genes or lifestyle?

Obesity often seems to run in families, and researchers are using new tools to determine which has a bigger impact:

By Markian Hawryluk / *The Bulletin*

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The concern about the obesity crisis and the observation that excess weight seems to run in families is raising an age-old question. Are similarities between parents and children due to the same lifestyle or the same genes?

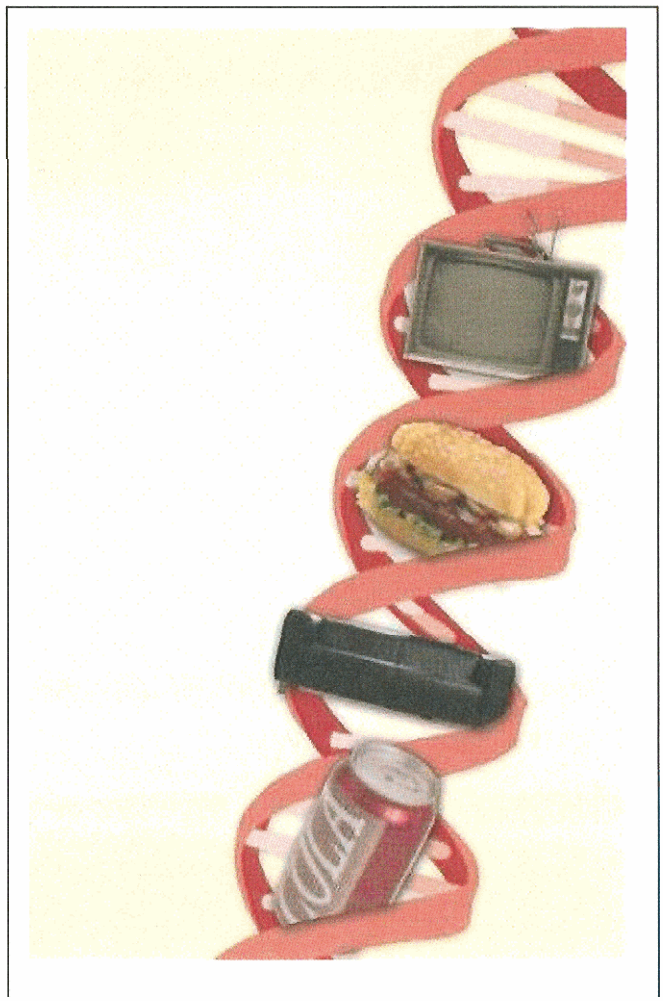
In recent years, researchers have developed new tools that might help to quantify the extent of the genetic contribution. New techniques that allow scientists to look at the entire human genome are uncovering more and more genetic links to obesity. They've identified at least a dozen genetic variations that increase a person's risk for being overweight.

But lest you think you can blame your weight solely on your DNA, researchers stress it's the rare case of obesity that can be attributed to bad genes.

So how much of the obesity crisis is due to genetics and how much to environment?

"I think it's hard to answer the question," said Amy Zlot, a researcher with the Oregon Genetics Program at the Oregon Department of Human Services. "If you're looking at the controversy over nature versus nurture, it's both."

Traditionally, scientists seeking to quantify the genetic component of obesity have tracked how excess weight runs in families, a concept known as heritability. They've concluded on the basis of studies with twins that about 60 percent of a person's weight depends on genetics and 40 percent on environment.



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Identical twins share the same genes, while fraternal twins share up to half of their genes. But when they live in the same home, they've shared an almost identical environment. Thus comparing the correlation in weight among identical twins to the rate among fraternal twins gives researchers a good estimate of how much of weight is attributable to genetics.

The genetic link is so strong that researchers have found the percentages hold up even when identical twins are raised in completely different households. Moreover, the studies showed that it was eating behavior that led to similar weights in twins, suggesting that genes impact things such as appetite and satiety.

Studies of parents and non-multiple children — who obviously have plenty of genes in common — came to similar conclusions. The strongest predictors of child obesity was parental obesity, even after accounting for things like diet and physical activity.

Of mice and men

Photo illustration by Andy Zeigert / The Bulletin

But all these correlations couldn't tell scientists which genes were responsible for weight and obesity, or how they could identify those individuals whose genes set them up to gain weight.

Working with mice, researchers discovered a genetic defect that blocks production of a hormone called leptin. The hormone is produced within fat tissue and helps to signal the brain when enough energy has been stored away. Without the hormone, the mice ate insatiably. But when the mice were injected with leptin they returned to normal body weight in less than a month.

Several years ago, British doctors treated two young boys who had similar genetic defects. One boy weighed 90 pounds at age 4 and consumed about 1,125 calories per meal. His cousin weighed 200 pounds at age 8. When doctors started giving the younger boy leptin injections, his average calories per meal dropped to 180, and by age 6, he was back to normal weight. In this case, a single gene was responsible for the boys' obesity.

While researchers have identified more than a dozen genetic defects that can be the sole cause of obesity, few obese individuals can blame their weight on such defects, said Dr. Rodolfo Valdez, an epidemiologist with the Office of Public Health Genomics at the Centers for Disease Control and Prevention.

"There are only about 200 cases reported for obesity in which there was one major gene causing those," he said. "In the majority of cases, it is just interaction between genes and environment."

The common explanation for how those two factors have conspired to produce today's obesity crisis is known as the thrifty genotype hypothesis. The idea is that our ancestors were more likely to survive periods of drought or famine if they had genes that improved their ability to store fat. Those who survived passed on those thrifty genes to their descendants.

But now that the food supply has become more stable and the amount of physical work in our lives has declined, such genes have begun to work against us.

"Those genes that helped us to accumulate fat in those times, are now facing an environment in which we have calories all over the place for 24 hours a day," Valdez said. "So those genes, they are living in a mismatched environment."

But that doesn't mean that people with those thrifty genes are condemned to a life of excess weight.

"We tend to blame our genes for many things. 'I didn't do it, it was my genes,'" Valdez said. "The truth is that genes alone don't do anything if you don't have the (proper) environment."

Valdez uses the example of language. Our genes provide all the physical tools we need to speak a language and might provide a mental capacity for learning new languages, but unless we're in the right environment, we won't learn new languages.

"In the case of obesity, the genes might be there, but if we don't find the proper environment, they won't develop," Valdez said. "By modifying the environment we can change a lot about how our genes are expressed."

The mismatched environment theory could also explain why the obesity crisis has emerged only in recent decades. The rise in obesity rates has been too sudden to attribute to a change in genetics alone.

Genetic tangle

The more researchers learn about the links between obesity and genetics, the more they understand how complex the genetic link is. The

effects of the relevant genes might be very subtle. The process may play out through small genetic variations that just slightly alter a protein's activity. Few will result in the complete shut down of an enzyme or protein, such as in the leptin example.

Research continues to support the notion that weight is controlled not by a single gene or two, but by as many as 600 different genes that work in combination to predispose certain people toward obesity and others toward normal weight.

Genetic research has been greatly facilitated by the mapping of the human genome and new technology that has allowed researchers to look at genetic variations throughout a person's DNA. Known as genome-wide association studies, or GWAS, the technology allows researchers to quickly compare genetic variations in people with a condition or disease with the genes of healthy people.

"Prior to about mid-2005, if you read that somebody had found a gene for a disease, generally it didn't hold up," said Dr. Struan Grant, associate director of the Center for Applied Genomics at the Children's Hospital of Philadelphia. "Now with this GWAS approach, you can robustly find these associations, and more importantly, your peers, other academic groups, agree with you."

It was only five years ago that GWAS studies became possible, and in a short time, researchers have already identified scores of gene variations that are linked with obesity.

One of the more promising findings was the discovery of the so-called FTO gene by British researchers in 2007. They found that individuals with one copy of the FTO gene variant had a 30 percent higher risk for obesity, and individuals with two copies had a 70 percent higher risk. Among people of white European descent, about one in six people carry two copies.

"Our findings suggest a possible answer to someone who might ask, 'I eat the same and do as much exercise as my friend next door, so why am I fatter?'" said Dr. Andrew Hattersley, a medical professor at the University of Exeter, and one of the scientists who identified the FTO gene. "There is clearly a component to obesity that is genetic."

German researchers took the research further, breeding mice that lacked the FTO gene. They ate large amounts of food but were relatively sedentary. But without the FTO gene, the mice produced large amount of adrenaline and gained no weight. "You had a real nervous mouse but it was slim. It could lead the couch potato life and still look great," Grant said. "That was one of the more remarkable breakthroughs in the genetics of obesity and it's the first real tangible example that indeed there is a real genetic basis to obesity. We see FTO behaving very strongly with respect to childhood obesity here in Philadelphia. It's clearly a key player."

Discovery of the gene variations, such as FTO, also gives researchers a target for developing treatments for obesity. Because FTO impacts production of an enzyme, researchers are now trying to develop drugs that would affect levels of those proteins, providing individuals with the FTO gene variants some additional help in battling their predisposition for obesity.

"The challenge is there are many genes, so you have to look at the mixture, the bad variants and the good variants as a sum, and how they work together," Grant said. "The most robust thing will be when you have the entire repertoire of the genetic area, the whole cocktail."

Unfinished business

But researchers still have a long way to go. A study published last month in the American Journal of Clinical Nutrition concluded that the combined effect of the first 12 genetic variants linked to obesity explain only about one percent of the variation in weight.

Dr. Ruth Loos, a researcher at the Institute of Metabolic Science at the University of Cambridge, and the lead author of the study, said more genetic variants have been found since the completion of the study and she expects many other locations within the genome, or loci, that impact obesity will be identified.

"These new loci may have small direct effects on obesity risk and explain only a small part of the variation," she said. "But the most important aspect of these new discoveries are their indirect implications, with which I mean that these new loci have pointed us towards genes or loci that we would never have thought of as obesity-susceptibility genes."

Loos said that it's likely that even once all those new links are identified, they still might not fully explain why some people gain more weight

than others. It may be, she said, that researchers will have to unravel the interaction between different genes or the interaction between genes and environment, to completely explain the differences.

"Once we understand that biology better, we might be better in treating obese individuals or even preventing (young people from becoming) obese," she said. "It will take time though — physiologists take many years to elucidate new pathways — to fully appreciate the impact of these new discoveries."

Grant argues that tangible progress might come much sooner due to the incredible rate of discovery that technology now offers geneticists.

"Within five to 10 years, we'll have very robust diagnostics with these findings, (telling us) you're going to get fat or you're going to get slim," he said. "I think also within the decade you'll start to see some medications based on these targets that we're finding."

At the CDC, public health experts like Valdez argue that we don't even need to wait for the estimated 600 genes affecting obesity to be identified. Family history already gives us a very good idea of whose genes predispose them for obesity.

"If we see obese people, it's very likely that children of those people will be obese too, and not only because they share their genes," he said.

"It is also the same familial environment. They live in the same house and eat the same food and have the same habits. So we don't need to wait until we have all these 600 markers identified. We can do something about it right now."

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