Genetic research shows single approach to obesity won't work

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Abstract
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The holy grail of obesity research is a simple, single solution that could stem the tide of this epidemic. But research we published in PLOS ONE today shows that this is an implausible, if not impossible, goal.

Using careful definitions and measurements of body fatness, we've shown that obesity that runs in families of people with type 2 diabetes is due to a large number of rare variants in many different genes.

This decreases prospects for a single drug treatment. And it highlights the key role of our affluent social environment in the development of obesity.

Type 2 diabetes and obesity

Type 2 diabetes is a growing problem in the developed world, linked to a similar increase in obesity, which is present in 80% to 90% of cases. Obesity and type 2 diabetes can both be inherited and have very strong genetic influences, but the link between the two conditions isn’t quite clear.

Researchers have found many common gene sequence variants linked to obesity, but, so far, these only account for about 5% of its total heritability.

There are many possible explanations for obesity’s “missing” heritability. But we have shown
that, in families with type 2 diabetes (and probably more generally), this absence is mostly due to a large number of rare (<0.5% of the population) genetic variants that can’t be detected in conventional genetic sequencing studies.

Our finding, which appears surprising, is actually consistent with current understanding of the human genome; it’s now clear that about 90% of all human genetic variation is rare.

It’s difficult to know how many different genes could be involved in obesity susceptibility, but it can’t be less than 50 and may be hundreds.

The situation is probably similar in type 2 diabetes genetics because in that situation also, known common genetic variants still only account for about 10% of heritability.

**Real-world applications**

A better understanding of the genetic causes of obesity will lead to more effective treatment and prevention. But the fact that so many genes are involved makes it theoretically much harder to suggest that a single drug would be effective in a large number of people.

How the current first-world environment impacts the genetics underlying behaviour, especially appetite-regulation, is not fully understood. But if people are genetically predisposed to a “strong” appetite, the enormous amounts of easily available, energy-dense food that we are surrounded by is likely to make them fat.

We have shown in a previous study that people with diabetes in the family tend to gain more weight in tempting situations with high-calorie foods (being provided with high-calorie snacks and being asked to over-consume over 28 days).

An important implication of our research is the belief that the family environment is responsible for obesity (by promoting bad eating habits or low levels of activity) is not true. Obesity runs in families predominantly because of inherited genes, not learned behaviours.

**Small differences, big impacts**

The importance of rare genetic variants is becoming clear in a number of diseases and researchers are redoubling their efforts to sequence the genomes of more people in greater detail to identify them.

In our work, it was very important to have a carefully defined measure of body fatness that reflected biology more accurately than other measures. If we’d analysed only the commonly used measure of body mass index (BMI, which is weight divided by height squared), for instance, we would’ve had no clear findings.

Much more attention should be paid to careful, biologically plausible measurements of body fatness before, or at least in parallel with, the massive investments in gene sequencing that are planned or underway.

Our result strongly suggests a need for a change in the approach to gene discovery in obesity and type 2 diabetes. We need to place more emphasis on accurate measurements and on family studies, and combine the effects of closely-related rare variants in analyses.

Research should also put more weight on the biological plausibility of proposed links to disease processes. The potential reward is results offering a rational basis for targeting therapy to the various defects likely to be responsible.

In the meantime, we know a family history of type 2 diabetes or obesity, or both, signals a much higher risk of developing obesity in our current environment. This should be the focus of
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attention for individuals, doctors and researchers.