Genes have a time clock, new obesity study reveals

In the search for the genetic underpinnings of obesity, large scale gene association studies in 2007 identified variations in a gene called FTO that was quite robustly linked to increases in body mass index (BMI). The findings were then replicated in future studies and the FTO gene gained widespread acceptance as the obesity gene.

Now new findings published in the journal *Proceedings of the National Academy of Sciences* adds another factor that should be taken into account when studying genetic associations – time. Carl Zimmer explains further,

> [The research] raises questions that extend far beyond obesity. Genes clearly influence our health in many ways, but so does our environment; often, it is the interplay between them that makes the difference in whether we develop obesity or cancer or another ailment. But the relative importance of certain genes may shift over the years, the new study suggests, as our environment changes.

Using data from the multigenerational Framingham Heart Study which has been in existence since 1948, the researchers saw that variants in the FTO gene that correlated with an increased risk of obesity in fact had no correlation in the subset of the study population born before the early 1940s. In contrast, the variation had a stronger association than previously predicted on people born later, particularly in the latter half of the 20th century. Simply put, the study says that year of birth modifies the correlation previously seen between an increase in BMI and particular single nucleotide changes in the FTO gene.

The mechanism of how the variation in the FTO gene alters BMI is still being worked out and hence the implications of this finding might not become clear until later. Some research suggests that it might act by altering appetite and food intake levels and more recently, research published in the journal *Nature* showed that the genetic variation may not have anything to do with the FTO gene, exerting its effects instead through a completely different gene known as IRX3.

Whatever the mechanism, the study findings brings up the intriguing question – what changed between the two populations that allowed the variant to have an effect on body mass index? The researchers speculated that a sedentary lifestyle combined with modern diets may have had an impact, though it is something that the study did not investigate further. There is some evidence for this however, as previous research has shown that physical activity can dampen the effect of the deleterious FTO variant by as much as 30 percent.

As easy and compelling as it is to look for a simple cause for a disease like obesity or diabetes, the findings shouldn't be misinterpreted to mean that you are more likely to become fat because you were born after 1942, as this headline erroneously implies. The reality is that this is a multigenic disease that has a large environmental component. In fact despite the robust association between FTO gene mutations and increased BMI, it still is quite poor at *predicting* the risk of obesity. And as this study suggests, when the environment changes over time so does the effect of genetic variations associated with disease

making it much more of a moving target than we previously thought.

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