Diabetologia (2012) 55:873–876
DOI 10.1007/s00125-012-2478-4

COMMENTARY

Is *FTO* a type 2 diabetes susceptibility gene?

D. Meyre

Received: 25 November 2011 / Accepted: 23 December 2011 / Published online: 2 February 2012

Keywords Association · Biology · Causality · Ethnicity · Molecular genetics · Obesity · Type 2 diabetes

Abbreviations
DXA Dual-emission X-ray absorptiometry
FTO Fat mass and obesity-associated

Obesity is a major predictor of future risk of type 2 diabetes [1] and the escalating prevalence of type 2 diabetes worldwide is mainly attributable to the continued rise in obesity observed over the last decades [2]. Identification of the complex interactions and shared molecular pathways linking obesity and type 2 diabetes is an area of intense research [3]. Human molecular genetics in particular has led to the identification of numerous molecular determinants of obesity and type 2 diabetes and to the global conclusion that the genes involved in genetic predisposition towards type 2 diabetes influence pancreatic beta cell function/mass and, to a lesser extent, insulin action, whereas obesity predisposing genes modulate hypothalamic sensing and control of energy balance [4, 5]. To date, few loci have been convincingly associated with both obesity- and type 2 diabetes-related traits, and *FTO*, in addition to *IRS1* [6, 7], *ENPP1* [8–10] or *GIPR* [11, 12], may be one of the molecular determinants linking obesity and type 2 diabetes.

D. Meyre (✉)
Department of Clinical Epidemiology and Biostatistics,
Michael DeGroote Centre for Learning & Discovery,
McMaster University,
Room 3205, 1280 Main Street West,
Hamilton, ON L8S 4L8, Canada
e-mail: meyred@mcmaster.ca

In 2007, four independent teams found that variation in intron 1 of *FTO* (which encodes fat mass and obesity-associated protein) is the major contributor to polygenic obesity in European populations [13–16]. Three of these studies investigated obesity phenotypes [14–16], whereas the other one initially identified *FTO* through a genome-wide association study for type 2 diabetes [13]. As the strong association between the intronic variant rs9939609 and type 2 diabetes (OR 1.09–1.23, $p=9\times10^{-6}$) observed in 3,757 type 2 diabetes cases and 5,346 controls from the UK was abolished after the adjustment for BMI (OR 0.96–1.10, $p=0.44$), the authors concluded that the association of *FTO* rs9939609 with type 2 diabetes was mediated through BMI and that *FTO* may be primarily considered as an obesity susceptibility locus [13]. However, in contrast with the UK data, Hertel et al recently reported that the association of *FTO* rs9939609 with type 2 diabetes was partly independent of its effect on BMI [17]. They prospectively followed 20,686 non-diabetic Scandinavian individuals at baseline and followed them up for over 10 years. Overall, 3,153 individuals developed type 2 diabetes and the *FTO* rs9939609 polymorphism was strongly associated with the incident risk of type 2 diabetes after adjustment for age and sex (OR 1.10–1.22, $p=3.2\times10^{-8}$). Further adjustment for BMI or change in BMI during the follow-up attenuated, but did not remove, the association of rs9939609 with incident type 2 diabetes (OR 1.05–1.18, $p=1.1\times10^{-4}$; OR 1.05–1.18, $p=1.5\times10^{-4}$, respectively).

In this issue of *Diabetologia*, Li and colleagues provide convincing evidence that *FTO* variation is associated with type 2 diabetes, and that this association is partly independent of BMI in East and South Asian populations [18]. In a meta-analysis of 22 studies, including 33,744 type 2 diabetes cases and 43,549 controls, they found that the *FTO* rs9939609

variant was associated with type 2 diabetes under an allelic model and after adjusting the OR for sex and age (OR 1.09–1.21, $p=5.5\times10^{-8}$). Interestingly, further adjustment for BMI attenuated, but did not abolish, the association of *FTO* rs9939609 with type 2 diabetes (OR 1.05–1.16, $p=6.5\times10^{-5}$). The authors also confirmed that *FTO* rs9939609 was associated with risk for obesity and for overweight, variation for BMI, waist-to-hip ratio and percentage body fat in Asians. The frequency of the obesity/type 2 diabetes risk allele (the minor allele) was lower in East Asians (12–20%) than in South Asians (30–33%), but the effects of the variant on obesity-related traits and type 2 diabetes were similar in both subgroups. The study by Li and colleagues is subject to several limitations. First, the authors adjusted the OR for type 2 diabetes with BMI, but the ability of this adjustment to account for the degree of adiposity has been questioned. BMI is significantly correlated with fat mass in obese individuals, but there is little or no correlation between BMI and fat mass in normal weight and underweight individuals. BMI does not distinguish between lean and fat body mass and, for a given BMI, fat mass may vary by more than 100% [19]. Adjustment for body fat content estimated by dual-energy X-ray absorptiometry (DEXA) or for the recently proposed body adiposity index [20] may better account for the degree of adiposity of the participants.

Another limitation of this study is the cross-sectional nature of the meta-analysis (data have been collected at one time point). There is indeed an important source of bias in cross-sectional studies of *FTO* and type 2 diabetes, as BMI measured after the diagnosis of type 2 diabetes is unlikely to be identical to BMI prior to the onset of the disease. Some patients tend to lose weight prior to being diagnosed with type 2 diabetes because of the presence of glycosuria [21], a phenomenon amplified if health systems are less efficient at identifying type 2 diabetes at an early stage (as is the case in some parts of Asia). Insulin therapy [22] or rosiglitazone treatment [23] promote weight gain, whereas lifestyle intervention [24], glucagon-like peptide 1 agonists or amylin analogues [25] promote weight loss. The major impact of type 2 diabetes and its treatments on body corpulence may introduce some noise into the analysis and tend to result in an overestimation of genetic effects. Longitudinal studies that compare newly diagnosed type 2 diabetes cases to matched controls are undoubtedly more suited to exploration of the complex and dynamic nature of the *FTO* genetic association on adiposity and glucose homeostasis evolution across the lifespan [17, 26].

This study adds to the growing body of evidence that *FTO* may be a type 2 diabetes susceptibility locus independently of BMI. Beyond genetic association studies for type 2 diabetes status, additional reports provide strong arguments in favour of this hypothesis. The *FTO* intronic variant has been associated both with cerebrocortical [27] and peripheral [28–31] insulin resistance, the association being abolished after BMI adjustment in some [28–30], but not all [27, 31], studies. *FTO* mRNA levels in several key tissues involved in the pathogenesis of type 2 diabetes (pancreatic beta and alpha cells, liver, skeletal muscle, adipose tissue) are modulated by type 2 diabetes status [32, 33], glucose levels [34, 35], glucose oxidation rate [36] or treatment by the hypoglycaemic drug rosiglitazone [33]. The *FTO* mRNA level is related to the expression of genes involved in gluconeogenesis in the liver [35], with *TNF* and *NFKB1* (also known as *NF-κB*) mRNA levels in subcutaneous adipose tissue [34] and with insulin and *KCNJ11* mRNA levels in beta cells [32]; all these genes/pathways are involved in the regulation of glucose homeostasis. Adenoviral overexpression of *FTO* in myotubes increases basal protein kinase B phosphorylation, enhances lipogenesis and oxidative stress and reduces mitochondrial oxidative function—a cluster of metabolic defects associated with type 2 diabetes [33]. Conditional overexpression of *FTO* in INS-1 pancreatic beta cells enhances first-phase insulin secretion in response to glucose [37], and transcription factor 7-like 2 (TCF7L2), a major determinant of type 2 diabetes risk [38], binds to the *FTO* promoter in this cell line [39]. FTO function may relate to the demethylation of single-stranded DNA and nucleic acid repair or modification processes [40, 41]. FTO has been proposed to be a transcriptional coactivator that enhances the transactivation potential of the CCAAT/enhancer binding proteins from unmethylated as well as methylation-inhibited promoters, suggesting a role in epigenetic regulatory processes [42]. In addition, the *FTO* intronic gene variant is associated with a distinct methylation pattern over a 7.7 kb region at the *FTO* locus that includes a highly conserved non-coding element validated as a long-range enhancer [43, 44]. The role of FTO in general mechanisms of nucleic acid repair and epigenetic regulation is consistent with the notion that FTO may be a pleiotropic factor involved in various diseases such as obesity or type 2 diabetes [45].

Although the findings listed above are encouraging, there are several lines of evidence that are less supportive of a role of FTO in susceptibility to type 2 diabetes. Complete or partial inactivation of the *Fto* gene in mice protects them from obesity [46, 47], whereas overexpression of *Fto* in mice increases food intake and results in obesity [48]. However, despite a careful phenotypic examination, no striking type 2 diabetes phenotype has been observed in these genetic mouse models [46–48]. A mild improvement in the insulin sensitivity of *Fto*-deficient mice has been observed and a reduction in the glucose tolerance of mice with increased *Fto* expression in response to a high-fat diet has been reported, likely as a result of the body weight differences of these animals compared with wild-type controls [46, 48]. Li et al recently constructed an obesity genetic predisposition score using information on 12 validated obesity predisposing gene variants, and tested whether this score was associated with the

incident risk of type 2 diabetes in 20,428 individuals from the European Prospective Investigation of Cancer (EPIC)-Norfolk cohort with an average follow-up of 12.9 years, during which 729 individuals developed type 2 diabetes [49]. The score was modestly associated with the incident risk of type 2 diabetes (OR 1.005–1.078 by additional obesity risk allele, $p=0.02$), but adjustment for BMI completely abolished the association (OR 0.967–1.039, $p=0.89$). These data suggest that, when analysed together, obesity predisposing gene variants lead to an increased risk of developing type 2 diabetes, almost completely through their effect on BMI [49]. Obesity-susceptibility genes predisposing to type 2 diabetes partly by mechanisms independent of adiposity may therefore represent an exception.

Is *FTO* a type 2 diabetes susceptibility gene? Even if a growing body of evidence supports this hypothesis, including the study by Li et al in this issue of *Diabetologia*, further data are needed at this stage and I propose few directions to feed the debate in the future. Large-scale type 2 diabetes case–control studies in which cases and controls are matched at the individual level, not only for sex and age, but also for BMI or ideally for body fat content or body adiposity index, may help to investigate whether the *FTO* rs9939609 polymorphism is associated with type 2 diabetes when there is a similar degree of adiposity among cases and controls. Genetic association studies performed in large-sized longitudinal cohorts with careful collection of obesity and type 2 diabetes-related deep phenotypes (e.g. body fat content evaluated by DEXA, OGTT-derived variables) and the comparison of newly diagnosed type 2 diabetes cases to nested controls may give a more complete picture of the effect of *FTO* gene variation on adiposity and glucose homeostasis. As the relationships between adiposity and risk of type 2 diabetes vary with ethnicity [50], it would be important to perform these studies in individuals with different ethnic backgrounds. The involvement of genes adjacent to *FTO* (such as *RBL2*, *AKTIP*, *RPGRIP1L* or *IRX3*) in the pathogenesis of type 2 diabetes should also be further investigated. The first intron of *FTO* has been involved in long-range gene regulation of *IRX3*, a gene potentially involved in pancreatic alpha and beta cell function [51]. One cannot exclude the possibility that gene variation in intron 1 of *FTO* may predispose to type 2 diabetes independently of *FTO* itself but through the regulation of adjacent genes. This may explain the lack of type 2 diabetes-related phenotypes observed in *Fto*-deficient mice and *Fto*-overexpressing mice.

Acknowledgements I thank Y. Gerrard (McMaster University, Hamilton, ON, Canada) for the editing of the manuscript. I thank the reviewers for their helpful comments.

Duality of interest The author declares that there is no duality of interest associated with this manuscript.

Contribution statement In accordance with ICMJE requirements, the author was responsible for the conception and design of the manuscript, drafted and revised the article and approved the final version to be published.

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