

HEALTH & SCIENCE Dynamic duos

As genetic-sequencing tools reveal more about human biology, pairs make ideal study subjects

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Twins are ideal subjects for scientists studying nature vs. nurture.



Mom needed pain relief. The ER ignored her.

BY ERSILIA M. DEFILIPPIS

I felt a shake and opened my eyes. The clock read 1:30 a.m.

"We need to go to the hospital," my mother whispered in my ear, clutching her stomach.

She knew; it was the same pain she had experienced many times before. We were in California, many miles from home, many miles from my father (a doctor), who always knew what to do. At the time, I was early in my medical school training, although I knew all the intricate details of my mother's medical history and realized she needed to get medical attention.

When we arrived at the local emergency room in an affluent neighborhood, my mother was placed in a wheelchair and taken to the waiting

PAIN CONTINUED ON E6

Taking it slow for back pain? I gave it a try.

BY LISA REIN

In my first Feldenkrais class, we lay on our backs with eyes closed and drifted our eyeballs left to right and back again. We shifted our feet from side to side as our eyes followed in their sockets. Then we changed up, moving our eyes in the opposite direction from our heads.

This may sound like a simple sequence. It's deceptively challenging. And it continued for an hour, with sitting variations, eyes alternating open and shut, a brain workout that included tracking our thumbs as our best arms moved at eye level from left to right and back again.

These eye calisthenics were supposed to relieve my years of back

FELDENKRAIS CONTINUED ON

Every August for the past 43 years, Twinsburg, Ohio, has hosted the biggest gathering of twins in the world. Two decades ago, organizers added an attraction to the lineup of parade, talent show and hot-dog dinner that drew more than 2,000 pairs this year: the chance to participate in research. Scientists vie for tent spots to test such things as twins' exposure to the sun, their stroke risk and their taste preferences. "Every year we get more [research] requests than we can handle," says Sandy Miller, a Twins Day Festival organizer

and mother of 54-year-old twins. “We just don’t have room for all the scientists who want to come.”

Since English scientist Francis Galton published a paper on the heritability of traits in 1875, researchers have been fascinated by how the behavior and health of identical twins differ throughout their lifetimes.

“Twins are nature’s experiment,” says Australian neuropsychiatrist Perminder Sachdev, who runs the Older Australian Twins Study, which was started 10 years ago and has recruited more than 300 pairs of twins older than 65 to analyze how physical activity, psychological trauma, alcohol use and nutrition affects their brains, psyches, metabolisms and hearts.

Because identical twins are the result of a single egg that splits into two, they share the same DNA and provide a perfect laboratory to answer age-old questions about the roles of genes and environment: Why does one twin get breast cancer and not the other? How does obesity increase one’s risk of Type 2 diabetes? Do genetics really determine whether you are more likely to own a gun or go to college?

“When you do a study in the general population, you’re comparing people of different ages, sex, backgrounds, dietary histories, educational and socioeconomic levels,” Sachdev says. “But with twins, you automatically control for many of these variables.”

Genetic-sequencing tools that plumb our biology in more detail than ever are providing new answers to why we get sick or act and look the way we do. In this era of molecular genetics, scientists can pinpoint which genes are linked to diseases — and more recently, whether certain genes are turned on and off over time, a field known as epigenetics.

“We can tease out more of the genetic components of nature versus nurture,” says Christopher Mason, a geneticist at Weill Cornell Medicine in New York. When identical twins are born, they’re 99.999 percent the same, but as they age, the effects of lifestyle, trauma, stress or disease cause their genes to be expressed in distinct ways. “They experience the slings and arrows of the environment differently,” he says. “Twin studies help you see the drivers of change.”

Twin astronauts

In one of the purest twins experiments ever designed, Mason was part of the team that compared the effects of a year spent in space on 52-year-old astronaut Scott Kelly with the Earth-based experience of his identical twin, Mark. Researchers discovered that Scott Kelly’s time on the International Space Station had altered the expression of 7 percent of his genes, including those involved in blood oxygenation and DNA repair. “It was surprising how many genes responded to the stress of spaceflight,” Mason says.

Mason says the research offers insight into how to study the effects of harsh environments. “We want to leverage the capacity of twin studies to understand human physiology at extremes, such as scuba diving, climbing Mount Everest or flying fighter jets,” he says. The intense interest in how genes affect our lives has inspired scientists around the world — including in the United States, the Netherlands, Denmark, China and Cuba — to create large national registries of twins. The largest of these, which has data on 85,000 pairs of Swedes, is being used to research allergies, cancer, dementia, cardiovascular disease and other topics.

One of the goals of the Older Australian Twins Study is to discover the genetic underpinnings of cognitive decline as people age. Using brain scans of 92 pairs of identical twins and other tests, Sachdev concluded that 70 percent of cerebral small vessel disease, a type of brain lesion associated with dementia, is genetically determined. He hopes that mapping the twins' whole genome and then comparing their epigenomes to see which genes were turned on will reveal the mechanisms behind the development. "The ultimate goal would be a drug that would prevent or stop the disease from progressing," he says.

Twins studies have been so popular that one 2015 meta-analysis found that researchers had looked at no fewer than 17,800 traits — including depression, cardiovascular disease and gun ownership — involving more than 14.5 million twin pairs over the past 50 years. It concluded that both "nature" (what you're born with) and "nurture" (what you've been exposed to as you age) are nearly equally important for understanding people's personalities and health: The variation for traits and diseases was, on average, 49 percent attributable to genes and 51 percent to environment.

Still, the debate is far from over, experts say, because genetic and environmental influences change over time. For example, a 2017 study that crunched BMI measurements from 140,000 twin pairs from around the world found that the role of environment (translation: your ability to lose weight through diet and exercise) increases as you get older — offering hope for anyone blaming their genes for a stuck scale.

One of the biggest promises of twins research is explaining why people with identical DNA don't get sick at the same rate.

In a 2016 study, University of Southern Denmark researchers looked at the epigenomes of 28 identical twins in which one had rheumatoid arthritis and the other didn't. Smoking is a leading cause of the disease, and the researchers found that some of the smokers in the group had damaged DNA function in regions associated with inflammation and autoimmunity even long after they had stopped smoking. The findings also identified important biological markers that will help future research, says co-author Qihua Tan, a biostatistician who studies epigenetics in twins.

Despite a consensus on the value of twins studies, there's disagreement over where research dollars should be focused. Some scientists believe genetically sequencing large numbers of unrelated people — in what are called genome-wide association studies, or GWAs — will result in the next wave of scientific progress.

"Instead of doing another study looking at the heritability of schizophrenia with twins, let's do a very large GWA study with 250,000 people and identify where it exists in the genome," says University of North Carolina psychiatrist Patrick Sullivan, who founded a consortium of 800 researchers studying mental-health disorders. "We can get directly into the biology. That's something twin studies can't do." He says the technology is cost-effective now: About \$30 per person, compared with \$1,000 more than a decade ago.

Perhaps the ideal genetics study of the future contains both the power of the GWA and the insight that can come from focusing on a smaller group of twins. In a 2017 study on the link between obesity and Type 2 diabetes and heart disease, researchers analyzed the epigenomes of 5,400 unrelated people from Europe and India. They found that DNA expression in people with heavier BMIs was different in 187 locations, including locations in-

volved in cholesterol metabolism and inflammation. The results suggested that obesity turned on genes associated with these diseases.

Yet the paper also included the work of researchers from the TwinsUK registry who studied blood and fat tissue samples from 200 twins. “We saw that identical twin sisters with different BMIs had different risks of developing Type 2 diabetes,” says Jordana Bell, an epigenomics researcher at King’s College London. “This is exciting work. Twin research helped us understand how obesity is a risk factor.”

Life experience

Twins also add important context about their life experiences that might be missed in what John Hopper, an epidemiologist and director of Twins Research Australia, calls the “sledgehammer” approach of sequencing people by the thousands. For example, to assist an international study based at the University of Southern California, he is recruiting pairs in which one twin has breast cancer and the other doesn’t. “We’ll be able to fill in the gaps by asking, ‘Who went through puberty first? Who developed breasts first?’ ” says Hopper. “The magic of studying twins is that you get insights into the causes of disease that you couldn’t get any other way. There’s gold among twins.”

Sandy Miller of the Twins Days Festival says the research tents are a big hit. “The area is always crowded, and every year, people call in advance to see which programs will be featured,” she says. “The twins do it because they want to. They know the outcomes help everyone — not just twins, but you and me as well.”

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