Researchers uncover molecular mechanisms linked to autism and schizophrenia

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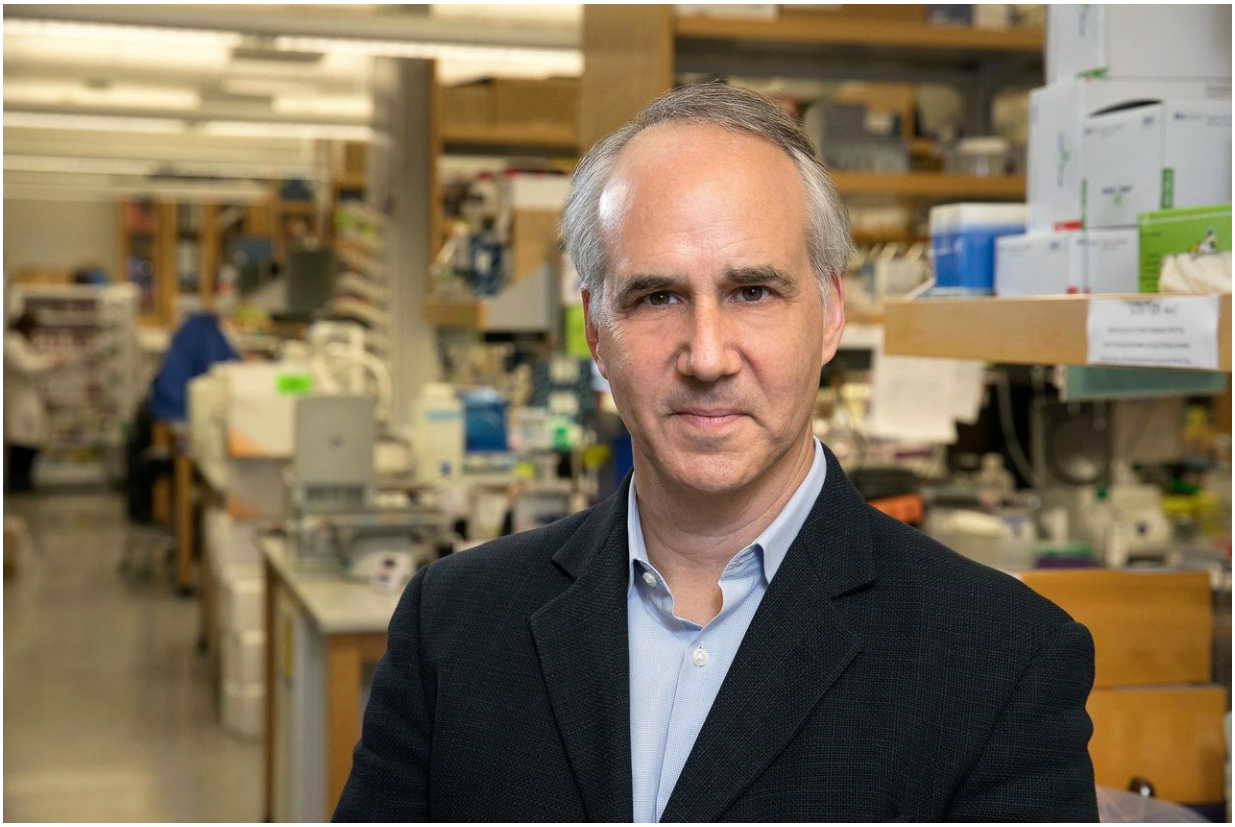

Daniel Geschwind is a Gordon and Virginia MacDonald Distinguished Professor of Human Genetics at the David Geffen School of Medicine at UCLA. Credit: UCLA Health/Reed Hutchinson

Since the completion of the groundbreaking Human Genome Project in

2003, researchers have discovered changes to hundreds of places in the DNA, called genetic variants, associated with psychiatric diseases such as autism spectrum disorder and schizophrenia. Now, new findings from a major study has linked many of these changes in DNA to their molecular effect in the brain, revealing new mechanisms of diseases.

In the new papers published in *Science*, UCLA researchers and collaborators from more than a dozen institutions from around the world provide the largest-ever datasets on the molecular workings of the brain. The findings provide a roadmap for development of a new generation of therapies for psychiatric conditions.

"This work provides several missing links necessary for understanding the mechanisms of psychiatric diseases," said Dr. Daniel Geschwind, a senior author on two of the new papers, and the Gordon and Virginia MacDonald Distinguished Professor of Human Genetics in the David Geffen School of Medicine at UCLA.

Other institutions collaborating on the new papers include University of California, San Diego; the Icahn School of Medicine at Mount Sinai, Yale University, University of North Carolina, Chapel Hill; University of Chicago, Duke University, Johns Hopkins School of Medicine, SUNY Upstate Medical University, and Central South University in China.

During the last decade, scientists have conducted genetic studies of people with psychiatric diseases, comparing the results to healthy individuals to find genes that have different sequences in those with disease. Often, however, their findings led to more questions than answers. Scientists not only discovered genes linked to the diseases, they also uncovered hundreds of areas of DNA found in between genes, called regulatory DNA, that also seemed to have an association.

Scientists know these sections of DNA can control when, where and how genes are turned on and off in many ways. However, figuring out which "regulatory regions" affect which genes— and therefore the RNA and proteins encoded by the genes— is not straightforward.

In 2015, researchers at 15 institutions around the country, including UCLA, came together in the PsychENCODE Consortium to study in more detail the brain's regulatory DNA. An earlier project, known as ENCODE, already had uncovered the roles sections of regulatory DNA, but it was clear that these might be different in the brain than other organs. The PsychENCODE has analyzed not just genetic variants linked to psychiatric diseases, but also patterns of RNA and proteins in 2,188 brain bank samples from both healthy individuals and those with a psychiatric disorder.

In one new paper, Geschwind and collaborators describe this new data, which helps explain the roles of tens of thousands of sections of regulatory DNA in affecting RNA and proteins in the brain. The data also reveals which genes are most often expressed at the same time as each other, suggesting new biological processes and pathways. The dataset—essentially a detailed model of the inner molecular workings of the human brain— is now publicly available as a starting point for other researchers to mine mechanisms of disease and potential drug targets.

"This resource is so vast that you can start by choosing one interesting disease associated genetic variant and begin digging into that and discovering how it impacts molecular networks in the brain," Geschwind said. "Having robust data of this scope provides a foundation for countless new studies."

In a second paper, Geschwind, first author Dr. Michael Gandal, assistant professor of psychiatry and biobehavioral Sciences at the Geffen School of Medicine, and other collaborators, used that new data to look

specifically at how RNA molecules are dysregulated—either present at higher levels, lower levels, or in altered conformations— in autism spectrum disorder, schizophrenia and bipolar disorder.

Using nearly 1,700 brain bank samples, the researchers revealed thousands of RNA molecules that are either spliced differently— with different sections of genetic material—or present at higher or lower levels in the brains of people with one of the psychiatric diseases.

"You can't look at the brain under a microscope and see substantial differences in these disorders," Gandal said. "But we've now shown that if you look finely at patterns of how genes are expressed, you see pathways that are clearly dysregulated."

Among the surprises in the data— altered levels of RNA linked to neuroinflammation and the brain's immune cells showed very different trajectories in people with schizophrenia, autism spectrum disorder and bipolar disorder.

Additionally, the study showed the importance of looking at individual cell types within the brain when parsing the new RNA data— in some cases, alternately spliced RNA was linked to disease but only when the RNA was found in certain cell types and not others.

Finally, new genes were implicated in the diseases based on the RNA results; five were linked to autism spectrum disorder, 11 to bipolar disorder, and 56 to schizophrenia.

Once again, the data is mostly important as a jumping off point for future studies, the researchers said.

"This is the tip of the iceberg," Gandal said. "The ability to compile together 2,000 brains has been revolutionary in terms of revealing new

genetic mechanisms, but it also points to how much we don't know."

More information: M.J. Gandal el al., "Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder," *Science* (2018). science.sciencemag.org/cgi/doi … 1126/science.aat8127

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