The bigger picture of *FTO*—the first GWAS-identified obesity gene

Ruth J. F. Loos and Giles S. H. Yeo

Abstract | Single nucleotide polymorphisms (SNPs) that cluster in the first intron of fat mass and obesity associated (*FTO*) gene are associated obesity traits in genome-wide association studies. The minor allele increases BMI by 0.39 kg/m^2 (or 1,130 g in body weight) and risk of obesity by 1.20-fold. This association has been confirmed across age groups and populations of diverse ancestry; the largest effect is seen in young adulthood. The effect of *FTO* SNPs on obesity traits in populations of African and Asian ancestry is similar or somewhat smaller than in European ancestry populations. However, the BMI-increasing allele in *FTO* is substantially less prevalent in populations with non-European ancestry. *FTO* SNPs do not influence physical activity levels; yet, in physically active individuals, *FTO*'s effect on obesity susceptibility is attenuated by approximately 30%. Evidence from epidemiological and functional studies suggests that FTO confers an increased risk of obesity by subtly changing food intake and preference. Moreover, emerging data suggest a role for FTO in nutrient sensing, regulation of mRNA translation and general growth. In this Review, we discuss the genetic epidemiology of FTO and discuss how its complex biology might link to the regulation of body weight.

Loos, R. J. F. & Yeo, G. S. H. *Nat. Rev. Endocrinol.* **10**, 51–61 (2014); published online 19 November 2013; doi:10.1038/nrendo.2013.227

Introduction

In the general population, an estimated 40–70% of the variation in obesity susceptibility arises from interindividual genetic differences.[1,2] Despite this substantial genetic contribution, the identification of genetic variants associated with obesity traits has been limited by our poor understanding of genome architecture and of the biological pathways implicated in obesity, as well as by small, insufficiently powered studies.[3] However, the development of genome-wide association studies (GWAS)—a hypothesis-free approach made possible by advances in high-throughput genotyping technology—has dramatically increased the speed of gene discovery. GWAS have identified approximately 2,000 genetic loci with robust associations for more than 300 common traits and diseases,[4,5] including at least 75 obesity susceptibility loci.[6,7] The *FTO* (fat mass and obesity associated) gene was the first obesity susceptibility gene identified by GWAS.[8,9] This locus has the largest effect on BMI and obesity risk and is most widely replicated with a variety of obesity traits throughout the life course and across diverse ancestries.[7] In this Review we discuss the discovery of *FTO* as an obesity gene and the insights gained through epidemiological and functional follow-up studies to elucidate the biological pathways that underlie the association between *FTO* and obesity.

Genetic epidemiology of *FTO*

FTO—the first obesity susceptibility gene

In 2007, two studies reported the discovery of *FTO* as the first GWAS-identified obesity susceptibility gene.[8,9] *FTO* was first discovered in a GWAS of type 2 diabetes mellitus (T2DM) in Europe that compared 1,924 patients with 2,938 healthy individuals.[8] A cluster of single nucleotide polymorphisms (SNPs) in the first intron of the gene showed robust association with T2DM risk ($P = 5 \times 10^{-8}$), which was convincingly replicated in an independent case–control study ($P = 9 \times 10^{-6}$).[8] However, after adjusting for BMI in the replication samples, the association with T2DM was abolished ($P = 0.44$), suggesting that the association of *FTO* with T2DM was mediated through effects on BMI. Follow-up analyses in 38,759 individuals confirmed that *FTO* is associated with BMI and obesity risk.[8] 8 weeks after the initial report, the first GWAS for BMI demonstrated the most significant associations for SNPs in the first intron of *FTO* ($P = 9 \times 10^{-7}$) in 4,741 individuals from Sardinia. These results were subsequently replicated in 2,335 European and Hispanic Americans ($P = 10^{-3}$).[9] A third study identified the same *FTO* locus when testing for population stratification in case–control obesity data.[10] These three studies firmly established *FTO* as the first gene with common polymorphisms that affect obesity susceptibility in the general population.

The *FTO* locus

The first two GWAS that reported *FTO* as an obesity susceptibility gene each identified different SNPs in the gene's first intron that most significantly associated with BMI (rs9939609,[8] rs9930506;[9] Figure 1). Subsequent GWAS for obesity-related traits in populations with European ancestry all confirmed *FTO* as an obesity susceptibility locus, but each identified different *FTO* SNPs that showed the most significant association.[11–22] For example, data

The Genetics of Obesity and Related Metabolic Traits Program, The Charles Bronfman Institute for Personalized Medicine, The Mindich Child Health and Development Institute, The Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1003, New York, NY 10029-6574, USA (**R. J. F. Loos**).
MRC Metabolic Diseases Unit, University of Cambridge Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, Box 289, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK (**G. S. H. Yeo**).

Correspondence to:
R. J. F. Loos
ruth.loos@mssm.edu
G. S. H. Yeo
gshy2@cam.ac.uk

Competing interests
The authors declare no competing interests.

Key points

- A cluster of single nucleotide polymorphisms (SNPs) in intron 1 of fat mass and obesity associated (*FTO*) gene was the first obesity susceptibility locus identified by a genome-wide association study (GWAS)
- FTO is an RNA demethylase that links amino acid availability and mTORC1 signalling to regulate growth and mRNA translation
- Of all GWAS-identified obesity susceptibility loci, the *FTO* locus has the largest effect; SNPs in the *FTO* locus are associated with obesity traits, throughout life and across diverse ancestries
- SNPs in *FTO* are also associated with non-adiposity traits, such as cardiometabolic traits, type 2 diabetes mellitus and osteoarthritis; most of these associations are mediated through FTO's effect on BMI
- Evidence from epidemiological and functional studies suggests that *FTO* confers an increased risk of obesity through subtle changes in food intake and preference

from 247,796 individuals of European ancestry, found SNP rs1558902 is most significantly associated with BMI ($P<10^{-60}$, Figure 1).[16] However, multiple neighbouring SNPs (Figure 1a) also show highly significant associations with BMI ($P<10^{-50}$).

Linkage disequilibrium (LD) is a measure of association between two alleles (Box 1). All GWAS-identified *FTO* SNPs belong to the same highly correlated cluster, with an LD of $r^2>0.80$, and consequently are associated with BMI at similar significance levels (Figure 1a), as well as with other obesity-related traits. In populations with European ancestry, the SNP cluster that includes all GWAS-identified *FTO* SNPs covers ~46,000 base pairs in the first intron of *FTO* that likely include the functional variant that explains the risk and associated phenotype, known as the causal variant. The cluster of BMI-associated *FTO* SNPs in East Asian populations is very similar to that of European ancestry populations (Figure 1b). Three large-scale GWAS in Korean[23], Chinese[24] and Japanese[25] populations each identified different *FTO* SNPs (rs9939609, rs17817449, rs12149832, respectively) as the most significantly associated with BMI, all of which are highly correlated (LD $r^2>0.90$) in both East Asian and European populations (Figure 1b). However, in populations of African ancestry, the correlation between SNPs in the first intron of *FTO* is substantially weaker than in those with European or East Asian ancestry (Figure 1b). This difference in LD allows refinement of the chromosomal region in which the causal variant(s) might be located. For example, a large-scale GWAS in a group with African ancestry combined data from 45,849 individuals and identified rs17817964 as the most significantly BMI-associated *FTO* SNP.[26] In populations of European and East Asian ancestry, rs17817964 is part of the same large cluster in *FTO* intron 1, whereas in African ancestry populations it represents a cluster of fewer SNPs across a smaller region, thus narrowing the locus that harbours the causal *FTO* variant (Figure 1b). In a targeted fine-mapping by the Population Architecture using Genomics and Epidemiology (PAGE) study,[27] the genotypes of 3,756 SNPs across a 646 kb region at chromosomal location 16q12.2, encompassing *FTO* and the neighbouring *RPGRIP1L*, were tested in >20,000 African Americans. In this study, rs56137030 is most significantly associated with BMI.[27] In individuals of Europeans ancestry, this SNP represents a cluster (LD r^2 for European ancestry >0.50) of 103 (out of the 3,756 total) SNPs, whereas in African Americans this cluster includes only 29 SNPs (due to weaker LD between SNPs).[27] Six of the 29 SNPs are found within intronic regulatory elements, two of which are predicted to have allele-specific binding affinities for different transcription factors, including cut-like homeobox 1, which might influence the transcriptional regulation of *FTO*.[28,29]

Taken together, the BMI-associated *FTO* region, initially identified in European populations, has been refined using the weaker correlation between SNPs in populations with African ancestry. These insights will help focus studies to pinpoint the causal variants.

Effect and variance across populations

At least 75 obesity susceptibility loci have been identified in addition to *FTO* using large-scale GWAS.[7] However, among individuals of European ancestry, the *FTO* locus has the greatest effect on obesity, is the most common, and has the largest explained variance. Specifically, each additional minor risk allele is associated with a 0.39 kg/m^2 higher BMI (equivalent to 1.13 kg for a person who is 1.70 m tall) and a 1.2-fold increase in obesity risk (Table 1).[16] Approximately 43% of the European-ancestry population carries one risk allele and 20% carry two, with small variations in genotype frequencies within these populations (Figure 2). Although the *FTO* locus explains the interindividual variation in BMI better than any other BMI-associated loci identified to date, its contribution is low at only 0.34%.[16] Consequently, the ability to predict a person's obesity risk based on *FTO* genotype is poor—only slightly better than tossing a coin.[30]

Soon after the discovery of *FTO* in European populations, other studies investigated its effects in groups with non-European ancestry, supporting the association of *FTO* as a general obesity susceptibility locus. The most consistent replications have been observed for individuals with Asian ancestry. Three large-scale GWAS in East Asian populations identified *FTO* SNPs as significantly associated with BMI.[23–25] Furthermore, targeted studies of specific population groups consistently confirmed the association of FTO with obesity-related traits in Chinese,[31–39] Japanese,[40–44] Koreans,[45,46] Vietnamese,[47] Filipino,[48] Malay[31] and Indian Asian populations.[49–57] In a meta-analysis that combined data of 96,551 individuals of Asian ancestry, each additional minor allele increases the risk of obesity (using Asian BMI cut-off values) by 1.25-fold, which is similar to the effect seen in European populations.[58] BMI increases by 0.26 kg/m^2 (equivalent to 750 g for a person who is 1.70 m tall) for each additional minor allele,[58] which is substantially less than in those with European ancestry and might reflect the fact that BMI represents a different adiposity phenotype in Asian populations compared with Europeans. Effect sizes of East and South Asian populations were similar, but the minor allele frequency was lower in East Asians (Chinese Hans and South Koreans, 12–14%; Japanese and Filipinos, 18–20%) than in South Asians (30–33%), which in turn are both lower than in European individuals (42%; Table 1). As a

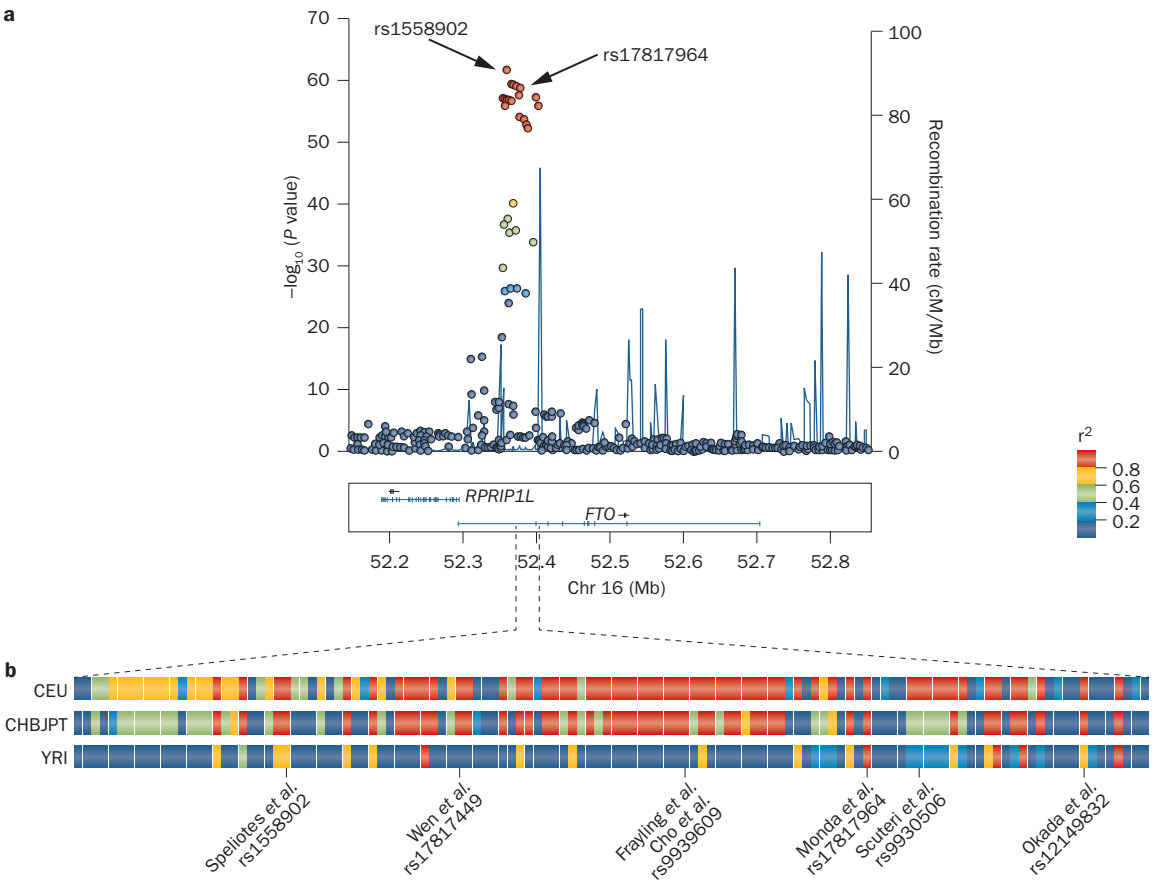

Figure 1 | A cluster of BMI-associated SNPs in the first intron of FTO. **a** | Regional plot of the *FTO* locus in populations with European ancestry. SNPs are plotted by position on chromosome 16 against association with BMI (–log10 P-value).[16] Recombination rates (from the European [CEU] HapMap) reflect the local LD structure (cyan). SNPs surrounding rs17817964 (red) are colour-coded to reflect their LD with this SNP (r^2 values from the CEU HapMap data). **b** | The LD structure of SNPs surrounding rs17817964, based on LD r^2 values from the CEU, Asian (CHBJPT) and African (YRI) HapMap data. Each colour block represents a SNP in the first intron of FTO (between position 52,355,019 and 52,407,580 according to NCBI Build 36). SNPs highly correlated with rs17817964 (LD r^2>0.80) are shown in red. Abbreviations: CEU, Utah residents with Northern and Western European ancestry from the CEPH collection; CHBJPT, Han Chinese in Beijing, Japanese in Tokyo; LD, linkage disequilibrium; YRI, Yoruba in Ibadan, Nigeria.

consequence of the smaller effect size and lower minor allele frequency (Figure 2), *FTO* SNPs in Asian populations explain less of the variation in BMI (0.16–0.20%) than in European ancestry populations.[58]

Results of targeted replication of *FTO* in Africans and African Americans have been inconsistent,[27,59–74] which might be due to the substantial differences in the LD between *FTO* SNPs in African compared with European or Asian ancestry populations (Figure 1b). As such, an *FTO* SNP that is part of the larger European–Asian cluster, but that does not overlap with the African cluster, will probably not show association with obesity-related traits. However, in a large-scale GWAS in populations of African ancestry, SNPs in *FTO* were among the most significantly associated with BMI ($P = 10^{-10}$), further establishing *FTO* as an obesity susceptibility locus in this ancestry.[26] While the effect of *FTO* on BMI in African populations was similar to that observed in those European ancestry, the minor allele frequency was much lower (12%; Figure 2), such that only 0.10% of the variation of BMI in those of African ancestry was explained (Table 1).[26] SNPs in *FTO* are also associated with BMI and other obesity-related traits in Hispanic and Latino populations[74–77] and American Pima Indians.[78]

Taken together, SNPs in *FTO* are associated with obesity-related traits across many ancestries. However, the allele frequency of the BMI-associated *FTO* SNPs differs substantially across ancestries, with the highest prevalence of minor (risk) allele carriers observed in those with European ancestry, but substantially fewer in Asian and African populations (Figure 2).

Box 1 | Linkage disequilibrium

Linkage disequilibrium (LD) measures the nonrandom association between alleles of different variants. LD is often expressed by the squared correlation co-efficient r^2, which ranges between 0 and 1. The higher the r^2, the closer the alleles are linked and the more likely they are to be inherited together. Any two alleles that are always inherited together, and are therefore closely linked, have an r^2 of 1. An allele inherited independently of another will have an r^2 of 0.

Table 1 | Effect size and explained variance of BMI-associated FTO SNPs

Ancestry	BMI-increasing allele frequency (%)	Effect on BMI (kg/m^2 per allele)	Explained BMI variance (%)	Effect on obesity risk‡ (OR per allele)	Reference
European	42	0.39	0.34	1.20	Speliotes *et al.*[16]
East Asian	12–20	0.25	0.16	1.27	Li *et al.*[58]
Indian Asian	30–33	0.29	0.20	1.18	Li *et al.*[58]
African	12	0.41*	0.10	ND	Monda *et al.*[26]

*Derived from the stage 2 effect size (inverse variance units) reported by Monda *et al.*[26] (assuming an SD of 6 kg/m^2). ‡Obese versus normal weight; in European ancestry populations the obesity cut-off level is 30 kg/m^2, in Asian ancestry populations the cut-off level is 28 kg/m^2. Abbreviations: ND, not determined; OR, odds ratio.

FTO and obesity risk over the life course

The association of *FTO* with obesity-related traits has also been confirmed in studies of children and adolescents.[8,19–21,38,39,56,59–61,79–89] Although SNPs in *FTO* do not influence birth weight,[88–92] studies with multiple measures over the life course show that *FTO* SNPs already affect body weight during early childhood (as early as 3 years old), after which the effect increases to reach its largest effect in young adulthood, followed by a subsequent weakening of the effect throughout adulthood.[86–90,93,94] Interestingly, a meta-analysis of eight BMI studies including children aged from 2 weeks to 13 years, showed that before 2.5 years, the BMI-increasing *FTO* allele was associated with reduced BMI.[94] This study further showed that individuals carrying the *FTO* allele associated with increased BMI in adults displayed an earlier childhood adiposity rebound, suggesting faster maturation, than those carrying other *FTO* alleles.[94]

FTO and lifestyle factors

To gain insight into the potential mechanisms through which variation in *FTO* leads to increased risk of obesity, many studies have examined whether SNPs in *FTO* are associated with food intake and physical activity, the two major mediators of body weight regulation.

Evidence supporting a role for *FTO* in the regulation of food intake is increasing. The BMI-increasing allele of *FTO* is associated with increased energy,[80,95–97] dietary fat[96,98,99] or protein intake,[97,100] increased appetite and reduced satiety,[101,102] poor food choices and eating habits,[103,104] and loss of control over eating.[105] A GWAS of macronutrient intake, in more than 70,000 individuals, found the BMI-increasing allele of *FTO* SNPs to be associated with increased protein intake ($P = 10^{-9}$), even after accounting for *FTO*'s effect on BMI ($P = 3 \times 10^{-7}$).[106] Despite this increasing evidence, some studies could not confirm the association of *FTO* with dietary traits.[43,60,107–111]

Other studies have consistently shown that SNPs in *FTO* are not associated with levels of physical activity,[43,100,110–114] which has been convincingly confirmed in a large-scale meta-analysis of published and unpublished data of 218,166 adults and 19,268 children.[115] Although physical activity does not seem to mediate the association between *FTO* and obesity susceptibility, this meta-analysis showed that the effect of *FTO* on BMI and obesity risk is approximately 30% lower in physically active than in sedentary adults.[115] These results confirm the observations of many individual studies[43,73,112–114,116,117] and emphasize the importance of physical activity in body weight regulation in adults—even those who are genetically susceptible to obesity benefit from being active. The mechanism that mediates the interaction between FTO and physical activity or other lifestyle factors, and whether this effect attenuation is observed only with physical activity or also with other lifestyle factors, is unclear. Some studies suggest that dietary habits, energy intake[97,100,108] and smoking[72] might also attenuate the effects of *FTO* on obesity susceptibility. SNPs in the first intron of *FTO* are associated with methylation capability, and some investigators speculate that this region might be sensitive to epigenetic effects.[118–120]

Studying lifestyle factors such as physical activity and food intake is challenging because their measurement can be inaccurate. Nevertheless, increasing evidence suggests that physical activity attenuates the association between *FTO* and obesity susceptibility, whereas food intake might mediate this association. However, which components of food intake are predominantly targeted by *FTO* still needs to be confirmed.

Obesity-related comorbidities

SNPs in the first intron of *FTO* associate with a number of adiposity-related traits. Although there has been little support for a role of FTO in body fat distribution, assessed by waist-to-hip ratio adjusted for BMI,[121] a GWAS in >10,000 individuals with CT measures of adipose depots observed convincing association between *FTO* SNPs and subcutaneous ($P = 6.2 \times 10^{-7}$), but not visceral ($P = 0.17$) adipose tissue.[122] Obesity is an important risk factor for cardiovascular and metabolic disease. Hence, it comes as no surprise that, because of the robust association between *FTO* and BMI, *FTO* SNPs are also associated with a range of cardiometabolic traits (Supplementary Table 1). A large-scale meta-analysis of 36 studies ($n = 198,502$) examined the effect of *FTO* on 24 cardiometabolic traits. In this study, the BMI-increasing allele of *FTO* was associated with increased risk of T2DM, heart failure, coronary heart disease, all-cause and ischaemic stroke, hypertension, dyslipidaemia, metabolic syndrome and mortality, as well as with increased fasting glucose and insulin levels, 2 h oral glucose tolerance test glucose levels, HbA_{1c}, blood pressure, lipid levels, liver enzymes and inflammation markers (Supplementary Table 1).[123] For most traits, these associations were mediated by *FTO*'s effect on BMI.[123] However, some evidence suggested that *FTO* might, at least in part, increase the risk of T2DM independently of its effect on BMI,[123] which is consistent with earlier observations.[57,58,124]

Obesity is also considered a risk factor for certain cancers, which motivated researchers to also test if the BMI-associated *FTO* SNPs were associated with cancer. Whereas some studies found *FTO* SNPs to influence the risk of some cancers,[125–131] other studies could not confirm this.[132–135] Interestingly, two large-scale GWAS identified SNPs in the second and eighth intron of *FTO* that are robustly associated with risk of estrogen

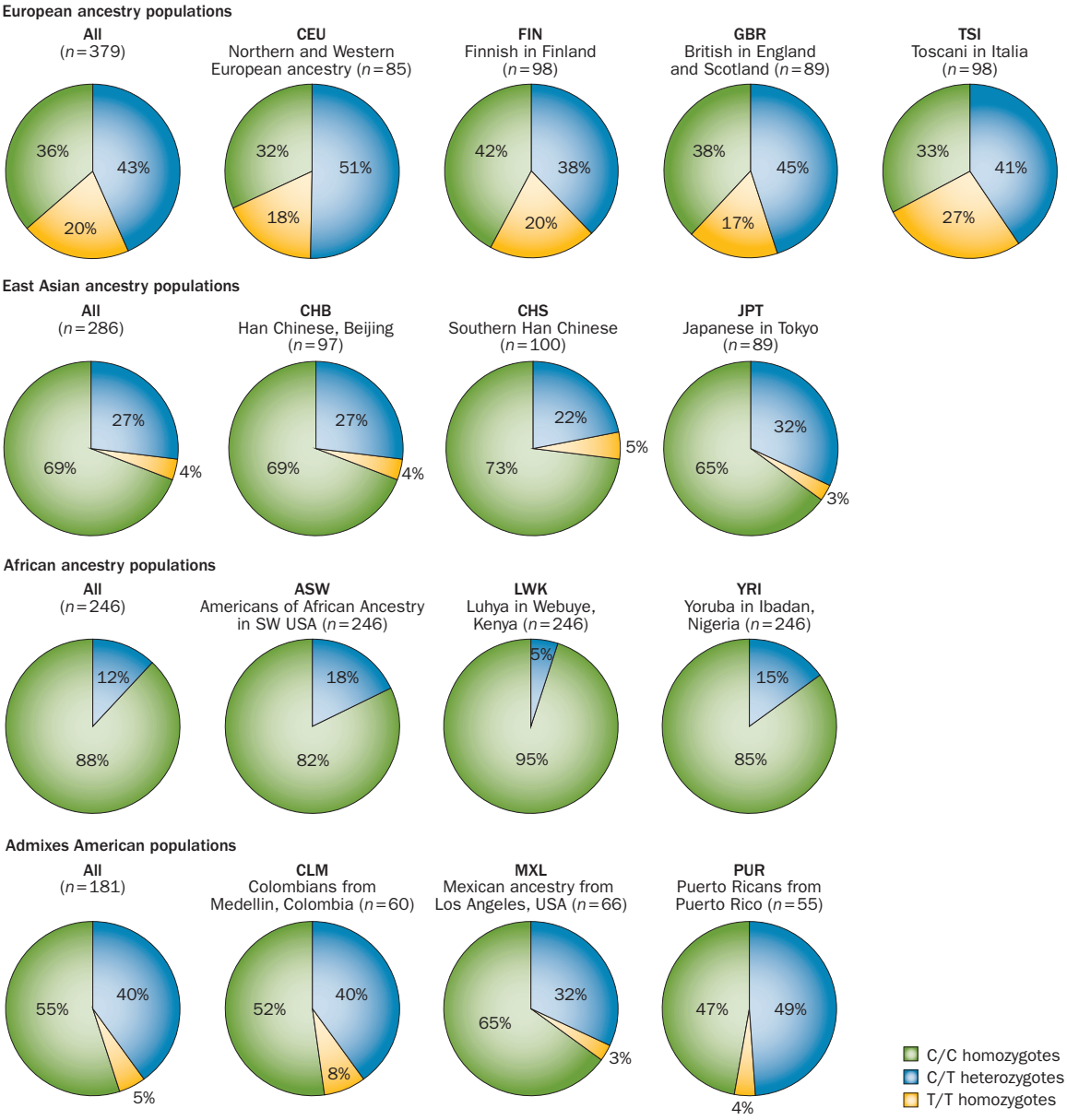

Figure 2 | Genotype frequencies for rs17817964 within and across ancestries based on the 1000 Genomes Project.[176] The T-allele is the BMI-increasing allele. The 'ALL' group for each ancestry combines genotype frequencies from the different populations within the same ancestry.

receptor negative breast cancer[136] and melanoma[137] (Supplementary Table 1). These two cancer-associated loci are independent (LD r^2 for European ancestry <0.10) from the BMI-associated locus in intron 1 of *FTO* and of each other. Their association with cancer risk is not mediated via an effect on BMI,[136,137] indicating that FTO influences pathways other than those associated with body weight regulation.

FTO mutations and obesity risk

Three studies, have examined whether rare variants in *FTO* are disproportionally represented in obese or lean individuals.[138–140] At least 45 low-frequency coding variants were identified, but no study found evidence of an enrichment of any particular variant, (individually or combined) in individuals with or without obesity, even though some are predicted to have deleterious effects on FTO function.[138–140]

FTO biology

FTO is a nucleic acid demethylase

FTO is a 2-oxyglutarate and Fe(II) dependent demethylase, closely related to the bacterial DNA demethylase AlkB and the mammalian AlkB homologues, ABH1 and ABH2.[141] *In vitro*, recombinant FTO catalyses the Fe(II)-dependent and 2-oxyglutarate-dependent demethylation of 3-methylthymine in single-stranded DNA,[141,142] and 3-methyluracil[141,142] and N6-methyladenosine (known as m6a in short)[143] in RNA. This functionality suggests a potential role for FTO in nucleic acid repair

or modification. The crystal structure of FTO shows an N-terminal catalytic domain and a C-terminal domain of unknown function.[144] The catalytic site contains five obligate amino acid residues found in all members of this enzyme superfamily: a histidine and an aspartic acid, required for binding Fe(II); and three residues, a histidine and two arginines, separated by six amino acids, required for 2-oxyglutarate binding.[138,144] The specificity for single-stranded nucleic acids is provided by an L1 loop, not present in other members of the AlkB family, which prevents double-stranded nucleic acids from entering the catalytic pocket by steric hindrance.[144]

FTO demethylates N6-methyladenosine, the most common modified nucleoside in mRNA,[145] with 50-fold greater affinity than 3-methyluracil,[143] which is found largely in ribosomal RNA.[146] However, because the vast majority of total RNA is ribosomal RNA there is, in absolute terms, far more 3-methyluracil than N6-methyladenosine in any given cell (Loos and Yeo, unpublished observations). Whether one or both of these modified bases are the endogenous substrate for FTO is still not clear.

FTO deficiency

Multiple examples exist where common variants close to a particular gene, such as *MCR4*,[11,147–149] *POMC*,[150,151] *BDNF*[13,152] and *PCSK1*,[153,154] are associated with alterations in risk of common phenotypes, such as increased fat mass and obesity. Rare loss-of-function mutations in these same genes can lead to a highly penetrant severe early-onset obesity. However, FTO is more complicated. *Fto* was originally identified as one of six contiguous genes in a 1.6 Mb chromosomal deletion causing the fused-toe phenotype in mice.[155] This deletion included *Ftm*, *Ftl,* the iroquois B cluster (consisting of *Irx3*, *Irx5*, and *Irx6*), as well as *Fto*. Mice homozygous for the deletion are embryonically lethal, whereas heterozygous fused-toe mutants have severe developmental abnormalities including defective left–right asymmetry,[156] impaired hypothalamic development,[156,157] as well as fused digits and hyperplasia of the thymus without any metabolic alterations. By contrast, mice with a specific targeted deletion of *Fto* did not display such severe developmental abnormalities, but had retarded postnatal growth, decreased fat and lean body mass, and elevated food intake when corrected for lean body mass.[158] Postnatal lethality is also high, with only 50% of homozygous pups reaching weaning age.[158,159]

In humans, a loss-of-function *FTO* mutation leads to a complex phenotype of postnatal growth retardation, microcephaly, severe psychomotor delay, functional brain deficits and facial dysmorphism.[160] In some patients, structural brain malformations, cardiac defects, genital anomalies and cleft palate are also seen. The Arg316Gln mutation, which swaps an arginine necessary for 2-oxyglutarate binding for a glutamine, leads to a loss of FTO demethylase activity. The importance of FTO's ability to demethylate is underlined by the severe phenotype; moreover, no affected individual has survived past the age of 30 months.[160] In both humans and mice, therefore, a fully functional FTO is critical for normal physiology.

The role of *RPGRIP1L*

SNPs in *FTO* associated with the highest risk of obesity are close to the transcriptional start site of *RPGRIP1L*, the human orthologue of mouse *Ftm*, which is adjacent to *FTO* but coded for on the opposite DNA strand (Figure 1a).[28] Initial studies focused on FTO because it is nutritionally regulated in the hypothalamus,[141] whereas RPGRIP1L localizes in the primary cilia and centrosomes of ciliated cells.[161] Mutations in the *RPGRIP1L* gene lead to Joubert syndrome type 7, which presents with cerebellar and brainstem malformation and renal failure.[161] Patients with Joubert syndrome type 7 have no obvious body-weight-related phenotypes. However, a 'lean' phenotype is difficult to identify in a healthy individual, let alone a patient who is severely ill. In mice, deletion of *Ftm* recapitulates the cerebral, renal and hepatic defects seen in patients with Joubert syndrome type 7.[161]

Some evidence suggests that *FTO* and *RPGRIP1L* are co-regulated. A region in intron 1 of *FTO* contains at least two putative cut-like homeobox 1 transcription factor binding sites, one of which overlaps with other obesity-associated SNPs.[27,28] Furthermore, *in vitro* evidence indicates that FTO can function as a transcriptional co-activator of CCAAT/enhancer-binding proteins.[162] The association between *FTO* and body-weight regulation might, therefore, be mediated through expression changes in both *FTO* and *RPGRIP1L*, but this hypothesis has yet to be proved.

FTO expression and energy homeostasis

Despite the severe phenotype seen in FTO deficiency, there is evidence that FTO might regulate energy homeostasis. For example, mice with a knockout of the *Fto* gene ($Fto^{-/-}$) have an apparent hyperphagia, and $Fto^{+/-}$ mice are resistant to obesity induced by a high-fat diet.[158] A knock-in mouse model, which expresses additional copies of *Fto*, shows that ubiquitous *Fto* overexpression leads to a dose-dependent increase in body and fat mass, irrespective of whether mice are fed a standard or a high-fat diet.[163] However, although this weight increase correlates with the lean phenotype of FTO deficiency, the increased food intake seen in these mice does not. Obese mice with increased fat mass would be expected to have increased leptin levels, but at 8 weeks, mice overexpressing *Fto* have reduced fasting leptin levels.[163] The hyperphagic phenotype might, therefore, plausibly be driven by hypoleptinaemia in these *Fto* mutant mice.

FTO is expressed ubiquitously in human and animal tissues,[141] which is consistent with the observation that multiple organ systems are affected by *FTO* deficiency. FTO expression is highest in the brain, including the hypothalamus, a region with a key role in the control of food intake.[141] Within the arcuate nucleus of the hypothalamus, nutritional status regulates FTO expression, which decreases following a 48 h fast[141] and increases after a 10-week exposure to a high-fat diet. Moreover,

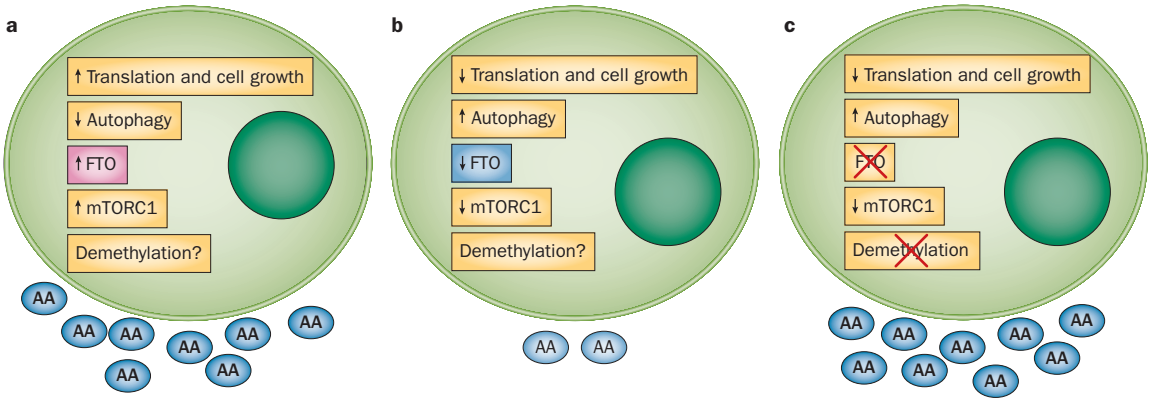

Figure 3 | Hypothetical role of FTO in amino-acid sensing. **a** | Under conditions of sufficient amino-acid levels, FTO levels and consequently mTORC1 activity are maintained, leading to appropriate translation and cell growth and inhibition of autophagy. **b** | In conditions of amino-acid deprivation, FTO levels drop, leading to decreased mTORC1 activity, mRNA translation and cell growth, whereas autophagy is increased. This mechanism ensures cellular survival by maintaining cellular energy levels. **c** | A cell with defective FTO (red X) interprets this as amino-acid starvation, thereby reducing mTORC1 signalling and increasing autophagy. Abbreviations: AA, amino acid; FTO, fat mass and obesity associated gene; mTORC1, mammalian target of rapamycin complex 1.

modulating FTO levels specifically in the arcuate nucleus can influence food intake.[164]

Despite inconsistencies between different mouse models, FTO seems to influence energy homeostasis by directly regulating food intake. Surprisingly, mouse lines, in which *Fto* has been specifically deleted in the brain recapitulate much of the phenotype of the whole-body knockouts,[165] suggesting that a substantial proportion of FTO function, particularly in regulating energy homeostasis, is mediated by the brain.

FTO as a nutrient sensor

Given that FTO is nutritionally regulated and can influence food intake, a role for FTO as a nutrient sensor is possible. With 2-oxyglutarate being a co-substrate of FTO and a key intermediate in the citric-acid cycle, initial studies explored whether FTO senses intracellular concentrations of this metabolite. However, typical intracellular concentrations of 2-oxyglutarate are more than 10-fold higher than its calculated dissociation constant (K_m) of 2.88 μM, so a physiological role for FTO in sensing 2-oxyglutarate seems unlikely.[166]

However, FTO mRNA and protein levels are dramatically downregulated by amino acid deprivation in mouse and human cell lines.[167] Strikingly, this regulation was seen only with essential amino acids.[167] Overall these results suggest that amino acids regulate *FTO* expression, which can lead to a growth retardation phenotype during *FTO* deficiency.

FTO and mTORC1 signalling

Mouse embryonic fibroblasts (MEFs) derived from *Fto*$^{-/-}$ mutants have slower rates of growth and reduced mRNA translation than wild-type MEFs,[168] which might result from maintenance of aminoacyl-tRNA synthetase levels, as part of a multimer known as the multi-synthetase complex (MSC).[169] The MSC tethers free amino acids to their cognate tRNAs and is a key modulator of translation. Consistent with reduced rates of translation, MEFs derived from *Fto*$^{-/-}$ mice have reduced levels of MSC components. In *Fto*$^{-/-}$-derived MEFs, mRNA translation and MSC levels are rescued by transfection with wild type FTO, implying that FTO can regulate translation by maintaining the MSC.[168]

In addition, cells lacking FTO have decreased activation of the mammalian target of rapamycin complex 1 (mTORC1) pathway, a key regulator of cell growth, mRNA translation and autophagy, the basic catabolic mechanism that involves cell degradation of unnecessary or dysfunctional cellular components via the lysosomal machinery. These cellular responses might explain the growth retardation seen in *Fto*$^{-/-}$ mice[158] and in humans with a homozygous loss-of-function *FTO* mutation.[160] The regulation of FTO by amino acids[167] seems to be necessary for the cellular response to changing amino-acid levels. Expression of exogenous *FTO* renders cells insensitive to amino-acid deprivation by preventing the expected reduction in mTORC1 signalling.[168]

A cell that lacks FTO cannot sense amino acids, thus responds by reducing mTORC1 signalling and increasing autophagy to maintain cellular energy levels and ensure survival (Figure 3). For example, whole-body deletion of *Fto* in adult mice led to a loss of weight, particularly in lean body mass.[159] Skeletal muscle is the largest mass of protein in the body and potentially the most sensitive to the sudden global FTO removal and subsequent increase in autophagy. By contrast, when FTO is postnatally deleted, specifically in the mediobasal hypothalamus, a more subtle weight loss occurs, due to a change in food intake.[159]

FTO and N6-methyladenosine

The link between amino-acid availability and mTORC1 signalling is dependent on FTO demethylase activity, although the how and why remain unclear.[168] One possibility could involve FTO's ability to demethylate N6-methyladenosine. Using antibodies against N6-methyladenosine to immunoprecipitate human and

mouse RNA transcripts that carry the nucleotide modification, two studies have mapped N6-methyladenosine in a transcriptome-wide manner.[170,171] N6-methyladenosines are common, enriched near stop-codons, highly conserved between mice and humans, and are dynamically, developmentally and tissue-specifically regulated.[170,171] The presence of N6-methyladenosine at appropriate mRNA sites seems to have a fundamental role in regulating gene expression, in addition to exerting varying effects on mRNA splicing and transport.[170,171] Methyltransferase-like 3 is currently the only enzyme identified that methylates adenosine to the N6-methyladenosine form,[172] wheres two enzymes are known to catalyse the removal of this methyl group: ALKBH5[173] and FTO.[143] In fact, transient overexpression of *FTO* in HEK293 cells decreases the total amount of N6-methyladenosine in the transcriptome.[171]

However, FTO does not globally target all N6-methyladenosine-modified mRNAs but demethylates only a specific subset.[174] The midbrain and striatum in $Fto^{-/-}$ mice have increased methylation in mRNAs encoding components of the dopamine signalling pathway, consequently dopaminergic signalling is reduced.[174] Dopaminergic signalling is crucial for the regulation of learning, reward behaviour and feeding. Outside the brain, FTO risk alleles can influence the methylation of ghrelin mRNA, which might affect levels of the circulating protein.[175] Ghrelin is a powerful orexigenic signal produced by the stomach, whose circulating levels normally peak before the onset of a meal. Further studies should determine the extent to which changes in dopamine and/or ghrelin signalling could be effectors of FTO's association with increased BMI.[175]

Conclusions

How does the biochemical function of FTO relate to the association between FTO SNPs and obesity? In truth, we still do not know. Little is known about if or how the *FTO* risk alleles influence the FTO protein. Considering their intronic location, SNPs are unlikely to cause functional mutations, but might regulate *FTO* transcription in a more subtle way, either by upregulating or downregulating FTO expression.

FTO is most highly expressed in the brain, where amino acids can influence the activity of pathways controlling food intake. We hypothesize that subtle effects of the risk alleles on *FTO* expression in regions of the brain, such as the hypothalamus, might influence how these cells sense amino-acid levels. Human carriers of the susceptible SNPs in *FTO* not only consume more food but also have altered nutrient preference, suggesting that FTO status influences the sensing of dietary macronutrient composition. The role of FTO in amino-acid sensing might aid our understanding of the cellular basis of this physiological phenomenon.

Considering that a substantial proportion of the world's population have their body weight subtly influenced by SNPs in *FTO*, can *FTO* ever be considered a realistic pharmaceutical target? Given the ubiquitous expression of FTO, the severe phenotype in humans and mice with FTO deficiency, and that adult FTO deletion leads to a dramatic loss of muscle mass, we do not believe FTO is a good target for future drugs. However, understanding the biology underpinning FTO function might reveal novel therapeutic targets to treat obesity. Furthermore, using the statistical association of *FTO* and BMI to understand the underlying biology can serve as a template for future GWAS of obesity genes with unknown function.

Review criteria

The PubMed database was searched for all English-language papers published since 2007 that listed "FTO" in their title and/or abstract. We subsequently focused on articles reporting large-scale human studies, typically with sample sizes of at least 1,000 individuals, or smaller studies where the results have been replicated by other studies. For articles on the biology of *FTO* we reviewed all six studies that have perturbed FTO expression in rodent models, and papers on the function of FTO, published since 2010.

1. Elks, C. E. *et al.* Variability in the heritability of body mass index: a systematic review and meta-regression. *Front. Endocrinol. (Lausanne)* **3**, 29 (2012).
2. Maes, H. H., Neale, M. C. & Eaves, L. J. Genetic and environmental factors in relative body weight and human obesity. *Behav. Genet.* **27**, 325–351 (1997).
3. Loos, R. J. F. in *Adipose Tissue Biology* (ed. Symonds, M. E.) 317–378 (Springer, 2012).
4. Hindorff, L. A. *et al.* Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proc. Natl Acad. Sci. USA* **106**, 9362–9367 (2009).
5. Hindorff, L. A., MacArthur, J., Morales, J., Junkins, H. A., Hall, P. N., Klemm, A. K. & Manolio, T. A. A catalog of published genome-wide association studies [online], http://www.genome.gov/gwastudies (2013).
6. Day, F. R. & Loos, R. J. Developments in obesity genetics in the era of genome-wide association studies. *J. Nutrigenet. Nutrigenomics* **4**, 222–238 (2011).
7. Lu, Y. & Loos, R. J. Obesity genomics: assessing the transferability of susceptibility loci across diverse populations. *Genome Med.* **5**, 55 (2013).
8. Frayling, T. M. *et al.* A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* **316**, 889–894 (2007).
9. Scuteri, A. *et al.* Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. *PLoS Genet.* **3**, e115 (2007).
10. Dina, C. *et al.* Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat. Genet.* **39**, 724–726 (2007).
11. Loos, R. J. *et al.* Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nat. Genet.* **40**, 768–775 (2008).
12. Willer, C. J. *et al.* Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat. Genet.* **41**, 25–34 (2009).
13. Thorleifsson, G. *et al.* Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat. Genet.* **41**, 18–24 (2009).
14. Lindgren, C. M. *et al.* Genome-wide association scan meta-analysis identifies three loci influencing adiposity and fat distribution. *PLoS Genet.* **5**, e1000508 (2009).
15. Heard-Costa, N. L. *et al.* NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. *PLoS Genet.* **5**, e1000539 (2009).
16. Speliotes, E. K. *et al.* Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat. Genet.* **42**, 937–948 (2010).
17. Kilpelainen, T. O. *et al.* Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. *Nat. Genet.* **43**, 753–760 (2011).
18. Berndt, S. I. *et al.* Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. *Nat. Genet.* **45**, 501–512 (2013).
19. Meyre, D. *et al.* Genome-wide association study for early-onset and morbid adult obesity

identifies three new risk loci in European populations. *Nat. Genet.* **41**, 157–159 (2009).
20. Scherag, A. *et al.* Two new loci for body-weight regulation identified in a joint analysis of genome-wide association studies for early-onset extreme obesity in French and German study groups. *PLoS Genet.* **6**, e1000916 (2010).
21. Bradfield, J. P. *et al.* A genome-wide association meta-analysis identifies new childhood obesity loci. *Nat. Genet.* **44**, 526–531 (2012).
22. Wheeler, E. *et al.* Genome-wide SNP and CNV analysis identifies common and low-frequency variants associated with severe early-onset obesity. *Nat. Genet.* **45**, 513–517 (2013).
23. Cho, Y. S. *et al.* A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nat. Genet.* **41**, 527–534 (2009).
24. Wen, W. *et al.* Meta-analysis identifies common variants associated with body mass index in east Asians. *Nat. Genet.* **44**, 307–311 (2012).
25. Okada, Y. *et al.* Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. *Nat. Genet.* **44**, 302–306 (2012).
26. Monda, K. L. *et al.* A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry. *Nat. Genet.* **45**, 690–696 (2013).
27. Peters, U. *et al.* A systematic mapping approach of 16q12.2/FTO and BMI in more than 20,000 African Americans narrows in on the underlying functional variation: results from the Population Architecture using Genomics and Epidemiology (PAGE) study. *PLoS Genet.* **9**, e1003171 (2013).
28. Stratigopoulos, G. *et al.* Regulation of Fto/Ftm gene expression in mice and humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **294**, R1185–R1196 (2008).
29. Stratigopoulos, G., LeDuc, C. A., Cremona, M. L., Chung, W. K. & Leibel, R. L. Cut-like homeobox 1 (CUX1) regulates expression of the fat mass and obesity-associated and retinitis pigmentosa GTPase regulator-interacting protein-1-like (RPGRIP1L) genes and coordinates leptin receptor signaling. *J. Biol. Chem.* **286**, 2155–2170 (2011).
30. Li, S. *et al.* Cumulative effects and predictive value of common obesity-susceptibility variants identified by genome-wide association studies. *Am. J. Clin. Nutr.* **91**, 184–190 (2010).
31. Tan, J. T. *et al.* FTO variants are associated with obesity in the Chinese and Malay populations in Singapore. *Diabetes* **57**, 2851–2857 (2008).
32. Liu, Y. *et al.* Meta-analysis added power to identify variants in FTO associated with type 2 diabetes and obesity in the Asian population. *Obesity* **18**, 1619–1624 (2010).
33. Ng, M. C. Y. *et al.* Implication of genetic variants near NEGR1, SEC16B, TMEM18, ETV5/DGKG, GNPDA2, LIN17C/BDNF, MTCH2, BCDIN3D/FAIM2, SH2B1, FTO, MC4R, AND KCTD15 with obesity and type 2 diabetes in 7,705 Chinese. *J. Clin. Endocrinol. Metab.* **95**, 2418–2425 (2010).
34. Chang, Y. C. *et al.* Common variation in the fat mass and obesity-associated (FTO) gene confers risk of obesity and modulates BMI in the Chinese population. *Diabetes* **57**, 2245–2252 (2008).
35. Shi, J. *et al.* Evaluation of genetic susceptibility loci for obesity in Chinese women. *Am. J. Epidemiol.* **172**, 244–254 (2010).
36. Sun, Y., Sun, J., Wang, X., You, W. & Yang, M. Variants in the fat mass and obesity associated (FTO) gene are associated with obesity and C-reactive protein levels in Chinese Han populations. *Clin. Invest. Med.* **33**, E405–E412 (2010).
37. Wang, J. *et al.* Study of eight GWAS-identified common variants for association with obesity-related indices in Chinese children at puberty. *Int. J. Obes. (Lond.)* **36**, 542–547 (2012).
38. Wu, L. *et al.* Associations of six single nucleotide polymorphisms in obesity-related genes with BMI and risk of obesity in Chinese children. *Diabetes* **59**, 3085–3089 (2010).
39. Xi, B. *et al.* Associations of obesity susceptibility loci with hypertension in Chinese children. *Int. J. Obes. (Lond.)* **37**, 926–930 (2013).
40. Hotta, K. *et al.* Variations in the FTO gene are associated with severe obesity in the Japanese. *J. Hum. Genet.* **53**, 546–553 (2008).
41. Omori, S. *et al.* Association of CDKAL1, IGF2BP2, CDKN2A/B, HHEX, SLC30A8, and KCNJ11 with susceptibility to type 2 diabetes in a Japanese population. *Diabetes* **57**, 791–795 (2008).
42. Tabara, Y. *et al.* Prognostic significance of FTO genotype in the development of obesity in Japanese: the J-SHIPP study. *Int. J. Obes.* **33**, 1243–1248 (2009).
43. Karasawa, S. *et al.* Association of the common fat mass and obesity associated (FTO) gene polymorphism with obesity in a Japanese population. *Endocr. J.* **57**, 293–301 (2010).
44. Takeuchi, F. *et al.* Association of genetic variants for susceptibility to obesity with type 2 diabetes in Japanese individuals. *Diabetologia* **54**, 1350–1359 (2011).
45. Cha, S. W. *et al.* Replication of genetic effects of FTO polymorphisms on BMI in a Korean population. *Obesity (Silver Spring)* **16**, 2187–2189 (2008).
46. Hong, K. W. & Oh, B. Recapitulation of genome-wide association studies on body mass index in the Korean population. *Int. J. Obes. (Lond.)* **36**, 1127–1130 (2012).
47. Binh, T. Q. *et al.* Association of the common FTO-rs9939609 polymorphism with type 2 diabetes, independent of obesity-related traits in a Vietnamese population. *Gene* **513**, 31–35 (2013).
48. Croteau-Chonka, D. C. *et al.* Genome-wide association study of anthropometric traits and evidence of interactions with age and study year in Filipino women. *Obesity (Silver Spring)* **19**, 1019–1027 (2010).
49. Yajnik, C. *et al.* FTO gene variants are strongly associated with type 2 diabetes in South Asian Indians. *Diabetologia* **52**, 247–252 (2009).
50. Ramya, K., Radha, V., Ghosh, S., Majumder, P. P. & Mohan, V. Genetic variations in the FTO gene are associated with type 2 diabetes and obesity in south Indians (CURES-79). *Diabetes Technol. Ther.* **13**, 33–42 (2011).
51. Taylor, A. E. *et al.* Associations of FTO and MC4R variants with obesity traits in indians and the role of rural/urban environment as a possible effect modifier. *J. Obes.* **2011**, 307542 (2011).
52. Chauhan, G. *et al.* Common variants of FTO and the risk of obesity and type 2 diabetes in Indians. *J. Hum. Genet.* **56**, 720–726 (2011).
53. Vasan, S. K. *et al.* Associations of variants in FTO and near MC4R with obesity traits in South Asian Indians. *Obesity (Silver Spring)* **20**, 2268–2277 (2012).
54. Sanghera, D. *et al.* Impact of nine common type 2 diabetes risk polymorphisms in Asian Indian Sikhs: PPARG2 (Pro12Ala), IGF12BP2, TCF7L2 and FTO variants confer a significant risk. *BMC Med. Genet.* **9**, 59 (2008).
55. Moore, S. C. *et al.* Common genetic variants and central adiposity among Asian-Indians. *Obesity (Silver Spring)* **20**, 1902–1908 (2012).
56. Dwivedi, O. P. *et al.* Common variants of FTO are associated with childhood obesity in a cross-sectional study of 3,126 urban Indian children. *PLoS ONE* **7**, e47772 (2012).
57. Rees, S. D. *et al.* An FTO variant is associated with Type 2 diabetes in South Asian populations after accounting for body mass index and waist circumference. *Diabet. Med.* **28**, 673–680 (2011).
58. Li, H. *et al.* Association of genetic variation in FTO with risk of obesity and type 2 diabetes with data from 96,551 East and South Asians. *Diabetologia* **55**, 981–995 (2012).
59. Grant, S. F. *et al.* Association analysis of the FTO gene with obesity in children of Caucasian and African ancestry reveals a common tagging SNP. *PLoS ONE* **3**, e1746 (2008).
60. Liu, G. *et al.* FTO variant rs9939609 is associated with body mass index and waist circumference, but not with energy intake or physical activity in European- and African-American youth. *BMC Med. Genet.* **11**, 57 (2010).
61. Graff, M. *et al.* Estimation of genetic effects on BMI during adolescence in an ethnically diverse cohort: The National Longitudinal Study of Adolescent Health. *Nutr. Diabetes* **2**, e47 (2012).
62. Adeyemo, A. *et al.* FTO genetic variation and association with obesity in west africans and african americans. *Diabetes* **59**, 1549–1554 (2010).
63. Hennig, B. *et al.* FTO gene variation and measures of body mass in an African population. *BMC Med. Genet.* **10**, 21 (2009).
64. Hassanein, M. T. *et al.* Fine mapping of the association with obesity at the FTO locus in African-derived populations. *Hum. Mol. Genet.* **19**, 2907–2916 (2010).
65. Bressler, J., Kao, W. H., Pankow, J. S. & Boerwinkle, E. Risk of type 2 diabetes and obesity is differentially associated with variation in fto in whites and african-americans in the ARIC Study. *PLoS ONE* **5**, e10521 (2010).
66. Avery, C. L. *et al.* A phenomics-based strategy identifies loci on APOC1, BRAP, and PLCG1 associated with metabolic syndrome phenotype domains. *PLoS Genet.* **7**, e1002322 (2011).
67. Cauchi, S. *et al.* European genetic variants associated with type 2 diabetes in North African Arabs. *Diabetes Metab.* **38**, 316–323 (2012).
68. Hallman, D. M. *et al.* The association of variants in the FTO gene with longitudinal body mass index profiles in non-Hispanic white children and adolescents. *Int. J. Obes (Lond.)* **36**, 61–68 (2012).
69. Lombard, Z. *et al.* Appetite regulation genes are associated with body mass index in black South African adolescents: a genetic association study. *BMJ Open* **2**, e000873 (2012).
70. Hester, J. M. *et al.* Implication of European-derived adiposity loci in African Americans. *Int. J. Obes. (Lond.)* **36**, 465–473 (2012).
71. Ng, M. C. *et al.* Genome-wide association of BMI in African Americans. *Obesity (Silver Spring)* **20**, 622–627 (2012).
72. Fesinmeyer, M. D. *et al.* Effects of smoking on the genetic risk of obesity: the population architecture using genomics and epidemiology study. *BMC Med. Genet.* **14**, 6 (2013).
73. Demerath, E. W. *et al.* Interaction of FTO and physical activity level on adiposity in African-American and European-American adults: the ARIC study. *Obesity (Silver Spring)* **19**, 1866–1872 (2011).
74. Wing, M. R. *et al.* Analysis of FTO gene variants with measures of obesity and glucose homeostasis in the IRAS Family Study. *Hum. Genet.* **125**, 615–626 (2009).
75. Villalobos-Comparan, M. *et al.* The FTO gene is associated with adulthood obesity in the Mexican population. *Obesity (Silver Spring)* **16**, 2296–2301 (2008).
76. Dong, C. *et al.* Genome-wide linkage and peak-wide association study of obesity-related

quantitative traits in Caribbean Hispanics. *Hum. Genet.* **129**, 209–219 (2011).
77. Song, Y. *et al.* FTO polymorphisms are associated with obesity but not diabetes risk in postmenopausal women. *Obesity (Silver Spring)* **16**, 2472–2480 (2008).
78. Rong, R. *et al.* Association analysis of variation in/near FTO, CDKAL1, SLC30A8, HHEX, EXT2, IGF32BP2, LOC387761 and CDKN2B with type 2 diabetes and related quantitative traits in Pima Indians. *Diabetes* **58**, 478–488 (2009).
79. Haworth, C. M. A. *et al.* Increasing heritability of BMI and stronger associations with the FTO Gene over childhood. *Obesity* **16**, 2663–2668 (2008).
80. Cecil, J. E., Tavendale, R., Watt, P., Hetherington, M. M. & Palmer, C. N. A. An obesity-associated fto gene variant and increased energy intake in children. *N. Engl. J. Med.* **359**, 2558–2566 (2008).
81. Zhao, J. *et al.* Examination of all type 2 diabetes GWAS loci reveals HHEX-IDE as a locus influencing pediatric BMI. *Diabetes* **59**, 751–755 (2010).
82. Melen, E. *et al.* Genome-wide association study of body mass index in 23,000 individuals with and without asthma. *Clin. Exp. Allergy* **43**, 463–474 (2013).
83. den Hoed, M. *et al.* Genetic susceptibility to obesity and related traits in childhood and adolescence. *Diabetes* **59**, 2980–2988 (2010).
84. Lauria, F. *et al.* Prospective analysis of the association of a common variant of FTO (rs9939609) with adiposity in children: results of the IDEFICS study. *PLoS ONE* **7**, e48876 (2012).
85. Zhao, J. *et al.* Role of BMI-associated loci identified in GWAS meta-analyses in the context of common childhood obesity in European Americans. *Obesity (Silver Spring)* **19**, 2436–2439 (2011).
86. Graff, M. *et al.* Genome-wide analysis of BMI in adolescents and young adults reveals additional insight into the effects of genetic loci over the life course. *Hum. Mol. Genet.* **22**, 3597–3607 (2013).
87. Hardy, R. *et al.* Life course variations in the associations between FTO and MC4R gene variants and body size. *Hum. Mol. Genet.* **19**, 545–552 (2010).
88. Rzehak, P. *et al.* Associations between BMI and the FTO gene are age dependent: results from the GINI and LISA birth cohort studies up to age 6 years. *Obes. Facts* **3**, 180 (2010).
89. Cauchi, S. *et al.* Combined effects of MC4R and FTO common genetic variants on obesity in European general populations. *J. Mol. Med.* **87**, 537–546 (2009).
90. Jess, T. *et al.* Impact on weight dynamics and general growth of the common FTO rs9939609: a longitudinal Danish cohort study. *Int. J. Obes* **32**, 1388–1394 (2008).
91. Kilpelainen, T. O. *et al.* Obesity-susceptibility loci have a limited influence on birth weight: a meta-analysis of up to 28,219 individuals. *Am. J. Clin. Nutr.* **93**, 851–860 (2011).
92. Horikoshi, M. *et al.* New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism. *Nat. Genet.* **45**, 76–82 (2013).
93. Qi, L. *et al.* Fat mass-and obesity-associated (FTO) gene variant is associated with obesity: longitudinal analyses in two cohort studies and functional test. *Diabetes* **57**, 3145–3151 (2008).
94. Sovio, U. *et al.* Association between common variation at the FTO locus and changes in body mass index from infancy to late childhood: the complex nature of genetic association through growth and development. *PLoS Genet.* **7**, e1001307 (2011).
95. Speakman, J. R., Rance, K. A. & Johnstone, A. M. Polymorphisms of the FTO gene are associated with variation in energy intake, but not energy expenditure. *Obesity* **16**, 1961–1965 (2008).
96. Timpson, N. J. *et al.* The fat mass-and obesity-associated locus and dietary intake in children. *Am. J. Clin. Nutr.* **88**, 971–978 (2008).
97. Sonestedt, E. *et al.* Fat and carbohydrate intake modify the association between genetic variation in the FTO genotype and obesity. *Am. J. Clin. Nutr.* **90**, 1418–1425 (2009).
98. Lee, H. J. *et al.* Effects of common FTO gene variants associated with BMI on dietary intake and physical activity in Koreans. *Clin. Chim. Acta* **411**, 1716–1722 (2010).
99. Park, S. L. *et al.* Association of the FTO obesity risk variant rs8050136 with percentage of energy intake from fat in multiple racial/ethnic populations: The PAGE Study. *Am. J. Epidemiol.* **178**, 780–790 (2013).
100. Ahmad, T. *et al.* Lifestyle interaction with fat mass and obesity-associated (FTO) genotype and risk of obesity in apparently healthy, U. S. women. *Diabetes Care* **34**, 675–680 (2011).
101. Wardle, J. *et al.* Obesity associated genetic variation in FTO is associated with diminished satiety. *J. Clin. Endocr. Metab.* **93**, 3640–3643 (2008).
102. Wardle, J., Llewellyn, C., Sanderson, S. & Plomin, R. The FTO gene and measured food intake in children. *Int. J. Obes* **33**, 42–45 (2008).
103. McCaffery, J. M. *et al.* Obesity susceptibility loci and dietary intake in the Look AHEAD Trial. *Am. J. Clin. Nutr.* **95**, 1477–1486 (2012).
104. Brunkwall, L. *et al.* Genetic variation in the fat mass and obesity-associated gene (FTO) in association with food preferences in healthy adults. *Food Nutr. Res.* **57**, 20028 (2013).
105. Tanofsky-Kraff, M. *et al.* The FTO gene rs9939609 obesity-risk allele and loss of control over eating. *Am. J. Clin. Nutr.* **90**, 1483–1488 (2009).
106. Tanaka, T. *et al.* Genome-wide meta-analysis of observational studies shows common genetic variants associated with macronutrient intake. *Am. J. Clin. Nutr.* **97**, 1395–1402 (2013).
107. Bauer, F. *et al.* Obesity genes identified in genome-wide association studies are associated with adiposity measures and potentially with nutrient-specific food preference. *Am. J. Clin. Nutr.* **90**, 951–959 (2009).
108. Corella, D. *et al.* A high intake of saturated fatty acids strengthens the association between the fat mass and obesity-associated gene and BMI. *J. Nutr.* **141**, 2219–2225 (2011).
109. Hubacek, J. A., Pikhart, H., Peasey, A., Kubinova, R. & Bobak, M. FTO variant, energy intake, physical activity and basal metabolic rate in Caucasians. The HAPIEE study. *Physiol. Res.* **60**, 175–183 (2010).
110. Holzapfel, C. *et al.* Genes and lifestyle factors in obesity: results from 12,462 subjects from MONICA/KORA. *Int. J. Obes.* **34**, 1538–1545 (2010).
111. Franks, P. W. *et al.* Assessing gene-treatment interactions at the FTO and INSIG2 loci on obesity-related traits in the Diabetes Prevention Program. *Diabetologia* **51**, 2214–2223 (2008).
112. Rampersaud, E. *et al.* Physical activity and the association of common FTO gene variants with body mass index and obesity. *Arch. Intern. Med.* **168**, 1791–1797 (2008).
113. Ahmad, T. *et al.* The Fat-Mass and Obesity-Associated (FTO) gene, physical activity, and risk of incident cardiovascular events in white women. *Am. Heart J.* **160**, 1163–1169 (2010).
114. Vimaleswaran, K. S. *et al.* Physical activity attenuates the body mass index increasing influence of genetic variation in the FTO gene. *Am. J. Clin. Nutr.* **90**, 425–428 (2009).
115. Kilpelainen, T. O. Physical activity attenuates the influence of FTO variants on obesity risk; a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med.* **8**, e1001116 (2011).
116. Andreasen, C. H. *et al.* Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. *Diabetes* **57**, 264–268 (2008).
117. Sonestedt, E. *et al.* Association between fat intake, physical activity and mortality depending on genetic variation in FTO. *Int. J. Obes (Lond.)* **35**, 1041–1049 (2010).
118. Bell, C. G. *et al.* Integrated genetic and epigenetic analysis identifies haplotype-specific methylation in the *FTO* type 2 diabetes and obesity susceptibility locus. *PLoS ONE* **5**, e14040 (2010).
119. Toperoff, G. *et al.* Genome-wide survey reveals predisposing diabetes type 2-related DNA methylation variations in human peripheral blood. *Hum. Mol. Genet.* **21**, 371–383 (2012).
120. Almen, M. S. *et al.* Genome wide analysis reveals association of a FTO gene variant with epigenetic changes. *Genomics* **99**, 132–137 (2012).
121. Heid, I. M. *et al.* Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat. Genet.* **42**, 949–960 (2010).
122. Fox, C. S. *et al.* Genome-wide association for abdominal subcutaneous and visceral adipose reveals a novel locus for visceral fat in women. *PLoS Genet.* **8**, e1002695 (2012).
123. Fall, T. *et al.* The role of adiposity in cardiometabolic traits: a mendelian randomization analysis. *PLoS Med.* **10**, e1001474 (2013).
124. Hertel, J. K. *et al.* FTO, type 2 diabetes, and weight gain throughout adult life: a meta-analysis of 41,504 subjects from the Scandinavian HUNT, MDC, and MPP studies. *Diabetes* **60**, 1637–1644 (2011).
125. Brennan, P. *et al.* Obesity and cancer: Mendelian randomization approach utilizing the FTO genotype. *Int. J. Epidemiol.* **38**, 971–975 (2009).
126. Delahanty, R. J. *et al.* Association of obesity-related genetic variants with endometrial cancer risk: a report from the Shanghai Endometrial Cancer Genetics Study. *Am. J. Epidemiol.* **174**, 1115–1126 (2011).
127. Machiela, M. J. *et al.* Association of type 2 diabetes susceptibility variants with advanced prostate cancer risk in the Breast and Prostate Cancer Cohort Consortium. *Am. J. Epidemiol.* **176**, 1121–1129 (2012).
128. Lurie, G. *et al.* The obesity-associated polymorphisms FTO rs9939609 and MC4R rs17782313 and endometrial cancer risk in non-Hispanic white women. *PLoS ONE* **6**, e16756 (2011).
129. Long, J. *et al.* Evaluating genome-wide association study-identified breast cancer risk variants in African-American women. *PLoS ONE* **8**, e58350 (2013).
130. Pierce, B. L., Austin, M. A. & Ahsan, H. Association study of type 2 diabetes genetic susceptibility variants and risk of pancreatic cancer: an analysis of PanScan-I data. *Cancer Causes Control* **22**, 877–83 (2011).
131. Lewis, S. J. *et al.* Associations between an obesity related genetic variant (FTO rs9939609)

and prostate cancer risk. *PLoS ONE* **5**, e13485 (2010).
132. Gaudet, M. M. *et al.* No association between FTO or HHEX and endometrial cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **19**, 2106–2109 (2010).
133. Lim, U. *et al.* Susceptibility variants for obesity and colorectal cancer risk: the multiethnic cohort and PAGE studies. *Int. J. Cancer* **131**, E1038–E1043 (2012).
134. Li, G., Chen, Q., Wang, L., Ke, D. & Yuan, Z. Association between FTO gene polymorphism and cancer risk: evidence from 16,277 cases and 31,153 controls. *Tumour Biol.* **33**, 1237–1243 (2012).
135. Zheng, W. *et al.* Common genetic determinants of breast-cancer risk in East Asian women: a collaborative study of 23,637 breast cancer cases and 25,579 controls. *Hum. Mol. Genet.* **22**, 2539–2550 (2013).
136. Garcia-Closas, M. *et al.* Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nat. Genet.* **45**, 392–398 (2013).
137. Iles, M. M. *et al.* A variant in FTO shows association with melanoma risk not due to BMI. *Nat. Genet.* **45**, 428–432 (2013).
138. Meyre, D. *et al.* Prevalence of loss-of-function FTO mutations in lean and obese individuals. *Diabetes* **59**, 311–318 (2010).
139. Deliard, S. *et al.* The missense variation landscape of FTO, MC4R, and TMEM18 in obese children of African Ancestry. *Obesity (Silver Spring)* **21**, 159–63 (2013).
140. Zheng, Z. *et al.* Screening for Coding Variants in FTO and SH2B1 Genes in Chinese Patients with Obesity. *PLoS ONE* **8**, e67039 (2013).
141. Gerken, T. *et al.* The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science* **318**, 1469–1472 (2007).
142. Jia, G. *et al.* Oxidative demethylation of 3-methylthymine and 3-methyluracil in single-stranded DNA and RNA by mouse and human FTO. *FEBS Lett.* **582**, 3313–3319 (2008).
143. Jia, G. *et al.* N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. *Nat. Chem. Biol.* **7**, 885–887 (2011).
144. Han, Z. *et al.* Crystal structure of the FTO protein reveals basis for its substrate specificity. *Nature* **464**, 1205–1209 (2010).
145. Desrosiers, R., Friderici, K. & Rottman, F. Identification of methylated nucleosides in messenger RNA from Novikoff hepatoma cells. *Proc. Natl Acad. Sci. USA* **71**, 3971–3975 (1974).
146. Kowalak, J. A., Pomerantz, S. C., Crain, P. F. & McCloskey, J. A. A novel method for the determination of post-transcriptional modification in RNA by mass spectrometry. *Nucleic Acids Res.* **21**, 4577–4585 (1993).
147. Chambers, J. C. *et al.* Common genetic variation near MC4R is associated with waist circumference and insulin resistance. *Nat. Genet.* **40**, 716–718 (2008).
148. Vaisse, C., Clement, K., Guy-Grand, B. & Froguel, P. A frameshift mutation in human MC4R is associated with a dominant form of obesity. *Nat. Genet.* **20**, 113–114 (1998).
149. Yeo, G. S. *et al.* A frameshift mutation in MC4R associated with dominantly inherited human obesity. *Nat. Genet.* **20**, 111–112 (1998).
150. Challis, B. G. *et al.* A missense mutation disrupting a dibasic prohormone processing site in pro-opiomelanocortin (POMC) increases susceptibility to early-onset obesity through a novel molecular mechanism. *Hum. Mol. Genet.* **11**, 1997–2004 (2002).
151. Krude, H. *et al.* Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat. Genet.* **19**, 155–157 (1998).
152. Gray, J. *et al.* Hyperphagia, severe obesity, impaired cognitive function, and hyperactivity associated with functional loss of one copy of the brain-derived neurotrophic factor (BDNF) gene. *Diabetes* **55**, 3366–3371 (2006).
153. Benzinou, M. *et al.* Common nonsynonymous variants in PCSK1 confer risk of obesity. *Nat. Genet.* **40**, 943–945 (2008).
154. Jackson, R. S. *et al.* Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. *Nat. Genet.* **16**, 303–306 (1997).
155. Peters, T., Ausmeier, K. & Ruther, U. Cloning of Fatso (Fto), a novel gene deleted by the Fused toes (Ft) mouse mutation. *Mamm. Genome* **10**, 983–986 (1999).
156. Anselme, I., Laclef, C., Lanaud, M., Ruther, U. & Schneider-Maunoury, S. Defects in brain patterning and head morphogenesis in the mouse mutant Fused toes. *Dev. Biol.* **304**, 208–220 (2007).
157. van der Hoeven, F. *et al.* Programmed cell death is affected in the novel mouse mutant Fused toes (Ft). *Development* **120**, 2601–2607 (1994).
158. Fischer, J. *et al.* Inactivation of the Fto gene protects from obesity. *Nature* **458**, 894–898 (2009).
159. McMurray, F. *et al.* Adult onset global loss of the fto gene alters body composition and metabolism in the mouse. *PLoS Genet.* **9**, e1003166 (2013).
160. Boissel, S. *et al.* Loss-of-function mutation in the dioxygenase-encoding FTO gene causes severe growth retardation and multiple malformations. *Am. J. Hum. Genet.* **85**, 106–111 (2009).
161. Delous, M. *et al.* The ciliary gene RPGRIP1L is mutated in cerebello-oculo-renal syndrome (Joubert syndrome type B) and Meckel syndrome. *Nat. Genet.* **39**, 875–881 (2007).
162. Wu, Q., Saunders, R. A., Szkudlarek-Mikho, M., Serna Ide, L. & Chin, K. V. The obesity-associated Fto gene is a transcriptional coactivator. *Biochem. Biophys. Res. Commun.* **401**, 390–395 (2010).
163. Church, C. *et al.* Overexpression of Fto leads to increased food intake and results in obesity. *Nat. Genet.* **42**, 1086–1092 (2010).
164. Tung, Y. C. *et al.* Hypothalamic-specific manipulation of Fto, the ortholog of the human obesity gene FTO, affects food intake in rats. *PLoS ONE* **5**, e8771 (2010).
165. Gao, X. *et al.* The fat mass and obesity associated gene FTO functions in the brain to regulate postnatal growth in mice. *PLoS ONE* **5**, e14005 (2010).
166. Ma, M., Harding, H. P., O'Rahilly, S., Ron, D. & Yeo, G. S. Kinetic analysis of FTO (fat mass and obesity-associated) reveals that it is unlikely to function as a sensor for 2-oxoglutarate. *Biochem. J.* **444**, 183–187 (2012).
167. Cheung, M. K., Gulati, P., O'Rahilly, S. & Yeo, G. S. FTO expression is regulated by availability of essential amino acids. *Int. J. Obes (Lond.)* **37**, 744–747 (2013).
168. Gulati, P. *et al.* Role for the obesity-related FTO gene in the cellular sensing of amino acids. *Proc. Natl Acad. Sci. USA* **110**, 2557–2562 (2013).
169. Quevillon, S., Robinson, J. C., Berthonneau, E., Siatecka, M. & Mirande, M. Macromolecular assemblage of aminoacyl-tRNA synthetases: identification of protein-protein interactions and characterization of a core protein. *J. Mol. Biol.* **285**, 183–195 (1999).
170. Dominissini, D. *et al.* Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq. *Nature* **485**, 201–206 (2012).
171. Meyer, K. D. *et al.* Comprehensive analysis of mRNA methylation reveals enrichment in 3' UTRs and near stop codons. *Cell* **149**, 1635–1646 (2012).
172. Bokar, J. A., Shambaugh, M. E., Polayes, D., Matera, A. G. & Rottman, F. M. Purification and cDNA cloning of the AdoMet-binding subunit of the human mRNA (N6-adenosine)-methyltransferase. *RNA* **3**, 1233–1247 (1997).
173. Zheng, G. *et al.* ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility. *Mol. Cell* **49**, 18–29 (2013).
174. Hess, M. E. *et al.* The fat mass and obesity associated gene (Fto) regulates activity of the dopaminergic midbrain circuitry. *Nat. Neurosci.* **16**, 1042–1048 (2013).
175. Karra, E. *et al.* A link between FTO, ghrelin, and impaired brain food-cue responsivity. *J. Clin. Invest.* **123**, 3539–3551 (2013).
176. Abecasis, G. R. *et al.* An integrated map of genetic variation from 1,092 human genomes. *Nature* **491**, 56–65 (2012).
177. Freathy, R. M. *et al.* Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected, given its effect on BMI. *Diabetes* **57**, 1419–1426 (2008).
178. Asselbergs, F. W. *et al.* Large-scale gene-centric meta-analysis across 32 studies identifies multiple lipid loci. *Am. J. Hum. Genet.* **91**, 823–838 (2012).
179. Robiou-du-Pont, S. *et al.* Contribution of 24 obesity-associated genetic variants to insulin resistance, pancreatic beta-cell function and type 2 diabetes risk in the French population. *Int. J. Obes. (Lond.)* **37**, 980–985 (2013).
180. Morris, A. P. *et al.* Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat. Genet.* **44**, 981–990 (2012).
181. Hubacek, J. A. *et al.* The FTO gene polymorphism is associated with end-stage renal disease: two large independent case-control studies in a general population. *Nephrol. Dial. Transplant.* **27**, 1030–1035 (2012).
182. Franceschini, N. *et al.* The association of genetic variants of type 2 diabetes with kidney function. *Kidney Int.* **82**, 220–225 (2012).
183. Timpson, N. J. *et al.* Does greater adiposity increase blood pressure and hypertension risk?: Mendelian randomization using the FTO/MC4R genotype. *Hypertension* **54**, 84–90 (2009).
184. Elks, C. E. *et al.* Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat. Genet.* **42**, 1077–1085 (2010).
185. Zeggini, E. *et al.* Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. *Lancet* **380**, 815–823 (2012).
186. Panoutsopoulou, K. *et al.* The effect of FTO variation on increased osteoarthritis risk is mediated through body mass index: a mendelian randomisation study. *Ann. Rheum. Dis.* http://dx.doi.org/10.1136/annrheumdis-2013-203772.
187. Samaan, Z. *et al.* The protective effect of the obesity-associated rs9939609 A variant in fat mass- and obesity-associated gene on depression. *Mol. Psychiatry* http://dx.doi.org/10.1038/mp.2012-178.
188. Bressler, J. *et al.* Fat mass and obesity gene and cognitive decline: the Atherosclerosis Risk in Communities Study. *Neurology* **80**, 92–99 (2013).

Author contributions

Both authors contributed equally to all aspects of the article.