Genetics of fat intake in the determination of body mass

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Abstract

Body mass and fat intake are multifactorial traits that have genetic and environmental components. The gene with the greatest effect on body mass is *FTO* (fat mass and obesity-associated), but several studies have shown that the effect of *FTO* (and of other genes) on body mass can be modified by the intake of nutrients. The so-called gene–environment interactions may also be important for the effectiveness of weight-loss strategies. Food choices, and thus fat intake, depend to some extent on individual preferences. The most important biological component of food preference is taste, and the role of fat sensitivity in fat intake has recently been pointed out. Relatively few studies have analysed the genetic components of fat intake or fatty acid sensitivity in terms of their relation to obesity. It has been proposed that decreased oral fatty acid sensitivity leads to increased fat intake and thus increased body mass. One of the genes that affect fatty acid sensitivity is *CD36* (cluster of differentiation 36). However, little is known so far about the genetic component of fat sensing. We performed a literature review to identify the state of knowledge regarding the genetics of fat intake and its relation to body-mass determination, and to identify the priorities for further investigations.

Key words: **Fat intake: Body mass: Gene polymorphisms: Fat sensitivity: *FTO***

Introduction

Most traits related to metabolism, as well as susceptibility to diet-related diseases, show complex determination in the general population[1]. Such multifactorial traits depend on genetic and environmental factors and on the interactions between them. Yet for different traits, the involvement of each factor may be different. In the great majority of cases, the development of obesity depends on both genetic and environmental factors, which simply means that body mass depends on individual genetic makeup and on energy balance.

The genetic architecture of complex traits includes the distribution of effects, the number of loci affecting a phenotype, and the interactions between the loci[2]. Heritability (H^2) is a parameter that indicates the degree to which the variability of each trait in a population can be attributed to genetic factors. The H^2 of the genetic component of BMI and of abdominal obesity ranges from 0·4 to 0·7 and from 0·4 to 0·55, respectively[3,4]. Genetic variation is the result of many combinations of alleles in the population. Millions of genomic loci can occur in different variants, and the most frequent type of polymorphism found in the genome is the SNP[5]. Regarding metabolism, DNA polymorphism can influence the dynamics between nutrients and their molecular targets, which contributes to the differences in individual responses to diet, and consequently to phenotypic variability. So far, at least 100 loci have been identified for BMI[6,7]. However, any one gene involved in body-mass determination has a relatively small effect on phenotype. The average BMI increase per allele ranges from 0·06 to 0·39 kg/m^2[8].

As mentioned above, one of the components that affects body mass is energy balance; this depends on the individual's metabolic rate, physical activity and food intake. Each of these elements can be considered a separate trait, again with complex determination. The main focus of this review is fat intake in relation to body-mass determination; for that reason, individual differences in metabolic rate and physical activity are not discussed here.

Genetic determination of fat intake: linkage and genome-wide association studies and candidate genes

Heritability of fat intake

The considerable individual differences that undoubtedly exist in overall food intake, as well as in the intake of particular foods or specific nutrients, are partly explained by genetic variation. Relatively few studies have been undertaken to identify the genes associated with macronutrient intake, but familial aggregation of intakes has been demonstrated. The magnitude of the reported genetic effects differs from study to study (due to different populations and methods), but typically ranges from about 20 to 40 %. For fat intake measured as a percentage of energy intake, the correlation was 0·61 for monozygotic twins, 0·59 for dizygotic twins and 0·36 for siblings[9].

Monozygotic twins share 100 % of their genes, so the magnitude of correlations shows the degree of the influence of genes on a trait of interest. Patterns for family correlations for fat intake may depend on the method of data collection. Values from a food diary method were higher than those from FFQ, with the mean H^2 values being 0·33 and 0·16, respectively. Due to methodological issues (for example, the limited number of possible responses and broad generalisation of food categories), FFQ may poorly represent actual overall intake, which can lead to both overestimation and underestimation of macronutrient intake[10], which is in this case an analysed phenotype. The results may also be affected by age-related effects, because family correlations among individuals of the same generation were higher (with a mean value of 0·40) than for individuals of different generations (with a mean value of 0·24)[11].

The H^2 values for the preference for fat or high-fat foods have been estimated in a few studies. Some results demonstrate that the preference for dietary fats is independent of genetic factors[12], but high H^2 (0·78) was shown for liking meat and fish[13].

Genome-wide approach

Genome-wide linkage studies have identified several chromosome regions for macronutrient and energy intake. The Quebec Family Study has identified evidence for the presence of six quantitative trait loci (QTL) that influence total energy and macronutrient intakes. The best evidence of linkage was found at region 3q27·3, where one of the markers was linked to energy, lipid and carbohydrate intakes. A candidate gene located in this region is the adiponectin gene (*ADIPOQ*)[14]. In the San Antonio Family Heart Study, a QTL for macronutrient consumption (total energy, total protein, total fat, and saturated and unsaturated fats) was identified on chromosome 2p22. The pro-opiomelanocortin gene (*POMC*) was tested as a candidate, but no association was demonstrated[15]. In the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study, the strongest evidence of linkage for energy intake appeared on chromosomes 1p21·2 and 20q13·13, and for fat intake on chromosome 12q14·1[16].

More recently, a few genome-wide association studies (GWAS) have been undertaken to identify the loci associated with macronutrient intake (http://www.ebi.ac.uk/gwas/)[17]. A two-stage genome-wide association meta-analysis of macronutrient intake in populations of European descent has been carried out[18]. In this study, the H^2 estimates for protein, carbohydrate and fat intakes were 17, 20 and 20–23 %, respectively. Genome-wide significant associations for fat intake were observed on 19q13·33. The minor allele of rs838145 was associated with a lower percentage of energy intake from fat. The *FGF21* (fibroblast growth factor 21) gene was proposed as a candidate located in this region, and it was shown that its minor allele was associated with higher concentrations of FGF21 protein. Moreover, the BMI-increasing allele (rs1421085) of the *FTO* (fat mass and obesity-associated) gene was found to be associated with higher protein intake[18]. A study based on the DietGen Consortium identified rs838133 in *FGF21* (19q13·33), rs197273 near TRAF family member-associated NF-κB activator (*TANK*) (2p24·2), and rs10163409 in *FTO* (16q12·2) as the top associations for

the percentage of total energy intake from protein and carbohydrates[19]. A genome-wide significant association for the percentage of total energy intake from carbohydrates was identified in SNP in an intron of the *FTO* gene. The rs838133 variant at the *FGF21* locus was associated with increased carbohydrate intake and decreased fat intake. A GWAS of adolescents from a French–Canadian population identified the *OPRM1* (opioid receptor mu 1) gene as a fat intake gene[20]. The minor *OPRM1* allele (rs2281617) was associated with lower fat intake (by 4 %) and lower body fat mass (by about 2 kg). The rs822396 SNP in intron 1 of the adiponectin (*ADIPOQ*) gene, which encodes adiponectin, was identified as being associated with confectionery intake[21]. This polymorphism was not directly associated with circulating adiponectin levels, but could be linked with other causative SNP. Heritability analyses have shown that the common SNP tested in this study explain a modest proportion (6–8 %) of the genetic variance in carbohydrate, protein and fat intake.

Genome-wide association studies on fat intake

In 2014, the results of the above-mentioned GWAS, which sought loci associated with fat intake, were published[20]. One gene found to have a great effect on fat intake and body fat mass is the *OPRM1* gene, which encodes a receptor expressed in the brain's reward system. This opioid receptor is also the primary receptor for the endogenous opioid peptide β-endorphin, encoded by the *POMC* gene, which is well known for its function in appetite regulation. The rs2281617 and rs518596 polymorphisms of the *OPRM1* gene have been associated with fat intake and body adiposity[20]. Moreover, the results suggest that these polymorphisms are not functional SNP. The questions that remain are whether such associations also exist in other populations, and which of them are causative mutations. One of the SNP identified in the *OPRM1* gene is the A118G functional polymorphism, which affects this gene's mRNA and protein yield[22]. The potential role of this polymorphism in the preference for fatty foods was examined by Davis *et al.*[23], who measured fat preference with the food preference questionnaire. The food preference questionnaire reflects attitudes to different food items. The researchers suggested that part of the variability in the preference for palatable foods can be explained by this polymorphism. However, this result needs to be replicated in other populations and with more ecologically valid assessments of food preferences[23]. The effects of the A118G polymorphism on the frequency of high-fat food consumption, obesity and lipid metabolism have not yet been determined. Interestingly, it has been shown that prenatal exposure to cigarette smoking interacts with the *OPRM1* genotype (rs2281617), with T-allele carriers showing lower fat intake in non-exposed individuals, but not in exposed individuals[24].

Functional candidate genes

Several functional candidate gene approaches have also addressed the question of genetic variation in fat intake. Some of these have focused on genes involved in the central control

of food intake, including the melanocortin 4 receptor (*MC4R*) gene[25,26], dopamine receptor 2 (*DRD2*)[27], the 5-HT$_{2A}$ receptor gene[28] and the *FTO* gene[29]. The role of the *FTO* gene is discussed in more detail in the next section.

One gene with a great effect on body mass is the *MC4R* gene; this encodes a receptor for melanocortin, which binds α-MST – a product of the *POMC* gene. The rs17782313 polymorphism near the *MC4R* gene has been found to be associated with obesity among European adults[30], but also with high intakes of total energy and total fat[31]. Yilmaz *et al.*[26] showed that rs17782313 is significantly associated with depressed mood and overeating behaviours, while Khalilitehrani *et al.*[25] have reported an association between the same polymorphism and fat intake (Table 1).

It is worth mentioning that associations between genetic variants and traits may change over time. For example, the association between the *FTO* genotype and BMI strengthens during childhood and adolescence, reaching its peak at the age of 20 years. Similarly, the *MC4R* polymorphism shows an association with body weight that is strong during childhood and adolescence, but which weakens with increasing adult age[32,33].

FTO is the gene with the greatest effect on body mass

FTO was the first obesity-susceptibility gene to be identified in a GWAS, and is the gene with by far the largest effect and which explains the largest phenotypic variance among individuals of European ancestry[34,35]. A cluster of SNP in the first intron of *FTO* has been identified (linkage disequilibrium $r^2 > 0.80$); they are all significantly associated with BMI[29]. Each additional minor allele is associated with a 0.39 kg/m^2 higher BMI and a 1.20-fold increase in the risk of obesity[36]. Approximately 43% of the population of European ancestry carry one minor allele, while 20% carry two minor alleles[29]. The *FTO* locus accounts for 0.34% of interindividual variation in BMI[37].

The biological role of FTO has recently been described. The *FTO* gene encodes for the Fe(II) and 2-oxoglutarate-dependent demethylase of single-stranded DNA and RNA[38], and is capable of demethylating single-stranded DNA and RNA at m6A, m3U or 3 mT[39]. It has been shown that FTO itself regulates body weight and that its overexpression leads to obesity[40,41], while Fto$^{-/-}$ mice show postnatal growth retardation and are resistant to high-fat diet-induced obesity[42]. The role of FTO in the cellular sensing of amino acids has been described[43]. The sensing of amino acid levels in the brain regulates the orexigenic and anorexigenic pathways controlling energy balance[44]. *FTO* is highly expressed in the hypothalamus, but data on the regulation of its expression by nutritional status are confusing[45–48]. It has been shown in a rodent model that food deprivation up-regulates hypothalamic *Fto* expression, and that these changes are associated with cues related to energy intake rather than with feeding reward[49]. It was recently described that *FTO* affects body weight by regulating thermogenesis[50,51]. There are direct interactions between the *FTO* locus and the distant *IRX3* (Iroquois-related homeobox 3) and *IRX5* (Iroquois-related homeobox 5) regions, which are developmental regulators affecting adipocyte differentiation. The *FTO* variants regulate the expression of *IRX3* and *IRX5*, and the risk allele of the causal SNP rs1421085 disrupts a conserved motif for the ARID5B repressor,

which doubles the expression of *IRX3* and *IRX5* during adipocyte differentiation. One result of this is a developmental shift from beige to white adipocytes and a consequent reduction in mitochondrial thermogenesis and increase in lipid storage[50,51].

Several studies have shown that *FTO* polymorphism is associated with food intake and body mass, but a comprehensive understanding of how it affects the functioning of the body still needs to be reached through investigations. Subjects homozygous for a risk A allele of *FTO* rs9939609 have dysregulated levels of the orexigenic hormone acylghrelin and attenuated postprandial appetite reduction[52]. In a 2-year trial entitled 'Preventing Overweight Using Novel Dietary Strategies', it was shown that dietary protein significantly modifies the genetic effects on food cravings and appetite scores; in particular, this risk A allele of *FTO* (rs9939609) was associated with a greater decrease in food cravings and appetite scores in participants with high-protein diet intakes[53]. Brunkwall *et al.*[54] indicated that carriers of the risk A allele of *FTO* reported a higher consumption of biscuits and pastry, but a lower consumption of soft drinks, than TT genotype carriers. They thus concluded that *FTO* polymorphism may be associated with certain food preferences. Most studies on food intake and *FTO* variation were conducted in children and have shown that individuals carrying the A allele at rs9939609 consumed more fat and total energy than those not carrying the variant[55]. Some of the studies did not find such an association. For example, Hakanen *et al.*[56] concluded that the *FTO* gene is not directly associated with energy intake at age 15 years (Table 1). Similarly, there was no evidence for association between the risk A allele and dietary energy density[57]. Hardy *et al.*[58] also concluded that the relationship between *FTO* variants and BMI does not occur primarily through the mediation of food intake. On the contrary, Cecil *et al.*[59] reported an association between the risk A allele and increased energy intake. A combined analysis of over 16 000 children and adolescents has suggested that the risk A allele is associated with higher total energy intake, and that lower dietary protein intake attenuates the association between the *FTO* genotype and adiposity[60]. Moreover, in the Multiethnic Cohort Study, percentage of energy from fat was a partial mediator of the rs8050136 effect on BMI[61]. A randomised cross-over trial in forty overweight men showed that *FTO* polymorphism is related to variation in the feeling of postprandial fullness[62]. Together, these may suggest that interactions between the intakes of different macronutrients and micronutrients are important for the overall results. Further studies are needed for a comprehensive understanding of *FTO* biology in different cell types. It could be hypothesised that, in addition to a developmental shift favouring lipid-storing adipocytes over beige adipocytes, *FTO* may exert its effect on body mass through the regulation of appetite and food preference[29].

Food intake as environmental exposure in gene–environment association studies of body mass

As mentioned earlier, genetic variation significantly contributes to body-mass variation, but fat intake may modify the effect of the genotype. The genetic variability described so far explains only about 5% of the interindividual BMI variance[8].

Table 1. Candidate gene studies on fat intake and fat sensitivity

Population analysed	Number of individuals analysed (n)	Sensory analysis	Food intake assessment	Polymorphism analysed	Effect	References
Fat intake						
Caucasian population	1078	Not analysed	DHQ, a FFQ	APOA2; rs5082	Total fat and protein intakes (expressed as g/d) were statistically higher in CC individuals than in T allele carriers. CC individuals had higher BMI values	Corella et al. 2007[138]
Caucasian population	3641	Not analysed	3 d dietary records	FTO; rs9939609	Individuals carrying the A allele at rs9939609 had higher BMI and consumed more fat and total energy than those without this variant	Timpson et al. 2008[55]
Caucasian population	5724	Not analysed	Semi-quantitative FFQ	MC4R; rs17782313, rs17700633	Carriers of the C allele at rs17782313 had an increased risk of type 2 diabetes, a higher intake of total energy and dietary fat, and higher BMI. The SNP rs1770833 was not significantly associated with either dietary intake or obesity	Qi et al. 2008[31]
Caucasian population	97	Not analysed	Test meal: lunch	FTO; rs9939609	The children who carried the A allele had significantly greater energy intake and BMI than those not carrying it	Cecil et al. 2008[59]
Caucasian population	640	Not analysed	4 d food records of children's food consumption	FTO; rs9939609	The FTO genotype was associated with BMI but not with energy intake in children older than 7 years of age. Children homozygous for the A allele had higher BMI than children with one or two T alleles	Hakanen et al. 2009[56]
Caucasian population		Not analysed	3 d unweighed food diaries	FTO; rs9939609	Dietary energy density and FTO were correlated with greater BMI. Allele A at rs9939609 was associated with greater fat mass	Johnson et al. 2009[57]
Caucasian population	300	Not analysed	Food preference questionnaire	OPRM1; rs1799971, rs510769, rs495491, rs563649, rs675026, rs9322447, rs558948	Only SNP rs495491 and rs563649 were associated with food preferences. Subjects homozygous for rs495491G-allele had lower fat preference compared with the GA and AA genotypes, while subjects homozygous for the rs1799971 G allele had higher fat preference compared with AA and GA genotypes	Davis et al. 2011[23]
Multiple ethnic populations	36 990	Not analysed	Study-specific quantitative FFQ	NEGR1; rs2815752 TMEM18; rs6548238 BDNF; rs6265 FTO; rs8050136 MC4R; rs17782313 KCTD15; rs11084753	FTO's obesity-risk allele rs8050136 was positively associated with the percentage of energy from fat and was most strongly associated with BMI among European Americans	Park et al. 2013[61]
Japanese population	977	Not analysed	Self-administered questionnaire (recording the usual frequency of consumption of forty-three food items)	ADIPOQ; rs822396	Adiponectin may play an important role in the regulation of energy homeostasis, including appetite stimulation	Wakai et al. 2013[21]
Caucasian population	22 799	Not analysed	A modified interview-based diet history method	FTO; rs9939609	Carriers of the A allele consumed a higher number of meals per d and ate more servings of energy-dense foods. The AA genotype carriers consumed fewer soft drinks than the TT genotype carriers	Brunkwall et al. 2013[54]
Caucasian population	40	Not analysed	Ad libitum food intake was monitored by determining total food consumed (g) and energy consumed (kJ)	FTO; rs9939609 LEP; rs7799039 LEPR; rs1137101 MC4R; rs17782313	The FTO and LEP polymorphisms were associated with a feeling of fullness and decreased prospective food consumption	Dougkas et al. 2013[62]
Caucasian population	598	Not analysed	24 h food recall, analysed with Recipe File (USDA)	OPRM1; rs2281617	OPRM1 may be involved in the regulation of dietary preference. At this locus, T-carriers compared with CC homozygotes showed lower fat intake	Haghighi et al. 2014[20]

Table 1 *Continued*

Population analysed	Number of individuals analysed (*n*)	Sensory analysis	Food intake assessment	Polymorphism analysed	Effect	References
Iranian population	400	Not analysed	3 d food record	*MC4R*; rs17782313	*MC4R* rs17782313 was associated with high energy intake and low carbohydrate and protein intakes	Khalilitehrani *et al.* 2015[25]
African-American and Asian population	16094	Not analysed	Validated FFQ (four studies), multiple-day dietary/food records (three studies), multiple-day 24 h recalls (four studies), both dietary records and 24 h recalls (one study), diet history determined by consulting and use of information systems (one study), or a brief self-administered diet history questionnaire (one study)	*FTO*; rs9939609	There was a significant association between the minor (A) allele of the *FTO* SNP rs9939609 and higher BMI and higher total energy intake in all participants. The association was significant in 15 352 Caucasians, but not in 478 African-Americans. Dietary protein intake may modify the influence of *FTO* variants on BMI	Qi *et al.* 2015[60]
Fat sensitivity						
African-American (*n* 19) and Caucasian (*n* 2) population	21	Triolein and OA were added at varying concentrations to double-distilled water	24 h diet recall with a multiple-pass system and the Fat Preference Questionnaire	*CD36*; rs1761667	Subjects homozygous for the rs1761667 G allele had lower detection thresholds for OA and triolein than did subjects homozygous for the A allele, which is associated with lower *CD36* expression. Total energy, fat consumption, fat preference scores and food cravings were similar among AA, AG and GG subjects	Pepino *et al.* 2012[134]
African-American population	317	Italian salad dressings were prepared with varying amounts of rapeseed oil (rich in long-chain fatty acids)	Fat preference analysis	*CD36*; rs1984112, rs1761667, rs1527483, rs1049673	The rs1761667 and rs1527483 SNP in the *CD36* gene were associated with oral fat perception. Carriers of the AA genotype perceived the Italian salad dressings to be creamier than did the GA and GG individuals	Keller *et al.* 2012[91]
Arab–Berber population	165	OA sensitivity analysis (one solution contained OA with acacia gum (0·01 %) while the other two served as controls with 0·01 % acacia gum only	Not analysed	*CD36*; rs1761667	The AA and AG genotypes were more frequent in obese teenagers, whereas the GG genotype was more common in lean participants. The A allele was more frequent in obese teenagers than in lean children	Daoudi *et al.* 2015[139]

DHQ, diet history questionnaire; *APOA5*, apolipoprotein A-V; *FTO*, fat mass and obesity-associated; *MC4R*, melanocortin 4 receptor; *OPRM1*, opioid receptor mu 1; *NEGR1*, neuronal growth regulator 1; *TMEM18*, transmembrane protein 18; *BDNF*, brain-derived neurotrophic factor; *KCTD15*, K channel tetramerisation domain containing 15; *ADIPOQ*, adiponectin; *LEP*, leptin; *LEPR*, leptin receptor; USDA, United States Department of Agriculture; OA, oleic acid; *CD36*, cluster of differentiation 36.

Several explanations for the hidden or missing H^2 have been proposed[63], including overestimation of body mass H^2 and inaccurate phenotyping, but also complex gene–gene or gene–environment interactions (G×E)[64]. One of the mechanisms proposed for G×E is changes in DNA methylation upon specific environmental triggers[65]. The standard GWAS ignores potentially useful information available in the form of environmental exposure data. It has been shown that power can be gained by accounting for possible G×E when scanning for marginal effects[66]. The design of G×E studies is more complex than that of classical association studies. They require bigger sample sizes which, beside allele frequency and effect size, also depend on the magnitude of the interaction. It has been suggested that smaller studies with repeated and more precise measurement of the exposure and outcome could be as powerful as studies that are as much as twenty times greater[67].

G×E in obesity were reviewed a few years ago by Qi & Cho[68]. Several genome-wide G×E association studies on body mass have been conducted. A genome-wide interaction meta-analysis produced evidence of age-dependent genetic effects on BMI[7]. Li et al.[69] provided a demonstration that a physically active lifestyle is associated with a 40% reduction in genetic predisposition to common obesity, as estimated by the number of twelve risk alleles. In a study of Goni et al.[70], significant interactions were found for genetic risk score on adiposity traits on the basis of twenty-three SNP and macronutrient intake (including consumption of energy, total protein, animal protein, vegetable protein, total fat and SFA). In several studies, fat intake was found to modify the genotype effect. Sonestedt et al.[71] observed that increases in BMI across FTO genotypes are restricted to those reporting a high-fat diet. Among TT and AA genotypes (including rs9939609), mean BMI of 25·3 and of 26·3 kg/m^2 were observed, respectively. Corella et al.[72] similarly found that SFA intake may strengthen the association between FTO gene polymorphism and BMI. Participants homozygous for the FTO risk allele (rs9939609) had higher mean BMI than the other genotypes only when they had high intakes of SFA[72]. Moreover, the consumption of fried food may modify a genetic risk score based on the effect of thirty-two BMI-associated variants on BMI[73]. The OR for obesity per ten risk alleles were 1·61 (95% CI 1·40, 1·87), 2·12 (95% CI 1·73, 2·59) and 2·72 (95% CI 2·12, 3·48) across three categories of fried food consumption, which means that the combined genetic effect on BMI among individuals who consumed fried foods more than four times per week was about twice as large as among those who consumed fried foods less than once per week. An interaction between total fried food consumption and an FTO variant (rs1558902) was also detected[73]. Fat intake was also shown to modulate the effect of the Pro12Ala polymorphism of the PPARG gene on BMI. Ala/Ala individuals had higher BMI than did Pro carriers among high-fat consumers[74]. Also, when the ratio of dietary polyunsaturated fat to saturated fat is low, the BMI of Ala carriers is greater than that of Pro homozygotes[75]. Increases in fat intake have been associated with increases in waist circumference in Pro/Pro homozygotes[76]. BMI was higher among Ala allele carriers only when the ratio of polyunsaturated fat to saturated fat was low, with the opposite being seen when this ratio was high.

There have been a limited number of studies that have considered food (fat) intake as exposure. One of the reasons for this is that it is likely that food intake assessment methods are often time-consuming and become more challenging in studies involving hundreds of participants. Since food intake measurement methods are inaccurate, some studies may fail to detect interaction effects, and for that reason may be less likely to be published.

Role of fat content in the diet and gene polymorphism in weight-loss strategies

The effectiveness of weight-loss strategies may depend on dietary composition (proportions between macronutrients). It has been demonstrated that a reduction in fat intake without intentional restriction of energy is associated with weight loss, and with more substantial weight loss in heavier subjects[77]. Sacks et al.[78] tested diets with different macronutrient compositions and did not observe any significant differences between their effects on body-weight decreases. A recent meta-analysis showed that low-fat interventions, as compared with higher-fat interventions, have a similar effect on weight loss, but that the effect of low-fat diet interventions on body weight depends on the intensity of the intervention in the comparison group[79]. Another meta-analysis has shown that low-carbohydrate diets may lead to greater reductions in body weight than do low-fat diets[80].

G×E effects are important for weight-loss strategies[68,81,82]. Fat intake modifies the effects of the genotype on body weight, BMI or lipid profile[83–86]. Greater reductions in body weight and total fat mass in response to a low-fat diet were observed in TT individuals (rs12255372) of the TCF7L2 (transcription factor 7 like 2) gene than in other genotype groups[83,84]. Stocks et al.[86] reported interactions between the TFAP2B (transcription factor AP-2β) rs987237 polymorphism and fat content in an energy-restricted diet. The AA genotype was associated with a 1·0 kg greater weight loss on the low-fat diet, and the GG genotype with a 2·6 kg greater weight loss on the high-fat diet. The effectiveness of a 2-year weight-loss dietary intervention was found to depend on the interactions between the APOA5 rs964184 polymorphism. In the low-fat intake group, carriers of the risk G allele exhibited greater reductions in TAG and LDL-cholesterol than did non-carriers, whereas in the high-fat diet group, participants with the G allele showed a greater increase in HDL-cholesterol than did participants without this allele[87]. Interactions between the hepatic lipase gene (LIPC) and dietary fat affected the results of a long-term weight-loss dietary intervention. In the low-fat diet group, the A allele of rs2070895 was associated with a decrease in TAG and LDL-cholesterol concentrations, and an opposite genetic effect was found in the high-fat diet group[88]. Different variants of CLOCK rs3749474 may influence the effect of a short-term dietary fat restriction on weight loss. The T-allele carriers showed a positive association between the change in the percentage intake of dietary fat and the change in BMI[89]. Changes in abdominal adipose tissue, visceral adipose tissue, and subcutaneous adipose tissue upon dietary intervention may also be modified by a neuropeptide Y (NPY) gene variant (rs16147). The rs16147 T allele appeared to be associated with more adverse change in the abdominal fat deposition in the high-fat diet group than in the low-fat diet group[90]. This type of

study is a step forward in personalised weight-loss strategies, which may be used in the near future.

Fat sensitivity, fat intake and gene polymorphism

Taste as a component of fat preference and fat intake

Fat consumption varies across individuals, and excess dietary fat consumption can be caused by a number of factors, including environmental triggers (for example, the broad availability of energy-dense foods) and the psychological, physiological and metabolic properties of an organism that depend on the many genes encoding hormones, enzymes and receptors involved in the regulation of food intake. However, the factors that contribute to increased fat intake are not well understood[91].

A preference for a certain food is defined as the selection of one food item over others when liking is the basis for the selection, though it may be only one of the motives[92]. A greater preference for fatty foods, as well as increases in the consumption of such food, have been documented in obese subjects[93]. It should be borne in mind that food preferences and food intake may not be correlated with each other[94]. Since food preferences are just one component of the food decision-making process, they usually provide only an approximation of actual food consumption[94,95]. Food choices depend on genetic and environmental determinants, with the latter including food availability and accessibility, as well as the social and cultural environment, but also several economic factors. Individual biological predispositions depend on several mechanisms – partly dependent on genotype – which determine the regulation of appetite as well as taste and sensory sensitivity[96,97]. The sensory qualities of food are critical to dietary preferences, and taste may be one of the most important determinants of food choice[98]. The fat content of food contributes to sensory properties that can guide food choice and energy intake[99]. However, sensory responses alone do not predict food consumption[100]. As mentioned by Mattes, several recent observations have drawn attention to the links between oral fat detection, fat intake, lipid metabolism and chronic disease risk[101].

Another important question is whether body mass affects fat sensitivity. However, experimental support for a hypothesis relating fat taste to fat intake and BMI remains equivocal[99]. The most commonly tested hypothesis states that decreased fatty acid sensitivity leads to increased fat intake and obesity, and the results of several studies have supported this hypothesis[102–105]. However, factors other than adiposity status – including genotype, salivary composition, and habitual or acute dietary fat intake – may influence fat taste intensity ratings[106]. In obese individuals, portion control or a low-fat diet may increase fat sensitivity, but the low-fat diet had the greatest effect[107]. It has been reported that obesity may shift the preference for oily solutions and orosensory detection of NEFA in diet-induced obesity (DIO) rats and mice[108]. The results suggest that, during behavioural tests, obese animals have a lesser ability to detect fatty acids through a cluster of differentiation 36 (CD36)-mediated mechanism than do lean animals.

Fat taste

Taste is a chemical sense whose mechanism involves chemical stimulation of sensory cells contained in taste buds[109]. The primary and commonly accepted tastes are sweet, bitter, salty, sour and umami[110]. In recent years, researchers have proposed another taste corresponding to fat, called pinguis[101] or oleogustus[111]. Although, some questions still remain (as pointed out by Besnard et al.[112]), accumulating evidence suggests that humans can taste fatty acids and that dietary fat consumption may be partially regulated by an oral detection mechanism[113]. The main compounds in dietary lipids are TAG[114], but there are reports that the primary stimuli for orosensory fat perception are fatty acids. The first evidence that taste receptors are activated by NEFA was provided in 1997 by Gilbertson et al.[115]. Moreover, Kawai & Fushiki[116] have demonstrated that NEFA bind directly to receptor CD36, at the same time disproving the idea that TAG could be recognised by CD36. The key protein involved in the conversion of TAG to NEFA in the oral cavity is lingual lipase. In rodents, this enzyme has strong lipolytic activity and plays a primary role in fat detection[98]. In vivo assays suggest that in humans the functional activity of LP is very weak (2 µmol/min·per l)[117], or even absent[118,119]. The secretion of lingual lipase is stimulated by chewing, which may suggest that lingual lipase contributes to oral fat detection in the case of fatty foods, which require a greater oral processing effort[117].

Knowledge on the transduction mechanism of fat taste is limited and most information has come from animal studies. Fatty acid perception is mediated by the proposed CD36 receptor, the G-protein-coupled receptors GPR120 and GPR40[120], and transient receptor potential channel type M5 (TRPM5)[121]. CD36, also known as FAT (fatty acid translocase), is an integral membrane protein with high affinity for long-chain fatty acids[122]. It is found on the apical side of the lingual taste-bud cells[123] and plays an important role in dietary lipids perception. In a mouse model it has been proved that in gustatory cells linoleic acid, by binding to CD36, induces the Src-PTK phosphorylation and initiates Ca signalling[124]. GPR40 and GPR120, members of the GPCR family, are specifically expressed in the mouse gustatory epithelium of the tongue[125]. Both CD36 and GPR120 exhibit similar binding specificities for long-chain fatty acids; however, GPR120 can only bind to specific types of fatty acid, while CD36 has a higher affinity for ligands and can respond to many types of fatty acid[109]. Mice lacking CD36, GPR120 or GPR40 have diminished preference for fatty acids[125,126]. However, GPR40 is not abundant in human gustatory tissues, while GPR120 is present in gustatory and non-gustatory epithelia[127]. For that reason a rodent model may not be appropriate to explore human fat taste transduction. Stimulation of the above-mentioned receptors leads to the generation of a specific signal and initiation of a second-messenger cascade, which in turn results in activation of the afferent nerve fibre, transferring the signal to the brain[124,128].

Orosensory sensitivity may be modulated by endogenous factors (endocannabinoids) and by hormones, as well as by fat consumption or appetite. Recent studies have shown that paracrine signalling within the taste buds may be regulated by

fat sensitivity[112]. It has been demonstrated that glucagon-like-peptide-1 (GLP-1) has a significant impact on taste sensitivity in mice[129]. GLP-1 and its receptor (GLP-1R) are expressed in two populations of mammalian taste cells: a subset of type II cells and a subset of type III cells[129]. Disruption of the *Glp-1r* gene may lead to a significant deterioration in fatty acid detection, as has been confirmed in two bottle preference tests in mice and through the licking test[130]. The molecular mechanism behind GLP-1's modulation of sensitivity to fatty acids is not yet fully understood, although it has been speculated that the intact *Glp-1r* gene may increase sensitivity to fatty acids by regulating lingual CD36 during eating[126].

Determination of fat sensitivity and its relation to body mass

There is interindividual variability in fat taste sensitivity, but there are methodological challenges involved in testing fat sensitivity, such as the lack of a commonly accepted test method. The specific testing methods and stimulus vehicle used vary across research groups, which makes comparison very difficult. In this way, several aspects of testing procedures may affect the results and contribute to the variability seen in them[99]. Tucker *et al.*[131,132] claim that repeated testing is required to properly assess associations between fat taste and outcomes such as BMI or food intake. Recently, a reliable and reproducible method of assessing oral chemoreception using an emulsion of milk and 18 : 1 has been proposed[133]. However, this method requires several unstable milk emulsions and may be too complex for large studies[99].

There is also a biological component to the individual ability to detect fatty acids, but the H^2 of fatty acid perception is unclear[7]. Pepino *et al.*[134] (Table 1) analysed twenty-two obese subjects with different *CD36* genotypes (rs1761667) and showed that GG homozygotes had an eight-fold lower oral detection threshold for oleic acid than did AA homozygotes; this was associated with lower gene expression. Although fat intakes and fat preferences were similar among subjects with different genotypes, the small number of individuals involved may explain this result. It could be assumed that the effect size of this single genotype on fat intake is too small to detect in such a group. Moreover, potential differences between lean and obese subjects were not considered in this study. Obese women with the *CD36* GG genotype (rs1761667) exhibited an oral detection threshold for oleic acid that was over three times lower than that of individuals with the AA genotype[135]. In one study alone, associations between gene polymorphism, fat sensitivity, fat preference (though not fat intake) and body weight were examined at the same time. Three polymorphisms of the *CD36* gene (rs1761667, rs3840546 and rs1527483) were reported to be associated with the outcomes in the study of Keller *et al.*[91] (Table 1). Participants were presented with salad dressings with three different fat concentrations and asked to rate perceived oiliness, fat content and creaminess on a visual analogue scale. As nose clips were not used in this experiment (to imitate a real eating experience), the ratings were based on both taste and smell. The test used in this study was thus not a discrimination test. Moreover, salad dressings are not pure stimuli and may not accurately reflect true fat sensitivity. On the other hand, a discrimination test with the use of salad dressing mimics food choices made during natural eating occasions. It was found that alleles of rs1761667, rs1527483 and rs3840546 were associated with perceived creaminess, fat content ratings and body weight, respectively For a few polymorphisms of *CD36*, no associations were detected with the examined traits, so the results were inconsistent, as might be anticipated for polymorphisms separated by about 2 kb[91]. Interestingly, the *Cd36* gene is expressed in the olfactory epithelium of mice, and *Cd36*-deficient animals display impaired preference for a lipid mixture odour[136]. Humans are able to detect slight differences between milk samples with varying grades of fat, and this ability is not affected by BMI or dairy intake[137]. It could thus be hypothesised that the effect of the *CD36* polymorphism on food choices involves sensing fats in the oral cavity and through olfactory perception, which might have played a role in the study of Keller *et al.*[91]. In summary, little is known so far about the genetic component of fat sensing. Methodological issues, including the lack of a rapid and valid test method for fatty acid sensitivity, may be the reason why no GWAS on this trait has been performed.

Conclusions

Fat intake is, to some extent, dictated by fat preference, which may in turn depend on individual sensory abilities. A genetic component has been demonstrated for all these parameters. However, many questions remain concerning the genetic determination of fat intake and its relation to body mass. There are several methodological issues that make studies of this topic more complicated: food intake measurements are labour-intensive and the results are only approximations of the real intake. In other words, precise phenotyping of food intake is extremely difficult, especially in GWAS. Additionally, more data are needed in order to come to a conclusion regarding the relationship between fat sensitivity and fat intake or the frequency of eating high-fat foods. One of the first steps in this field should be the development of a valid and relatively quick method of testing oral fat sensitivity. Usually, association studies need to be repeated in multiple populations if cause-and-effect relationships are to be identified between a polymorphic site and a trait. For all these reasons, there is still much work to be done in precisely describing the relationship between fat intake, fat sensitivity and body weight.

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