The Secret Life of FAT

Changes in our DNA can determine much more than the battle of thick versus thin.

BY **SYLVIA TARA**

It was a breezy Friday evening in the fall in San Diego. I was a biochemistry Ph.D. student out to dinner with friends after a full week of research, classes and teaching. I'd had a strong interest in biology since grade school, particularly in how the body malfunctions and the inventive ways we treat it. The idea that tiny molecules affected our health, thoughts and quality of life was fascinating to me.

Keeping my fat in check had never been easy, and I watched my weight closely. On this day, like every other, I had counted my calories since the morning. I ate a painstakingly balanced combination of grains, proteins and vegetables. I abstained from anything fun — no sugar, carb-heavy snacks or alcohol. I had run for 40 minutes, and lifted weights. As I sat down to dinner with my friends, I held steadfast — I ordered a small salad and water. My friend, Lindsey, ordered a beer and burrito and devoured it all.

That seemingly trivial event changed everything for me. Lindsey was 4 foot 11 inches and probably about 95 pounds. She never went to the gym. She drank sugary lattes and indiscriminately ate fast food. She worked in the lab all day like me, and hunched over a computer in the evening. Yet somehow this petite woman was able to pack in a large steak burrito, with beans, rice, sour cream, guacamole, cheddar cheese all wrapped in a flour tortilla, and then down a beer as if all this were nothing unusual. She had no guilt afterward, no appearance of worry, she made no comments about feeling sick after eating it or how she would need to run on the treadmill the next morning. Nothing.

I felt as though nature was cackling in my face. This was one of the moments in my life that made me realize that we are not all created equal, at least not when it comes to fat. Just as some people are taller, or produce more sweat, or grow more hair, there are some who simply produce more fat than others. And one of those people happened to be me.

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THE THRIFTY GENOTYPE

We have all come to accept that our genes determine everything from the color of our eyes to the straightness of our teeth to our height, our talents, even our moods. But strangely, when it comes to fat, we tend to underestimate the effect of genetics. For the most part, fat is considered a personal failing — a punishment for lack of willpower, for eating too much, and for being too lazy to exercise and burn off those calories.

Fortunately, science has come to the rescue by showing the many ways genes influence fat. This avenue of research is still new, since we have only recently begun to decode the mysteries of the human genome, but studies are emerging every year.

A good example of how our genes can determine fatness is the story of the Pima Indians who crossed the Bering Strait from northern Asia and settled in the Americas approximately 30,000 years ago. One population of the tribe settled near the Gila River in Phoenix, Ariz., and another kept migrating south, making their home in Maycoba, Mexico. The Pima sustained themselves by tilling dry soil to grow squash, corn, beans and cotton, and by hunting small animals and other game. This lifestyle provided them a natural, well-balanced diet, and required them to get plenty of exercise.

What worked against the Pima, however, was drought, which occurred several times each century, destroying crops and reducing animal

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populations. Famine would follow and only those who could withstand long bouts of hunger managed to survive. The Pima endured these conditions for millennia, and geneticists believe that, over time, their bodies evolved a "thrifty genotype" — a set of genes that enabled them to subsist on very few calories by increasing the efficiency of their metabolism and storing as much energy as possible as fat.

For centuries, this genetic adaptation helped to maintain the population. Then, during the mid-19th century, the fate of the two Pima settlements in Phoenix and Maycoba started to diverge, with fascinating consequences. The Arizona Pima started encountering Caucasian migrants in 1850 as they made their way to California in search of gold. The Pima assisted the weary travelers, offering food and protection. The outsiders, feeling welcomed, started staking claims along the Gila River, on which the Pima depended to irrigate their farms.

With the ongoing gold rush in California, more settlers arrived, and the new farmers and ranchers started diverting water and land from the Pima. Tensions arose, eventually leading the U.S. government to resettle the Native Americans on a reservation, though the Pimas' new land didn't include surrounding hunting lands or water rights to the Gila River. Without sufficient water for their farms, the Pima faced starvation.

The government offered food assistance starting as early as the 1930s. It included Western foods such as milk, bacon, cheese, canned meats and dry cereal, as well as flour and lard that the Pima used to make deep-fried bread. The lives of the Native Americans no longer included farming or hunting, and they became more sedentary. Some started to work in nearby factories, and others joined the armed services. Increasingly, they were introduced to the American lifestyle, and the Arizona Pima started gaining weight — lots of it.

The encroaching obesity among the tribe was noticed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 1963, while they were doing an area survey. The rate of obesity and diabetes in the Arizona Pima was so high that the institute established research programs focused on the group to understand why.

The institute measured the health of the Arizona Pima every two years. Since 1965, tribe members have voluntarily undergone physical examinations specifically looking at weight, height, body mass index (BMI) and factors for diabetes. The population of overweight Pima Indians was found to be more than three times higher than the U.S. national rate. The Arizona tribe also had drastically higher rates of diabetes. Yet Caucasians living nearby at the time led a similar lifestyle without the same ill effects.

The NIDDK researchers also became aware of the Pima who lived in Maycoba, Mexico. As they were genetically similar to the Arizona Indians, the researchers wanted to know if both groups had the same health problems.

SHEDDING THE GUILT

Eric Ravussin of the Pennington Biomedical Research Center, based in Baton Rouge, La., was one of the first

Pima Chief Antonio Azul (far left) led his tribe in the late 1800s, an era before Western food supplemented their diets. By 1908, a book of medical observations on the Pima and other Southwest tribes noted increased obesity incidence, and included this image of a Ute woman (left). This Pima family (above) was photographed around 1900 outside their adobe home in Arizona.

scientists to make the trek to Maycoba, high in the Sierra Madre. Ravussin remembers, "There were no paved roads. There was nothing there — no electricity, no running water, nothing. No one had cars."

It took researchers eight to 10 hours using a four-wheel-drive vehicle through the rocky terrain to get to the village. The Maycoba Indians still farmed and rode bicycles in lieu of driving cars. For the most part, they maintained the rural lifestyle followed by their ancestors. As a result, the Maycoba Indians were far healthier than their Arizona counterparts.

Compared with the Maycoba population, the Arizona Pima obesity rate was 10 times greater among the men, and three times for the women; diabetes was five and a half times higher among the tribe in Arizona. Clearly, the newly modernized lifestyle was taking its toll.

The tale of the two tribes illustrates the genetics of fat at work. The Pima would not have survived the frequent famines through the centuries without evolving their thrifty genotype. However, in the modern time of plenty, their genes are a liability, leading to high rates of obesity and diabetes compared with other races.

Eventually, analysis of DNA from the Pima suggested that they have variations on certain chromosomes that are linked to fatness. Thanks to their genetic inheritance, their bodies are storing away calories, anticipating a famine that never comes.

We can't change our genes, but science is learning that we can influence how they affect our health. And, as the Pima prove, there may be extra measures we need to adopt to accommodate our genetic peculiarities when it comes to fat. If we can't lose all the excess weight we've stored, at least we can shed some of the guilt associated with it.

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AMPED-UP METABOLISM

Claude Bouchard conducted some of the first studies showing that genes affect fat. After getting his Ph.D. in population genetics and physical anthropology in 1977 from the University of Texas at Austin, Bouchard returned to his native Quebec and started a laboratory at Laval University where he and his staff began studying obesity.

Bouchard, now at the Pennington Biomedical Research Center, and his team executed two foundational studies that upended the understanding of genetics and weight between 1986 and 1990, before the Human Genome Project was completed. The first study showed that our propensity to gain fat, and where the body stores it, are influenced by genetics. Bouchard put 12 male identical-twin pairs on a diet of an extra 1,000 daily calories above their normal eating pattern for 84 days. As he expected, the young men put on a significant amount of weight — the average gain was 13 percent. Bouchard observed that related twins were three times more likely to gain the same amount of total body weight, fat percentage and subcutaneous fat — fat just beneath the skin — than unrelated test subjects.

For a weight-loss experiment, Bouchard again isolated male identical twins in a research unit for four months. First, he measured the exact calories needed for the twins to maintain their current weights. He then imposed a standardized exercise routine of two hours per day, ultimately inducing a calorie deficit of 53,000 per person over the duration of the study.

As the twins slimmed down from exercise, Bouchard looked at body weight, lean mass and fat distribution and found the amount of energy burned during exercise was also influenced by genetics. If one twin burned 80 calories compared with 100 burned by a comparator group during a workout, then the other twin would likely suffer the same metabolic shortcoming.

Bouchard found that our genes influence our resting metabolism, fat mass, percent of fat and abdominal visceral fat, and cholesterol levels. He and his colleague Angelo Tremblay discovered one important exception, though — a vital piece of information for those seeking to control their weight. They found that when subjects performed vigorous exercise, genetics didn't matter as much. Bouchard's definition of "vigorous" was any exercise that caused metabolism to increase by six times or more over resting metabolism (which can be achieved by running about 4 to 6 mph or cycling about 12 to 16 mph, or doing other activities that produce rapid breathing and sweat within a few minutes).

FROM LEFT: MASSACRES OF THE MOUNTAINS: A HISTORY OF THE INDIAN WARS OF THE FAR WEST/JACOB PIATT DUNN/HARPER & BROTHERS/1886; BUREAU OF AMERICAN ETHNOLOGY BULLETIN 34 PLATE XXII/1908; GRANGER NYC

The lesson is clear: Once we enter a specific range of strenuous exercise, the body kicks in to lose fat, no matter what our genes want.

CALORIE HOARDING

New technological advances are allowing for more specific investigation of our genes. For example, individuals with variations in a gene called *FTO* tend to desire high-calorie foods more often and have more fat as a result. This genetic variation causes an almost twofold increased risk of obesity compared with those who don't inherit it.

Colin Palmer at the University of Dundee in Scotland conducted one study that shows the effects of the *FTO* gene. He assessed almost 100 schoolchildren to see whether they carried the *FTO* variant gene or the normal gene. He then evaluated what the children ate by allowing them to take food from a buffet that included an assortment of fruits and vegetables, as well as higher-calorie foods such as chips and chocolate. When he analyzed what they consumed, he noticed that children with the *FTO* gene variant had eaten more of the higher-calorie, energy-dense foods compared with children with the normal gene.

"They had the same amount of food, the same mass of food, it was just the higher-calorie foods," Palmer says. Not surprisingly, children with the variant gene also had about 4 pounds more body fat. The *FTO* gene is thought to be expressed not only in the brain, where it increases our desire to eat fattening foods, but also in fat tissue.

Harvard Medical School researcher Melina Claussnitzer and her team found that a single variation in the *FTO* gene caused fat cells that would normally become healthier beige to turn into white fat cells instead. Beige fat cells have the potential to turn into energy-burning brown fat cells when activated by exercise. But in people with the *FTO* mutation, fewer cells become beige and more turn into energy-storing white cells. So the result of the *FTO* mutations is a drive to eat higher-calorie foods paired with less calorie burning and more calorie hoarding — a challenging combination for any dieter.

Although individuals with variants in their *FTO* gene have almost double the risk of obesity compared with those who do not inherit the gene, "having the *FTO* variant doesn't mean one is destined to be fat. We can still control what goes in our mouths, though it may be more work for some than others," Palmer explains.

The good news is, unless you have one of the very rare genetic mutations that undeniably cause obesity, your genes are just one factor in your weight profile.

HEAVIER, HEALTHIER

Not all fat caused by genetics is a bad thing — and some of it may actually be protective. Ruth Loos is the director of the Genetics of Obesity and Related Metabolic Traits program at Mount Sinai Hospital in New York. She's slender, with short, wispy blond hair that frames her angular features.

Working with Bouchard, Loos grew fascinated with the genetics of fat and metabolism, and eventually went on to establish her own lab at Mount Sinai. As she set out to design her research, she noticed that many genes being identified were linked to high BMI, which simply compares someone's weight with their height. Loos realized BMI isn't the best measure of fatness because it doesn't separate fat mass from lean tissue like muscle.

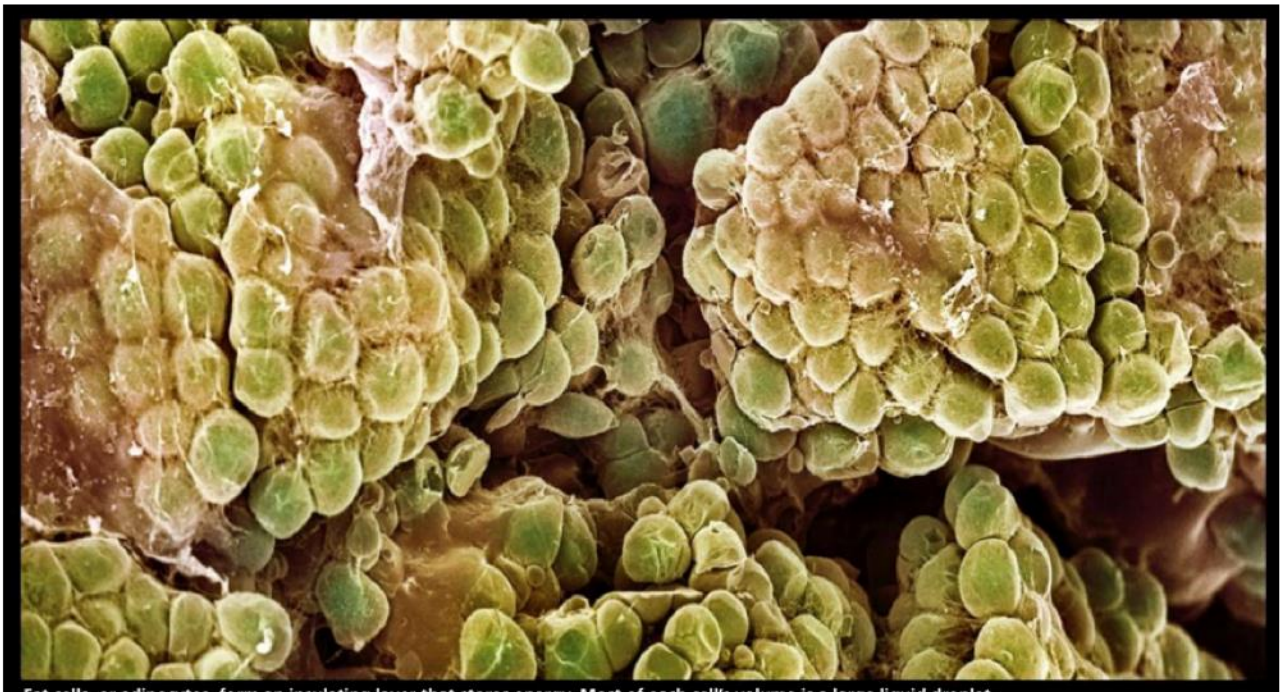
In other words, if you're a bodybuilder with only 7 percent fat but a lot of muscle, your BMI will be high, perhaps the same as that of someone who is obese with lower muscle mass.

Loos wanted to tease out which sections of DNA had to do with fatness, not just weight. So her team conducted an analysis of the genetic data from 36,626 individuals to see which genes were associated with body fat. From this research, Loos found that fatness was significantly linked to variations in the *FTO* gene and a gene called *IRS1*. It was already understood that *FTO* variations were associated with being overweight, encouraging kids to seek fattier foods, for example. But the linkage of the *IRS1* gene to fat was new.

As the team analyzed the data, they uncovered a mystery. One variation of the *IRS1* gene caused lower fat in men. At first, this seemed like a lucky gene to have. But as Loos analyzed the data further, she saw that while men with this variant indeed had less fat in their arms, legs and trunk, they also had higher triglycerides — fat found in the blood — and lower good cholesterol in their blood and increased insulin resistance, all signs of ill health.

How could this be? They were thinner than men without the variant, and thinness should lead to better health, not worse. More puzzling, this variant didn't seem to affect women in the same way.

Loos and her team looked further. Perhaps this adverse metabolic profile was linked to how fat was distributed. Her team reviewed measurements for subcutaneous fat, the healthier fat which sits under the skin, and visceral fat, the unhealthy fat that surrounds the organs. They



Fat cells, or adipocytes, form an insulating layer that stores energy. Most of each cell's volume is a large liquid droplet.

STEVE GSCHMEISSNER/SCIENCE SOURCE

found that men with one *IRS1* variant (let's call it variant A) had lower subcutaneous fat and more visceral fat compared with those without the variation.

However, the men with variant B were fatter but also healthier. Why would the gene that produces more fat protect you against disease, Loos wondered. Slowly, she and her team pieced together an answer. *IRS1* contains the code for a protein that's involved in mediating cells' sensitivity to insulin, a hormone that helps the body use sugar and store fats. She found that *IRS1* variant A was associated with lower expression of this protein in subcutaneous fat and visceral fat. So, cells in these areas weren't as sensitive to insulin and weren't internalizing glucose and fats. This occurred in men much more than in women.

In addition, *IRS1* variant A was inhibiting the expansion of fat tissue. With no place to go, more fat was hanging around in the blood, causing health issues. On the other hand, those with *IRS1* variant B were able to easily expand their fat tissue. So they were a little chubbier because the fats in the blood went where they belonged — into fat.

Loos' findings described a new kind of fat gene. Other gene variants — like mutations in *FTO* or the gene for leptin, an energy-balancing hormone — had been linked to overeating or fat cell type. But *IRS1* was the first that was linked specifically to fat cell creation. When we don't create new fat cells to house our circulating fats, we're prone to more diseases. With less fat, we may appear to be healthier, but may actually be in danger of developing diabetes and other diseases.

"Genes that increase your risk of obesity can also protect you from Type 2 diabetes [and] cardiovascular disease and give you an optimal lipid profile," Loos says. "These are what we call the healthy obesity genes. So these individuals who had the variant to increase fatness actually were good fat storers. They store the fat where it should be stored. And it protects their liver, it protects their muscle, it protects against visceral fat. And that fat protects them against disease as well. So these [good] genes, they do exist."

You can undergo a diagnostic test to find out whether you have any known gene variants that are associated with obesity. If you have such a variant, are you doomed to a life of flabbiness? The good news is, unless you have one of the very rare genetic mutations that undeniably cause obesity, your genes are just one factor in your weight profile.

In the end, daily actions matter more. How much we decide to eat, what we eat and how much we choose to exercise will, in the majority of cases, trump our genes. Fat genes like the *FTO* variant, however, make it harder to stay on track and keep weight down.

"You may be genetically susceptible to become obese, but it doesn't mean that you're destined to become obese," Loos says. "Genes load the gun, and environment pulls the trigger." D