Researchers find unexpected genetic mosaic in the brain

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(Medical Xpress)—Scientists at the University of Virginia and elsewhere have discovered that nerve cells in the brain are unexpectedly varied in their genetic makeup, a surprising finding that may help explain schizophrenia, depression, bipolar disorder, autism and other such conditions thought to be genetically linked but not yet tied to a single gene.

Researchers at U.Va.'s School of Medicine and their collaborators found that up to 41 percent of the neurons they examined displayed at least one significant variation in DNA – a percentage far greater than anticipated. This variation could be in the form of either a duplication or a deletion in the genetic code. A deletion could lead to reduced expression of the affected genes, while a duplication could lead to greater expression.

"That might be why it's been so hard to figure out the genetics of these complex diseases – because we've been building on the assumption that all the cells in there had the same genome," said Mike McConnell of U,Va.'s Department of Biochemistry and Molecular Genetics. "If we've been over- or under-representing some of the risk genes, now we might have a better understanding."

The work represents an important application of single-cell sequencing, allowing scientists to examine the genetic makeup of an individual cell. McConnell said this was, to his knowledge, the first time the approach had been applied to neurons.

Neurons, he noted, are unlike most cells, where genetic deletions and alterations occur during the cellular copying process. "For the most part, you have all these neurons you're born with and you don't really replace them. Whereas in the skin, a skin cell is there for maybe a week or two weeks, and in the intestine for less than a week. When you get mosaics in these places, that cell is gone soon. But when you get these unique genomes in neurons, then those cells stay there, and they continue to participate in that circuit forever."

More research is needed to determine exactly when and how the mosaic is occurring in neurons. "What we have observed here is surprising and potentially very important. But, in some sense, our results have raised more questions than they have answered," said U.Va. researcher Ira Hall of the Department of Biochemistry and Molecular Genetics. "For example, are neuronal genomes fundamentally different than genomes from other cell types? What is the effect of age and cell type? Do levels or specific patterns of cell-to-cell genomic variability correlate with age-dependent neuronal decline, or specific disease states? To answer these questions, we need to look at many more cells, in diverse contexts."

But the finding may offer answers to longstanding questions that have flummoxed researchers. "There are examples out there of identical twins where one has schizophrenia and the other one doesn't. One has autism and the other one doesn't," McConnell said. "These are identical twins who were raised together, they had the same nature and nurture, and it's not clear why one of them would get the disease and the other one wouldn't. And it could be because of the mosaic they wound up with in their brain."

The finding may also facilitate the development of new drugs and treatments for conditions connected to the variation. "It would be very far-fetched to think that you could actually fix the mosaic," McConnell said, "but if we can understand how the mosaic is causing disease, and

identify certain genes that become overrepresented or underrepresented in the mosaic, then we could start studying those genes and perhaps find better targets for some of these diseases."

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