Overactive FTO gene does cause overeating and obesity

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Study offers confirmation that it is the FTO gene that can predispose some people to obesity.

(PhysOrg.com) -- Scientists have gained strong confirmation of the direct connection between the FTO gene and obesity, obtaining the first direct evidence that overactivity of the gene leads to overeating and obesity in mice.

The research team from the University of Oxford and Medical Research Council (MRC), with funding from the Wellcome Trust and MRC, have published their results in the journal *Nature Genetics*.

The team's findings suggest that the gene could be a promising target for developing anti-obesity drugs that act by turning down the gene's activity.

‘This work makes us confident that FTO is an important gene that contributes to obesity,’ says Professor Frances Ashcroft of Oxford University’s Department of Physiology, Anatomy and Genetics, and one of the leaders of the research. ‘Too much activity of this gene can lead to putting on weight by overeating.

‘We can now think about developing drugs that turn down the activity of the FTO gene as potential anti-obesity pills. That’s a long way off and there’s no certainty of success, but it’s an enticing prospect,’ she adds.

In 2007, an international team of researchers, including Oxford scientists, announced that they had identified the first genetic variant that could be linked to increased likelihood of obesity in a large genome-wide study.

The single change in DNA sequence lay within the FTO gene. People with two copies of this genetic variant (around 16% of people of European descent have two copies) were 3 kg heavier on average than those without.

While this was an important result, genome-wide association studies are often first steps that then enable detailed research to pin down the mechanisms behind the observed connection, in this case to obesity.

In particular, genome-wide studies cannot be certain that the genetic variation identified directly increases obesity risk. The DNA change could be a flag or marker that the important gene lies nearby, or the DNA change could lie within a control element that regulates a different gene some distance away.

The researchers in the current study, led by Professor Roger Cox at MRC Harwell and Professor Frances Ashcroft at Oxford University, set out determine whether it was differences in the activity of the FTO gene

itself that was directly causing the increase in body weight.

The scientists bred mice with extra copies of the FTO gene. These mice were healthy, but ate more and became fatter than normal mice.

Female mice with two extra copies of the FTO gene, when fed a standard diet, became 22% heavier that normal female mice after 20 weeks. The difference in weight for male mice was 10%. The researchers also showed that the difference came because mice with FTO overactivity consumed more food. (There is no suggestion that weight differences in humans with FTO variants are, or would be, nearly as large, or would necessarily affect the sexes in a similar proportion.)

Chris Church, a PhD student from MRC Harwell and first author on the study, said: 'For the first time we have provided convincing proof that the FTO gene causes obesity. The next step is to understand how it does this, for instance whether it increases appetite by influencing our brain or alters messages from our fat stores and other tissues. Once we know how FTO causes obesity we have the potential to look at developing drugs to treat it.

'Genome-wide association studies have done a fantastic job narrowing down the areas in the genome responsible for obesity. They've provided signposts of where to look, but these areas still need pinning down to a precise gene, as we have done here for the first time with FTO. The mouse model has enabled us to achieve this in just a few years, and we hope the same process will now be applied to the other gene areas implicated in obesity, enabling scientists to confirm precisely which other genes can predispose us to become overweight.'

Almost 1 in 3 people in the UK are overweight or obese. Obesity predisposes people to numerous diseases, including heart disease, type 2 diabetes and cancer. The estimated cost of obesity to the NHS is

approximately £1 billion a year, with an additional £2.3 to £2.6 billion per year to the economy as a whole.

'This gene is novel to obesity research and it is going to be exciting to find out how it works,' says Professor Roger Cox of the Medical Research Council's Mammalian Genetics Unit at Harwell, and one of the leaders of the research. 'We have the mouse models now to address these questions.'

Provided by Oxford University