

# blue genes



Does your DNA decide the size of your jeans?

12

**Somewhat.** But you can do a lot to take control of your long-term health and weight, such as reaching for an apple and taking a walk.

13

John Kirwan, PhD, was baffled. While conducting a study on diabetes risk, he expected his study's older, overweight participants to become healthier after 12 weeks of supervised exercise. What he didn't expect was that a handful of people would virtually erase their diabetes risk — slashing it by 90 percent — with a simple hour of daily exercise.

What was different, he asked, about this small group of people? Was it diet? Was it good genes? After examining and rejecting several explanations, Dr. Kirwan and his research team at Cleveland Clinic's Lerner Research Institute decided to examine what people were eating. At the study's start, participants were all teetering dangerously close to developing type 2 diabetes, a major risk of being overweight. They had been told to stick with their normal diet and to record what they ate in a food diary. When the researchers compared food diaries, they were amazed at what they found.

By Karyn Hede | Photography by Marge Ely



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WERE OVERWEIGHT; TODAY, 66% ARE.

“The ones who had improved 90 percent had changed their food selection over the course of the study,” he says. “They had shifted to a low-glycemic diet,” which is lower in “white” carbs, processed and sugary foods. While the goal of the study was to reverse prediabetes, the participants also lost weight. Genetic predisposition was trumped by diet and exercise.

Over the past decade, researchers have begun to identify genes that play a part in establishing our body weight and the risks that go along with being overweight and obese. But should overweight people feel resigned to their fate?

No, say doctors who study obesity. With the exception of a few rare conditions, most of us can control our weight within a range that is in part determined by our genetic makeup. And Dr. Kirwan’s study points to exercise and the foods we eat as key to reaching the healthiest weight possible.

**LOOKING FOR A PROBLEM GENE**

About 20 genes likely play some role in weight gain, according to Claude Bouchard, PhD, an obesity researcher and Executive Director of the Pennington Biomedical Research Institute, Baton Rouge, La. Yet, “the epidemic of obesity is not driven primarily by our genes,” he says. “It’s driven by the environment. We have, hidden in our genes, a predisposition that does not become manifest until the environment changes, until it becomes obesogenic like it has today.”

Lots of genes can contribute to weight gain, and it takes the combined effect of those genes, along with that obesogenic lifestyle — a shorthand term for a set of factors, such as low levels of physical activity and high-carbohydrate diets — that produce

increasing numbers of overweight people. And those increases are indeed dramatic.

In the late 1970s, 47 percent of U.S. adults were overweight; today, 66 percent are. Obesity among adults has more than doubled, from 15 percent to 33 percent, according to the Centers for Disease Control and Prevention (CDC). During the same period, incidence of type 2 diabetes, the form closely associated with obesity, has surged. About 20 percent of people over age 60 have type 2 diabetes, according to the CDC, resulting in annual medical costs of \$92 billion and growing.

In the past year, Dr. Bouchard says, one gene variation has risen above the rest as a “strong player” in the average person’s weight troubles. That gene, called FTO, appears to be the first to predispose people to gain weight regardless of other risk factors.

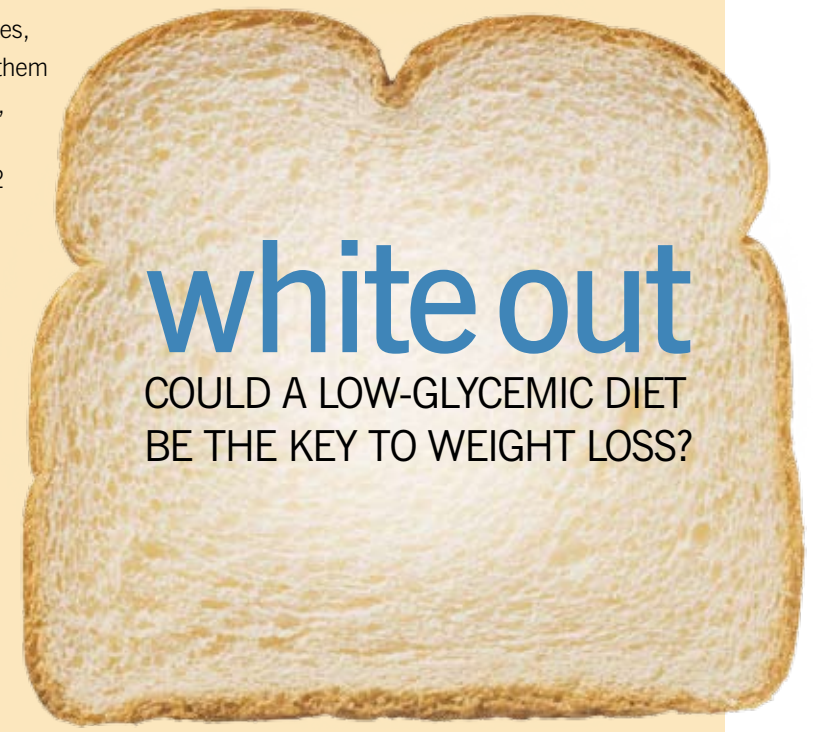
In 2007, three independent groups studying the FTO gene in tens of thousands of people in the United States and Europe came to the same conclusion: People with a specific variation of FTO are two-thirds more likely to be obese — carrying an average of 8 additional pounds — than those without the variation. Indeed, when Bouchard and his colleagues reexamined genetic evidence from the Quebec Family Study, a research project that looked for obesity genes, they confirmed that FTO contributes to obesity. However, the gene is linked with obesity among only Whites. Studies among Asians have so far shown no association with obesity; results among Blacks are mixed.

The gene appears to be particularly active in the areas of the brain that control appetite and energy expenditure, but it is unknown whether its activity reprograms the appetite center of the brain or changes how the brain responds to signals of fullness from the body.

What is it about a low-glycemic diet that helped the overweight study participants of Cleveland Clinic’s John Kirwan, PhD, lose weight and turn their backs on diabetes?

Fifty-four million people in the United States have prediabetes, according to the American Diabetes Association, and most of them don’t know it. The warning signs include elevated blood sugar, high blood pressure and excess weight. Prediabetes is part of a vicious cycle that, left unchecked, can lead directly to type 2 diabetes and all its risks for early death, says Dr. Kirwan.

The cycle begins at mealtime. A high-glycemic or high-carbohydrate meal, one that contains what are often called the “whites” — white bread and rice, pasta and sugary drinks — quickly releases sugars into the bloodstream, resulting in a spike in insulin, the hormone that helps regulate blood sugar levels. A low-glycemic meal, which releases sugars into the bloodstream more slowly over a longer time, requires less insulin. The so-called high-glycemic meals — think processed and fast foods — have become the U.S. norm, and doctors say these wild swings in blood sugar and insulin levels contribute to the body losing its ability to respond to insulin — a hallmark of type 2 diabetes.



SLICE OF BREAD: DIGITAL VISIONGETTY IMAGES

## ARE YOUR PARENTS' WAISTLINES YOUR GENETIC DESTINY?

GENES DO PLAY A PART IN ESTABLISHING BODY WEIGHT, BUT OVERWEIGHT PEOPLE DO NOT HAVE TO RESIGN THEMSELVES TO AN UNHEALTHY FATE, SAY OBESITY EXPERTS.

16

Dr. Bouchard points out that the gene appears to have its strongest effect in people who don't exercise. In January 2008, researchers from Denmark reported in the journal *Diabetes* that carriers of the high-risk version of the gene who were inactive weighed about 5 pounds more than those with the high-risk version who exercised more than one hour per week.

"We are far from genetic determinism here," says Dr. Bouchard. "People who exercise from time to time [more than one hour per week] appear to have some protection from the effects of the FTO gene."

Genetics certainly is one of the underlying factors that drives weight gain, says Cleveland Clinic's Dr. Kirwan. And excess weight is definitely a risk factor for debilitating health conditions such as diabetes and heart disease, he says. But not all fat is created equal.

Doctors have known for years that between two people who are 5 feet 6 inches tall and weigh 200 pounds, the one who carries most of that weight around the middle, like an apple, is at higher risk for all kinds of ailments, including heart disease and diabetes, than the one who carries the weight around the hips, like a pear. Doctors are beginning to understand why it's healthier to be a pear with fat at the hips than an apple with fat around the internal organs.

"It is really the visceral fat, the deep fat that deposits around internal organs such as the liver, that causes the problem," says Dr. Kirwan. Detailed measurements of body fat among his study participants, taken with sophisticated CT scanning techniques, revealed that those with the strongest reductions in diabetes risk had lost visceral fat. He has launched a study to test whether



combining exercise and low-glycemic meals can help more people trim the visceral fat and reverse course on the road to type 2 diabetes.

### FAT TALKS

Fat is more than unsightly ripples on the back of our thighs or stubborn love handles. It is not just an inert blob. Fat can communicate. The cells that store and release fat produce small molecules that influence our organs and even our brain. That's right, our fat is talking back to us.

Scientists have identified dozens of molecules, such as a protein called rbp4, produced by fat. Proteins such as rbp4 send signals to distant organs that change our metabolism, says

Dr. Kirwan. The levels of some of these appear to be influenced by our genes, but others can change quite dramatically depending on what we eat or how active we are during the day.

To understand why visceral fat seems to be linked to diabetes, Dr. Kirwan went to Cleveland Clinic's bariatric surgery group to obtain samples of visceral fat removed from patients during gastric bypass surgery. Comparing the proteins produced in the fat cells of patients with and without diabetes, Dr. Kirwan found higher levels of rbp4 in the visceral fat of the obese patients with diabetes. While doctors don't yet know rbp4's exact role, it is clear that these fat-associated proteins influence the body's response to the foods we eat and contribute to diabetes.

### LEAN GENES

We all know people who seem to indulge in whatever foods they want, never set foot on a treadmill and yet stay lean and healthy. Joseph Nadeau, PhD, a geneticist collaborator of Dr. Kirwan's at Case Western Reserve University in Cleveland, wants to know what makes those people so genetically blessed. He is studying the genetics of health in search of genes that can protect us from gaining weight and becoming diabetic.

"We've learned from studying mice that there are some variations of genes that will protect against disease," says Dr. Nadeau. "We often focus on the individuals with disease, and that's important, but at the same time our observations tell us that there are genetic solutions. How is it that your friends who eat all the time get to stay

17

## The Inside Story

Are gut bugs making you fat?

ur bodies are home to tens of trillions of bacteria

that inhabit our 25- to 30-foot-long gut, our food digestion factory. Although they do a lot of good — easing our digestion and keeping us healthy — some of these minuscule factory workers can make us sick — or even fat, according to recent studies.

Heavy people harbor a different population of gut microbes than thin people, according to scientists at Washington University in St. Louis. And those differences matter, as explained by their studies in mice. When the researchers introduced the bacteria from obese mice into the guts of mice raised in a germ-free environment, the mice gained more weight than when they received bacteria from slender mice. The researchers weren't able to say how or why, but the gut microbes were altering the amount of stored fat — the bugs from the rotund creatures turned formerly trim rodents into candidates for a diet program.

“Establishing a link between gut microbes and weight gain was a ‘eureka’ moment in science,” says John Kirwan, PhD, of Cleveland Clinic’s Lerner Research Institute. “The discovery is likely to drive further research into how different types of microbes contribute to obesity and metabolic diseases such as type 2 diabetes that are associated with being overweight.”

There may be good news for the unwitting victims of mischievous microbes: yogurt.

Jeremy Nicholson, PhD, of Imperial College, London, and his collaborators there and at Nestle Research Center, Lausanne, Switzerland, replaced normal mouse gut bugs with human microbes and then gave the mice probiotic drinks. With probiotics, the mice absorbed less fat from their meals. The findings, reported in the January 2008 issue of the journal *Molecular Systems Biology*, suggest that probiotics could transform those microbe-fattened Washington University mice back to their former svelte selves. People too? If confirmed in people, Dr. Nicholson thinks it may be possible to create functional foods that help us reprogram our microbial workforce. However, he notes, probiotics make some people ill, and the ratio of various probiotic components will need to be carefully controlled before they can safely be given to people.

“The potential to bring body weight to a healthy level by eating specific foods that alter the gut’s microbe population is an exciting prospect,” says Dr. Kirwan, “and one that is likely to be embraced by millions of overweight Americans.”

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lean? What genes are involved, and how do they do what they do?”

Dr. Nadeau is working with researchers in Wisconsin and San Diego to study the genetics of healthy elderly people with an eye toward finding health-promoting genes. “We hope to take advantage of this kind of genetic information to tip the genetic balance in a good way that benefits people,” he says.

Even people who feel they have been dealt a bad genetic hand when it comes to gaining weight can improve their odds of staying healthy by building and maintaining muscle. Standard advice encourages people to focus on calorie-burning exercises such as running or biking. But as we age, we lose muscle mass each year even if we continue fat-burning aerobic activity. Studies show people who work out regularly with weights gain less of the dangerous abdominal fat and maintain more muscle as they age. And weight training appears to keep even overweight people from gaining abdominal fat.

Researchers at the University of Pennsylvania recently completed a two-year study of 164 overweight and obese women between ages 25 and 44 and showed that those who lifted weights twice a week lost a moderate amount of weight, while the non-weight lifters lost none. More important, the researchers reported in the September 2007 issue of the *American Journal of Clinical Nutrition*, although both groups gained some abdominal fat, the weight lifters added only 7 percent fat to their midsections, while those who didn't lift weights experienced a 21 percent gain in abdominal fat — the worst kind.

Boston University researcher Ken Walsh, PhD, has been studying the link between losing muscle mass after age 50 and gaining dangerous abdominal fat. He says the importance of the type of muscle we use to lift objects and maintain our core body strength is only now becoming clear.

“If you poll average 50-year-olds who go to a gym, they would say that ‘I’m in good shape. I jog, I play tennis,’ but if you measure their grip strength, it is probably being drastically reduced,” says Dr. Walsh. They may be doing aerobic exercise, but without strength training, their muscle mass and strength is declining.

The good news is: “You can get muscle back with weight training,” he says. “And, you don’t have to become a body builder.”

What all these studies boil down to, says Dr. Bouchard, is “what your mother always told you: Eat right and get some exercise.” ■

**Karyn Hede** is a freelance science and medical writer whose work has appeared in *Science Magazine*, *The Scientist*, and other publications.