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

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Abstract

In 2007, SNPs that cluster in the first intron of *FTO* showed highly significant association in the first two genome-wide association studies for obesity traits of which the minor allele increases body mass index (BMI) by 0.39 kg/m^2 (or 1,130 g in body weight) and risk of obesity by 1.20 fold. Subsequent studies convincingly confirmed this association across populations of diverse ancestry and throughout the life course, with the largest effect seen in young adulthood. The effect of *FTO* SNPs on obesity traits in African and Asian ancestry populations is similar or somewhat smaller than in European ancestry populations, but the BMI-increasing allele is substantially less prevalent in non-European ancestry populations. *FTO* SNPs do not influence physical activity levels, yet, in physically active individuals, *FTO's* effect on obesity susceptibility is attenuated by ~30%. Growing evidence from epidemiological and functional studies suggests that FTO confers an increased risk of obesity through subtle changes in food intake and preference. In addition, recent emerging data now points to a role for FTO in the sensing of nutrients and the regulation of translation and growth. In this review, we explore the genetic epidemiology of FTO and discuss how its complex biology might link to the regulation of body weight.

Introduction

An estimated 40 to 70% of the variation in obesity susceptibility observed in the population is due to inter-individual genetic differences.[1,2] Despite this substantial genetic contribution, the identification of genes associated with obesity traits was, for many years, hampered by a limited understanding of the genetic architecture of the human genome and the biological pathways implicated in obesity.[3] However, the advent of the genome-wide association approach in 2005, a hypothesis-free approach made possible through advances in high throughput genotyping technology, has dramatically increased the pace of gene discovery. To date, genome-wide association studies (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] *FTO* (fat mass and obesity associated

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gene) was the first obesity-susceptibility gene identified through GWAS,[8,9] and continues to be the locus with the largest effect on body mass index (BMI) and obesity risk, most widely replicated with variety of obesity traits throughout the life course and across diverse ancestries.[7] Here, we review the discovery of *FTO* as an obesity gene and the insights that have been gained over the past six years through epidemiological and functional follow-up studies to elucidate the biological pathways that underlie the association between *FTO* and obesity.

I. The genetic epidemiology of *FTO*

The discovery of *FTO* as the first obesity susceptibility gene

In 2007, within a time period of three months, two studies claimed the discovery of *FTO* as the first GWAS-identified obesity-susceptibility gene.[8-10] *FTO* was first discovered through a GWAS of type 2 diabetes in Europeans, comparing 1,924 cases and 2,938 controls.[8] A cluster of single nucleotide polymorphisms (SNPs) in the first intron of the gene showed highly significant association with risk of type 2 diabetes. However, after adjusting for BMI, the association with type 2 diabetes completely abolished, suggesting that the *FTO* - type 2 diabetes association was mediated through *FTO*'s effect on BMI. Follow-up analyses in 38,759 individuals confirmed the association with BMI and obesity risk.[8] Eight weeks after the first discovery, a GWAS for BMI in 4,741 Sardinians observed highly significant associations for SNPs from the same intronic cluster in *FTO*, which was subsequently replicated in 2,335 European and Hispanic Americans.[9] A third study, published at around the same time as the two GWAS, identified the same *FTO* locus serendipitously, while testing for population stratification in their case-control obesity data.[10]

Together, these studies firmly established *FTO* as the first gene with common variants that affect obesity susceptibility in the general population.

The *FTO* locus - a cluster of BMI-associated SNPs in *FTO*'s first intron

The two GWAS that first reported on *FTO* as an obesity susceptibility gene each identified a different SNP in the first intron as the most significantly associated with BMI; i.e. rs9939609[8], rs9930506[9] (Figure 1b). Subsequent GWAS studies for obesity-related traits in European ancestry populations all confirmed the *FTO* locus, but reported a number of other *FTO* SNPs, located in the same chromosomal region.[11-22] For example, the most recent GWAS for BMI, which included data from up to 247,796 individuals of European ancestry, found rs1558902 to be most significantly associated SNP ($P_{GWAS} < 10^{-60}$) as shown in Figure 1a.[16] But also the neighboring SNPs (Figure 1a, in red) show highly significant associations with BMI ($P_{GWAS} < 10^{-50}$). All these GWAS-identified *FTO* SNPs are part of the same cluster of highly correlated SNPs (linkage disequilibrium (LD) $r^2>0.80$) and, as a consequence, they are all highly significantly associated with BMI (Figure 1a) and other obesity related traits. In European ancestry populations, this SNP cluster stretches across ~46,000 base pairs in *FTO*'s first intron that likely harbors the causal variant(s).

The cluster of BMI-associated *FTO* SNPs in East Asian populations is very similar to that of European ancestry populations (Figure 1 b). Three large-scale GWAS in East Asian populations (Korean[23], Chinese[24], Japanese[25]) each identified different *FTO* SNPs

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(rs9939609, rs17817449, rs12149832, respectively) as the most significantly associated with BMI, all of which are highly correlated ($r^2 > 0.90$) in East Asian as well as in European ancestry populations (Figure 1b).

However, in populations of African ancestry, the correlation between SNPs in *FTO*'s first intron is substantially weaker than in European or East Asian ancestry populations (Figure 1b). This looser correlation structure provides the opportunity to narrow down to chromosomal region in which the causal variant(s) might be located. For example, a large-scale GWAS in African ancestry populations that combined data from 45,849 individuals, 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 described above, whereas in African ancestry populations, rs17817964 represents a cluster of much fewer SNPs across a smaller region, thus narrowing the locus that harbors the causal *FTO* variant (Figure 1b). In a targeted fine-mapping effort by the PAGE (Population Architecture using Genomics and Epidemiology) study, genotypes of 3,756 SNPs across a 646kb-region at 16q12.2, encompassing *FTO* and the neighboring *RPGRIP1L*, were tested in more than 20,000 African Americans, identifying rs56137030 as the SNP with the most significant association with BMI.[27] In Europeans ancestry populations, this SNP represents a cluster ($r^2_{CEU} >0.50$) of 103 (of the 3,756) SNPs, whereas in African Americans – due to weaker correlations between SNPs – this cluster includes only 29 SNPs.[27] Six of the 29 SNPs locate within intronic regulatory elements, two of which are predicted to have allele-specific binding affinities for different transcription factors, including Cut-like homeobox 1 (CUX1) that possibly influences the transcriptional regulation of FTO.[28,29]

Taken together, the BMI-associated *FTO* region, initially identified in European ancestry population, has been narrowed down through taking advantage of a weaker correlation between SNPs in African ancestry populations. These insights will help focus further efforts needed to pinpoint the causal variant(s).

Effect size and explained variance across ancestries

Since the discovery of *FTO* in 2007, at least 75 additional obesity-susceptibility loci have been identified through large-scale GWAS efforts. However, the *FTO* locus stands out, as it has by far the largest effect size, is very common, and has the largest explained variance among individuals of European ancestry. More specifically, each additional minor (risk) allele is associated with a 0.39 kg/m^2 higher BMI (equivalent to 1,130 g for a person of 1.70m tall) and a 1.20 fold increased risk of obesity (Table 1).[16] Approximately 43% of the population carries one risk allele and 20% carries two risk alleles, with small variations in genotype frequencies within European ancestry populations (Figure 2). Of all BMI-associated loci identified thus far, the *FTO* locus explains the most of the inter-individual variation in BMI, yet only a mere 0.34%.[16] As a consequence, the ability to predict a person's risk of obesity based on their FTO genotype is poor and only slightly better than tossing a coin.[30]

Soon after the discovery of *FTO* in European ancestry populations, many replication efforts examined its effects in non-European ancestry populations, showing convincing support for the generalizability of *FTO* as an obesity-susceptibility locus across most ancestries studied

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so far. The most consistent replications have been observed for Asian ancestry populations. Besides the fact that the three large-scale GWAS in East Asians identified *FTO* SNPs as the most significantly associated with BMI[23-25], targeted efforts consistently confirmed association with obesity-related traits in Chinese,[31-39] Japanese,[40-44] Koreans,[45,46] Vietnamese,[47] Filipino,[48] Malays,[31] and Indian Asians.[49-57] A meta-analysis that combined data of 96,551 individuals of Asian ancestry, showed that each additional minor allele increases risk of obesity (using Asian BMI cut-offs) by 1.25 fold, which is similar to effects observed in European ancestry populations.[58] BMI increases by 0.26 kg/m^2 (equivalent to 750g for a person 1.7m tall) for each additional minor allele,[58] which is substantially less than in European ancestry populations and might reflect the fact that BMI represents a somewhat different adiposity phenotype in different Asians. Effect sizes of East and South Asians were not significantly different, but the minor allele frequency was lower in East Asians (Chinese Hans and Koreans: 12-14%; Japanese and Filipinos: 18-20%) than in South Asians (30-33%), which both are lower than in Europeans (42%) (Table 1). As a 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 may be due to the substantial differences in correlation structure between *FTO* SNPs in African compared to European/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 likely not show association with obesity related traits. However, in the recent large-scale GWAS in African ancestry populations, SNPs in *FTO* were among the most significantly associated with BMI, firmly establishing *FTO* as an obesity-susceptibility locus also in this ancestry.[26] While *FTO*'s effect on BMI was similar to that observed in European ancestry populations, the minor allele frequency was much lower (12%) (Figure 2), such that only 0.10% of the variation of BMI in African ancestry populations was explained (Table 1).[26]

SNPs in *FTO* also show association with obesity-related traits in Hispanic/Latino populations[74-77] and in Pima Indians.[78]

Taken together, SNPs in *FTO* show association with obesity-related traits across many ancestries. Noteworthy is that the genotype frequency distribution of the BMI-associated *FTO* SNPs differs substantially across ancestries, with the highest prevalence of minor (risk) allele carriers observed in European ancestry populations, and substantially fewer in Asian and African ancestry populations (Figure 2).

FTO and obesity risk over the life course

Although *FTO* was first discovered as an obesity-susceptibility locus in adults,[8-10] its associations with obesity related traits were promptly confirmed in studies of children and adolescents.[8,19-21,38,39,56,59-61,79-89]

While SNPs in *FTO* do not influence birth weight[88-92], longitudinal studies have shown that they affect body weight already during early childhood, as early as age 3yrs, after which

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FTO's effect increases to reach its largest impact at around young adulthood, followed by a subsequent weakening of the effect throughout adulthood.[86-90,93,94].

The role of lifestyle factors in the association between *FTO* and obesity-susceptibility

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

The evidence supporting a role for *FTO* in the regulation of food intake is slowly growing. The BMI-increasing allele of *FTO* SNPs has been found to be associated with increased energy intake,[80,95-97] increased intake of dietary fat[96,98,99] or protein[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 recent GWAS of macronutrient intake in more than 70,000 individuals identified the BMI-increasing allele of *FTO* SNPs to be highly significantly associated with increased protein intake.[106] Despite the growing evidence, other studies have not been able to confirm associations with dietary traits.[43,60,107-111]

Studies have consistently shown that *FTO* SNPs are not associated with physical activity levels,[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% smaller in physically active than in sedentary individuals, at least in adults,[115] thereby firmly confirming observations of a growing number of individual studies.[43,73,112-114,116,117] This observation emphasizes the importance of physical activity in body weight regulation in adults, showing that even those who are genetically susceptible benefit from being active. It remains unclear what the biological mechanisms are behind the observed interaction between physical activity and *FTO* and whether this effect attenuation is observed only with physical activity or also with other lifestyle factors. Some studies have suggested that also dietary habits and energy intake[97,100,108] and smoking[72] might attenuate the effects of FTO on obesity susceptibility. Variants in the first intron of FTO have been shown to be associated with methylation capability, such that some have speculated that this region might be sensitive to epigenetic effects.[118-120]

Thus, while studying lifestyle factors such as physical activity and food intake is challenging because of the inaccuracy of their measurement, there is growing evidence that physical activity attenuates the association between *FTO* and obesity susceptibility, whereas food intake might be mediating this association. It remains to be confirmed which components of food intake are predominantly targeted by *FTO*.

FTO and obesity-related comorbidities

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.[16,121,122] In a recent large-scale meta-analysis of 36 studies (n = up to 198,502) that examined *FTO*'s effects on 24

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cardiometabolic traits, the BMI-increasing allele of the *FTO* SNP was associated with increased risk of type 2 diabetes, heart failure, coronary heart disease, ever all-cause and ischemic stroke, hypertension, dyslipidemia, metabolic syndrome, and mortality, and also with increased fasting glucose and insulin levels, 2h-OGTT glucose levels, HbA1c, blood pressure, lipid levels, liver enzymes, and inflammation markers.[122] For most traits, these associations were fully mediated through *FTO*'s effect on BMI.[122] However, there was evidence that *FTO* may, at least in part, increase the risk of type 2 diabetes independently of its effect on BMI,[122] which is consistent with earlier observations.[57,58,123]

Obesity is also considered a risk factor for certain cancers, which motivated researchers to also test whether the BMI-associated FTO SNPs associated with cancer. While some studies found *FTO* SNPs to influence the risk of some cancers,[124-130] others could not confirm this.[131-134] Interestingly, two recent large-scale GWAS identified SNPs in the second and eight intron of *FTO* to be robustly associated with risk of estrogen receptor negative breast cancer[135] and melanoma,[136] respectively. These two cancer-associated *FTO* loci are independent (LD $r^2_{CEU} < 0.10$) from each other and from the BMI-associated locus in the first intron. Their association with cancer risk was not mediated through an effect on BMI,[135,136] indicating that FTO's function reaches beyond body weight regulation.

FTO mutations and obesity risk

So far, three studies have examined whether rare variants in *FTO* are disproportionally represented in obese or lean individuals through sequencing of the exons.[137-139] Together, they identified at least 45 low-frequency coding variants, but none of the studies found evidence of an enrichment of any of these variants, individually or combined, in either obese or lean indiviudals, even though some of the variants are predicted to have deleterious effects of FTO's function.[137-139]

II. The biology of FTO

FTO is a nucleic acid demethylase

Soon after its identification, utilizing bioinformatics tools, FTO was predicted to be a 2-oxyglutarate (2-OG) Fe(II) dependent demethylase, closely related to the bacterial DNA demethylase AlkB and the mammalian AlkB homologues 1 & 2 (ABH1 and ABH2).[140] *In vitro*, recombinant FTO is able to catalyze the Fe(II)- and 2OG-dependent demethylation of 3-methylthymine in single-stranded DNA,[140,141] as well as 3-methyluracil (3meU)[140,141] and 6-methyl adenosine (6meA)[142] in single-stranded RNA, suggesting a potential role for FTO in nucleic acid repair or modification. The crystal structure of FTO is available and shows an N-terminal catalytic domain and a C-terminal domain of unknown function.[143] The catalytic pocket contains five obligate amino acid residues found in all members of this enzyme superfamily; two residues, a histidine (H) and an aspartic acid (D), required for binding Fe(II); and three residues, an H and two arginines (R) separated by six amino acids, required for 2OG binding.[137,143] The specificity for single stranded nucleic acids is provided by an L1 loop, not present in other members of the AlkB family, which sterically hinders double stranded nucleic acids from entering the catalytic pocket.[143]

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FTO demethylates 6meA, which is the most common modified nucleoside found in mRNA,[144] with 50-fold greater affinity than 3meU,[142] is found largely in ribosomal RNA.[145] However, because the vast majority of total RNA is rRNA, there are in absolute terms actually a hundred fold more 3meU than 6meA in any given cell. The question of whether one or both of these modified bases are the endogenous substrate/s for FTO is still not entirely clear.

FTO deficiency

There are several examples where common variants close to a particular gene, such as *MCR4*,[11,146-148] *POMC*,[149,150] *BDNF*,[13,151] and *PCSK1*,[152,153] are associated with alterations in risk of common phenotypes such as fat mass or risk of obesity, whereas rare loss-of-function mutations in these same genes result in highly penetrant severe early onset obesity. FTO however, has proven to be far more complicated. *Fto* was originally identified as one of six contiguous genes in a 1.6Mb deletion causing the 'fused-toe' phenotype.[154] This deletion included not only *FTO*, but also *Ftm*, *Ftl* and the Iroquois B cluster consisting of *Irx*3, 5, and 6. Homozygotes are embryonically lethal, while heterozygous fused toes mutants display severe developmental defects including left-right asymmetry,[155] defects in hypothalamic development,[155,156] as well as fused digits and hyperplasia of the thymus without any metabolic alterations. In contrast, mice with a specific targeted deletion of *Fto* did not display these severe developmental abnormalities, but exhibited a phenotype of postnatal growth retardation, decreased fat and lean body mass, and elevated food intake when corrected for lean body mass.[157] There was also a significant level of post-natal lethality, with only 50% of homozygous pups reaching weaning age.[157,158]

In humans, a loss-of-function mutation in *FTO* leads to an even more complex phenotype of postnatal growth retardation, microcephaly, severe psychomotor delay, functional brain deficits, and characteristic facial dysmorphism.[159] In some patients, structural brain malformations, cardiac defects, genital anomalies, and cleft palate were also observed. The R316Q mutation, which disrupts one of the obligate arginines necessary for 2-OG binding, results in loss of FTO's demethylase activity. The importance of FTO's ability to demethylate is underlined not only by the severe phenotype detailed above, but also by the tragic fact that none of the affected individuals survived past the age of 30 months.[159] So in both humans and mice, a fully functional FTO certainly appears to be critical for normal physiology.

Is it FTO?

Given the very close proximity of the risk SNPs to the transcriptional start site of *RPGRIP1L* (human ortholog of mouse *Ftm*), which is adjacent to and coded for on the opposite DNA strand to *FTO*,[28] it was reasonable to query the possible role of RPGRIP1L in the control of body-weight. There were two main reasons why the focus of study began with *FTO* and not *RPGRIP1L*. Firstly, while FTO was found to be nutritionally regulated within the hypothalamus,[140] this was not true for RPGRIP1L, which is known to localize in the primary cilia and centrosomes of ciliated cells. Secondly, human defects in RPGRIP1L exist and cause Joubert syndrome type 7 (JBTS), which presents clinically with cerebellar and brainstem malformation and renal failure.[160] The patients do not present with any obvious

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body weight-related phenotypes, with the caveat that any potential 'lean' phenotype is difficult to ascertain in a healthy individual, let alone someone who is severely ill. Deletion of the mouse ortholog *Rpgrip1l* (*Ftm*) recapitulates the cerebral, renal and hepatic defects seen in Joubert's patients.[160]

There is evidence for co-regulatory mechanisms between *FTO* and *RPGRIP1L*, with a possible overlapping regulatory region within intron 1 of *FTO* that contains at least two putative transcription factor binding sites (CUX1), as mentioned above, one of which overlaps with other obesity associated SNPs.[27,28] It remains a possibility that the association between *FTO* SNPs and body weight regulation is mediated through changing the expression of both *FTO* and *RPGRIP1L*.

Perturbation of FTO expression points to role in energy homeostasis

Even despite the severe phenotype seen in FTO deficiency however, there are compelling pieces of evidence that support a role of FTO in the control of energy homeostasis. For one thing, *Fto*−/− mice have an apparent hyperphagia, and there is the fact that *Fto*+/− mice are resistant to high-fat diet induced obesity.[157]

Church and colleagues have generated a 'knock-in' mouse model carrying one or two additional copies of *Fto*, and show that ubiquitous overexpression of FTO leads to a dose-dependent increase in body and fat mass, irrespective of whether mice are fed a standard or a high-fat diet.[161] That said, although the increase in weight with the overexpression of FTO seems consistent with the 'lean' phenotype of FTO deficiency, the increase in food intake seen in these mice is not. At 8 weeks, the mice overexpressing Fto do have reduced fasting leptin levels, which is odd given that obese mice with increased fat mass are normally expected to have increased leptin levels. One could speculate that the hyperphagic phenotype seen in this model is driven by the hypo-leptinaemia.

FTO is expressed ubiquitously in human and animal tissues,[140] which is consistent with multiple organ systems being affected in FTO deficiency. Its highest expression is seen in the brain, including the hypothalamus, where control of food intake is centred[140]. As touched on above, within the arcuate nucleus of the hypothalamus (ARC), FTO is bi-directionally regulated as a function of nutritional status; decreasing following a 48hr fast[140] and increasing after 10 weeks of exposure to a high fat diet, while modulating FTO levels specifically in the ARC can influence food intake.[162]

Thus, although there are some inconsistencies between the different mouse models to be worked out, the weight of evidence supports the notion that FTO itself can influence energy homeostasis by having direct effect on food intake. These findings are in keeping with the association between the *FTO* risk alleles and increase in food intake. Central nervous system (CNS) specific *Fto* deleted mice have now been generated.[163] Surprisingly, these brain-specific *Fto* deficient mice recapitulate much of the phenotype of the whole-body knock-outs,[163] suggesting that an important proportion of FTO's function, particularly its link to the regulation of energy homeostasis is mediated in the brain.

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FTO as a nutrient sensor?

Given the evidence above that FTO is nutritionally regulated and can influence food intake, could FTO be acting as a nutrient sensor? Initial attention focused on 2-OG, a key intermediate in the citric-acid cycle, and a co-substrate of FTO. It was plausible that FTO could function as a sensor for intracellular concentrations of this metabolite and thus cellular metabolism. However, since typical intracellular concentrations of 2-OG are more than 10-fold higher than its calculated Km of 2.88μM, it is unlikely that FTO's physiological role is to sense 2-OG, even if it is required as a co-factor for FTO activity.[164]

FTO mRNA and protein levels however, are dramatically down-regulated by total amino-acid deprivation mouse and human cell-lines.[165] Strikingly, this regulation was seen only with essential amino-acids, suggesting that FTO might play a role in the sensing of essential amino-acid availability.[165] Could the regulation of FTO expression by amino acids then be linked to the growth retardation phenotype seen in FTO deficiency?

FTO links amino acid availability and mTORC1 signaling to regulate growth and translation

In a recent study, it was shown that mouse embryonic fibroblasts (MEFs) derived from $Fto^{-/-}$ mice exhibit slower rates of growth and have reduced mRNA translation when compared to WT MEFs.[166] This seems to occur, at least in part, by maintenance of levels of Aminoacyl-tRNA synthetases (AARSs), as part of a large multimer complex known as the Multi-Synthetase Complex (MSC),[167] which tether free amino-acids to their cognate tRNAs and are one of the key modulators of translation. Consistent with the reduced rates of translation, $Fto^{-/-}$ *MEFs* have reduced protein levels of MSC components. The defects in mRNA translation and reduced levels of MSC components in $Fto^{-/-}$ MEFs are rescued by re-expressing FTO in these cells, implicating a role for FTO in regulating translation rates through maintenance of MSC protein levels within the cell.[166]

In addition, cells lacking FTO display decreased activation of the mTORC1 pathway and increased autophagy, all of which makes mechanistic sense in explaining the growth retardation phenotype seen in *Fto*−/− mice[157] and in humans homozygous for loss-of-function *FTO* mutations.[159] The dramatic regulation of FTO by AAs[165] seems to be necessary for the cellular response to changing AA levels, as expression of exogenous FTO in cells renders them insensitive to AA deprivation by preventing the expected reduction in mTORC1 signaling.[166]

Thus, a cell without FTO is one that thinks it is starving of amino acids, reducing mTORC1 signaling and increasing autophagy in an effort to ensure cellular survival by maintaining cellular energy levels. The consequence of this in a whole organism is clearly illustrated in another recent study, when a targeted deletion of *Fto* in adult mice results in a loss of body weight, with all of the change in weight down to a dramatic loss in lean mass.[158] As skeletal muscle is the largest depot of protein in the body, it appears to be the most sensitive to the sudden removal of FTO and subsequent increase in autophagy. In contrast, when FTO is postnatally deleted specifically from the mediobasal hypothalamus, there is a more subtle weight loss, resulting from a change in food intake.[158]

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FTO and the 6meA methylome

Critically, the link between AA availability and mTORC1 signaling is dependent upon FTO's demethylase activity, although the question of how and why this occurs remains to be answered[166]. One possibility could involve FTO's ability to demethylate 6meA. Using antibodies against 6meA to immunoprecipitate human and mouse transcripts that carry the modification and coupling this to RNA-seq, two recently published studies have mapped the presence of 6meA in a transcriptome-wide manner.[168,169] 6meAs, as it turns out, are common, enriched near stop-codons, highly conserved between mice and man, and are dynamically, developmentally and tissue specifically regulated. These studies have far reaching implications, as the decoration of 6meA at appropriate mRNA sites appears to play a fundamental regulatory role in gene expression, in addition to exerting varying effects on mRNA splicing and transport. To date, methyltransferase like 3 (METTL3) is the only enzyme identified to catalyse the conversion of adenosine to 6meA,[170] while two enzymes are known to catalyse the removal of this methyl group; one is ALKBH5[171] and the other is FTO. In fact, Meyer and colleagues show that transient overexpression of FTO in HEK293 cells decreases the total amount of 6meA found in the transcriptome[169].

A recent paper has demonstrated that FTO does not globally target all 6meA-modified mRNAs but instead demethylates specific mRNA subsets[172]. They show for instance, that the midbrain and striatum of *Fto*−/− mice show increased methylation in mRNAs from genes encoding components of the dopamine signalling pathway, resulting in reduced dopaminergic signalling tone[172]. Outside of the brain, FTO risk alleles have also been reported to influence the methylation status of ghrelin mRNA. By doing so, Karra and colleagues have postulated that FTO may affect levels of circulating ghrelin. Further studies will be required to determine the extent to which changes in dopamine and/or ghrelin signalling could be effectors of FTO's association with increased BMI.[173]

Future Perspectives

So how do the findings on the biochemical function of FTO relate to the association between FTO SNPs and obesity? In truth, we still do not know. In particularly, little is known about if or how the *FTO* risk alleles are influencing the FTO protein. Considering their intronic location, they are unlikely to cause functional mutations, but are more likely to be playing a subtle transcriptional regulatory role, either to up- or down-regulate FTO expression.

What we do know is that FTO is most highly expressed in the brain, where the sensing of amino acids can influence the activity of pathways controlling food intake. We would hypothesize that subtle effects of the risk alleles on expression of FTO in key brain regions, such as the hypothalamus, are likely to influence the way in which these cells sense amino acid levels. As we discuss above, there is evidence that human carriers of the susceptible SNPs in *FTO* not only consume more food, but also show an alteration in nutrient preference, perhaps suggesting that FTO status can influence the central sensing of dietary macronutrient composition. Thus the role of FTO in amino acid sensing may provide some clues towards understanding the cellular basis for this physiological phenomenon.

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Given the fact that a substantial proportion of the world's population have their bodyweight subtly influenced by SNPs in *FTO*, can *FTO* ever be considered a realistic pharmaceutical target? Given its ubiquitous expression, the severity of the phenotype seen in human and murine FTO deficiency, and the fact that adult deletion of FTO results in a dramatic loss of muscle mass, we believe it is unlikely. However, the understanding of FTO biology could potentially reveal novel therapeutic targets in our battle against the increasing epidemic of obesity. We also believe that the efforts to date in turning the statistical association of *FTO* with BMI into a deeper understanding of its biology and could form a template into how we approach the many other emerging GWAS obesity genes of unknown function.

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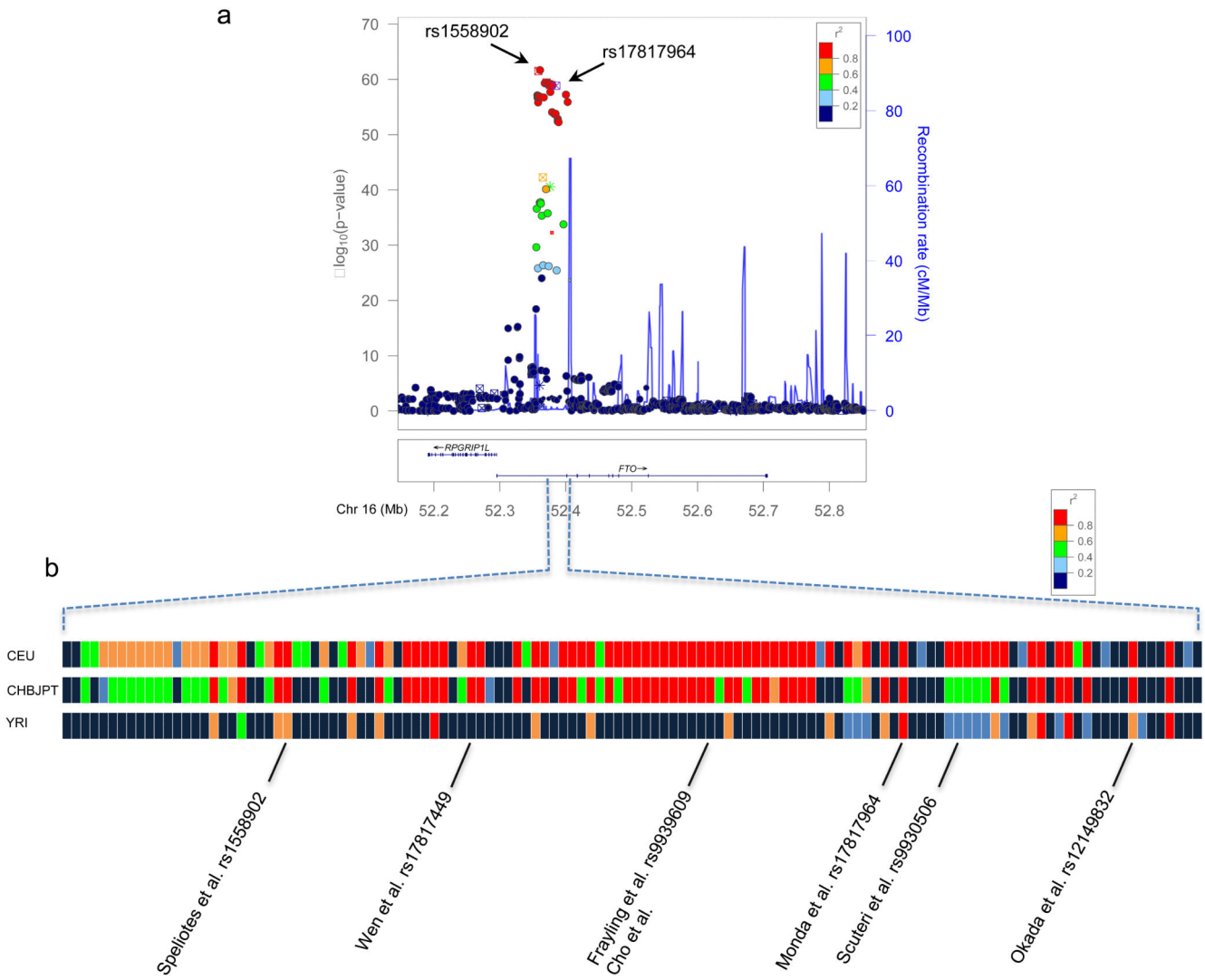

Figure 1. A cluster of BMI-associated SNPs in FTO's first intron.

a | Regional plot of the *FTO* locus in European ancestry populations. SNPs are plotted by position on chromosome 16 against association with BMI (−log10 P-value).[16] Recombination rates (from CEU HapMap) are plotted in cyan to reflect the local LD structure. The SNPs surrounding the rs17817964 (in purple) are color coded to reflect their LD with this SNP (r2 values from the HapMap CEU data). **b** | The LD structure of SNPs surrounding rs17817964, color coded to reflect their LD with this SNP in European (CEU), East Asian (CHBJPT) and African (YRI) ancestry populations. Based on LD r2 values from the HapMap CEU, CHBJPT and YRI data. Each "cell" represents a SNP in the first intron of FTO (between position 52,355,019 and 52,407,580 according to NCBI Build 36). SNPs in "red" are highly correlated (r^2>0.80) with rs17817964.

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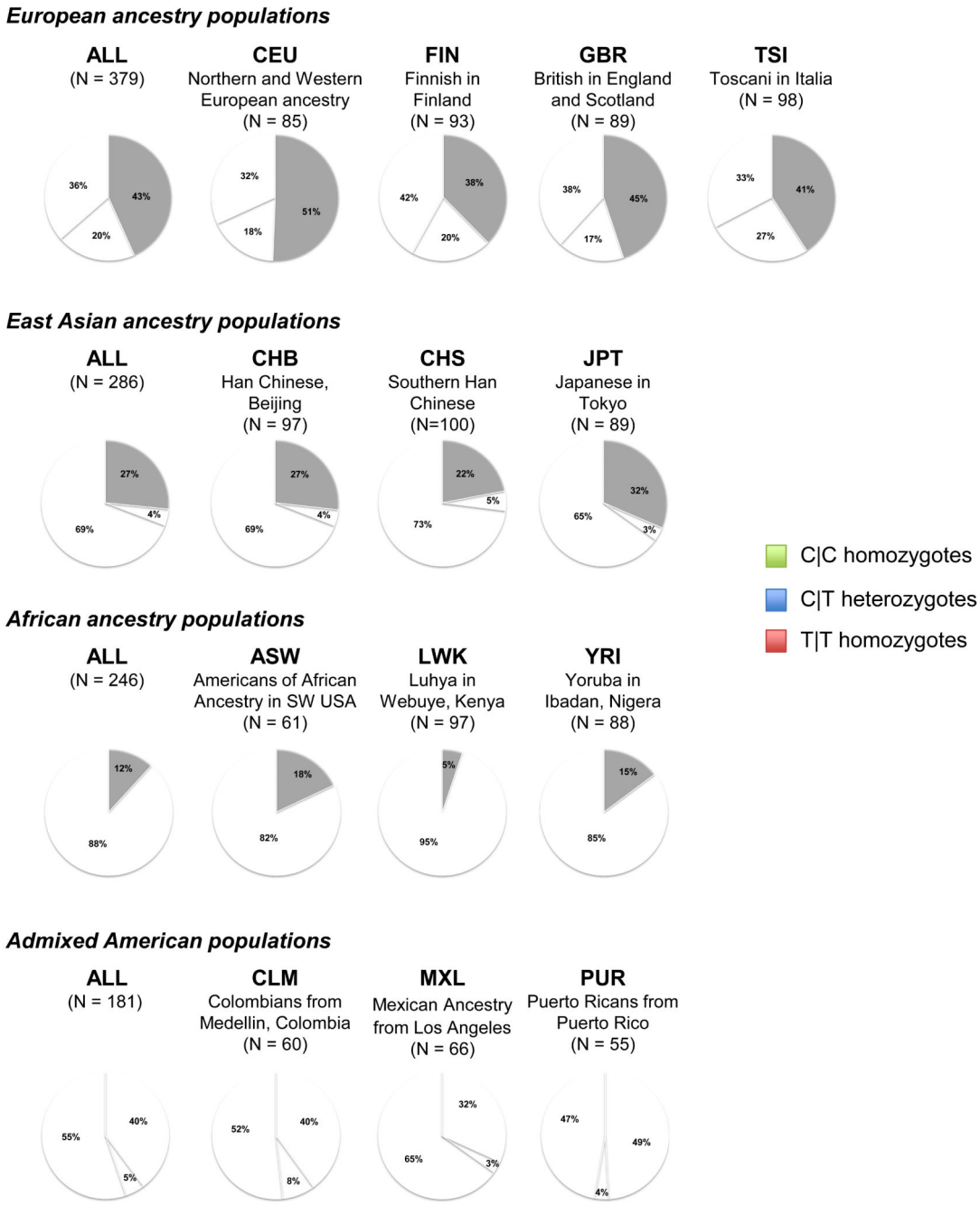

Figure 2. Genotype frequencies for rs17817964 across populations of different ancestry based on data from the 1000 Genomes Project.[174] The T-allele is the BMI-increasing allele.

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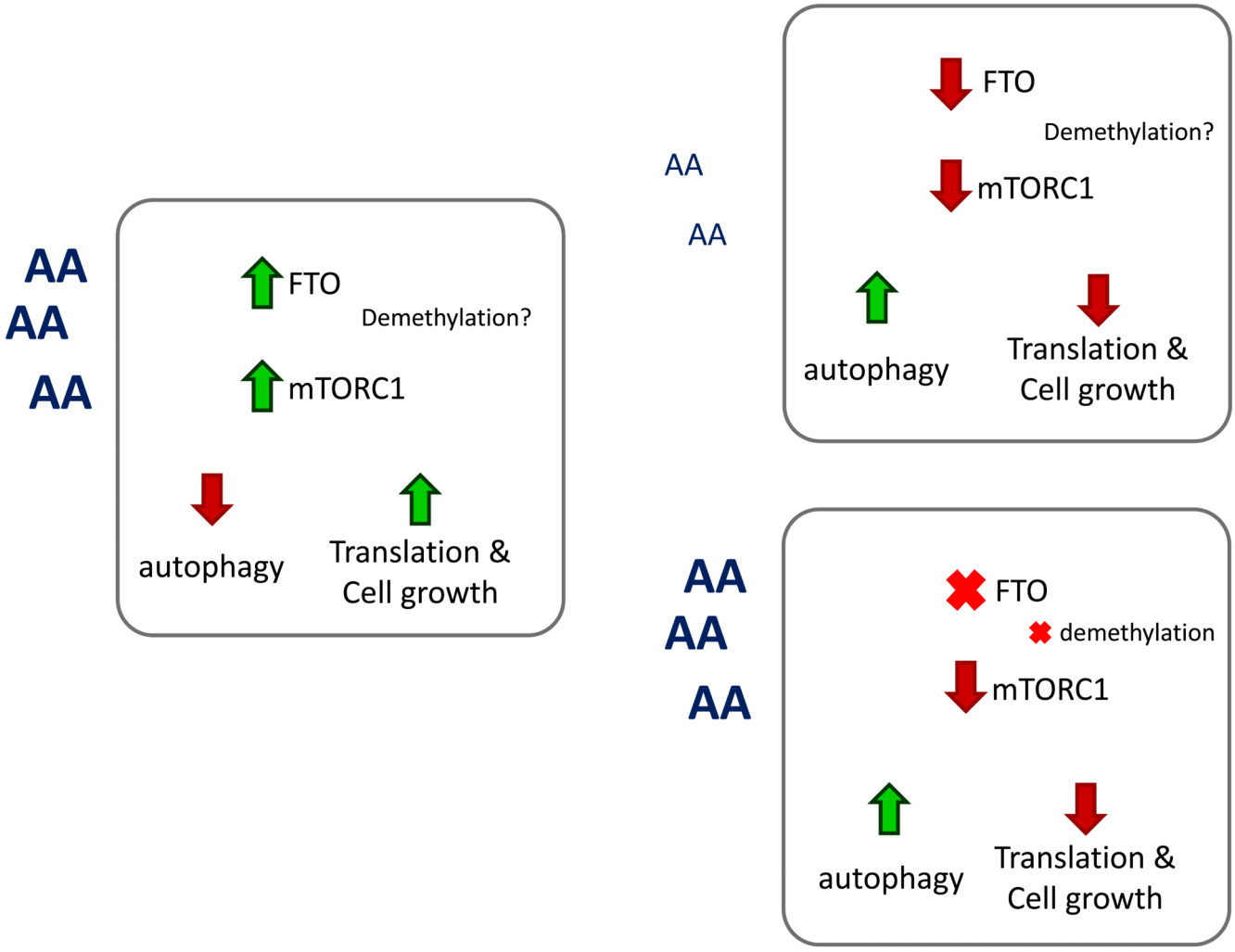

Figure 3. Model of FTO's role in the cellular sensing of amino acids (AAs).

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Table 1

Effect size and explained variance of BMI-associated FTO SNPs in European, Asian and African ancestry populations.

Ancestry	BMI-increasing allele frequency (%)	Effect on BMI (kg/m^2 per allele)	Explained BMI variance (%)	Effect on obesity risk** (OR per allele)	Source
European	42%	0.39	0.34	1.20	16
East Asian	12-20%	0.25	0.16	1.27	58
Indian Asian	30-33%	0.29	0.20	1.18	58
African	12%	0.41*	0.10	-	26

* Derived from the stage 2 effect size (inverse variance units) reported by Monda et al.[26] (assuming a SD of 6 kg/m^2).

** Obese vs normal weight; in European ancestry populations the obesity cut off is 30 kg/m^2, in Asian ancestry populations the cut off is 28kg/m^2.