Probe of DNA repeats reveals genetic link to schizophrenia

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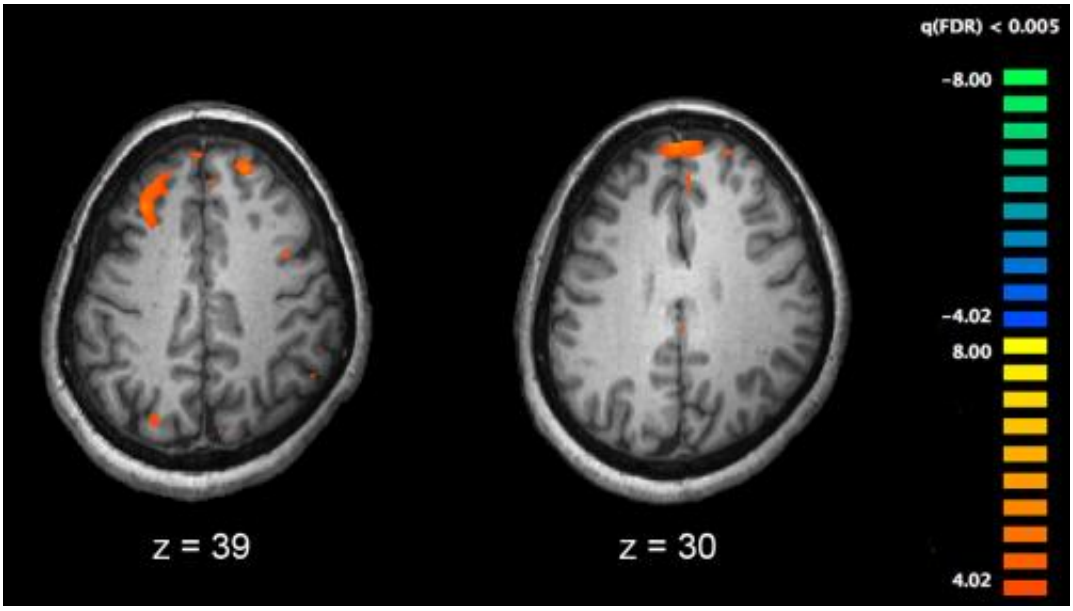

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown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

Researchers at The Hospital for Sick Children (SickKids) and Centre for Addiction and Mental Health (CAMH) have found that repeated DNA sequences in the genome may contribute to an individual's risk of developing schizophrenia.

Tandem repeats are a class of DNA sequence where two or more nucleotides, known as the building blocks of DNA, are repeated adjacent to one another. Sometimes these repeats can expand when they are passed from one generation to the next. As a repeat sequence expands, the likelihood that it may disrupt a gene's function increases.

Tandem repeat expansions are known to contribute to more than 50 conditions, including Huntington's Disease. Less is known about the role of these tandem repeats in a complex disorder like schizophrenia, which is influenced by the effects of many variants in different genes.

Led by Dr. Ryan Yuen, Scientist in the Genetics & Genome Biology program at SickKids, and Dr. Anne Bassett, a Senior Scientist at CAMH and University Health Network, a study published May 12, 2022 in *Molecular Psychiatry* found that individuals with schizophrenia have a high number of rare tandem repeat expansions that are not typically found in the general population. These tandem repeat expansions are located near genes, and often together with other genetic variants, that are known to be associated with schizophrenia.

As part of the study, the team found that the expansions were also present in the sequenced genomes of individuals with a family history of schizophrenia.

"This is the first time these rare repeat expansions have been assessed genome-wide in schizophrenia. Our findings suggest that the tandem repeat expansions are an important class of variants that contribute to schizophrenia risk," says Yuen.

Tandem repeat expansions contribute to errors in how neurons in the brain communicate

Tandem repeats are generally found in non-coding DNA, which means their function is unclear and they can be difficult for researchers to study. The researchers applied a novel computational approach developed by Yuen and his team at SickKids to search and find rare long tandem repeat expansions across the entire genome of 257 adults with schizophrenia carefully assessed by Bassett's team. They compared the data to genomes of 225 individuals with no psychiatric conditions as well as to a cohort of over 2,500 individuals from the 1000 Genomes Project, an international genome database.

The study found that tandem repeat expansions contribute to dysfunction at the synapse—where neurons connect and communicate with each other in the brain—likely by disrupting the regulatory process of their associated genes.

The research follows other recently published studies that describe other contributors to schizophrenia risk—one that identified common variant regions and the second that focused on rare protein-disrupting variants.

"We found that genes with tandem repeat expansions are overlapping with other discoveries we're seeing in the field. Our study helps to fill some of the gaps in our knowledge and underlines the important function of the synaptic functions in schizophrenia as well as the complex way in which schizophrenia is affected by different types of genetic variants," says Yuen, whose team previously used the same approach to link tandem repeat expansions to autism spectrum disorder.

Findings help expand understanding of the genetic underpinnings of schizophrenia

Bassett says the findings provide more evidence for the array of genetic risk underlying schizophrenia and related psychiatric disorders.

"Given the biological complexity of schizophrenia, we hope that our findings, in combination with other recent studies in the field, can be used to further advance understanding of this disorder as a brain disease to help destigmatize the illness," says Bassett. "These findings are a major step forward for the future of schizophrenia research."

Yuen notes future studies with a larger cohort size are required to further characterize the role of the rare tandem repeats in the condition.

"As we unlock greater understanding of the genetic underpinnings of schizophrenia, we could one day move toward a future in which genetic risk factors can be used to individualize treatment approaches for patients."

More information: Genome-wide tandem repeat expansions contribute to schizophrenia risk, *Molecular Psychiatry* (2022). www.nature.com/articles/s41380-022-01575-x

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