/m, 17 years)	BMI z-score increase per A-allele: 0.2–0.5 kg/m ² ; $p = 0.0343$	obesity risk for AA genotype: 1.59; 95% CI (1.11–2.27); $p = 0.016$	Jacobsson et al., 2008 [31]
3,337 UK children from TEDS: a population-based twin cohort. Case-control from SCOOP-UK (926 obese), and ALSPAC (4,022 normal weight control subject) cohorts (7–11 years)	BMI z-score increase per A-allele: 0.13–0.18 kg/m ² ; $p < 0.001$ WC increase per A-allele: 0.60–0.95 cm; $p < 0.001$ AA homozygotes had reduced satiety responsiveness scores ($p = 0.008$)	overweight/obesity risk for A-allele: 1.76; 95% CI (1.59–1.94); $p = 9 \times 10^{-28}$	Wardle et al., 2008 [39]
4,318 UK children (10–13 years) from the ALSPAC study	fat mass increase per A-allele: 0.68 ± 0.25 kg (13 years) No association with DED	greater fat mass independently of DED	Johnson et al., 2009 [38]
97 Scottish children (4–10 year)	A-allele carriers: 1.78 kg greater fat mass; $p = 0.01$ the A-allele was associated with higher energy intake ($p = 0.006$) independently of body weight	confirm the association with BMI and greater fat mass	Cecil et al., 2008 [40]
3,589 children from UK from the ALSPAC study (10–11 years).	total energy intake increase per A-allele: 1.01 kcal/day; $p = 0.03$ total fat intake increase per A-allele: 1.01 g/day; $p = 0.02$	significant association with total fat and energy intake after adjustment for BMI	Timpson et al., 2008 [37]
Other <i>FTO</i> variants, main effect			
700 lean children and 283 obese children from France, Germany and Switzerland.	C allele for rs1421085 was significantly associated ($p = 0.01$) with increased BMI z-score		Dina et al., 2007 [11]
450 obese Swedish (6–21 years) and 512 normal weight Swedish (15–20 years).	no association between c.896+223A>G variant and BMI z-score; obese subjects with GG genotype had increased fasting serum insulin levels ($p = 0.017$) and insulin resistance ($p = 0.025$)		Jacobsson et al., 2008 [35]

ALSPAC = Avon Longitudinal Study of Parents and Children; NFBC1966 = Northern Finland 1966 Birth Cohort; TEDS = Twins' Early Development Study; SCOOP-UK = Severe Childhood Onset Obesity Project UK; DED=dietary energy density; w/m=women/men.

found again, but only among girls [35]. Similar results were reported by Lappalainen et al. [36] who found the difference in BMI associated with the AA genotype of rs9939609 to be more evident in women than in men.

Apart from the association of rs9939609 *FTO* variant with adiposity, a number of trials conducted in children have aimed to investigate the effects of rs9939609 of *FTO* gene on energy intake [37, 38]. In two such studies the association with adiposity was confirmed. Furthermore, Wardle et al. [39] reported an increase in waist circumference of 0.60–0.95 cm per A-allele. Cecil et al. [40] and Johnson et al. [38] found an in-

crease in fat mass in A-allele carriers of about 1.78 and 0.68 kg, respectively.

Specifically, Timpson et al. [37] found positive associations between rs9939609 of the *FTO* gene and energy and fat daily intake in a large representative sample of children aged 10–11 years before and after adjustment for BMI. Total energy and total fat intake increase per A-allele was approximately 1.01 kcal/day and 1.01 g/day, respectively.

Wardle et al. [29] indicated that AA homozygote subjects had significantly reduced satiety responsiveness scores (table 1). Children with two copies of the lower-risk *FTO* allele (T-allele)

Table 2. Studies on the role of *FTO* gene variants and its interaction with physical activity

Subjects	Mean age $\pm$ SD, years	Main effect	Reference
<i>FTO</i> : rs9939609 variant			
Children			
349 healthy children participants of the STRIP study and randomly assigned to lifestyle intervention or control groups	15 years	at age 15 years, leisure-time-PA was not associated with the variant	Hakanen et al., 2009 [44]
Adults			
234 Danish obese men and 323 Danish controls	obese: 47.5 ± 5.1 control: 49.9 ± 6.0	the positive association between this variant and fatness is not explained by an effect of this variant on REE, GIT, VO_2 max or LTPA	Berentzen et al., 2008 [45]
5,722 Danish individuals from the population-based Inter99 study sample	TT subjects: 46.2 ± 8 TA subjects: 45.9 ± 8 AA subjects: 46.5 ± 8	association of the A-allele with both overweight and obesity; in homozygous carriers of the A-allele, physical inactivity associates with a relatively large increase in BMI compared with noncarriers and heterozygous for the A-allele	Andreasen et al., 2008 [34]
2,511 Finnish and 15,925 Swedish non-diabetic middle-aged adults	at baseline: 45.5 ± 6.9 follow-up: 68.5 ± 5.6	no evidence of an interaction between the <i>FTO</i> variant and physical activity on BMI	Jonsson et al., 2009 [46]
743 obese individuals from eight clinical centers in seven European countries	37.1 ± 7.9	the association between this variant and obesity may not be mediated by modulation of EE in obese individuals	Goosens et al., 2009 [47]
Other <i>FTO</i> variants			
Adults			
Participants from the EPIC-Norfolk Study. 20,374 participants at baseline and 11,909 participants during follow-up	at baseline: men: 59.1 ± 9.3 women: 58.6 ± 9.3 follow-up: men: 63.0 ± 9.0 women: 61.9 ± 9.0	T risk allele of rs1121980 was significantly associated with BMI and WC; PA level attenuated this effect on BMI and WC	Vimalaswaran et al., 2009 [43]
704 healthy Old Order Amish adults, selected from the HAPI study	43.6 ± 3.4	26 <i>FTO</i> SNPs were associated with BMI; the increased risk of obesity due to <i>FTO</i> variants can be blunted through PA; the association is much smaller and no significant in subjects having higher physical activity levels	Rampersaud et al., 2008 [42]

REE = Resting energy expenditure; EE = energy expenditure; GIT = glucose-induced thermogenesis; VO_2 max = maximum oxygen uptake; LTPA = leisure-time physical activity; STRIP = Special Turku Coronary Risk Factor Intervention Project; PA = physical activity; EPIC = European Prospective Investigation into Cancer and Nutrition-Norfolk Study; HAPI = Heredity and Phenotype Intervention Heart Study.

ate less than those with one or two higher-risk alleles. However, carriers of A-allele had significantly higher consumption of a highly palatable food independently of BMI in a home-based study of eating behavior.

Moreover, Cecil et al. [40] explained that the A-allele was associated with increased energy intake independently of body weight, although the amount of food ingested by children who had the allele was similar to that in children without the allele.

It appears that the *FTO* variant, rs9939609 may have a role in the control of food intake and food choice, suggesting a possible link to a hyperphagic phenotype or a preference for

energy-dense foods. However, Johnson et al. [38] found no association between the *FTO* variant rs9939609 and dietary energy density in a prospective cohort, the ALSPAC study.

Besides focusing on the relationship between *FTO* polymorphisms and energy intake, several other studies have analyzed if these variants are associated with energy expenditure (table 2).

In regard to the rs9939609 *FTO* variant, Andreasen et al. [34] found that physical inactivity is associated with a larger BMI increase in AA subjects compared with non-carriers or heterozygous subjects [34]. In this sense, Sonestedt et al. [41] have shown that high-fat diets and low physical activity lev-

Table 3. Effect of *FTO* gene polymorphisms in lifestyle intervention programs

Subjects	Mean age $\pm$ SD, years	Duration	Main effect	Reference
<i>FTO</i> : rs9939609 variant				
Children				
280 overweight children. 154/126 w/m	10.8 $\pm$ 2.7	1-year lifestyle intervention	the AA genotype + CC genotype (INSIG2) was associated with the lowest degree of overweight reduction, even with increase in overweight ($p < 0.05$)	Reinehr et al., 2009 [49] ^a
640 healthy children (299/341 w/m). 324 intervention group/316 control group	7 months to 15 years	Follow-up from 7 months to 15 years	the effects of this genotype on BMI changed over time as the children homozygous for the A-allele had progressively higher BMI ($p = 0.029$); AA genotype was associated with elevated serum total ($p = 0.05$) and LDL-cholesterol ($p = 0.04$); no association between <i>FTO</i> and weight change in a lifestyle intervention	Hakanen et al., 2009 [44]
Children and adults				
207 overweight or obese children and adolescents (cases), 178 normal weight adults (controls)	cases: 10.79 $\pm$ 2.52 controls: 24.58 $\pm$ 2.56	12-month program (Obeldicks)	association of the A-allele with overweight and early onset obesity ($p = 0.036$); no association with body weight loss, glucose, triglycerides, LDL and HDL cholesterol levels	Muller et al., 2008 [48] ^a
Adults				
502 overweight subjects with impaired glucose tolerance. 337/165 w/m	TT subjects: 55.3 $\pm$ 6.9 TA subjects: 55.2 $\pm$ 7.3 AA subjects: 55.3 $\pm$ 7.1	4-year follow-up (diet and exercise)	AA subjects had higher BMI ($p = 0.006$) and WC ($p = 0.025$); during the follow-up, women with the AA genotype had higher BMI ($p = 0.021$)	Lappalainen et al., 2009 [36]
Other <i>FTO</i> variants				
Adults				
204 subjects with increased risk for type 2 diabetes. 122/82 w/m	AA subjects: 44.1 $\pm$ 1 CX subjects: 46.7 $\pm$ 0.9	9-month intervention program (exercise and diet)	C allele of rs8050136 was associated with higher BMI and higher prevalence of obesity ($p < 0.0001$), body fat and lean body mass at baseline ($p \leq 0.01$); no influence on changes in body weight or fat distribution after 9 month intervention	Haupt et al., 2008 [30]

INSIG2 = Insulin-induced gene-2; BP = blood pressure; w/m=women/men.

^aSubjects of these studies belongs to the same cohort.

els may accentuate the susceptibility to obesity by the *FTO* variant. In a study of other gene variants, Rampersaud et al. [42] reported that the association between *FTO* genotype and body composition was much smaller and not statistically significant in subjects with higher physical activity levels. In addition, Vimalaswaran et al. [43] found a similar effect for the rs1121980 *FTO* variant.

However, other studies on the effect of *FTO* rs9939609 polymorphism on energy expenditure showed that the link between the gene variants and fatness is not explained by physical activity level either in children [44] or in adults [45–47].

Interventional Studies in Children and Adults

Evidence concerning the potential modifying effect of the *FTO* gene on body weight changes achieved by lifestyle intervention is limited. A summary of the latest scientific work is presented in table 3.

Recent studies have suggested that there is no association between rs9939609 alleles and weight loss [30, 36, 44, 48] or change in fat distribution [30]. Hakanen et al. [44] recruited healthy infants who were followed up from 7 months of age up to 15 years of age. The program was aimed at reducing coronary risk factors by dietary counseling at 3- to 12-month

intervals. Subjects were also genotyped for rs9939609 of *FTO* gene, but no effect of this (rs9939609) variant was observed after the intervention (table 3).

Meanwhile, Müller et al. [48] revealed that variation in the first intron of *FTO* is a risk factor for early onset obesity but there was no association between the rs9939609 genotype and body weight loss after 1-year lifestyle intervention program in 207 overweight and obese individuals who were from the same cohort studied by Reinehr et al. [49] (table 3).

Recently, Reinehr et al. [49] analyzed the effect of two different SNPs (INSIG2: rs7566605 and *FTO*: rs9939609) on weight status change in a 1-year lifestyle intervention program. The results showed that the INSIG2 CC genotype was associated with a significantly lower degree of overweight reduction during the lifestyle intervention, while a trend towards lower weight loss was observed for AA carriers in *FTO*. Most importantly, the combination of INSIG2 CC genotype and *FTO* AA genotype was significantly associated with the lowest degree of overweight reduction, suggesting that the effects of INSIG2 and *FTO* potentiate each other [49] (table 3).

In adults, Lappalainen et al. [36] reported that subjects with the AA genotype (rs9939609) showed the highest BMI at baseline. After the intervention program, no influence of the genotype on changes in body weight or fat distribution was found.

Conclusions

Evidence on the potential modifying effects of the *FTO* gene on adiposity from observational and lifestyle intervention studies in children, adolescents, and adults is still limited. Further research into the genetic factors involved in the development of obesity, including epigenetics, will improve the knowledge of the still unclear functions of the *FTO* gene, and thus its contribution to potential therapies to target obesity.

Disclosure

The authors declared no conflict of interests.

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