

Researchers find high-risk genes for schizophrenia

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Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

Using a unique computational framework they developed, a team of scientist cyber-sleuths in the Vanderbilt University Department of Molecular Physiology and Biophysics and the Vanderbilt Genetics Institute (VGI) has identified 104 high-risk genes for schizophrenia.

Their discovery, which was reported April 15 in the journal *Nature Neuroscience*, supports the view that [schizophrenia](#) is a developmental disease, one which potentially can be detected and treated even before the onset of symptoms.

"This framework opens the door for several research directions," said the paper's senior author, Bingshan Li, Ph.D., associate professor of Molecular Physiology and Biophysics and an investigator in the VGI.

One direction is to determine whether drugs already approved for other, unrelated diseases could be repurposed to improve the treatment of schizophrenia. Another is to find in which [cell types](#) in the brain these genes are active along the development trajectory.

Ultimately, Li said, "I think we'll have a better understanding of how prenatally these genes predispose risk, and that will give us a hint of how to potentially develop intervention strategies. It's an ambitious goal ... (but) by understanding the mechanism, [drug development](#) could be more targeted."

Schizophrenia is a chronic, severe mental disorder characterized by hallucinations and delusions, "flat" emotional expression and cognitive difficulties.

Symptoms usually start between the ages of 16 and 30. Antipsychotic medications can relieve symptoms, but there is no cure for the disease.

Genetics plays a major role. While schizophrenia occurs in 1% of the population, the risk rises sharply to 50% for a person whose identical twin has the disease.

Recent genome-wide association studies (GWAS) have identified more than 100 loci, or fixed positions on different chromosomes, associated

with schizophrenia. That may not be where high-risk genes are located, however. The loci could be regulating the activity of the genes at a distance—nearby or very far away.

To solve the problem, Li, with first authors Rui Chen, Ph.D., research instructor in Molecular Physiology and Biophysics, and postdoctoral research fellow Quan Wang, Ph.D., developed a computational framework they called the "Integrative Risk Genes Selector."

The framework pulled the top genes from previously reported loci based on their cumulative supporting evidence from multi-dimensional genomics data as well as gene networks.

Which genes have high rates of mutation? Which are expressed prenatally? These are the kinds of questions a genetic "detective" might ask to identify and narrow the list of "suspects."

The result was a list of 104 high-risk genes, some of which encode proteins targeted in other diseases by drugs already on the market. One gene is suspected in the development of autism spectrum disorder.

"Schizophrenia and autism have shared genetics," Chen said.

Much work remains to be done. But, said Chen, "Our framework can push GWAS a step forward ... to further identify [genes](#)." It also could be employed to help track down genetic suspects in other complex diseases.

Also contributing to the study were Li's lab members Qiang Wei, Ph.D., Ying Ji and Hai Yang, Ph.D.; VGI investigators Xue Zhong, Ph.D., Ran Tao, Ph.D., James Sutcliffe, Ph.D., and VGI Director Nancy Cox, Ph.D. Chen also credits investigators in the Vanderbilt Center for Neuroscience Drug Discovery—Colleen Niswender, Ph.D., Branden

Stansley, Ph.D., and center Director P. Jeffrey Conn, Ph.D.—for their critical input.

More information: Quan Wang et al. A Bayesian framework that integrates multi-omics data and gene networks predicts risk genes from schizophrenia GWAS data, *Nature Neuroscience* (2019). [DOI: 10.1038/s41593-019-0382-7](https://doi.org/10.1038/s41593-019-0382-7)

Provided by Vanderbilt University

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