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## SUMMARY

It is an inescapable fact that obesity results from consuming more energy than you burn. The interesting question however is why some people eat more than others? Recent genetic analyses have revealed that variations in the fat mass and obesity-associated (*FTO*) gene are robustly associated with obesity and increased food intake. This association is replicable across different age groups in multiple populations and attention is now turned to studying the complex biology of *FTO*.

Fasting decreases while a high-fat diet increases *FTO* expression levels specifically within the arcuate nucleus of the hypothalamus. In keeping with this, reducing *FTO* expression in the arcuate nucleus increases food intake, while overexpressing *FTO* decreases food intake.

## FTO and Obesity: a problem for a billion people

### A problem of our time

Obesity is one of the greatest public health challenges of the 21st century. The prevalence of obesity has tripled in many countries since the 1980s. The number of those affected continues to rise at an alarming rate. Within the European Union for example, nearly 150 million adults and 15 million children are considered obese. The problem is not with obesity itself per se, but with the accompanied increased risk to a host of nasty diseases, including type-2 diabetes, heart-disease, high-blood pressure and certain cancers.

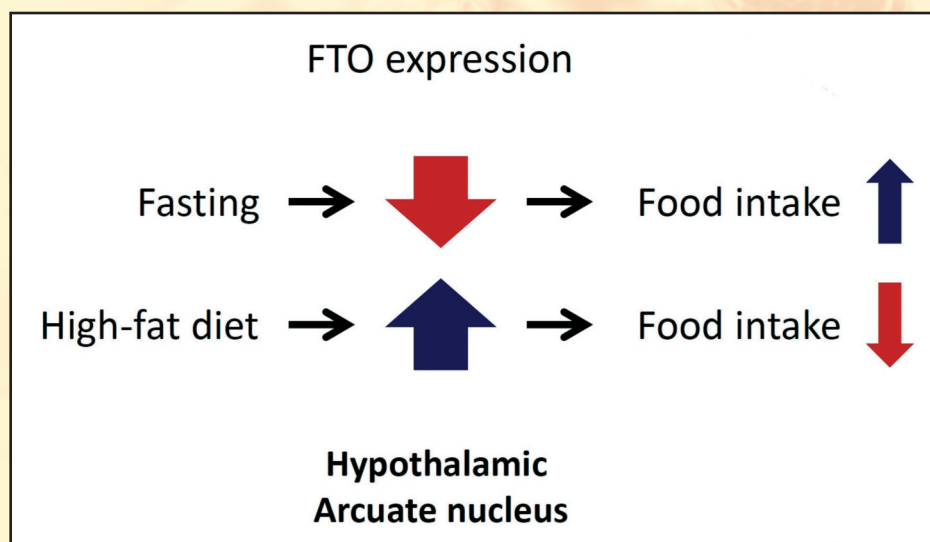
So how can we explain this rapid increase of body-weight in the population? Have our genes changed? Have we suddenly evolved? Clearly not. These dramatic changes have occurred over the past 25 years, against a constant gene pool and well within

the lifetime of most of you reading this article. This would put the smoking gun in the guilty hands of 'environmental changes', an all-encompassing term used to describe changes in lifestyle, working practices and perhaps most of all, diet. Sadly, no matter how much we protest, the only way you can gain weight, is if you eat more than you burn.

However, it is also clear that different people have responded rather differently to these changes in environment. Some have become over-weight or obese to varying degrees, while others have not gained a single gram over the past 25 years.

### A billion people 3kg heavier

Over the past 15 years, studies of Mendelian (single gene) inherited syndromes of obesity in humans and mice have been invaluable in



illuminating critical neuronal pathways controlling food intake and body-weight. In humans however, these monogenic causes of severe obesity are extremely rare. The major burden of disease is carried by those of us with 'common obesity', where in contrast to the Mendelian obesity syndromes, is likely to have a 'polygenic' aetiology, with multiple variations each having a subtle effect.

It was not until very recently that the required technology to interrogate more than a million different genetic variants in parallel was developed. In 2007, just such a genome-wide association study identified that multiple single nucleotide polymorphisms in a gene called *Fat mass and obesity related (FTO)* were associated with increased body-mass index (BMI): individuals homozygous for the 'risk' alleles weigh on average 3kg more than those homozygous for the 'protective' alleles. Subsequent studies have shown that *FTO* risk alleles are unequivocally associated with increased food intake.

While the effect of these *FTO* risk alleles appears modest, they are very common, with an estimated one billion homozygous carriers in the world that span multiple different ethnicities and populations. Yet the biological function of *FTO*, particularly its role in controlling energy balance, remains unknown. Nevertheless, *FTO* at last gives us a handle on a huge, worldwide, common problem and demands exploration.

## The complexity of *FTO* biology

*FTO* belongs to the family of enzymes (dioxygenases) which are involved in many cellular processes including, DNA and RNA repair. *In vitro*, *FTO* is able to remove methyl lesions from single-stranded DNA and RNA, suggesting that *FTO*'s physiological role could be linked with nucleic acid modification. However, we still do not know how this demethylation activity might be linked to obesity.

In 2009, it was reported that nine members of a large Palestinian Arab family were affected by a previously unknown polymalformation syndrome, and all of them turned out to be homozygous for an amino acid substitution at position 316 (R316Q) in *FTO*. Unfortunately for the affected individuals, this mutation rendered *FTO* completely inactive. The affected individuals showed retarded postnatal growth, severe functional brain deficits and cardiac abnormalities.

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*"...the only way you can gain weight, is if you eat more than you burn"*

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Tragically, the severity of the phenotype was such that all affected children died before reaching 30 months.

Mice homozygous for a targeted deletion in *FTO* display a complex phenotype. Like humans with *FTO* deficiency, they are post-natally growth retarded with decreased fat and lean body mass, and 50% die before weaning. Thus *FTO* seems to have a critical, but as yet undetermined role, in the development of several major organ systems, including the central nervous and cardiovascular systems.

## Obesity, it's 'all in your head'

*FTO* is expressed in many tissues, with the highest expression in the brain, in particular the hypothalamus. Intriguingly, if this gene is deleted just in neurones (neuronal-specific *FTO* deleted mice), the mice show the same phenotype as when the gene is deleted throughout the body, suggesting that much of *FTO*'s function, including its link to energy regulation, is mediated in the brain. Within the arcuate nucleus of the hypothalamus, *FTO* levels are

reduced in the fasting state and increase when animals are fed a high-fat diet. In contrast to the severe phenotype seen in complete *FTO* deficiency, perturbing *FTO* levels discretely within the arcuate nucleus bi-directionally influences food intake, with reducing *FTO* levels resulting in an increase in food intake and vice versa (Figure 1).

Thus, while *FTO* clearly has a broader biological function, it also has a role specifically within the hypothalamus to regulate food intake.



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