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PSYCHOLOGICAL ISSUES (M HETHERINGTON AND V DRAPEAU, SECTION EDITORS)

The 'Fat Mass and Obesity Related' (*FTO*) gene: Mechanisms of Impact on Obesity and Energy Balance

John R. Speakman

Abstract A cluster of single nucleotide polymorphisms (SNPs) in the first intron of the fat mass and obesity related (*FTO*) gene were the first common variants discovered to be associated with body mass index and body fatness. This review summarises what has been later discovered about the biology of *FTO* drawing together information from both human and animal studies. Subsequent work showed that the 'at risk' alleles of these SNPs are associated with greater food intake and increased hunger/lowered satiety, but are not associated with altered resting energy expenditure or low physical activity in humans. *FTO* is an FE (II) and 2-oxoglutarate dependent DNA/RNA methylase. Contrasting the impact of the SNPs on energy balance in humans, knocking out or reducing activity of the *Fto* gene in the mouse resulted in lowered adiposity, elevated energy expenditure with no impact on food intake (but the impact on expenditure is disputed). In contrast, overexpression of the gene in mice led to elevated food intake and adiposity, with no impact on expenditure. In rodents, the *Fto* gene is widely expressed in the brain including hypothalamic nuclei linked to food intake regulation. Since its activity is 2-oxoglutarate dependent it could potentially act as a sensor of citrate acid cycle flux, but this function has been dismissed, and instead it has been suggested to be much more likely to act as an amino acid sensor, linking circulating AAs to the mammalian target of rapamycin complex 1. This may be fundamental to its role in development but the link to obesity is less clear. It has been recently suggested that although the obesity related SNPs reside in the first intron of *FTO*, they may not only impact *FTO* but mediate their obesity effects via nearby genes (notably *RPGRIP1L* and *IRX3*).

Keywords *FTO* · GWAS · BMI · Body composition · Adiposity · Fatness · Obesity · Food intake · Energy expenditure · Physical activity · 2-oxoglutarate · Demethylation · DNA · RNA · Leptin · Ghrelin · Hypothalamus · Amino acid sensor · mTOR · Protein intake · Macronutrient intake · IRX3 · RPGRIP1L · FTM

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J. R. Speakman
Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, 1 Beichen xilu, Chaoyang Beijing, China

J. R. Speakman (✉)
Institute of Biological and Environmental Sciences, University of Aberdeen, Tillydrone Ave, Aberdeen, Scotland AB24 2TZ, UK
e-mail: J.speakman@abdn.ac.uk

Introduction: Background

The *FTO* gene has a curious early history of association with obesity. Insertional mutagenesis studies in mice resulted in a mutation involving the deletion of several hundred kB of genomic sequence on mouse chromosome 8 [1], subsequently established to contain six separate genes. This mutation resulted in a lethal phenotype during gestation in homozygous carriers, but in heterozygous individuals the phenotype included several morphological abnormalities including fusion of the toes. Hence the deletion was named *Ft* (Fused toes). One of the deleted genes in the Ft segment was later cloned and named *Fatso* (*Fto*) [2], not because of any phenotypic association to body fatness, but apparently because it was by far the largest gene in the deleted segment (according to OMIM, although this is not stated in the original publication). It was speculated that *Fto*'s function would be primarily developmental, and in particular associated with left-right asymmetry, limb development and craniofacial morphology [2]. This

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association of *FTO* with development was confirmed by a genome-wide linkage analysis, followed by candidate gene sequencing in a consanguineous family from Palestine, which phenotypically displayed severe growth retardation, developmental delay, and early death. The causal mutation was traced to a homozygous 947G-A transition in the *FTO* gene, resulting in an arg316-to-gln (R316Q) substitution in the derived protein [3]. Moreover, knock out of the *Fto* gene in the mouse also results in severe growth retardation and elevated early mortality [4••, 5]. These developmental defects are replicated in the conditional KO mouse where the gene is only absent in the CNS [5].

The name *Fatso* for the gene was prescient in the light of subsequent findings. In 2007, *FTO* became the first gene to emerge from genome wide association studies, single nucleotide polymorphisms adjacent to which were linked to variation in the risk of type 2 diabetes (OR=1.27) [6••, 7]. Type 2 diabetes risk is dependent on obesity, and it was shown that once adjusted for body mass index (BMI), a surrogate for body fatness, the association of *FTO* SNPs and diabetes disappeared (OR=1.03) [6••]. Hence *FTO* SNPs were primarily affecting BMI rather than type 2 diabetes risk directly. The primary SNP involved in the association studies was rs9939609, which was located in the first intron of the gene, but this actually is representative of a cluster of ten SNPs located close together that are highly correlated with each other (r^2=0.52 to 1.0) and also strongly linked to the BMI phenotype (p from 10^{-4} to 10^{-5}). rs9939609 has A or T alleles, with the A type being found at rates between 12 % (Han Chinese) and 52 % (Yorubans), with white Caucasians having a prevalence of 45 % (HapMap consortium data). The A-allele was shown to be associated with a median per allele effect on BMI of 0.36 kg/m^2, since replicated many times and averaging about 0.39 kg/m^2 [8]. Assessing the association across multiple case control studies (comprising >30,000 subjects) gave a combined probability for the link to obesity of 3×10^{-35} [6••]. Perhaps because of the unfortunate derogatory nature of the gene name *Fatso* for a gene linked to obesity, the acronym was retrofitted to a new name 'Fat mass and obesity related.' Since 2007 there have been over 600 papers published on the *FTO* gene (Web of Science: October 2014). The aim of the current review is to summarise this literature drawing together what we understand about the biology of *FTO* and its relation to obesity, from studies of both animals and humans.

Impact on food Intake in Humans

Since SNPs adjacent to *FTO* appeared to impact BMI, and by implication body fatness several questions immediately arose. In particular it was of interest what the exact function of the *FTO* protein was, and whether the important SNPs in it exerted their effects via an impact on either food intake or energy expenditure (or both). Many methods for the measurement of food intake in free-living individuals are beset by the problems of error in recall and self-reporting. Indeed the errors are so bad with these methods that calls have been made for the methods to be discontinued as scientific tools because the data they provide are so misleading [9]. Unsurprisingly then several studies utilising food frequency questionnaires and 24 h recall have mostly failed to establish any association of intake with *FTO* SNP genotypes [e.g. 10•, 11–14] (Appendix 1). Nevertheless, an association between at risk alleles of the *FTO* SNPs (rs1421085 and rs17817449) and greater fat and refined starch intakes was observed using food frequency questionnaires in 133 overweight/obese Caucasians [15]. Similarly, a link was established between the at risk variant at rs1421085 and protein intake using a food frequency questionnaire in 7724 subjects [16], and the *FTO* rs8050136 A allele (n=36,973) was positively associated with percentage of energy derived from fat and inversely associated with energy from carbohydrates in a cohort of 36,973 subjects [17]. McCaffery et al. [18] associated four different *FTO* SNPs with total energy intake and the number of eating episodes per day, with in all cases the at risk SNPs having greater intake and more eating episodes, although the effects of rs9939609 were the smallest and actually not significant for intake, while the most significant SNP was rs1421085. A meta-analysis combining data across 37 studies (predominantly based on FFQ methods) and involving a very large cohort of 177,330 subjects has indicated significant impacts of the *FTO* rs9939609 genotype on total energy and carbohydrate intake (with the at risk allele having significantly lower intakes!) but the at risk allele was linked to higher protein intake [19].

More objective measures based on weighed intake over 7 days have established that AA and AT genotypes of rs9939609 are associated with greater overall energy intake compared to the TT genotype (p=0.024) [20•] (Appendix 1). The effect on energy intake was reduced, but still significant, if adjusted for variations in BMR. The only macronutrient showing differences in intake by genotype was protein intake (p=0.02) although alcohol intake approached significance in a linear model (p=0.05) with the A allele being linked to lower intake [20•]. An impact of rs9939609 variants on alcohol intake and alcohol related behaviours was subsequently reported by multiple authors also with the A allele linked to lower intake [21–24]. Since the A allele is the 'at risk' allele for obesity, and the effect of this allele is evident down to at least age 4 years [25] and probably earlier [26], the impact on alcohol intake is unlikely to be causal in any association to obesity. Using detailed 3 day diary intake records for 3641 children similar impacts of the A allele of rs9939609 on the energy intake of children [27], but in this case there was also a significant impact on fat intake (with no significant impacts on protein or carbohydrates). These effects were attenuated but

still significant if the intake was adjusted for BMI [27]. Steemburgo et al. [28] using 3 day weighed intake records reported greater fat and lower fibre intake in the AA compared to the AT/TT genotype for rs9939609, particularly in females. Analogous effects for the A allele of the rs8050136 SNP on total energy intake were found using food diaries [29], and in the only study of Asian populations to date, there was an association of the rs9939609 A allele with greater fat intake in children based on 3 day diary records, but no effects on total energy or the other macronutrients, and no impact in adults (n=8842). The variants in the adjacent rs9939973 SNP had no effect [30]. Hence, despite many studies showing no effects on daily energy or macronutrient intake (Appendix 1), when sufficiently accurate intake tools are used there is an impact of both the *FTO* SNPs rs9939609 and rs8050136 (and potentially also rs1421085) on daily energy intake, with in both cases the 'at risk' A allele individuals having greater energy, and possibly greater protein and fat intakes and lower fibre intake.

Increasing evidence suggests that the *FTO* SNPs are associated with variation in appetite ratings and satiety, as well as eating in the absence of hunger, and loss of control over eating (Appendix 1). Cecil et al. [31] evaluated satiety in primary school aged children (n=76) by following the levels of consumption at a test meal, 1.5 hours after consuming three priming meals varying in their energy content and density. As expected ingested energy was lower when children had consumed either a low or high energy meal. There was, however, a significantly higher energy intake when the children were carriers of the A allele (AA or AT) compared to the TT allele, in the control and low energy priming conditions. A trend to the same effect in the high energy priming situation failed to reach significance. In contrast to the impacts on energy intake there was no difference in the weight of food ingested during the test meal between genotypes, suggesting A carriers were selecting more energy dense components of the test meal. This was confirmed by the significantly greater selection of fat by the A carriers (p=0.04 to 0.001 across the three conditions), but no effect on carbohydrate intake (p=0.05 to 0.75) and a marginal effect on protein intake (p=0.02 to 0.06) [31].

Wardle et al. [32] genotyped 3337 children for the rs9939609 SNP, and measured habitual appetitive behaviour using two parent completed psychometric measurements (Satiety Responsiveness and Enjoyment of Food) from the Child Eating Behaviour Questionnaire. They found the at risk AA homozygotes had significantly reduced Satiety Responsiveness scores (P=0.008, ANOVA), but there was no significant effect on enjoyment of food, although there was a trend to higher levels in the AA genotype. They followed up this study with a more detailed analysis of 131, 4–5 year old children in which eating in the absence of hunger (EAH) was measured [33]. The EAH paradigm involves feeding children to satiety and then 10 minutes later observing their consumption of biscuits, comprising a mix of savoury and sweet types, over a 10 minute period. The weight consumed provides a measure of eating in the absence of hunger. On average children with the rs9969309 TT genotype ate only 30 g of biscuits, compared with 37.9 g for the AT and 40 g for the AA genotype (p=0.014 for additive model) [33]. In adults, studies have shown that carriers of the A genotype of rs9939609 (i.e., AA or AT) have altered post-prandial satiety levels as recorded by visual analogue scales completed periodically after consuming a test meal [34•]. Interestingly this latter study suggested that the gene effects in *FTO* interacted epistatically (one gene dependent on others) with polymorphic variation in other genes including the leptin receptor and DNA methyl transferase 3B (*DNMT3B*) [34•].

Loss of control (LOC) of eating is a behaviour that is commonly reported by overweight adolescents, and it predicts excessive weight gain in children. In 190 children and adolescents, the impact of the rs9939609 SNP on the presence or absence of LOC eating was evaluated by interview [35]. In addition subjects participated in a lunch buffet test meal designed to model an LOC eating episode. Of the AA/AT subjects, 34.7 % reported LOC compared with only 18.2 % of the TT subjects (P=0.002). However, total energy intake at the test meal was independent of the genotype (P=0.61). Nevertheless, AA/AT subjects consumed a greater percentage of energy from fat at the test meal than did the TT subjects (P< 0.01) [35].

Eating in the absence of hunger is known to depend on levels of acute psychological stress. In a randomized cross-over design, the 'eating in absence of hunger' protocol was measured as a function of acute stress vs. a control task and of State Trait Anxiety Index (STAI) state scores [36]. In comparison with the rs9939609 T allele, the A allele was associated with an increased feelings of hunger after food intake in both the stress (p<0.01) and control condition (p<0.05). The effect of stress on this difference was not significant and subsequent food intake also was not different. Hence these data supported other studies implicating the A allele as being related to satiety but did not indicate any association with the stress component of the manipulation [36].

Dougkas et al. [37] studied the impact of rs9939609 SNPs on appetite ratings of overweight men. The study involved a randomised cross-over trial including 40 subjects who attended four sessions 1 week apart and received three isoenergetic and isovolumetric servings of dairy snacks or water (control) in a random order. Appetite ratings were determined using visual analogue scales (VAS) after the test meal consumption. The postprandial fullness rating over the full experiment following intake of the different snacks was 17.2 % (P=0.026) lower in the at risk AT or AA genotypes compared with the TT genotype for rs9939609. These observations supported the suggestions that the *FTO* polymorphisms are related to the variation in the feeling of fullness. It was similarly observed that post-prandial appetite levels

(VAS-Hunger) were elevated in AA homozygotes compared to TT homozygotes (for rs9939609) which were linked to an interaction between *FTO* genotype and levels of circulating ghrelin [38•]. This study also showed, using functional MRI (fMRI) that the *FTO* genotype modulates the neural responses to food images in both homeostatic and brain reward regions. AA and TT subjects exhibited divergent neural responsiveness to circulating acyl-ghrelin within brain regions that regulate appetite, reward processing, and incentive motivation. Hence it was inferred that the primary impact of the polymorphic variation was to impact on how *FTO* regulates ghrelin, which is a key mediator of ingestive behaviour [38•].

In perhaps the most comprehensive study of the *FTO* SNP family on feeding behaviour performed to date, the effects of 64 *FTO* SNPs on the relative reward value of food (RRVfood) and their relationship to food intake in an *ad libitum* snack test were studied [39]. The RRVfood task involves participants working for a food reward in a progressive ratio schedule of reinforcement. This basically involves doubling the work required to obtain an extra increment of intake and recording how hard subjects will therefore work for their favoured food. In total RRVfood scores explained 14.2 % of the variance in energy intake on the *ad libitum* snack test, and SNP alleles at 6 SNPS (rs9936768, rs8049933, rs7199716, rs1292170, rs12446047 and rs11076022) modulated this response to explain an additional 4.9 to 7.4 % of the variance. These SNPs also moderated the relationship between RRVfood and fat or carbohydrate intake, and a subset explained protein or sugar intake. Overall only alleles of two SNPs (rs1292170 and rs12446047) influenced intake of total energy and all macronutrients. It is perhaps important that the main *FTO* SNP that has been studied so far (rs9939609) was not among the most important SNPs when all were considered together [39]. This was also observed by McCaffery et al. [19] in their study where the most important SNP was rs1421085. Peters et al. [40] systematically dissected the *FTO* locus in 20,488 subjects locating a total of 3756 variants. Although there were links to BMI for all the SNPs located in the first intron the most significant association was with rs56137030 not rs9939609. A similar study of 527 lean and 524 obese children using ultra-deep sequencing of the *FTO* gene located 705 SNPs, 19 of which in intron 1 were associated with obesity, ten of these 19 were more closely associated ($p<.007$) than rs9939609 ($p=0.012$) [41•]. The implication is that future studies may discover more significant impacts of the *FTO* gene if they focus genotyping effort on these other SNPs rather than rs9939609.

In a rather different approach Sonestedt et al. [42•] explored whether the intake of high fat modified the association of the *FTO* genotypes and obesity levels. They concluded that the impact of the AA and AT variants of the rs9939609 SNP was dependent on the levels of fat intake. For individuals with high fat intake the BMI averaged 25.3 among TT carriers and 26.3 in AA carriers ($P=0.0001$). However, the variant was not associated with a higher BMI among subjects with lower fat intakes (BMI=25.7 and 25.9 in TT carriers and AA carriers, respectively; $P=0.42$) [42•]. They followed this up with similar measures in a much larger cohort of 22,799 individuals showing again that the impact of the *FTO* genotype interacted with fat intake ($p=0.01$) [43]. This mediation effect of high fat diet for rs9939609 has been replicated in two further independent studies [44, 45], and also shown for specific dietary fatty acids [46] and total energy intake [47] and with respect to other *FTO* SNPs [48]. Interactions have also been suggested with respect to consumption of fried foods [19], meal skipping behaviour [49], and adherence to a Mediterranean diet [50] and PUFA intake [51]. An interaction of the effect of *FTO* on children's growth/adiposity was also found with vitamin D status [52]. A modulating effect has even been suggested for education level [53]. These studies also point therefore to epistatic [34•] or gene-environment interactions, affecting the impact of the *FTO* gene variants. In contrast to these studies modulating effects of diet on the impact of rs9939609 *FTO* genotypes on obesity were not observed in a large cohort of Europeans (n=6566) [54].

Impact on Energy Expenditure and Physical Activity in Humans

Simultaneous to the explosion of studies attempting to discover if *FTO* SNPs affects food intake there was similar interest in their role with respect to energy expenditure. Because thermoregulation costs are normally minimal, human energy demands can be roughly divided into that for basal or resting expenditure and that for physical activity [55]. Resting or basal costs are more easily measured but physical activity expenditure has also been assessed using indirect markers (Table 1). Studies of basal and resting expenditure, when appropriately normalised for differences in body weight/composition, indicate that the *FTO* SNP genotypes do not affect resting or basal metabolic rates [10•, 11–19, 20•, 29, 31, 56•, 57]. Unadjusted measures do occasionally show significant differences (10, 31, 56, 58) but only because the genotype impacts body composition. Only one study has suggested an impact on adjusted basal metabolism [14] but in that case the BMR was predicted from an equation based on anthropometry, rather than being measured directly. Given the precision of the calorimetry methodology relative to food intake determination, and the repeated demonstration of no effect across multiple cohorts when adjusted for body weight and composition we can be confident that the obesity linked *FTO* SNPs have no impact on basal energy demands.

Relatively fewer studies have explored the impact on physical activity. All of the indirect measures and questionnaire based monitoring show no significant genotype effects (Table 2). Moreover there were no effects of the genotype

Table 1 Effects of variants of FTO SNPs on energy expenditure and related parameters (ordered by date of publication)

Reference	Date	Population	n	SNP	Parameter measured	Genotype effect
Do et al [10•]	04.2008	Caucasian adult	908/507F	rs17817449	BMR	$p = 0.042$ (A lower)
					BMR adj	ns ($p = 0.53$)
Berentzen et al [56•]	07.2008	Caucasian Adult	557/0F	rs9939609 (rs8050136, rs7193144)	VO_2max	ns ($p = 0.954$)
					VO_2 max (adjusted)	ns ($p = 0.662$)
					REE	REE higher in AA ($p = 0.033$)
					REE (adjusted)	ns ($p = 0.712$)
					Glucose induced thermogenesis	ns ($p = 0.948$)
					GIT (adjusted)	ns ($p = 0.767$)
Grunnet et al [125]	07.2008	Caucasian Adult	46/0F	rs9939609	24h EE in room calorimeter	ns ($p = 0.48$)
					24h fat oxidation	ns ($p = 0.90$)
					24h Glucose oxidation	ns ($p = 0.22$)
					24h protein oxidation	ns (p =0.33)
					RQ	ns ($p = 0.41$)
					BMR	ns ($p = 0.58$)
Speakman et al [20•]	08.2008	Caucasian adult	150/103F	rs9939609	BMR	ns ($p = 0.544$)
					VO_2 max	ns (p = 0.243)
					BMR (mass adj)	ns ($p = 0.502$)
					VO_2max (mass adj)	ns ($p = 0.675$)
Cecil et al [31]	12.2008	Caucasian children (4-10y)	75	rs9939609	BMR	TT lower ($p = 0.03$)
					BMR adj	ns (p = 0.216)
Haupt et al [29]	04.2009	Caucasian Adult	151	rs8050136	BMR adj	ns ($p > .05$)
Goosens et al [57]	04.2009	Caucasian Adult	743/190F	rs9939609	REE	ns ($p = 0.87$)
					lipid induced REE	ns ($p = 0.89$)
Corpeleijn et al [126]	07.2010	Caucasian Adult	722/541F	rs9939609	REE	ns ($p > .05$)
					post prandial REE (lipid meal)	ns ($p > .05$)
					Fasting fat oxidation	ns ($p > .05$)
					Post prandial fat oxidation	ns (p> .05)
Zavattari et al [127]	09.2011	Caucasian Children (10y)	912/486F	rs9939609	free T3 and T4	ns ($p > .05$)
Hubacek et al [14]	2011	Caucasian Adult	6024	rs17817449	predicted BMR from Schofield eqn	at risk GG allele higher ($p < .008$)
					predicted BMR/kg	at risk GG allele lower ($p < .006$)
Kowalska et al [128]	07.2012	Caucasian Adult	93/93F	rs9939609	Fat oxidation	greater in TT carriers in PCOS patients (p =0.018) but nsd in controls
					Insulin stimulated fat oxidation	ns
Huuskonen et al [129]	12.2012	Caucasian adult	846/0F	rs8050136	VO_2 max	no gene effect on relation of VO_2max to BMI
Arrizabalaga et al [58]	03.2014	Caucasian Adult	77/77F	rs 9939609	unadjusted REE	A allele lower ($p < .001$)
					Thyrotropin levels	A allele higher ($p < .05$)

BMR Basal metabolic rate, *BMRadj* Basal metabolic rate adjusted for body weight or body composition, *VO_2max* Maximal oxygen consumption, *VO_2max adj* maximal oxygen consumption adjusted for body mass or composition, *REE* Resting energy expenditure; *T3* Triiodothyronine, *T4* thyroxine, *PCOS* poly-cystic ovary syndrome, *EE* energy expenditure

Table 2 Effects of FTO SNPs on physical activity and related parameters (ordered by date of publication)

Reference	Date	Population	n	SNP	Parameter measured	Genotype effect
Berentzen et al [56•]	07.2008	Caucasian Adult	557/0F	rs9939609 (rs8050136, rs7193144)	leisure time PAQ <2h/week 2-4h/week >2-4h light/week >4h/week	 ns ($p = 0.319$) ns ($p = 0.525$) ns ($p = 0.468$) ns ($p = 0.546$)
Cecil et al [31]	12.2008	Caucasian children (4-10y)	71	rs9939609	TEE by DLW AEE by DLW	TT lower ($p = 0.009$) TT lower ($p = 0.02$)
Wardle et al [33]	01.2009	Caucasian children (4-5y)	131	rs9939609	Maternal rating of child's fidgeting Maternal rating of child's PA Maternal rating of child's enjoyment of PA	ns ns ns
Hakanen et al [112]	01.2009	Caucasian children (15y)	382	rs9939609	Self report Questionnaire Physical activity level	 ns ($p = 0.99$)
Liu et al [13]	04.2010	Caucasian & African am.	1978	rs9939609	Vigorous PA self-report Vigorous PA (accelerometry)	ns ($p = 0.62$) ns ($p = 0.26$)
Corpeleijn et al [126]	07.2010	Caucasian adult	722/541F	rs9939609	PA questionnaire Habitual physical activity	 ns ($p > .05$)
Hubacek et al [15]	2011	Caucasian adult	6024/3244F	rs17817449	self-reported PA hours per week in sports games etc	ns (males $p = 0.79$) ns (females $p = 0.99$)
Prats-Puig et al [130]	05.2013	Caucasian children	297/146F	rs9939609	modulation of association of sleep to BMI	association in TT but not AA ($p < .05$)
Eynon et al [131]	2013	Caucasian adult	551	rs9939609	link to athletic status in elite athletes	ns

PAQ Physical activity questionnaire, *TEE* Total energy expenditure, *AEE* activity energy expenditure, *DLW* Doubly-labelled water, *PA* Physical activity, BMI: Body mass index

on maximal oxygen consumption rates [20•, 21–33, 34•, 35–37, 38•, 39, 40, 41•, 42•, 43–55, 56•]. Intriguingly, however, measures of the energy expenditure of 71 children [31] using the doubly-labelled water method [59] suggested that there was a genotype effect (rs9939609) on both total and activity energy expenditure. The impact of this genotype was, however, in the opposite direction to that anticipated, with the TT genotype having significantly lower total and activity related energy expenditure. No adjustment for body composition was made, so this remains a rather enigmatic finding. Overall, while the data seem fairly solid with respect to the lack of an impact on physical activity levels (although more accelerometry data are required), the jury is still out on an effect of *FTO* SNPs on activity energy expenditure, and this is an area in need of further data.

Although the impact of *FTO* on activity energy expenditure is uncertain it has been well established that physical activity levels can ameliorate the detrimental impact on BMI of the at risk *FTO* SNPs [22, 30, 42•, 43, 47, 60•, 61–66]. This is normally reported in terms of how lifestyle choices can overcome ones genetic programming. However, since physical activity may well be affected by other genetic factors this effect could as likely reflect genetic epistasis rather than an environment by gene interaction. The combination of these epistatic and environmental modulators results in a change in the variation of body fatness with the *FTO* genotype [67]. The protective effect of exercise does not appear to also extend to the association between *FTO* genotypes at rs9939609 and coronary heart disease [68].

Food Intake and Expenditure (Rodent Studies)

Fischer et al. [4••] knocked out the *Fto* gene in the mouse. As noted above this had a major impact on development and the resultant *Fto*(−/−) mice while viable were stunted relative to wild-types and showed elevated early life mortality. This impact was unfortunate because it complicates elucidation of other energy balance parameters since the normalisation for body weight and composition differences is not straightforward [69–71]. The *Fto* null mice had lower levels of both fat and lean tissue reflecting their developmental stunting, but relative adiposity was reduced. There were no significant impacts on total food intake, but a significantly greater intake expressed per gram lean body mass because the null mice were smaller ($p=0.015$). Similarly mass specific oxygen consumption and CO_2 production both showed significant elevations in the *Fto*(−/−) mice, both during the day and at night ($p=0.0034$ to 0.013). Physical activity on the other hand was significantly reduced. Analysis difficulties aside [71] the overall impression of the impact of inactivation of *Fto* was the complete opposite of the *FTO* 'at risk' obesity SNPs in humans. That is food intake was unaffected, but energy expenditure was elevated and physical activity diminished, and inactivation of the gene led to a lean phenotype. However, note that in a similar global knockout model replicated the developmental defects but the body composition of their mice was 'relatively normal' [5]. Rather than completely knocking out the gene, a mouse generated from ENU chemical mutagenesis screens that had a point mutation in the *Fto* gene resulting in partial loss of function has been studied [72]. The mutation in exon 6 resulted in a phenylalanine for isoleucine change at AA 367 which potentially impacted on the ability of the protein to dimerise, and its catalytic ability was reduced to about 40 % of wild-type individuals. These mutant mice with reduced, rather than abolished, *Fto* activity were not developmentally compromised in the same way as the animals global knockout [4••, 5], but they did develop a lean phenotype from the age of about 12 weeks onwards. These mice also showed elevated energy expenditure at 18 weeks of age (but again in this analysis expenditure was normalised to lean body mass rather than using ANCOVA for the analysis as recommended [69, 70]). The mice showed an elevated respiratory exchange ratio (RER), particularly in the dark phase, but no change in physical activity levels. Food intake was unaffected. Again the phenotype differs markedly from the impact of the human SNPs by influencing the expenditure side of the energy balance equation rather than the input side. Another way of avoiding the developmental impacts of the gene is to use an adult onset knockout model. McMurray et al. [73•] generated mice with loss of function initiated at different ages. Germline loss (i.e. loss through the whole of development) recapitulated the global KO phenotype [4••, 5] including a significant effect on energy expenditure, when adjusted by lean mass. However, this effect was abolished when using more appropriate analysis approaches based on regression models [69, 70]. Loss of function at age 6 weeks overcame the major impacts on stunting and early mortality, but the mice developed relative adiposity because of a loss of lean tissue at the same time as expanding fat mass. This change was not linked to obvious effects on either expenditure or intake.

The effect therefore of reducing the activity of *Fto* in some studies was an increase in leanness [4••, 5, 6••, 7–9, 10•, 11–19, 20•, 21–33, 34•, 35–37, 38•, 39, 40, 41•, 42•, 43–55, 56•, 57–59, 60•, 61–72] but in others an increase in adiposity [73•]. In addition, supposed effects on energy expenditure [4••, 5, 6••, 7–9, 10•, 11–19, 20•, 21–33, 34•, 35–37, 38•, 39, 40, 41•, 42•,

43–55, 56•, 57–59, 60•, 61–72] were potentially due to using inappropriate analysis approaches [71, 72, 73•] Overall these studies paint a rather confusing picture of *Fto*'s effects on energy balance. In contrast, transgenic global overexpression of *Fto* in mice, with 1 or 2 extra copies of the gene, resulted in a dose dependent elevation in body fatness [74]. In this instance the impact did include an increase in food intake, on both standard and high fat diets. Moreover, using a regression model analysis it was shown that energy expenditure was not significantly impacted by the copy number of *Fto*. Hence in this model the mode of impact on body composition mirrored exactly that in humans with the susceptible SNP genotypes impacting energy intake but with no effect on energy expenditure. This asymmetry in the impact of over- and reduced expression may explain the apparent conflict between the loss of function studies in rodents and the human studies of the SNP impacts.

Potential Mechanisms of the Association to food Intake

FTO is a Fe(II) and 2-oxoglutarate dependent DNA/RNA demethylase [75••]. Subsequent studies emphasised that it has a stronger affinity for RNA than DNA and a preference for thiamine or uracil, and that this site specificity is dependent on its crystal structure [76••]. The gene and protein are widely expressed but are particularly expressed in the brain including the hippocampus, brain stem and hypothalamus, notably among nuclei previously implicated in the regulation of food intake. Functional coupling analysis has suggested a link to the brain derived neurotrophic factor (BDNF) signalling pathway [77]; known also to be linked to food intake regulation. In rodents, gene expression of *Fto* in the hypothalamus is responsive bidirectionally to nutritional status [78–81] and exercise [82]. For example, fasting reduced both *Fto* mRNA levels and the number of *Fto*-immunoreactive cells in the hypothalamus, but this effect could be reversed by intraperitoneal glucose injection. Moreover, intracerebroventricular injection of glucose increased hypothalamic *Fto* mRNA levels in fasted mice [80]. These data strongly implicated *Fto* gene expression in the hypothalamic regions of the brain that is linked to homeostatic regulation of intake, rather than the reward system. Emphasising this hypothalamic role Tung et al. [83] explored the impact of regional up- or down-regulation of *Fto* in the rat hypothalamus by using stereotactic injections coupled with adenoviral technology. An over expression of *Fto* protein by 2.5-fold in the arcuate nucleus of the hypothalamus resulted in a 14 % decrease in average daily food intake in the first week. In contrast, knocking down Arcuate nucleus (ARC) *Fto* expression by 40 % increased food intake by 16 %. Surprisingly, the mRNA levels of Agouti-related protein (Agrp), Pro-opiomelanocortin (Pomc) and Neuropeptide y (Npy), ARC-expressed genes that have been classically associated with the control of food intake, were not affected by the manipulation. Yet STAT3 which mediates the link between these genes and leptin was significantly affected. This is all the more confusing because in cell culture *Fto* knockdown decreased NPY mRNA expression in SH-SY5Y cells (−21 %) through upregulation of pSTAT3 (118 %) [84].

Olzewski et al. [78, 79] have strongly emphasised the colocalisation of *Fto* with oxytocin expressing neurons and the absence of an impact of *Fto* on the NPY/AgRP/POMC axis of food intake regulation. However, yet other studies implicate *Fto* in the regulation of leptin levels [85] and leptin sensitivity [86], or CREB (cAMP response element binding protein) signalling and hence links to NPY1R and BDNF [77, 87], Ghrelin signalling [38•] and the dopaminergic midbrain circuitry [88].

In contrast to these studies of mRNA, McTaggart et al. [89] focused on the effects of starvation on protein levels following 18 h starvation in the hypothalamus, cerebellum and rostral brain. Contrary to the studies on mRNA they found protein levels were relatively uniform, and that fasting for 18 hours did not alter the expression pattern, or levels, of *FTO* protein (and mRNA). However, contrasting this work, other studies showed that after 48 h starvation both *FTO* mRNA and protein levels were significantly elevated in the lateral hypothalamic area, paraventricular, ventromedial and arcuate nuclei [90]. In addition starvation also altered the intracellular distribution of *Fto*. This was particularly evident in some neurons of paraventricular and ventromedial nucleus, as well as lateral hypothalamic area, but not the arcuate nucleus, and resulted in the majority of the enzyme being localized outside the cell nuclei. Both *Fto* mRNA and catechol-O-methyltransferase mRNA were upregulated in the identical time-dependent manner in fasting animals [90].

The action of *Fto* as a demethylase is dependent on 2-oxoglutarate levels. Since 2-oxoglutarate is an intermediate of the citric acid cycle one possible mechanism by which it may be linked to energy balance is as a sensor of 2-oxoglutarate levels and hence TCA cycle activity. Ma et al. [91•] developed an elegant fluorescent sensor for *Fto* demethylase activity and hence were able to measure its activity and dependence on 2-oxoglutarate concentrations. They were able to show that the K_m of *Fto* for 2-oxoglutarate was 2.88 uM which is about tenfold lower than the estimated intracellular concentrations of 2-oxoglutarate [91•]. Hence this convincingly demonstrated

that it is highly unlikely to act as a sensor of citric acid cycle activity.

Most recently it has been suggested that rather than acting as a sensor of 2-oxoglutarate *Fto* may actually be a sensor of circulating amino acids [81–90, 91•, 92, 93•]. This interpretation was prompted by the fact that *Fto*(−/−) mice [4••, 5] show severe growth retardation, a phenotype replicated in human loss of function mutants [6••]. Cultured cells from *Fto*(−/−) mutants show reduced growth and impaired survival under AA deprivation. The action of *Fto* seemed to be linked to impairment of the translation of mRNA via impacts on the multi-tRNA synthetase complex (MSC) made up of aminoacyl-tRNA synthetases (AARSs) and several accessory proteins. Since AARSs are also implicated in linkage of circulating amino acid levels to the mammalian target of rapamycin complex 1 (mTORC1) signalling, *Fto*/*FTO* could potentially play a role in amino acid sensing. In cell culture *FTO* gene expression is critically regulated by the supply of essential, but not non-essential, amino acids across a range of cell types including hypothalamic N46 cells [81]. This suggests that *FTO* may play a role in sensing specific amino acid availability, probably acting upstream of AARSs and mTORC1. The fact some studies have suggested that the A allele of rs9939609 influences not only energy intake but also protein intake [19, 20•], that A allele carriers respond more positively to high protein diets in terms of reduced cravings and hunger [94], and that AA/AT carriers have a strong preference for meat consumption (OR=4.04) [95] may be significant in this regard. However, it is worth noting that some studies that have otherwise diagnosed a link between genotype and total energy intake have not found an impact on protein intake [e.g. 27, 28].

Is the Critical gene Affected by the Obesity Linked SNPs Really *FTO*?

In their seminal paper where the role of *FTO* as an obesity gene was first discovered, Frayling et al [7] pointed out that *FTO* is close to other genes, and that the important SNP cluster may actually exert its effects via such genes, in particular *KIAA1005* (also called *FTM* and subsequently *RPGRIP1L*) which is only 200 bp away from *FTO*, and transcribed in the opposite direction. This is 65 kb from the cluster of important obesity SNPs in intron 1 of *FTO*. More recently two studies have suggested that the SNPs in the first intron of *FTO*, actually exert their impact via this gene and more distant genes. Stratigopoulos et al. [96] found that a CUX1-regulatory element within the implicated *FTO* region might control expression not only of *FTO* but also *RPGRIP1L* (see also 40). Indeed the expression patterns of these two genes in response to perturbations of energy balance seemed to suggest they are coregulated [97]. Since ciliary genes are known to play a role in energy homeostasis, it was hypothesized that *RPGRIP1L* might actually be the critical target. This was despite the fact in knockout *Fto* mice it was established that there had been no impact of the KO on *Rpgrip1l* [4••]. Heterozygous *Rpgrip1l*(+/−) mice were found to be hyperphagic and fatter, and displayed diminished suppression of food intake in response to leptin administration. In the hypothalamus of Rpgrip1l(+/−) mice, the number of AcIII-positive cilia was diminished which impaired leptin signalling. They consequently suggested that *RPGRIP1L* may be partly or even exclusively responsible for the obesity resulting from the SNPs physically located within *FTO* [98•].

Another gene located nearby to *FTO* is the Iroquois Homeobox gene family member *IRX3*. It has been demonstrated that the obesity-associated SNPs in the first intron of *FTO* are functionally connected, at megabase distances, with *IRX3* [99••]. The obesity-associated SNPs directly interact with the promoters of both *FTO* and *IRX3* in the human, mouse and zebrafish genomes. In addition, long-range enhancers within this region recapitulate aspects of *IRX3* gene expression. Consistent with this, obesity-associated single nucleotide polymorphisms in the first intron of *FTO* are associated with expression of *IRX3* in the human brain, but importantly not with *FTO* expression. Supporting this mode of action, *IRX3* deficient mice have a 25-30 % lower bodyweight suggested to be linked also to an increase in basal metabolic rate. Although the method used to analyse the effect on BMR was a simple ratio to lean body mass and this analysis approach is known to have problems [70]. This strongly suggests that *IRX3* is a long-range target of obesity-associated SNP variants within *FTO*. These findings are remarkable because the relevant SNPs actually lie inside the first intron of *FTO* and *IRX3* is 500 kb downstream, almost 10× more distant than *RPGRIP1L*. Clearly the mechanism of action of the SNPs located by the GWAS procedure is substantially more complex than actions at a single gene. Hence while the function of *FTO* may prove to be as an amino acid sensor, this may ultimately be more significant for its developmental functions, and not its relation to obesity.

Conclusions: What we know and what we don't

We definitely know that a cluster of SNPs in the first intron of the *FTO* gene are strongly linked to obesity. In humans these SNPs seem to act on food intake and not resting energy expenditure. We need more detailed studies of the impacts of the SNPs on macronutrient selection. Current studies sometimes show fat preference or protein preference is affected, but there is little consistency. We have only one study using accelerometry, and another using doubly labelled water, regarding the impact on activity levels and activity expenditure and these give conflicting results. Almost all the studies of the

impacts on human energy balance have been made in Caucasians (Appendix 1, and Tables 1 and 2). Given the different abundances of the minor alleles and the magnitude of their impact in different ethnic populations more studies of non-Caucasians are required. Impacts of the gene on obesity seem to be exacerbated by fat intake, and ameliorated by physical activity. Whether this is due to epistatic gene interactions with other genes that drive fat intake and physical activity, or gene-by-environment interactions is unknown. The impact of the SNPs on food intake seems to be related to reduced post-prandial satiety, fullness and elevated hunger, and this is probably linked to both post-prandial leptin and ghrelin levels. We need more evidence in these respects of the roles of these and other satiety and hunger signals, plus there is no indication at present how *FTO* mediates its impacts on these other pathways. The absence of an effect on the main feeding related neuropeptides NPY/AgRP/POMC in the hypothalamus is perplexing, given its effects on leptin and STAT3 signalling. A role mediated via oxytocin in the hypothalamus is implicated but has not been pursued. Given the widespread distribution of *FTO* in the brain, actions outside the hypothalamus are likely but have not been well explored (but see [88] for impacts on the dopamine system). *FTO* is also expressed peripherally (e.g. [100]) but its role there is less studied than its central distribution, although the rs9939609 polymorphism does have an impact on fat cell lipolysis [101]. Some evidence suggests *FTO* acts as an amino acid sensor linked to mTORC1. Is that function only associated with its developmental role? or does it play a key part of the link to obesity? We know *FTO* is a DNA/RNA demethylase that localises to the nucleus. We know very little about the molecular mechanism(s) by which such demethylase activity exerts its actions presumably on transcription and translation efficiency via specific methylation events [102–108]. These likely influence splicing, stability and export of mRNA [109] and interact with transcriptional regulators such as CEBP [110] but the details are unclear. Finally the SNP cluster may have actions not only on *FTO*, but on more distant genes as well, including *RLGRIP1L* and *IRX3*. At present it is unknown whether even more distant genes are involved. In addition we do not know how the effects on these other genes interact to produce the feeding and obesity phenotypes.

Compliance with Ethics Guidelines

Conflict of Interest John R. Speakman declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Appendix 1

Table 3

Table 3 Effects of variants of the FTO SNPs on food and macronutrient intakes and related parameters (ordered by date of publication)

Reference	Date (mm.yyyy)	Population	n	SNP	Parameter measured	Genotype effect
Do et al [10•]	04.2008	Caucasian adult	908/507F	rs17817449	Food questionnaire energy intake	ns ($p = 0.37$)
					lipid intake	ns ($p = 0.51$)
					CHO intake	ns ($p = 0.87$)
Speakman et al [20•]	08.2008	Caucasian adult	150/103F	rs9939609	1 week weighed intake energy intake	Greater intake in AT and AA relative to TT ($p = .024$)
					Protein intake	highest in AT (p=0.02)
					Sat fat intake	ns ($p = 0.535$)
					PUFA intake	ns ($p = 0.08$)
					CHO intake	ns ($p = 0.095$
					Alcohol intake	ns ($p = 0.149$) linear model ($p = 0.05$) A intake lower

Table 3 (continued)

Reference	Date (mm.yyyy)	Population	n	SNP	Parameter measured	Genotype effect
Timpson et al [28]	10.2008	Caucasian children	3641/ 1881F	rs9939609	3 day diary total energy all foods Protein intake Fat intake At fat intake PUFA intake Carbohydrate intake	(all p values below for model adjusted for BMI) Greater intake with A allele ($p = 0.03$) ns ($p = 0.8$) A allele higher ($p = 0.02$) ns ($p = 0.05$) trend A higher ns ($p = 0.06$) trend A higher ns ($p = 0.4$)
Cecil et al [31]	12.2008	Caucasian Children (4-10y)	97	rs9939609	energy intake at test meal after priming meal Weight ingested after priming meal	A carriers higher ($p = 0.06$ to 0.002) dependent on priming meal energy ns ($p > 0.05$)
Wardle et al [33]	01.2009	Caucasian Children (4-5y)	131	rs9939609	Weighed intake after meal	AA ($p = 0.02$) and AT ($p = 0.03$) ate more than T
Johnson et al [111]	03.2009	Caucasian Children (10-13y)	2275	rs9939609	3 day diary dietary energy density	FTO genotype did not modify the association between fatness and energy density,
Hakanen et al [112]	01.2009	Caucasian Children (15y)	382	rs9939609	4d food record mean daily energy intake Energy /kg Fat % Protein % Carbohydrate %	 ns ($p = 0.99$) ns ($p = 0.69$) ns ($p = 0.27$) ns ($p = 0.81$) ns ($p = 0.97$)
Haupt et al [29]	04.2009	Caucasian adult	151	rs8050136	Food diary	Greater total energy intake in A allele carriers $p = 0.01$
Bauer et al [11]	10.2009	Caucasian adult	1700/ 1700F	rs1121980	77 item FFQ energy intake Fat intake Carbohydrate intake Protein intake Alcohol intake	 ns ($p = 0.2$) ns ($p = 0.12$) trend ($p = 0.08$) T allele eats less ns ($p = 0.49$) ns ($p = 0.47$)
De Hoed et al [34•]	11.2009	Caucasian adult	103/62F	rs9939609	postprandial hunger and satiety using visual analog scale (VAS)	lower responses in A carriers (Additive model $p = 0.02$)
Tanofsky-Kraff et al [35]	12.2009	Caucasian Children (6-19y)	190	rs9939609	Questionnaire on loss of eating control lunch buffet test (energy intake) Fat consumption in test meal	greater loss of control in AT and AA ($p = 0.002$) ns ($p = 0.61$) AA/AT greater than TT ($p < .01$)
Hasselbalch et al [12]	04.2010	Caucasian adult	1119	rs9939609	validated 247 item FFQ Energy intake, Protein, fat, CHO, Alcohol and fiber intake	 all ns ($p > .05$)

Table 3 (continued)

Reference	Date (mm.yyyy)	Population	n	SNP	Parameter measured	Genotype effect
Liu et al [13]	04.2010	Caucasian & African am. adult	1978/ 1025F	rs9939609	>4 × 24h recalls	
					Energy intake	ns (p =0.79)
					% carbohydrate	ns (p = 0.9)
					% protein	ns (p = 0.41)
					% fat	ns (p = 0.62)
Rutters et al [36]	06.2010	Caucasian adult	98/47F	rs9939609	food intake after stress and non-stress manipulations	
					Hunger feelings after food intake	AA/AT increased relative to TT (p < .05)
					Intake at test meal	ns
Papathanasopoulos et al. [113]	07.2010	Caucasian adult	62	rs9939609	Gastric functioning tests	
					gastric emptying	ns (p > .05)
					gastric volume	ns (p > .05)
					maximal tolerable volume	greater in AA than AT/TT (p = 0.0075)
Lee et al [30]	11.2010	Asian children	463	rs9939609	3 day food record	
					energy intake	ns (p = 0.116)
					Carbohydrate intake	ns (p = 0.294)
					Fat intake	A allele higher (p = 0.008)
					Protein intake	ns (p = 0.106)
				Rs9939973	energy intake	ns (p = 0.477)
					Carbohydrate intake	ns (p = 0.670)
					Fat intake	trend heterozygote > (p = 0.089)
					Protein intake	ns (p = 0.589)
		Adults	8842	rs9939609	energy intake	ns (p = 0.768)
					Carbohydrate intake	ns (p = 0.625)
					Fat intake	ns (p = 0.783)
					Protein intake	ns (p = 0.734)
				Rs9939973	energy intake	ns (p = 0.867)
					Carbohydrate intake	ns (p = 0.887)
					Fat intake	ns (p = 0.343)
					Protein intake	ns (p = 0.984)
Hubacek et al [14]	2011	Caucasian adult	6024/ 3244F	rs17817449	140 item FFQ	
					Energy intake	ns (p = 0.75)
					Fat intake	ns (p = 0.38)
					Protein intake	ns (p = 0.61)
					Alcohol intake	ns (p =0.82)
Sobczyk-kopciol et al. [21]	2011	Adult	6584	rs9939609	alcohol consumption	lower in AA (p = 0.012)
					various other alcohol related behaviour	lower in AA
Jonassaint et al [114]	06.2011	Adult	1762	7 SNPs	Eating disorder phenotypes and traits linked to eating disorder pathology	all ns (p?)

Table 3 (continued)

Reference	Date (mm.yyyy)	Population	n	SNP	Parameter measured	Genotype effect
Lear et al [115]	12.2011	Adult Multi-ethnic	706	rs9939609	Dietary intake Europeans. ns in Chinese or south Asians % calories from fat	greater intake for A allele in aboriginals all populations combined $p = 0.064$
Muller et al [116]	06.2012	Caucasian Adults	6101	rs9939609	link to eating disorders AN and BN	A allele greater risk of BN (OR 1.142 p 0.049) A allele greater risk of AN (OR 1.181 p 0.020)
Lappalainen et al. [117]	11.2012	Caucasian Adults	479/319F	rs9939609	3 day food diary Total energy Fat % Carbohydrate % Fiber intake	 ns ($p = 0.726$) ns ($p = 0.985$) ns ($p = 0.611$) ns ($p = 0.109$)
McCaffery et al [18]	2012	Caucasian Adults	2075/1163F	rs1421085	FFQ eating episodes per day total energy intake	 > in at risk C allele ($p = 0.001$) $p = 0.031$, $p = 0.067$ adj for Bwt
				rs9939609	eating episodes per day total energy intake	> in at risk A allele (p =0.018) ns ($p = 0.101$)
				rs9922708	eating episodes per day total energy intake	> in at risk A allele ($p = 0.039$) $p = 0.033$ (0.068 adj for Bwt)
				rs3751812	eating episodes per day total energy intake	> in at risk A allele ($p = 0.014$) $p = 0.035$ (0.067 adj for Bwt)
Velders et al [118]	11.2012	Caucasian children (age 5)	1718	rs9939609	food responsiveness impulsivity and AHDH Emotional control	A allele greater (OR = 1.21, $p = 0.03$) A lower (OR = 0.74, $p = 0.01$) A better (OR = 0.64, $p = 0.01$)
Corella et al [22]	2012	Adult	7052	rs9939609	alcohol intake	lower in A genotype carriers ($p = 0.001$)
Brunkwall et al [119]	2013	Caucasian Adults	22799	rs9939609	food preference for 27 food groups 7 day cooked food records	A genotype greater consumption of biscuits and lower intake of soft drinks ($p = .0001$)
Steemburgo et al [28]	2013	Hispanic adults	236/126F	rs9939609	3 day weighed diet Fat intake Fiber intake	 A allele higher than AT/TT (OR 2.17) A allele lower than AT/TT (OR 2.42)
Chu et al [120]	05.2013	Caucasian adult	33533	rs10163409	Meta-analysis of FFQ data % calories from CHO % calories from fat % calories from protein	 $p < 5 \times 10^{-8}$ independent of adjustment for BMI $p = 1.6 \times 10^{-4}$ marginal $p = 0.068$
Ibba et al [121]	05.2013	Caucasian children	412	rs9939609	Childhood eating behaviour Q	ns all factors

Table 3 (continued)

Reference	Date (mm.yyyy)	Population	n	SNP	Parameter measured	Genotype effect
Tanaka et al [16]	2013	Caucasian adults	7724	rs1421085	FFQ (meta-analysis) protein intake	'at risk' allele higher $p = 9.96 \times 10^{-10}$
Karra et al [38•]	08.2013	Caucasian adult	20	rs9939609	post-prandial (PP) appetite fasting hunger pre-test Fasting fullness pretest PP hunger suppression PP suppression of ghrelin	(VAS) ns ($p = 0.33$) ns ($p = 0.34$) Attenuated in AA ($p = 0.037$) AA impaired ($p = 0.028$)
		Caucasian adult males	24	rs9939609	fMRI responses to food images neural responsivity to food	 $p < .05$
Dougkas et al [37]	09.2013	Caucasian adult	40/0F	rs9939609	appetite by VAS after 4 test meals	Fullness 17.2% lower in AA/AT ($p = 0.026$)
Park et al [17]	09.2013	Multiethnic adult	36973	rs8050136	180 item FFQ and 24h recall % calories from fat % calories from carbohydrate	 A higher ($p = 0.0004$) A lower ($p = 0.00008$)
Wang et al [23]	10.2013	Caucasian adult	2699	128 SNPs	Alcohol dependence	AD shown to depend on at least 3 SNPs $p < .001$
Huang et a [94]	05.2014	Caucasian adult	737	rs9939609	Appetite related traits Cravings Hunger Fullness	 A allele lower when on HP diet ($p = 0.027$) A allele lower when on HP diet ($p = 0.047$)
Kjeldahl et al [122]	05.2014	Caucasian adult	1116	rs9939609	Plasma metabolite profiles	no FTO genotype effect in multivariate model
Scheid et al [39]	06.2014	Adults Mixed ethnic	237/120F	68 FTO SNPs	relative reinforcing value of food snack consumption test	modulation of association between RRVfood and food intake. 6 FTO SNP genotypes explain 4.9 to 7.4% of variance in food intake in the test
Wahl et al [123]	06.2014	Caucasian adult	56/0F	rs9939609	metabolomic responses to high CHO and fat meals	minor effects on metabolite profiles/fluxes
Qi et al [19]	08.2014	Mixed ethnic adult	177330	rs9939609	meta-analysis of 37 studies FFQ (31 studies), recall (2 studies) dietary record (2 studies) mixed (2 studies) Total energy Protein % energy carbohydrate % energy Fat % energy	 A allele lower $p = 0.001$ across all ethnicities A allele higher $p = 2.4 \times 10^{-16}$ A allele lower $p = 0.004$ not significant $p = 0.24$
Harbron et al [15]	08.2014	Caucasian adult	133	rs 1421085 rs17817449	FFQ eating behaviour Q	at risk alleles linked to poorer eating behaviour score Higher intake of high fat foods and refined starch

Table 3 (continued)

Reference	Date (mm.yyyy)	Population	n	SNP	Parameter measured	Genotype effect
Yang et al [95]	08.2014	Chinese children		rs9939609	preference for meat based diet	AA/AT genotypes prefer meat (OR 4.04)
Roswall et al [124]	10.2014	Caucasian adult	6548	rs9939609	Response to Nordic or Mediterranean diets	not modified by FTO genotype

CHO carbohydrate, *FFQ* Food frequency questionnaire, *PUFA* Poly-unsaturated fatty acids, *VAS* Visual analog scale, *RRV* relative reinforcing value, *PP* post-prandial, *OR* Odds ratio

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