The New York Times

September 16, 2013

DNA Double Take

By CARL ZIMMER

From biology class to "C.S.I.," we are told again and again that our genome is at the heart of our identity. Read the sequences in the chromosomes of a single cell, and learn everything about a person's genetic information — or, as 23andme, a prominent genetic testing company, says on its Web site, "The more you know about your DNA, the more you know about yourself."

But scientists are discovering that — to a surprising degree — we contain genetic multitudes. Not long ago, researchers had thought it was rare for the cells in a single healthy person to differ genetically in a significant way. But scientists are finding that it's quite common for an individual to have multiple genomes. Some people, for example, have groups of cells with mutations that are not found in the rest of the body. Some have genomes that came from other people.

"There have been whispers in the matrix about this for years, even decades, but only in a very hypothetical sense," said Alexander Urban, a geneticist at Stanford University. Even three years ago, suggesting that there was widespread genetic variation in a single body would have been met with skepticism, he said. "You would have just run against the wall."

But a series of recent papers by Dr. Urban and others has demonstrated that those whispers were not just hypothetical. The variation in the genomes found in a single person is too large to be ignored. "We now know it's there," Dr. Urban said. "Now we're mapping this new continent."

Dr. James R. Lupski, a leading expert on the human genome at Baylor College of Medicine, wrote in a recent review in the journal Science that the existence of multiple genomes in an individual could have a tremendous impact on the practice of medicine. "It's changed the way I think," he said in an interview.

Scientists are finding links from multiple genomes to certain rare diseases, and now they're beginning to investigate genetic variations to shed light on more common disorders.

Science's changing view is also raising questions about how forensic scientists should use DNA evidence to identify people. It's also posing challenges for genetic counselors, who can't assume that the genetic information from one cell can tell them about the DNA throughout a person's body.

Human Blueprint

When an egg and sperm combine their DNA, the genome they produce contains all the necessary

information for building a new human. As the egg divides to form an embryo, it produces new copies of that original genome.

For decades, geneticists have explored how an embryo can use the instructions in a single genome to develop muscles, nerves and the many other parts of the human body. They also use sequencing to understand genetic variations that can raise the risk of certain diseases. Genetic counselors can look at the results of genetic screenings to help patients and their families cope with these diseases — altering their diet, for example, if they lack a gene for a crucial enzyme.

The cost of sequencing an entire genome has fallen so drastically in the past 20 years — now a few thousand dollars, down from an estimated $3 billion for the public-private partnership that sequenced the first human genome — that doctors are beginning to sequence the entire genomes of some patients. (Sequencing can be done in as little as 50 hours.) And they're identifying links between mutations and diseases that have never been seen before.

Yet all these powerful tests are based on the assumption that, inside our body, a genome is a genome is a genome. Scientists believed that they could look at the genome from cells taken in a cheek swab and be able to learn about the genomes of cells in the brain or the liver or anywhere else in the body.

In the mid-1900s, scientists began to get clues that this was not always true. In 1953, for example, a British woman donated a pint of blood. It turned out that some of her blood was Type O and some was Type A. The scientists who studied her concluded that she had acquired some of her blood from her twin brother in the womb, including his genomes in his blood cells.

Chimerism, as such conditions came to be known, seemed for many years to be a rarity. But "it can be commoner than we realized," said Dr. Linda Randolph, a pediatrician at Children's Hospital in Los Angeles who is an author of a review of chimerism published in The American Journal of Medical Genetics in July.

Twins can end up with a mixed supply of blood when they get nutrients in the womb through the same set of blood vessels. In other cases, two fertilized eggs may fuse together. These so-called embryonic chimeras may go through life blissfully unaware of their origins.

One woman discovered she was a chimera as late as age 52. In need of a kidney transplant, she was tested so that she might find a match. The results indicated that she was not the mother of two of her three biological children. It turned out that she had originated from two genomes. One genome gave rise to her blood and some of her eggs; other eggs carried a separate genome.

Women can also gain genomes from their children. After a baby is born, it may leave some fetal cells behind in its mother's body, where they can travel to different organs and be absorbed into those tissues. "It's pretty likely that any woman who has been pregnant is a chimera," Dr.

Randolph said.

Everywhere You Look

As scientists begin to search for chimeras systematically — rather than waiting for them to turn up in puzzling medical tests — they're finding them in a remarkably high fraction of people. In 2012, Canadian scientists performed autopsies on the brains of 59 women. They found neurons with Y chromosomes in 63 percent of them. The neurons likely developed from cells originating in their sons.

In The International Journal of Cancer in August, Eugen Dhimolea of the Dana-Farber Cancer Institute in Boston and colleagues reported that male cells can also infiltrate breast tissue. When they looked for Y chromosomes in samples of breast tissue, they found it in 56 percent of the women they investigated.

A century ago, geneticists discovered one way in which people might acquire new genomes. They were studying "mosaic animals," rare creatures with oddly-colored patches of fur. The animals didn't inherit the genes for these patches from their parents. Instead, while embryos, they acquired a mutation in a skin cell that divided to produce a colored patch.

Mosaicism, as this condition came to be known, was difficult to study in humans before the age of DNA sequencing. Scientists could only discover instances in which the mutations and the effects were big.

In 1960, researchers found that a form of leukemia is a result of mosaicism. A blood cell spontaneously mutates as it divides, moving a big chunk of one chromosome to another.

Later studies added support to the idea that cancer is a result of mutations in specific cells. But scientists had little idea of how common cases of mosaicism were beyond cancer.

"We didn't have the technology to systematically think about them," said Dr. Christopher Walsh, a geneticist at Children's Hospital in Boston who recently published a review on mosaicism and disease in Science. "Now we're in the midst of a revolution."

Benign Differences

The latest findings make it clear that mosaicism is quite common — even in healthy cells.

Dr. Urban and his colleagues, for example, investigated mutations in cells called fibroblasts, which are found in connective tissue. They searched in particular for cases in which a segment of DNA was accidentally duplicated or deleted. As they reported last year, 30 percent of the fibroblasts carried at least one such mutation.

Michael Snyder of Stanford University and his colleagues searched for mosaicism by performing autopsies on six people who had died of causes other than cancer. In five of the six people they autopsied, the scientists reported last October, they found cells in different organs with stretches of DNA that had accidentally been duplicated or deleted.

Now that scientists are beginning to appreciate how common chimerism and mosaicism are, they're investigating the effects of these conditions on our health. "That's still open really, because these are still early days," Dr. Urban said.

Nevertheless, said Dr. Walsh, "it's safe to say that a large proportion of those mutations will be benign." Recent studies on chimeras suggest that these extra genomes can even be beneficial. Chimeric cells from fetuses appear to seek out damaged tissue and help heal it, for example.

But scientists are also starting to find cases in which mutations in specific cells help give rise to diseases other than cancer. Dr. Walsh, for example, studies a childhood disorder of the brain called hemimegalencephaly, in which one side of the brain grows larger than the other, leading to devastating seizures.

"The kids have no chance for a normal life without desperate surgery to take out half of their brain," he said.

Dr. Walsh has studied the genomes of neurons removed during those surgeries. He and his colleagues discovered that some neurons in the overgrown hemisphere have mutations to one gene. Two other teams of scientists have identified mutations on other genes, all of which help to control the growth of neurons. "We can get our hands on the mechanism of the disease," said Dr. Walsh.

Other researchers are now investigating whether mosaicism is a factor in more common diseases, like schizophrenia. "This will play itself out over the next 5 or 10 years," said Dr. Urban, who with his colleagues is studying it.

Moving Cautiously

Medical researchers aren't the only scientists interested in our multitudes of personal genomes. So are forensic scientists. When they attempt to identify criminals or murder victims by matching DNA, they want to avoid being misled by the variety of genomes inside a single person.

Last year, for example, forensic scientists at the Washington State Patrol Crime Laboratory Division described how a saliva sample and a sperm sample from the same suspect in a sexual assault case didn't match.

Bone marrow transplants can also confound forensic scientists. Researchers at Innsbruck Medical University in Austria took cheek swabs from 77 people who had received transplants up to nine

years earlier. In 74 percent of the samples, they found a mix of genomes — both their own and those from the marrow donors, the scientists reported this year. The transplanted stem cells hadn't just replaced blood cells, but had also become cells lining the cheek.

While the risk of confusion is real, it is manageable, experts said. "This should not be much of a concern for forensics," said Manfred Kayser, a professor of Forensic Molecular Biology at Erasmus University in Rotterdam. In the cases where mosaicism or chimerism causes confusion, forensic scientists can clear it up by other means. In the Austrian study, for example, the scientists found no marrow donor genomes in the hair of the recipients.

For genetic counselors helping clients make sense of DNA tests, our many genomes pose more serious challenges. A DNA test that uses blood cells may miss disease-causing mutations in the cells of other organs. "We can't tell you what else is going on," said Nancy B. Spinner, a geneticist at the University of Pennsylvania, who published a review about the implications of mosaicism for genetic counseling in the May issue of Nature Reviews Genetics.

That may change as scientists develop more powerful ways to investigate our different genomes and learn more about their links to diseases. "It's not tomorrow that you're going to walk into your doctor's office and they're going to think this way," said Dr. Lupski. "It's going to take time."