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Schizophrenia genetic networks identified: Connection to autism found

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Although schizophrenia is highly genetic in origin, the genes involved in the disorder have been difficult to identify. In the past few years, researchers have implicated several genes, but it is unclear how they act to produce the disorder. A new study by researchers at Columbia University Medical Center identifies affected gene networks and provides insight into the molecular causes of the disease.

The paper was published today in the online edition of the journal Nature Neuroscience.

Using an unbiased collection of hundreds of mutations associated with schizophrenia, the Columbia researchers applied a sophisticated computational approach to uncover hidden relationships among seemingly unrelated genes. The analysis revealed that many of the genes mutated in schizophrenia are organized into two main networks, which take part in a few key processes, including axon guidance, synapse function, neuron mobility, and chromosomal modification.

The study also uncovered an intriguing connection between schizophrenia and autism. "If we hadn't known that these were two different diseases, and had put all the mutations into a single analysis, it would have come up with very similar networks," said the study's senior author, Dennis Vitkup, PhD, associate professor in the Department of Biomedical Informatics, the Center for Computational Biology and Bioinformatics, and the Columbia Initiative in Systems Biology at Columbia University Medical Center. "It shows how closely the autism

and schizophrenia genetic networks are intertwined," he added.

Although it will take time to translate the findings into practical treatments, the study provides insight into the molecular causes of schizophrenia. It also suggests that mutations associated with schizophrenia, autism, and probably many other psychiatric disorders, are likely to converge on a set of interrelated molecular processes.

Computer analysis uncovers genetic networks

To discover potential connections among genes mutated in schizophrenia, Dr. Vitkup and colleagues developed a computational approach, called NETBAG+, to identify networks of genes likely to be responsible for the same genetic phenotype. They then gathered the strongest mutations that had been observed in schizophrenia by other researchers—including a set of de novo mutations recently described by a team of Columbia researchers led by Maria Karayiorgou, MD, and Joseph A. Gogos, MD, PhD—and fed them into the program.

The program uncovered two genetic networks. Genes in the first network are involved primarily in axon guidance, synapse function, and cell migration. Genes in the second network are involved in chromosomal organization and remodeling.

Parts of both networks are highly active during prenatal development, suggesting that changes in the brain that cause schizophrenia later in life are laid down very early in life.

Connection to autism

Dr. Vitkup also compared his schizophrenia networks with networks found in neurodevelopmental disorders such as autism. One

schizophrenia network is strongly related to an autism network he described in a study published last year. Both networks contain genes involved in axon guidance, synapse function, and cell migration.

"Our recent mutational analysis showed that this overlap includes primarily genes that are important for early fetal development. This is not surprising, because some cases of schizophrenia and likely many cases of autism have neurodevelopmental origin," said Dr. Karayiorgou.

The close relationship between genetic networks involved in autism and schizophrenia raises an intriguing question: How can mutations in the same or related genes cause two different disorders?

"I like to use the analogy of car brakes," said Dr. Vitkup. "Different mechanical malfunctions of the brake mechanism can have very different functional consequences, from rapid acceleration to stalling."

Dr. Vitkup looked at large mutations called copy number variants (CNVs) that can lead to either schizophrenia or autism. CNVs involve long stretches of the genome containing several genes that have been either duplicated or deleted. Duplication of a region increases the "dosage" of its genes; deletion of a region decreases the dosage.

In CNVs involved in the growth of dendrites, or dendritic spines, at the ends of neurons, he found decrease in growth to be more common in schizophrenia and increase in growth more common in autism. "That's consistent with what's been found by postmortem brain studies," he said.

"Evidence of functional convergence among risk genes is consistent with the notion that schizophrenia and autism are both primarily diseases of neuronal communication. However, they have distinct clinical features and the challenge remains to identify the critical neural circuits and mechanisms that differentiate them," said Dr. Joseph A. Gogos. "This is

a step in that direction."

Dr. Vitkup predicts that many more genes involved in schizophrenia and autism will eventually be found—possibly up to 1000 genes for each disorder—but a significant fraction of them will likely fall into the networks and pathways identified in the current study.

"Until a few years ago, people were looking for just a handful of genes responsible for autism and schizophrenia, so the idea that many hundreds of genes are involved is a big change in thinking," Dr. Vitkup said. "Our study and the studies of our collaborators suggest that in the search for the causes of complex genetic disorders, it will be more productive to look for common pathways and gene circuits than for a handful of causal genes. This type of network analysis gives us a way to begin to make sense of what's happening."

Study points way to future approaches to gene discovery

"To uncover all of the processes and molecular pathways involved in schizophrenia and related disorders, more gene searches are clearly necessary," said Dr. Vitkup.

Until recently, the hunt for disease genes was focused primarily on analyses of common genetic mutations, using so-called genome-wide association studies (GWAS). But according to Drs. Vitkup, Karayiorgou, and Gogos, a complementary, possibly less expensive, approach may be more fruitful. "By looking at individuals with schizophrenia who are born into families with no history of the disorder," Dr. Vitkup said, "we can identify de novo mutations that are likely to have caused their disorder."

Drs. Karayiorgou and Gogos recently used this approach to uncover many dozens of new schizophrenia mutations from several hundred families; nearly every mutation was unique to one patient.

"Our study demonstrates that through network-based analyses of rare de novo mutations, it is possible to implicate relevant molecular processes," said Dr. Vitkup. "Applying similar methods to larger cohorts of patients, we should be able to delineate all of the pathways and molecular processes underlying complex psychiatric disorders such as schizophrenia."

More information: The paper is titled, "Diverse types of genetic variation converge on functional gene networks involved in schizophrenia."

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