Landmark study reveals clearest genetic signals yet for schizophrenia risk

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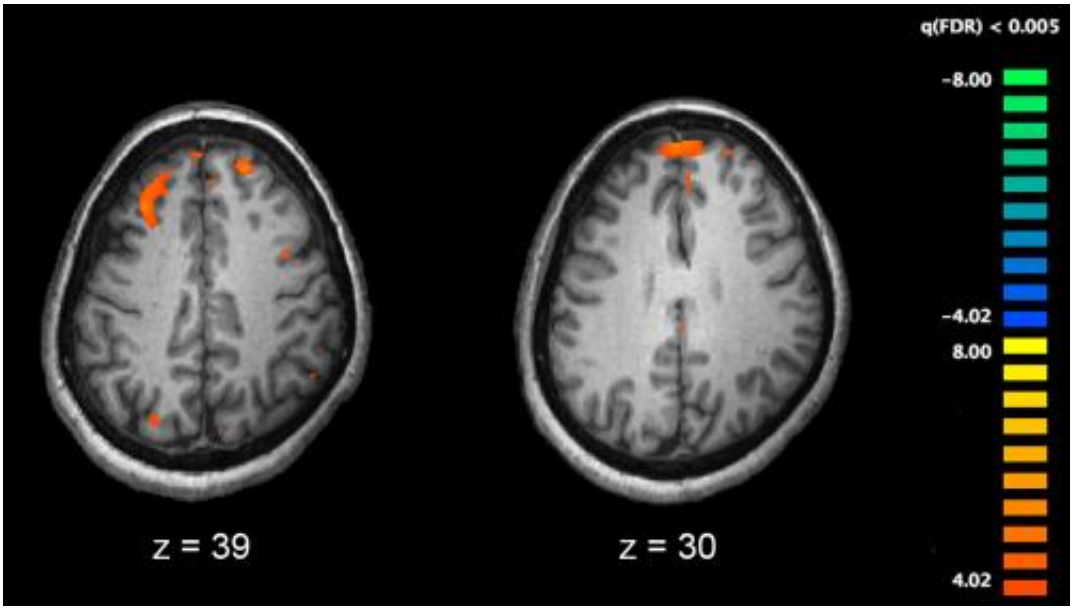

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown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

In a landmark genetic study of more than 121,000 people, an international consortium called SCHEMA, led by researchers at the Broad Institute of MIT and Harvard, has identified extremely rare protein-disrupting mutations in 10 genes that strongly increase an

individual's risk of developing schizophrenia—in one instance, by more than 20-fold. A second, complementary study in a larger but overlapping group of 320,400 people, conducted by the Psychiatric Genomics Consortium (PGC) and including the same Broad researchers, brings to 287 the number of regions of the genome associated with schizophrenia risk, including ones containing genes identified by SCHEMA.

Together, these studies underscore an emerging view of schizophrenia as a breakdown in communication at the synapse (the junction between neurons), and illustrate how different kinds of genetic variation affecting the same genes can influence the risk for different psychiatric and neurodevelopmental disorders. The two studies appear together in the journal *Nature*.

"Psychiatric disorders have been a black box for a very long time. Unlike cardiovascular disease or cancer, we have had very few biological clues to disease mechanisms," said Tarjinder Singh, a postdoctoral fellow in the Stanley Center for Psychiatric Research at the Broad Institute. "As a result, we have lacked the necessary insights for development of much needed new treatments. Instead we have been iterating on the antipsychotic drugs serendipitously discovered more than 70 years ago." Singh, who is also in the Analytic and Translational Genetics Unit (ATGU) at Massachusetts General Hospital, is a collaborator on the PGC study, and a co-corresponding author of the SCHEMA study.

"Identifying these 10 genes is a watershed moment in schizophrenia research because each one of them provides a solid foundation for launching biological inquiry," said Benjamin Neale, another co-corresponding author on the SCHEMA study, a PGC collaborator, an institute member and director of genetics in the Stanley Center, co-director of the institute's Program in Medical and Population Genetics, and faculty of the Mass General ATGU. "By sequencing the DNA of

thousands of people, we are starting to see exactly which genes matter. These discoveries are the starting point for developing new therapies that treat the root cause of this devastating condition."

"We've tried for years and years to gain this kind of traction on the biology of schizophrenia," said Broad core institute member and Stanley Center director Steven Hyman. "Realistically, it will take yet more years to translate these results into biomarkers and treatments that will make a difference in the lives of people who are suffering with this devastating illness. But it is highly motivating to have a compelling path forward."

A global collection

The SCHEMA and PGC findings are the fruit of a decade-long push led by researchers in the Stanley Center and nearly four dozen other institutions around the world. Both projects aim to gather and compare DNA from large numbers of people with and without schizophrenia. By working together, investigators across the PGC have built a dataset that now includes more than 320,400 people from collections across the world, including people of European, Finnish, African American, LatinX, East Asian, and Ashkenazi Jewish descent. The SCHEMA cohort comprises a subset of that, representing more than 121,000 people.

The two groups have followed complementary paths in their study of schizophrenia genetics. Since 2009, the PGC team has conducted increasingly larger genome-wide association studies cataloging common genetic variations called single nucleotide polymorphisms (or SNPs) that contribute to schizophrenia risk.

The SCHEMA (SCHizophrenia Exome Meta-Analysis) Consortium—which came together in 2017—focuses on the exome, the nearly two-percent of the genome that encodes proteins. Specifically, the

SCHEMA Consortium looked for variants that would either knock out or markedly alter a gene's ability to produce functioning proteins.

"There's 10 years worth of data represented in these studies," said Sinéad Chapman, the director, global genetics project management in the Stanley Center who, along with team members Christine Stevens, Caroline Cusick, and many others, spent hundreds of hours ensuring that the samples and data from the SCHEMA collaborators were properly processed and tracked for these analyses. "It was quite a manual process, as there isn't one magic system to connect all the samples and data and all of their related regulatory and clinical information."

According to Singh, these two studies were possible because the necessary pieces were finally in place. "The genomic technologies, the sequencing infrastructure, the computational tools needed to understand the data they produce, have advanced dramatically in the last two decades," he said. "The most important piece was the global commitment on the part of PGC and SCHEMA members to share samples and data across institutions and nations to achieve the numbers of people needed to bring these rare mutations to light."

Emerging convergence

By sequencing whole exomes from 24,248 people with schizophrenia and 97,322 without, the SCHEMA team identified ultra-rare variants in 10 genes that dramatically increased a person's risk of developing schizophrenia. These variants, called PTVs for "protein truncating variants," prevent cells from producing a gene's full-length functional protein.

"In general, any given person has a roughly one percent chance of developing schizophrenia in their lifetime," said Neale. "But if you have one of these mutations, it becomes a 10, 20, even 50 percent chance."

Their findings also hint at an additional 22 genes that also likely influence schizophrenia risk, and which may prove significant after further study. Data from the SCHEMA study are available at schema.broadinstitute.org.

Together, these genes point to dysfunction at the synapse -- where neurons connect and communicate with each other -- as a possible cause of schizophrenia. This idea first emerged several years ago, thanks in part to a 2016 study from researchers at the Broad's Stanley Center, Harvard Medical School, and Boston Children's Hospital. In that study, they described for the first time how variations in a single gene -- complement component 4, or C4 -- raises schizophrenia risk by triggering excessive "pruning" of synapses.

Insights into two of the 10 genes from the SCHEMA study, *GRIN2A* and *GRIA3*, further implicate the synapse as a key part of schizophrenia's mechanistic roots. These two genes encode portions of the glutamate receptor, a cellular antenna found at the synapse that allows neurons to receive chemical signals from neighboring neurons. Pharmacological studies have previously suggested that glutamate signaling may be involved in schizophrenia, but the SCHEMA study provides the first solid genetic evidence of this. Additionally, *GRIN2A* activity in the brain peaks during adolescence, around the time people suffering schizophrenia begin to experience symptoms.

Most of the SCHEMA genes, however, have never before been associated with a brain disorder or neuron-specific functions. One gene (*SETD1A*) is involved in transcriptional regulation. Another (*CUL1*) helps the cell recycle old or unneeded proteins, while yet another (*XPO7*) helps chaperone molecules out of the cell's nucleus. Yet in the SCHEMA analysis, PTVs in these genes drive a 20- to 52-fold increase in schizophrenia risk.

"We don't yet have a well-developed framework for understanding how these genes might play a role in schizophrenia," said SCHEMA co-corresponding author and PGC collaborator Mark Daly, who is also an institute member in the Stanley Center, Mass General ATGU faculty, and director of the Institute for Molecular Medicine, Finland. "These genes will ultimately lead to some new insights, but are going to require a lot of experimental follow-up to see where they might fit in the puzzle."

Separately, the PGC team examined common genetic variations in 76,755 people with schizophrenia and 243,649 without, finding 287 regions of the genome (or loci) as having some involvement in schizophrenia risk, an increase of 94 loci since the last PGC analysis released in 2019. With further analysis they identified 120 genes that potentially increase risk for schizophrenia. Several of these genes were also identified in the SCHEMA study.

The PGC team also found that the genomic regions they implicated are largely active only in neurons, only in the brain, and affect mechanisms that directly impact neuron function, such as synaptic structure and organization.

The nature and effect of the variants detected by PGC differed in some ways from the SCHEMA findings. For instance, the damaging protein-coding *GRIN2A* mutations SCHEMA identified are extremely rare and raise schizophrenia risk 24-fold. The variants found in the PGC study are far more common and change *GRIN2A* expression, increasing risk by only 1.06-fold.

However, the fact that both studies' findings converge similar groups of genes and similar biological mechanisms suggests that genetic discoveries are beginning to home in on core aspects of schizophrenia biology, and are close to broader insights into the mechanisms

underlying schizophrenia progression.

"Our hope was that we would end up with some amount of overlap in the stories that the common and rare variant associations were telling us," said Neale. "And we see overlap pointing to a relationship between synaptic biology and schizophrenia risk."

Revelations into shared risk

The SCHEMA data also shed light on how psychiatric and neurodevelopmental disorders more broadly can share genetic risk. For instance, several SCHEMA genes, including *GRIN2A*, have previously been implicated with neurodevelopmental conditions such as epilepsy, developmental delay, and intellectual disability.

But by comparing their data from that of other large-scale studies, the SCHEMA team noted that the overlaps they saw were driven by different kinds of mutations: PTVs for schizophrenia, missense mutations (which can lead to amino acid swaps that modify a protein's activity) for the neurodevelopmental conditions.

"We see that a spectrum of consequences can arise from different kinds of mutation in the same genes," Neale noted. "We have a lot more to do and a lot more to learn about what these genes do, what variations in these genes do, and what the biological consequences of genetic variation really are writ large."

"This point is critical for gaining insight into how genetics works across brain disorders," Daly added. "We need to make sure that we don't take a siloed view of these data, and instead remain open to learning what these genetics has to teach us across phenotypes."

And indeed, this perspective is already bearing fruit. In a separate study

published in *Nature Genetics*, members of the international Bipolar Exome Consortium (BipEx), including Neale, report how comparisons of SCHEMA and BipEx data have helped reveal rare PTVs in the gene *AKAP11* gene that raise the risk of bipolar disorder several-fold, making it the strongest genetic risk factor found for bipolar disorder to date.

Fitting the puzzle pieces together

Already a great deal of work is being done to model the effects of the SCHEMA mutations in the laboratory. Researchers also recognize that there are many additional genetic discoveries waiting to be found.

"These first 10 genes are really only the beginning of genetic discovery," Neale said. "There is pretty clear evidence that there are many more genes to discover using the same kind of approach. But we fundamentally need bigger sample sizes to be able to reveal those additional genes.

"But, if you have more pieces of the puzzle," he continued, "it might be a little bit easier to fit them together and come into a slightly more coherent mechanistic view of schizophrenia, and how we might start to approach those processes with the hope of improving patient's lives."

"The biological complexity of schizophrenia is truly daunting, but this combination of rare protein altering variants from exome sequencing and common variants from GWAS have put us on our way to understanding the roots of that complexity," said Hyman. "In these results, we may be seeing how synaptic abnormalities or losses begin in schizophrenia, giving us openings to diagnosing and treating people much earlier than we can today."

"With schizophrenia, like with other complex disorders, I think we will ultimately find that many processes are involved in risk or protection,"

Daly added. "Understanding that may turn out to be one of the most complex undertakings in genetics and biology."

More information: Mark Daly, Rare coding variants in 10 genes confer substantial risk for schizophrenia, *Nature* (2022). DOI: 10.1038/s41586-022-04556-w. www.nature.com/articles/s41586-022-04556-w

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