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Genetic determinants of thinness and obesity: cards of the same deck

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ABSTRACT

Obesity is a major public health concern. While most genetic studies have focused on obesity, we opted to look at the contribution of genetic variation to healthy thinness. In this study, we found that propensity to obesity or thinness is affected mostly by the same genes.

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Obesity is a major public health concern worldwide, with high prevalence paralleling an increasingly "obesogenic" environment that promotes a sedentary lifestyle and poor-quality food choices. However, even within this environment, some people are able to maintain a healthy body mass index (BMI, defined as weight in Kg divided by height squared (m^2) >18.5Kg/m^2 and <25Kg/m^2), while others struggle to do so. This has long supported the idea that there is a heritable component to both obesity and thinness, which means that some of the observed variation in BMI in the population can be attributed to genetic factors (for example, thin children are more likely to have thin parents). Therefore, one can use genetic studies as a tool to better understand how biological networks regulate both energy consumption and expenditure and use that information potentially to develop novel anti-obesity treatments. Genetic studies test millions of genetic variants - variations in our DNA that may differ from person to person - in large numbers of people and ask the question: do certain variants occur more commonly in individuals with a particular trait (for example, obesity) than in those who are healthy ("controls")?

In this study, we wanted to study two things: do genetic variants influence healthy human thinness to

the same degree as they influence obesity? And do the same genes affect obesity and thinness, or are there genes that are exclusively linked to one but not the other?

To this end, we studied ~1,400 thin individuals (BMI < 19) that had a family history of thinness, claimed they had been thin all their life and that were confirmed by a general practitioner to be healthy. In parallel, we also studied ~1,400 individuals that had severe obesity since early childhood and we contrasted the thin and obese participants against each other, as well as against a common group of ~6,400 individuals in the middle of the BMI distribution (people who were not overly thin or overly obese). We also used genetic variants known to influence BMI to construct a "genetic risk score", where one quantifies how many of BMI increasing variants each individual has and tests if the difference in scores is significantly different between groups of people (for example, between thin and obese people). One can think of this risk score as a hand at a poker game. The majority of people will have an average hand, some really lucky people will have a particularly good hand (a straight flush), and some really unlucky people will have a particularly bad hand (a high card ten). A good hand means you are more likely to win (easily thin) and a bad hand means you are more likely to lose (easily obese).

The first result we found is that thinness and obesity are similarly influenced by genetic variants, that is, they are equally heritable (in both cases genetic variants influence these conditions by about 30%). The second important finding is that for the most part the same genes influence both thinness and obesity, and we have not found any "obesity" or "thinness" specific genes. Lastly, we found that those who are thin have on average a lower genetic risk score, while those who are obese have on average a higher genetic risk score, which means that on average thin people have "better poker hands" than obese people do.

Overall, our study shows that there is a significant genetic component to healthy thinness and that on average, these individuals are "luckier" in the genetic lottery. In other words, these people have an easier time maintaining a low body weight thanks to their genetic makeup. This might be due to a lower threshold for satiety or through influences on exercising behaviour but at this point we do not know enough about the biological mechanisms through which most of these variants exert their effect on BMI to give a definite answer.

While finding new anti-obesity drugs is still very much in the horizon, the old advice of good diet and exercise is still the best way to maintain a healthy BMI. After all, we have seen some people with a very high genetic risk score with a low BMI (<20) just like some people win poker games with a pair of twos.