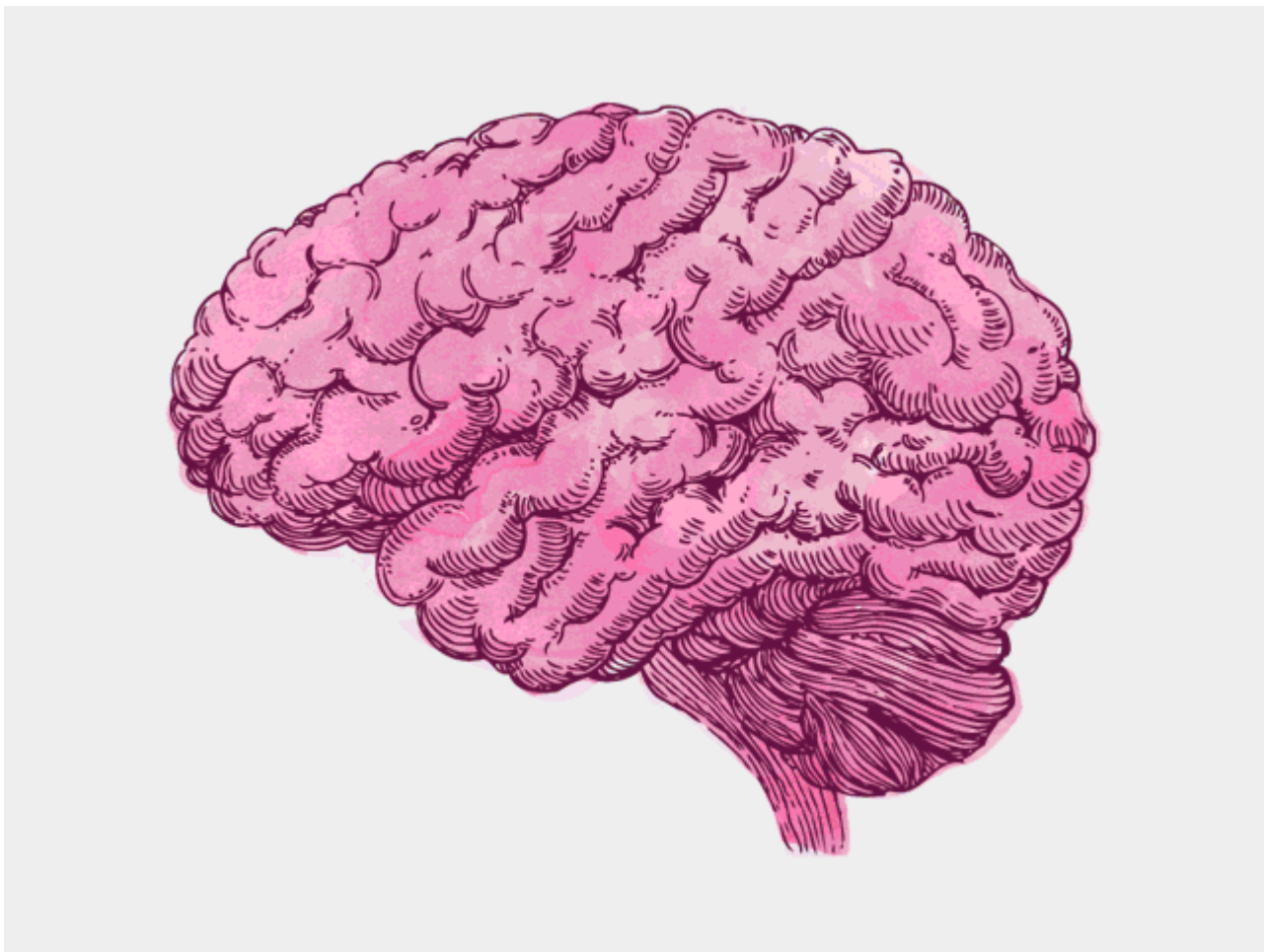




I Contain Multitudes

Our bodies are a genetic patchwork, possessing variation from cell to cell. Is that a good thing?

By Kat McGowan



Even healthy brains harbor genetic diversity, though scientists disagree over the extent.

Your DNA is supposed to be your blueprint, your unique master code, identical in every one of your tens of trillions of cells. It is why you are you, indivisible and whole, consistent from tip to toe.

But that's really just a biological fairy tale. In reality, you are an assemblage of genetically distinctive cells, some of which have radically different operating instructions. This fact has only become clear in the last decade. Even though each of your cells supposedly contains a replica of the DNA in the fertilized egg that began your life, mutations, copying errors and editing mistakes began modifying that code as soon as your zygote self began to divide. In your adult body, your DNA is

peppered by pinpoint mutations, riddled with repeated or rearranged or missing information, even lacking huge chromosome-sized chunks. Your data is hopelessly corrupt.

Most genome scientists assume that this DNA diversity, called “somatic mutation” or “structural variation,” is bad. Mutations and other genetic changes can alter the function of the cell, usually for the worse. Disorderly DNA is a [hallmark of cancers](#), and genomic variation can cause a suite of brain disorders and [malformations](#). It makes sense: Cells working off garbled information probably don’t function very well.

Most research to date has focused on how aberrant DNA drives disease, but even healthy bodies harbor genetic disorder. In the last few years, some researchers report that anywhere from [10 to 40 percent of brain cells](#) and between 30 and 90 percent of human liver cells are aneuploid, meaning that one entire chromosome is either missing or duplicated. Copy number variations, in which chunks of DNA between 100 and a few million letters in length are multiplied or eliminated, also seem to be widespread in healthy people.

Our vulnerabilities and our resilience are all bound up together, two sides of one coin.

The exact extent of cell-to-cell diversity is still unclear and a matter of some debate. It’s only in the last two years that scientists have been able to look carefully at just one genome at a time, with the advent of [new methods of single-cell DNA sequencing](#). (Earlier methods averaged the results of thousands or millions of cells and could only detect huge aberrations or relatively common ones.) Because this work is so new, each study includes surprises: A [single-cell genome sequencing study](#) of 97 neurons from healthy brains, published today by [Christopher Walsh](#), a neurologist at Boston Children’s Hospital and Howard Hughes Medical Institute, and the postdoctoral researcher Xuyu Cai found few that were aneuploid — less than 5 percent. But most had at least one good-sized copy number variation.

Walsh’s findings and others mark a third phase in human genomics. When the complete DNA of one human being was first sequenced in 2000, it was considered to be “the” human genome. Soon after, researchers began to explore the differences between individuals, launching the era of the “personal genome.” Now science is entering the age of the microgenome, in which research begins to explore the worlds within us, examining our inherent imperfections and contradictions, the multitudes we contain.

With that third phase comes a deeper question. What do our genetic contradictions mean? Do they play an important role in our biology? At this point, just about every genome scientist has a slightly different take. One surprising theory suggests that DNA diversity might be good for you. It’s a feature, not a bug.



Our genetically diverse brains might be one reason we are all so different, suspects Salk Institute neurobiologist Fred Gage.

According to this idea, genetic heterogeneity allows bodies to be more adaptive and resilient. The logic comes from evolutionary biology. Genetic diversity is clearly beneficial for a population or species, because a few individuals will likely be randomly equipped to survive unpredictable environmental changes, such as a drought or an epidemic. Along similar lines, some biologists have proposed that genetic diversity might also be beneficial within the individual. If new conditions demand new abilities or functions, such as surviving an environmental toxin or learning a new skill, genetic heterogeneity increases the odds that at least some cells will be able to thrive in this new situation. “I think of the body as a population of cells, similar to the population of human organisms walking this earth,” said [James Lupski](#), a geneticist at Baylor College of Medicine, who studies how DNA alterations shape human traits. In any such population, “there’s a lot to be said for generating variation, and allowing the most fit variation to be selected out.”

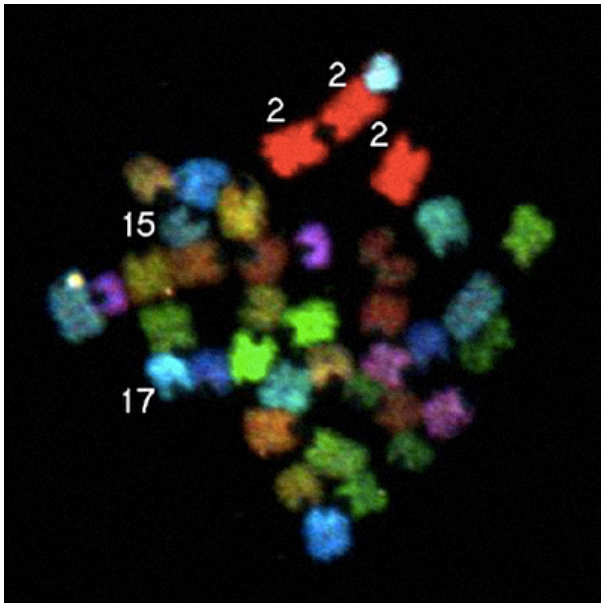
The most radical version of this argument comes from [Fred Gage](#), a Salk Institute neurobiologist best known for pioneering studies in neuroplasticity, the adult brain’s ability to adapt. His team has found several types of genetic variation to be common in normal adult human brains, and he thinks this diversity could help explain the organ’s amazingly complex structure and remarkable flexibility. “We can’t predict what will happen to us in our 80 years of life,” he said. “We have to build in mechanisms of diversity that will help us adapt to the things that happen to us.” Experts in liver biology propose a similar idea. They even have [preliminary evidence](#) that genetic diversity actually can make the organ more resilient.

The outcome of this research could also have practical consequences. If somatic mutations are common in healthy bodies, then biomedical researchers can no longer assume that DNA aberrations point toward the causes of disease. Doctors won’t be able to trust that the DNA found in a blood or saliva sample actually reflects the gene sequences in the heart or the liver. Should somatic variation turn out to be not just common but also good for you, it will undermine the longstanding presumption that the healthiest genome gets replicated with perfect fidelity. The most highly functional bodies may be the ones that permit a little mutation, that encourage a certain amount of

genetic wildness and disorder within.

A Patchwork Brain

In the immune system, DNA diversity is without a doubt essential to health — it's how our bodies recognize infectious invaders even if we've never encountered them before. Our immune cells produce hundreds of millions of unique and distinctive receptors, a vast library that can detect and combat just about any possible foreign agent. Amazingly, this variety is generated from just a handful of immunoglobulin genes, which are [reshuffled and recombined randomly](#) in each immune cell. Every unique mix of these gene fragments results in a slightly different receptor, a discovery that earned [Susumu Tonegawa](#) a Nobel Prize in 1987. "It was necessary to our survival as a species to randomly generate millions of types of variations to make us enough antibodies," said Lupski. "I wouldn't call that pathology; I'd call it normal biology."



A normal cell is supposed to have two copies of each chromosome, but this brain cell from an embryonic mouse has three copies of chromosome 2 and only one of 15 and 17.

But the immune system was thought to be just one fluky exception, and DNA variation elsewhere in the body was written off as error, the unfortunate result of imperfections in the copying machinery. Enzymes involved in copying and editing DNA during cell division may snip out, reinsert or make too many copies of stretches of the genome, creating copy number variations. Aneuploidies are the result of a different type of mistake. They occur when duplicated chromosomes are divvied up unevenly between two dividing cells.

Such mutations are termed "somatic" because they aren't inherited; instead, they spontaneously appear in non-reproductive cells. If a somatic mutation happens during development in a rapidly dividing tissue, it may be present in hundreds or millions of cells. By contrast, germline mutations are usually inherited: They were already in the egg or sperm at the moment of conception, which means they affect every cell in the body.

Some researchers suspected that something like what was happening with the immune system might be going on in the brain. Here, too, a limited set of genes somehow codes for a great diversity of cells — perhaps as many as 10,000 different types. "The brain is extraordinarily interesting, and people are always looking for elegant ways to explain how you get these amazing levels of diversity," said [Ira Hall](#), a molecular geneticist at the Washington University School of Medicine in St. Louis, who has studied mechanisms of DNA rearrangement for many years.

In 2001, neuroscientist [Jerold Chun](#) and other researchers at the University of California San Diego made the surprising discovery that about a [third of the immature cells](#) that give rise to neurons in an embryonic mouse brain were aneuploid. “People thought we were nuts,” said Chun, now a neuroscientist at Scripps Research Institute in San Diego. In follow-up papers, Chun and others found that full-grown aneuploid neurons were common in adult mouse brains, even forming circuits with other cells. They [showed up in humans too](#): In people who had died from causes unrelated to the brain, roughly 10 percent of their brain cells were found to be aneuploid.



Jerold Chun of the Scripps Research Institute discovered in 2001 that a third of the cells in an embryonic mouse brain had the wrong number of chromosomes.

If each brain harbored a subpopulation of idiosyncratic, genetically freakish neurons, some of which might respond in weird ways to stimulation or to injury, that might begin to account for the incredible variation between brains and individuals, Chun reasoned. “It gives you the ability to create a nervous system that’s almost infinitely diverse,” said Chun. “On top of the genetic diversity we have as a species, neural diversity places orders of magnitude more possibilities into the system.”

Along similar lines, Gage’s group found that tiny chunks of DNA, called mobile elements, could trigger small genetic changes to [newly born neurons](#) in the adult human brain. These insertions are too small to easily locate on a genome-wide basis, so his group looked for larger copy number variations (CNVs) in 110 neurons from postmortem brains. Gage teamed up with Hall, who has expertise in single-cell sequencing, and they reported last fall that 13 to 41 percent of adult human neurons had at least one major CNV, and some had ten or more.

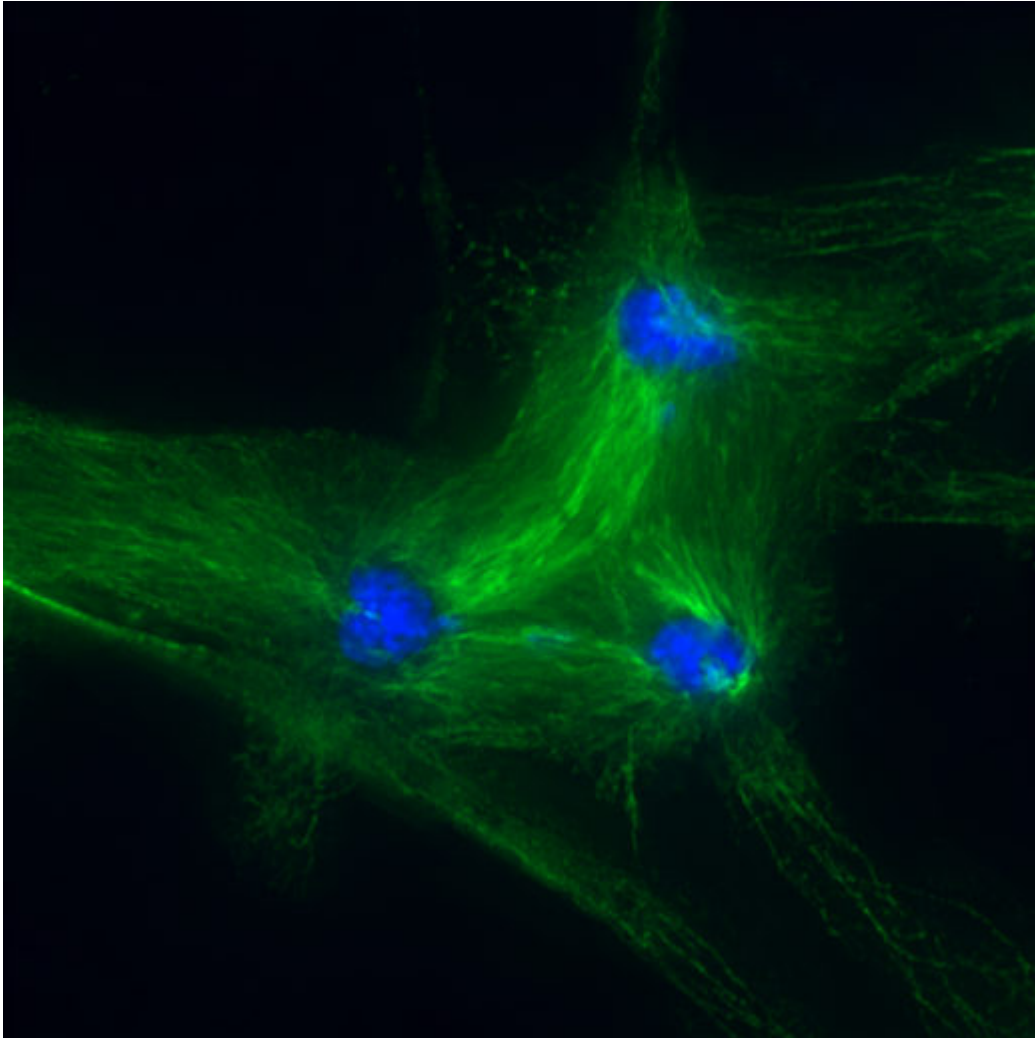
Gage proposes that the mobile elements and the CNVs exist for the same reason: They promote dynamic flexibility in the brain, which could turn out to be essential during times of rapid change. “You are provided with added diversity, which is preparation for unexpected changes. It may give you some adaptability that a stagnant, univalent genome would not.” The cells that provide advantages survive and make connections with other cells. Those that don’t, die off. It’s survival of the fittest, right there in our brains.

Bursting With Chromosomes

Whether other parts of the body are as riddled with genomic glitches is unclear. “It’s still very early,” said Hall. Outside of the brain, the best-documented genomic variability in healthy people is in the liver. More than a hundred years ago, biologists noticed that some hepatocytes (liver cells) were huge, swollen with two or more nuclei and bursting with chromosomes. Modern estimates are

that in humans, about [half of all hepatocytes are polyploid](#), meaning that instead of having the usual two copies of each chromosome, they have four, eight, even 16.

One theory is that the extra DNA serve as backup copies. The liver is like a waste processing plant: It deactivates and disposes of toxic substances, and its cells are constantly exposed to DNA-damaging chemicals. If an important gene on one chromosome in a liver cell gets knocked out by a DNA-disrupting poison, the extra copies of the chromosome will ensure that gene still functions.



This dividing liver cell apparently didn't read the textbook: It has multiple extra copies of its DNA (blue regions), and it is preparing to split into thirds.

But [Andrew Duncan](#), a cell biologist at the University of Pittsburgh, and colleagues noticed that when polyploid cells split, the daughter cells are often aneuploid, with oddball sets of chromosomes rather than the usual pairs: Some chromosomes are solitary, some come in threes. About half of all human hepatocytes are aneuploid, indicating that the backup-copy theory can't be the whole story. Duncan thinks that the liver, like the brain, benefits from genomic diversity for similar reasons. The liver has the ability to regenerate itself, should it become damaged by toxins or diseases like cirrhosis or hepatitis. A genetically diverse pool of cells means that some might be better equipped to survive. Those outliers will multiply, outcompete other cells and reconstruct the organ.

Duncan even has some proof this can happen, at least in a lab mouse. Mice that have been genetically modified to develop [hereditary tyrosinemia](#), a human liver disease, will resist the disease if they also lose another gene on chromosome 16 called homogentisic acid dioxygenase. Duncan found in 2012 that the livers of the sickly mice were selectively rebuilt by aneuploid cells that had randomly lost a copy of chromosome 16. "This genetic trick allowed them to resist the disease," he

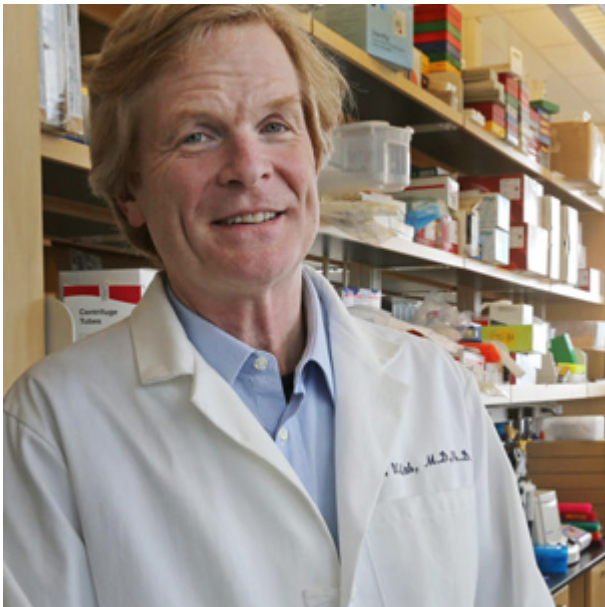
said.

He is now hoping to show that something similar can happen in other mouse models of human liver diseases, and is also looking for evidence that aneuploid cells can rebuild the livers of sick humans as well. “It’s becoming something people at least consider, that maybe these chromosomal variations could be playing a role” in disease recovery, he said. “It’s up to us and others to figure out what that role is.”

A Good Thing?

Meanwhile, not everyone is convinced that large-scale genetic aberrations are all that common in healthy bodies. Much of that doubt is related to technological shortcomings: The traditional method of identifying aneuploidy, fluorescent in situ hybridization, isn’t ideally suited to survey all 23 pairs of chromosomes, and deciding that one chromosome is aneuploid can be somewhat subjective. The newer single-cell sequencing methods can directly audit one entire genome, but they require the DNA to be chemically amplified, skewing results. Getting deep enough “coverage” of the genome (repeating the sequencing enough to correct most errors) is still time-consuming and expensive, so studies are done at low coverage. Even large CNVs are hard to detect, and the smaller ones are currently almost impossible to survey systematically.

For all these reasons, genome biologist [Angelika Amon](#) at MIT (and also a Howard Hughes scholar), whose research focuses on aneuploidy in cancer and aging, thinks that major genetic variation in healthy bodies has been overestimated. That’s in part because she thinks it is biologically implausible: Her studies shown that aneuploidy makes cells grow slowly and show signs of metabolic stress. “Everything we’ve studied about aneuploidy in yeast, mouse and humans shows us that having the wrong chromosome number is not a good thing,” she said.



Christopher Walsh of Harvard Medical School recently found that many cells in healthy brains have at least one big chunk of DNA missing or out of place.

Walsh thinks that the more plausible range of aneuploidy in the brain is less than 5 percent (in line with what’s seen in most other tissues, like skin), as opposed to Chun’s estimate of around 10 percent. (Amon believes it is closer to 2 percent.) With megabase-sized CNVs, the picture is even murkier. While Amon also suspects that current CNV estimates have been overinflated by the statistical methods used to analyze variation, Walsh’s most recent study is more or less consistent with the lower range of what Chun and Gage have found — that very roughly speaking, most brain cells have at least one substantial CNV. “CNV is pretty common, even in the normal developing

brain,” said Walsh. “I was impressed with that.”

These questions of where and how much will likely be resolved as the technology and methods to analyze genomes continue to improve. Whether somatic mutations are largely beneficial, or even an essential source of human diversity and adaptability, will be harder to answer. For now, the idea “is very theoretical, not based on real data,” admitted Gage.

[Another study from Walsh’s group published today](#) reveals that mutations in even a small number of cells can result in severe brain malformations, such as brains that have two cortexes, or are smooth as an egg. “As few as 10 percent of cells being mutated can give you all kinds of problems — seizures, intellectual disabilities,” said Walsh. In his eyes, the downsides of somatic mutation in the brain are obvious, and any potential benefit is yet to be proven. Likewise, while Lupski thinks that somatic variation is significant, he is not yet convinced that it’s helpful. More experiments like Duncan’s are needed to prove that genetically diverse brains or livers have measurable advantages over homogenous ones.

But even the skeptics appreciate the deep appeal of the idea that genomic diversity could be helpful. “People are excited about it, because it could provide an explanation for human variability,” said Amon. We possess a bewildering variety of habits and behaviors and a capacity to adjust to just about anything life throws at us. It’s compelling because it reflects a truth about human nature, that our vulnerabilities and our resilience are all bound up together, two sides of one coin. It just seems to fit with who we are.

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