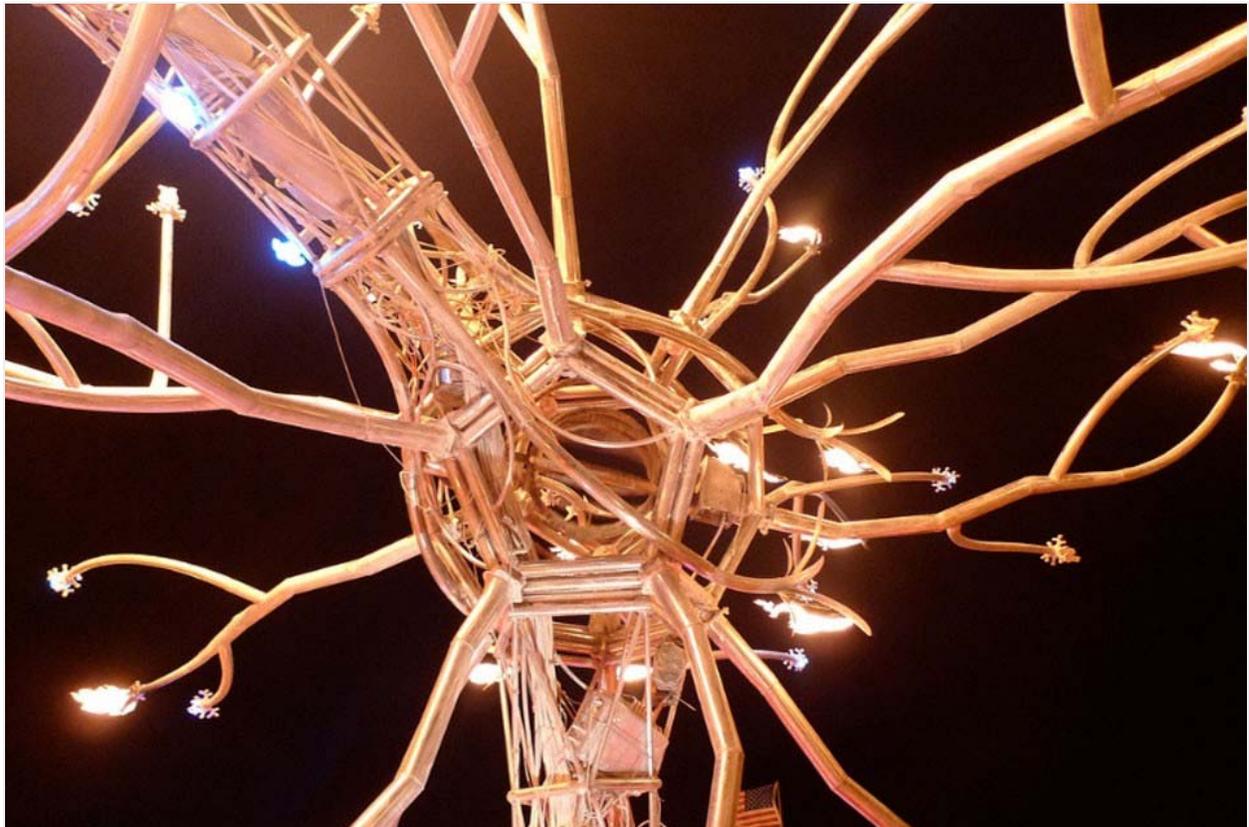


*The Atlantic*

# The Surprising Genealogy of Your Brain

Each of your neurons is more closely related to heart cells than to most of its neighbors. Why?



Ann Larle Valentine / Flickr

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People talk about an individual's genome as if it was a single consistent entity—but it isn't. Every one of us actually contains a cosmopolitan melting pot of different genomes. Our 37 trillion or so cells all arose from a single fertilized egg, and as this progenitor divided again and again, its daughters picked up mutations in their DNA that distinguished them, and their descendants, from their neighbors.

Scientists can now detect the subtle differences between these dynasties and trace their lines of ancestry. That is, they can reconstruct the genealogy of *a single body*. And they're finding that these family trees are more convoluted than anyone suspected.

Take the brain. You might expect that neighboring neurons would be closely related to one another, or that entire regions would arise from the same ancestral cells. But that's not the case. Christopher Walsh from Boston Children's Hospital has now shown that in one region, the prefrontal cortex, any given neuron is more closely related to cells from *the heart* than it is to three-quarters of its immediate neighbors.

Walsh has been building up to this since the early 1990s, when he charted the migration of neurons in rat brains, and found that closely related cells would often end up in very different places. Now, using powerful techniques that can sequence the DNA from individual cells, he can trace these lineages with much more precision, and in human brains.

His postdoc Michael Lodato sequenced the genomes of 36 single neurons, extracted from the preserved brains of three healthy people who had died in accidents. He found that each neuron contains around 1,500 unique mutations, making them more variable than the team had anticipated. Contra Pahlaniuk, each neuron really is a beautiful and unique snowflake.

These mutations are different than those that typically exist in, say, skin cells or cancer cells. Those arise when cells divide and make mistakes when duplicating their DNA, or when that DNA is bombarded by damaging stimuli like ultraviolet radiation or tobacco chemicals. By contrast, neurons pick up most of their

mutations through the simple act of switching on their genes. “When DNA isn’t being used, it is packed up and put away,” explains Walsh. “When a cell wants to use a gene, it unwinds the DNA and opens it up, and that unwinding is a little dangerous. It makes the DNA more vulnerable and can induce damage.”

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## **Perhaps by dispersing the descendants of early cells around the brain, we also spread the risk of neurological disease.**

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“The field will look back at this paper as a landmark study,” says Alexander Urban from Stanford University School of Medicine. “They have taken a phenomenon that was only vaguely known to exist and put it on a very firm foundation with solid numbers. Based on this foundation, we can now start to investigate the possible consequences of these [mutations] in health and in disease, during brain development, and in aging.”

Lodato also sequenced the genomes of 226 neurons from a single brain, known simply as Brain B. He found that these cells belonged to at least five distinct lineages, all of which were spread throughout the organ. More surprisingly, those lineages also included cells from other parts of the same person, including their liver, heart, lung, and pancreas.

To understand that weird pattern, cast your mind back by several decades to a time when Brain B’s owner was a recently conceived ball of embryonic cells. Five of those cells would eventually give rise to the lineages that Lodato discovered, and they had already acquired mutations that distinguished them from each other. As they divided, their progeny intermingled and gave rise to all kinds of tissues. Some produced neurons and found their way to the same pocket of prefrontal cortex that Lodato studied. Others made a living in distant organs.

Why such a complicated pattern? Imagine if that wasn't the case, and that a single early cell could give rise to all the neurons in a specific chunk of brain. If that cell developed a mutation in a critical gene, the resulting brain region would be in serious trouble. Indeed, in earlier studies, Walsh's team showed that mutations in small clusters of neurons can lead to debilitating disorders involving abnormal brain development and epileptic seizures.

So perhaps, by dispersing the descendants of early cells around the brain (and the body), we also spread the risk of neurological disease. "That's just a speculation," says Walsh—but a very plausible one. Given his new results, it seems likely that every site in every gene is mutated in at least one neuron, somewhere in the brain. Indeed, Lodato found that brain B harbored single neurons with mutations that confer a high risk of schizophrenia, seizure disorders, and other disorders. If these cells are few and far between, the consequences might be minimal.

Walsh's study is one of many which show that "probably every neuron is unique from a genomic perspective," says Michael McConnell from the University of Virginia. His own team have shown that up to 40 percent of neurons contain large stretches of DNA that have been either duplicated or deleted. Others have found that selfish-jumping genes can actively scatter copies of themselves throughout the genomes of their host neurons. All of these processes exacerbate the differences between neighboring neurons, and could potentially contribute to diseases.

Indeed, the National Institute for Mental Health has recently funded a collaborative project called the Brain Somatic Mosaicism Network, in which Walsh, Urban, and several other researchers will look at the role of these mosaics in schizophrenia, autism and Tourette syndrome.

"The assumption has always been that the genomes within every individual are identical," says McConnell. "Now that we know that assumption is false, it's forced a rethink."

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#### ABOUT THE AUTHOR

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