



The role of fat mass and obesity-associated gene (*FTO*) in obesity — an overview

Rola genu podatności na otyłość (*FTO*) w rozwoju otyłości — przegląd

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Abstract

Obesity is an epidemic of the 21st century. The magnitude of this problem stems from its increasing prevalence and numerous metabolic complications caused by excessive fat accumulation. The pathogenesis involves both environmental and genetic factors, and *FTO* (fat mass and obesity-associated gene) is one of the most significant among genes predisposing to obesity. The role of *FTO* polymorphism in the development of obesity has been confirmed in many studies, but the effect varies significantly in different ethnic groups. Moreover, the exact mechanisms of *FTO* influence are yet to be explained. The association between *FTO* and lifestyle factors such as diet and physical activity has been extensively studied in recent years. This paper presents current knowledge about the role of *FTO* gene in the development of obesity and type 2 diabetes in different ethnic groups and the association between *FTO* polymorphism and lifestyle modifications predisposing to adiposity. (*Endokrynol Pol* 2014; 65 (3): 224–230)

Key words: obesity; fat mass and obesity-associated gene; polymorphism; ethnicity; lifestyle modifications

Streszczenie

Otyłość jest epidemią XXI wieku. Znaczenie tego problemu wynika zarówno z jego narastającej częstości, jak i wielu powikłań zdrowotnych, którym sprzyja nadmiar tkanki tłuszczowej. W patogenezie otyłości istotną rolę odgrywają czynniki środowiskowe i genetyczne, a spośród tych ostatnich jednym z najbardziej znaczących jest gen *FTO* (gen podatności na otyłość). Wpływ polimorfizmu *FTO* na rozwój otyłości potwierdzono w wielu pracach, lecz jego bezpośredni efekt zależy od pochodzenia etnicznego osób badanych. Ponadto wciąż niejasny jest dokładny mechanizm działania tego genu. W ostatnich latach intensywnie badano związek polimorfizmu genu *FTO* ze środowiskowymi czynnikami ryzyka otyłości, takimi jak dieta i wysiłek fizyczny. W niniejszej pracy przedstawiono obecny stan wiedzy o roli genu *FTO* w rozwoju otyłości i cukrzycy typu 2 w różnych grupach etnicznych oraz jego związek ze stylem życia, który predysponuje do nadmiernego gromadzenia tkanki tłuszczowej. (*Endokrynol Pol* 2014; 65 (3): 224–230)

Słowa kluczowe: otyłość; gen podatności na otyłość; polimorfizm; etniczność; zmiany stylu życia

Introduction

Obesity is one of the most serious problems in public health worldwide, leading to cardiovascular diseases, type 2 diabetes and several types of cancer. The prevalence of obesity is constantly increasing. Since 1980, the number of obese people has nearly doubled. This problem concerns not only adults (in 2008 more than 1.4 billion were overweight), but also children (more than 40 million children under the age of five were overweight in 2011) [1].

That is why many scientific projects concentrate on the pathogenesis of excessive fat mass accumulation. Twin studies suggest the existence of genetic factors in human obesity [2] and estimate the heritability of obesity to be around 60-90% [3]. Recent advances in

genomic technology (GWAS, genome wide association studies) have revealed more than 40 candidate genes that predispose individuals to obesity. One of them is fat mass and obesity-associated gene (*FTO*) — accounting for approximately 22% of common obesity [4]. It is located on chromosome 16q12.2 and has nine exons. *FTO* is mainly expressed in the hypothalamus but also in other tissues (muscles, adrenal gland, and fat tissue). It encodes a 2-oxoglutarate-dependent nucleic acid demethylase and probably plays an important role in controlling energy homeostasis [5], nucleic acid demethylation and lipolysis [6].

FTO was first reported in 2007 by Frayling et al. for its association with type 2 diabetes and obesity [7]. Since then, the influence of *FTO* on obesity has been demonstrated in many studies in different ethnic groups. *FTO*



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contributes maximally to the variance in body mass index (BMI) in Europeans (0.34%) and East Asians (0.18%) [8, 9]. Although the role of *FTO* in the development of human obesity seems fairly certain, the exact mechanisms of this influence are yet to be explained. Another interesting problem is the interaction between genetic predisposition and lifestyle factors, such as diet and physical activity, which are currently the subject of extensive studies.

***FTO* and obesity in different ethnic groups**

In the initial work by Frayling et al., the 16% of European adults who were homozygous for the A allele had 1.67-fold increased odds of obesity compared to homozygous for low risk T allele (39% of the population) [7]. Later publications confirmed the association between *FTO* polymorphism and obesity risk in Caucasians [4, 10–14]. Meta-analyses [8, 15] have shown the effect of the predisposing genes on adiposity among individuals of European descent and are estimated to be 0.39 kg/m² per allele according to Speliopoulos et al. and 0.28 kg/m² according to Hertel et al. Most studies in the white population have concentrated on *FTO* rs9939609 polymorphism in the first intron [7, 12–15], which seemed to have the strongest influence on BMI mainly because of its prevalence — 45% for allele A due to *HapMap*. Only a few studies have referred to other introns — two, three [16], eight [17] and four [18].

Recently however, results of a new study have been released in which the entire *FTO* gene in total 412 Kbp has been amplified in a group of 524 morbid obese and 527 lean Swedish children [19]. This is the first comprehensive variation map of the *FTO* gene, including both SNPs and small indels (small deletions and insertions), using new generation sequencing of pooled DNA - massive parallel sequencing (SOLiD). Scientists identified 19 obesity-associated SNPs. All of them are located in intron one, thus the authors concluded that this is the only obesity-associated region of the *FTO* gene. Interestingly, ten of the identified SNPs have a stronger association than the commonly studied rs9939609, and rs62048402 has been shown to be the most significant one. This was confirmed in a recent study on a Latvian population [18] where SNPs rs62048402, rs9939609 and rs7561317 were associated with higher BMI with p-values of 0.0036, 0.0069 and 0.015 respectively. The four top obesity-associated SNPs in a study by Almen et al. [19], with rs62048402 being the strongest one, lie within the potential regulatory region of intron one. Some transcription factors, such as the glucocorticosteroid receptor, bind there and this is the only known functional region of the comprehensive *FTO* map which may potentially explain the pathomechanism of related obesity.

The effect of the variant of *FTO* on adiposity varies among different populations [20]. In an Asian population, initial studies did not confirm the role of *FTO*. Li et al. reported lower minor allele frequencies of *FTO* and no association with obesity in a Chinese population [21]. Similarly, a publication by Shimaoka et al. suggested no influence of *FTO* on BMI or other metabolic traits except for insulin resistance [22]. But subsequent studies did reveal an association between *FTO* polymorphism and obesity in people of Asian descent [23–25]. A meta-analysis has been performed using data from 32 populations, including 96,551 people from East and South Asia [26]. Each additional A-allele increased the odds of obesity by 1.25 and overweight by 1.13 compared to normal weight controls. The study revealed that the effects of *FTO* polymorphism are similar to those observed in Europeans. It is thus possible that the effect of the *FTO* gene polymorphism can only be observed in more extensive studies of greater statistical power. An important difference is the lower Minor Allele Frequency (MAF) of the *FTO* variant in South (0.32) and East (0.17) Asians than white Europeans (0.45), which results in a reduced role of *FTO* in propensity to obesity in general [26]. It should also be noted that the BMI cut-off values for obesity and overweight are lower for Asians than Europeans [27].

In African populations, the results of the studies are, so far, inconsistent. Bressler et al. [28] compared BMI and diabetes risk in Europeans and Africans. *FTO* polymorphisms were associated with higher BMI and diabetes risk in Europeans, while in Africans only rs1421085 was a determinant of obesity, but at the same time, a protective factor against diabetes. An interesting study carried out by Hennig et al. [29] showed that *FTO* variation did not influence BMI in a group of 2,208 Gambians who live in a traditional way and are leaner than typical Europeans. The authors suggested that the difference in lifestyle, especially in food excess and physical activity, might be the reason for the inconsistency in results with European studies. However, a study in postmenopausal women in the US [30] revealed no association between *FTO* risk alleles and obesity in black women, while in white women living in similar conditions, the influence was significant, and the MAF was comparable in both groups. This would suggest that ethnic differences predominate in influencing one's lifestyle. But recent studies established the positive effect of *FTO* variation and obesity risk in individuals of African descent. First, Wing et al. [31] proved that rs8050136 and rs9939609 were correlated with BMI in African-Americans. A study by Ademeyo et al. [17] showed effect size on BMI 0.77 kg/m² for rs9932411 and 0.70 kg/m² for rs7191513 in West Africans and African-Americans. Hassainen et al. [32] genotyped SNPs, which are correlated with BMI in

Europeans, in nearly 10,000 African subjects. Most SNPs did not show any significant association with obesity except for rs3751812, which explained 0.31% average proportion of variance in BMI and rs9941349 — 0.30% of variance. The authors also suggest ruling out rs9939609 and many other variants which are in linkage disequilibrium (LD) with this variant in Europeans.

The first study which focused on the Brazilian population was carried out in 2012 [33]. Ramos et al. confirmed the association of the *FTO* variant with BMI in multi-ethnic Brazilian subjects. The homozygous for the risk allele A weighed about 3.1 kg more than TT-carriers.

There are few reports about *FTO*-related obesity risk in Oceanians [34, 35]. No significant association between *FTO* variation and adiposity has been reported.

Peng et al. [20] meta-analysed 59 case-control studies and identified five polymorphisms (rs993609, rs17817449, rs1421085, rs8050136, rs1121980) associated with obesity in different ethnic groups. However, in some subgroups there was no correlation, for instance for rs993609 with Hispanic and Caucasian or rs8050136 with Asians and Africans. This may be an effect of differences in MAF or LD patterns in ethnic groups.

There have only been a few studies conducted in Poland. Kowalska et al. analysed the association between polycystic ovary syndrome and *FTO* polymorphism, showing its influence on weight, fat mass and insulin sensitivity [36], which is probably due to lower lipid oxidation in risk allele carriers [37]. Other authors have reported an association between rs9939609 polymorphism and obesity and cardiovascular risk in Polish children [38, 39]. The problem is becoming important, because the prevalence of adiposity - also in children - in our country is rapidly increasing.

Generally, the role of *FTO* gene in pathogenesis of obesity is proven, but the effect is variable in different ethnic groups. This partially explains the greater susceptibility of some groups to obesity. Moreover, studies concerning genetic predisposition to adiposity must include larger groups of subjects to achieve enough statistical power.

***FTO*-related obesity during lifetime**

Another interesting aspect would be to assess the time when the effect of genetic predisposition becomes significant. A recent meta-analysis showed only a nominally significant association between *FTO* loci and birth weight [40], and the results were abolished after correction for multiple testing. Similar conclusions were made in earlier studies [7, 41], suggesting that *FTO*-related obesity tends to manifest later. However, the genetic predisposition was significant in a group of two-week-old newborns in a work by Lopez-Bermejo

et al. [41]. The AA-homozygotes had 17% higher total, truncal, and abdominal fat mass than T-carrier neonates. A Danish longitudinal study, representing a wide range of BMI in adolescence, showed that AA genotype predisposes to weight gain from birth to the age of 7 years and later from adolescence and early adulthood onwards. [42] Generally, it seems that some alleles of *FTO* increase obesity risk since childhood [7, 41–43], but not due to higher birth weight. Another interesting observation was that the association between *FTO* and BMI is weaker in older men, probably because of loss of fat tissue connected with age [14]. At a younger age, the genetic predisposition has a stronger effect on BMI, which was also suggested in a recent work comparing *FTO* effect in four periods of adulthood [44]. No such works were conducted in Poland.

***FTO* and diabetes**

The *FTO* gene has been investigated for its potential influence on type 2 diabetes (T2D). According to Frayling et al., each minor allele increased the odds of diabetes by 1.15-fold [7]. Most subsequent studies have shown that this association is only a result of adiposity in risk allele carriers [7, 11, 13, 14, 23, 45] and was invalidated after BMI adjustment. In contrast with this data, the MONICA Study revealed that rs9939609 A allele carriers were 48% more likely to suffer from T2D; the risk persisted after BMI adjustment [12]. An observation carried out over a span of ten years in the HUNT study demonstrated higher T2D incidence in non-diabetic Scandinavians with risk allele. Although BMI adjustment attenuated this correlation, it did not eliminate it [15]. A recent study in a Latvian population confirmed the association of SNPs in the first intron (rs11642015, rs62048402 and rs9939609) of *FTO* with T2D, which remained significant after correction for BMI. Interestingly, the rs57103849 showed BMI independent association with younger age T2D diagnosis [18]. The rs57103849, which lies in the fourth intron outside the *FTO* gene cluster associated with obesity, was reported to correlate with insulin resistance independently of BMI [46].

Interesting results were also reported in studies among different ethnic groups [26, 47]. In an Indian population, rs9939609 showed an association with T2D but not with BMI. The authors concluded that Asians have generally lower BMI than Europeans and are more susceptible to T2D probably due to higher visceral obesity [47]. Other studies also reported that the association between *FTO* loci and T2D remains significant after a BMI adjustment [48, 49], but some showed BMI-dependent relation with T2D [23, 50]. A meta-analysis from Li et al. [26], combining data

of 96,551 Asians from 32 populations, confirmed the association of *FTO* variance and T2D, which was not abolished after an adjustment of BMI. However, this meta-analysis has been the subject of several limitations, mentioned by Meyre [51]. Firstly, the authors adjusted the risk of T2D with BMI value, which does not sufficiently reflect fat body mass (especially visceral fat mass) in normal weight subjects. Secondly, data collected at one time-point may also be of limited value, because body weight might change due to diabetes therapy. That is why longitudinal studies, comparing newly diagnosed T2D cases to matched controls (as in the HUNT study) seem to be the most reliable. In Poland, an association between *FTO* variation and insulin sensitivity in a group of 136 women with PCOS was found ($p = 0.025$), but this effect was mediated by adiposity [36].

FTO gene predisposes to obesity and in this way it definitely predisposes to T2D as well. However, it is difficult to establish if the association is only adiposity-dependent. Such studies would probably need to use methods like X-ray absorptiometry or MRI to assess fat mass volume rather than BMI.

***FTO* and diet**

Although *FTO*'s role as the obesity susceptibility gene is fairly certain, its exact mechanism of influence remains unknown. Initial works showed that *FTO* encodes a 2-oxoglutarate-dependent nucleic acid demethylase and its mRNA was detected in many tissues. The highest expression was found in the hypothalamic sites that govern feeding behaviour, such as arcuate (ARC), paraventricular (PVN), dorsomedial and ventromedial (VMN) nuclei [52, 53]. Recently, studies have suggested that methylated single-stranded RNA, rather than DNA, may be the primary *FTO* substrate [54]. In mice, fasting was reported to decrease expression of the gene [52], however in rats upregulation has been detected [53, 54]. Results in animals have given the basis to subsequent publications assessing the role of *FTO* in regulation of energy balance in humans.

Studies have suggested that *FTO*-dependent risk of obesity is increased through higher energy intake rather than lower energy expenditure [43, 55]. In a group of 2,726 Scottish children (4-10 years), the A allele of rs9939609 was associated with increased food intake in test meals independently of body mass. Genetically predisposed subjects ingested meals with a 16% greater energy density than wild types, while the weight of chosen food did not differ significantly between these groups [43]. Results of other studies were consistent with this data, for example Timpson et al. revealed that risk allele carriers ingested more dietary fat and more

dietary energy than non risk carriers [56]. This eating behaviour might be partially an effect of diminished satiety responsiveness, which has been reported both in children [57] and adults [58].

Interestingly, *FTO* may influence not only total energy, but also specific macronutrient ingestion. Increased fat intake in risk allele carriers was reported earlier [43, 55, 56]. Tanaka et al. performed recently a meta-analysis of macronutrient intake in populations of European descent and showed that rs1421085 variant was associated with higher protein intake independently of BMI [59]. Corresponding results were demonstrated by the Malmo Diet and Cancer Study, where a higher percentage of energy from protein in diet was observed for A-allele carriers [60]. Subsequent studies in the same population also showed different food preferences related to *FTO* gene [61]. Risk allele was associated with a higher consumption of pastry, biscuits, ice-cream and fruit. In line with these results, A-allele carriers were reported to consume more meals per day and eat more energy dense foods [62]. However, in study of Corella et al. [63], no association between *FTO* and general food intake or food groups was found, but alcohol consumption in variant allele carriers was significantly lower than in wild-type subjects. Interestingly, AA genotype subjects presented also the highest rate of under-reporting of energy intake (17%) compared to TT genotype (15.4%), which was also more frequent in obese population [61].

Generally, increased intake of energy dense foods, eaten additionally to main meals during the day, may partially explain *FTO*-related obesity development. Recently, an interesting work by Karra et al. [64] brought up a new possible explanation of *FTO*'s influence on diminished satiety. In this study 'obesity-risk' allele carriers (AA-homozygotes) exhibited attenuated postprandial suppression of both hunger and acyl-ghrelin levels compared to TT-homozygotes. Ghrelin is an orexigenic hormone, often called 'the hunger hormone', increasing the intake of food [65] and shifting preference into meals rich in fat. The feeding phenotype caused by ghrelin is very similar to *FTO* A-allele influence. Risk-allele carriers not only presented higher levels of ghrelin in blood, but they also displayed different neural responses to ghrelin in the brain regions known to regulate appetite, reward-processing and incentive motivation. With the use of functional MRI it was also shown that AA-subjects rated high-calorie food images as significantly more appealing in the postprandial state than TT-subjects. This study presents an interesting aspect of association between *FTO* gene and adipocytokines, which are known to manage eating behaviour. Further studies in this subject are required [64].

Some authors investigated also how a specific diet affects *FTO*-related obesity. For example, Razquin et al. [66] have demonstrated that a Mediterranean-based diet, rich in mono- and polyunsaturated fat, provides *FTO* risk allele carriers some protection against body weight gain after three years of nutritional intervention. Also Corella et al. showed that high adherence to a Mediterranean diet can counterbalance the genetic susceptibility to obesity [63]. In the Malmo Diet and Cancer Study, fat intake was shown to accentuate the effect of *FTO* on obesity. In a group with high fat ingestion, large differences in percentage body fat depending on *FTO* were observed, and in a group with smaller fat intake, *FTO* changed fat mass less significantly [60]. Similar results were yielded in studies by Moleres et al. [67]. In line with these findings, in the Finnish Diabetes Prevention Study, an increase in BMI across *FTO* genotypes was accentuated by a diet with high fat, low carbohydrates and low fibre intake [68]. In the three-year follow-up of the study, individuals with the AA genotype did not differ from the other genotypes when they followed a diet low in energy. And a recent study confirmed a higher weight loss in A carriers of *FTO* rs9939609 polymorphism than in TT genotype subjects after three months of a hypocaloric diet [69]. Such results give new strength to dietary interventions, especially in patients with an inherited predisposition to obesity.

***FTO* and physical activity (PA)**

Physical activity is another important lifestyle intervention, which may help to overcome the effect of the *FTO* gene on obesity-related traits. Vimalaswaran et al. showed a reduced, but still significant, effect of the rs1121980 polymorphism on both BMI and waist circumference in physically active individuals compared to an inactive group (20,374 European adults) [70]. Similarly, Andearsen et al. [11] found an interaction between the *FTO* rs9939609 genotype and self-reported physical activity on BMI levels in the Inter99 study sample. Not all studies, however, have confirmed the influence of physical activity on gene-related obesity [71, 72]. Nevertheless, it is important that all mentioned works were based on self-reported activity measurement, which is an important limitation. In the HELENA study, the physical activity was objectively assessed by accelerometry. Among adolescents who spent at least 60 minutes participating in moderate to higher physical activity every day, the A allele was not associated with higher BMI or waist circumference, in contrast with inactive subjects [73]. Also in the Malmo diet and cancer cohort, A-allele influence on fat mass was eliminated only in the group

with the highest leisure time activity (assessed with questionnaires and accelerometry) [60].

The objectivity of assessing physical activity is not the only problem in all these studies. Generally, identifying interactions between lifestyle and genetic variants requires much larger sample sizes than when detecting the simple effect of a gene on environment. The meta-analyses might partially help to solve this problem, although authors have to compare results of the studies in which different methods were used. Kilpelainen et al. analysed data from 45 studies of 218,166 adults and nine studies of 19,268 children and adolescents, categorising subjects as 'active' or 'inactive'. The effect of the *FTO* risk allele rs9939609 on BMI and obesity was almost 30% smaller in active adults than in inactive subjects. Interestingly, the *FTO* × PA interaction differed across geographical groups and was more significant in North Americans compared to Europeans. This may be caused by lower average physical activity in North Americans, so the lifestyle intervention may provide a greater reduction of obesity risk. Also, these differences might be caused by possible lower accuracy of PA measurement in Europeans (categorical variables) than in Americans (continuous variables). In children, no association between PA and *FTO* genes was found, what may be the effect of smaller sample size, but also inaccuracy of BMI as obesity measurement method in this age group [74].

Another important aspect of physical activity was reported in the population-based Malmo diet and cancer cohort [60]. The authors observed a tendency of interaction between leisure-time physical activity and *FTO* on total mortality ($P = 0.07$). Among TT-carriers, the highest vs lowest quintile of physical activity was associated with 33% reduced cardiovascular mortality, and 11% among A-allele carriers. These results suggest that *FTO* polymorphism modifies interaction between physical activity and cardiovascular mortality. There was no association between *FTO* and general mortality in a Swedish study [60]. Earlier, this correlation was significant in 362,200 Danish young men [75], where mortality was 42% reduced in TT genotype compared to A-allele carriers, independently of obesity.

Conclusions

Variations of the *FTO* gene are risk factors for common obesity. The exact influence differs among ethnic populations due to genetic differences. It is also suggested that the effect on body mass of many polymorphisms may combine [76], which makes the analysis more difficult. Moreover, lifestyle modifications — especially diet and physical activity — may accentuate or attenuate genetic predisposition to obesity.

Gene/lifestyle interactions have become an important aspect of understanding the pathogenesis of excessive fat accumulation, but they are very difficult to assess. Studies concerning this problem must have enough power to detect these interactions, and exclude many limitations (mostly caused by self-reported data). However, more studies are needed, as their results could help to create more effective obesity treatments.

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