# Brain background to body mass

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A genetic study of more than 90,000 people has identified six new genetic variants that are associated with increased Body Mass Index (BMI), the most commonly used measure of obesity. Five of the genes are known to be active in the brain, suggesting that many genetic variants implicated in obesity might affect behaviour, rather than the chemical processes of energy or fat metabolism.

Obesity is an increasing problem that results in individual risk to health as well as increasing burdens on health care systems. By identifying genetic variants that affect obesity, researchers hope to understand better the mechanisms regulating energy balance, which will guide the development of new therapies and help to develop improved diagnosis.

The study is published in *Nature Genetics* by the GIANT Consortium and includes authors from more than 60 institutions.

"It might seem remarkable that it is the brain that is most commonly influenced by genetic variation in obesity, rather than fat tissue or digestive processes," says Dr Ines Barroso, a senior author on the study, from the Wellcome Trust Sanger Institute. "Until 2007, no genetic associations had been found for 'common obesity', but today almost all those we have uncovered are likely to influence brain function."

Increase in weight occurs when calories taken in exceed calories burned, but behind that simple equation lie behavioural processes such as appetite and satiety, as well as the biochemical mechanisms our bodies use to process foods and use stores of energy, such as fat tissue. A part

of the brain called the hypothalamus controls many of our basic functions such as body temperature, hunger and fluid balance: it is programmed to maintain the status quo.

"Very occasionally, mutations in genes active in the hypothalamus have dramatic consequences for weight gain," explains Dr Ruth Loos, a leading author from the Medical Research Council Epidemiology Unit, "such that people carrying these mutations are severely obese. Such mutations might be considered exceptional.

"However, we suggest that the picture for common obesity is very similar: many or most genes associated with increased BMI are active in the brain."

Studies in twins suggest that genetics can account for 40-70% of the variation in BMI. Yet only one of the genes that were previously discovered had been thought to be linked to increased BMI or obesity in humans. The six new candidate genes provide a rich pool of resources to understand some of the processes in the brain that drive increased BMI and common obesity.

They also highlight the role of different types of mutation: intriguingly, one of the variants does not seem to mark a single-base change in the human genome, but rather the loss of a region of DNA of around 45,000 bases. The authors suggest that this lack of genome sequence near a gene called NEGR1might knock out genomic sequences that regulate activity of NEGR1. Such a variant has not been previously detected in studies of common obesity.

"It may seem surprising that we know so little about the biology of such an important medical and social issue," says Mark McCarthy, Robert Turner Professor of Diabetes at the University of Oxford, a senior author on the paper. "We can use genetics to open the door on some of

the processes that contribute to individual differences in the predisposition to obesity. We are finding that common diseases have complex causes, and it is only by understanding the biology that we can start to make rational attempts to treat and prevent conditions such as this.

"Studies such as this are uncovering more and more genetic changes that are involved in more and more diseases. This is a remarkable time for human genetics."

The authors point out that perhaps dozens of similar variants remain to be discovered. The effects of the variants identified in the new study are modest: someone who carries all the risk variants would typically be 1.5-2 kg heavier than an average person. The findings of this study will pave the way for future investigations to uncover more of the elusive variants, perhaps through sequencing of whole genomes, which has become more efficient and cost-effective in the past year or so.

The research also helps to set the stage to unravel the two influences of genetics and environment. Future research could harness the power of longitudinal cohort studies, which track the health of many subjects through time, thereby providing the tools to map gene-environment interactions.

Source: Wellcome Trust Sanger Institute

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