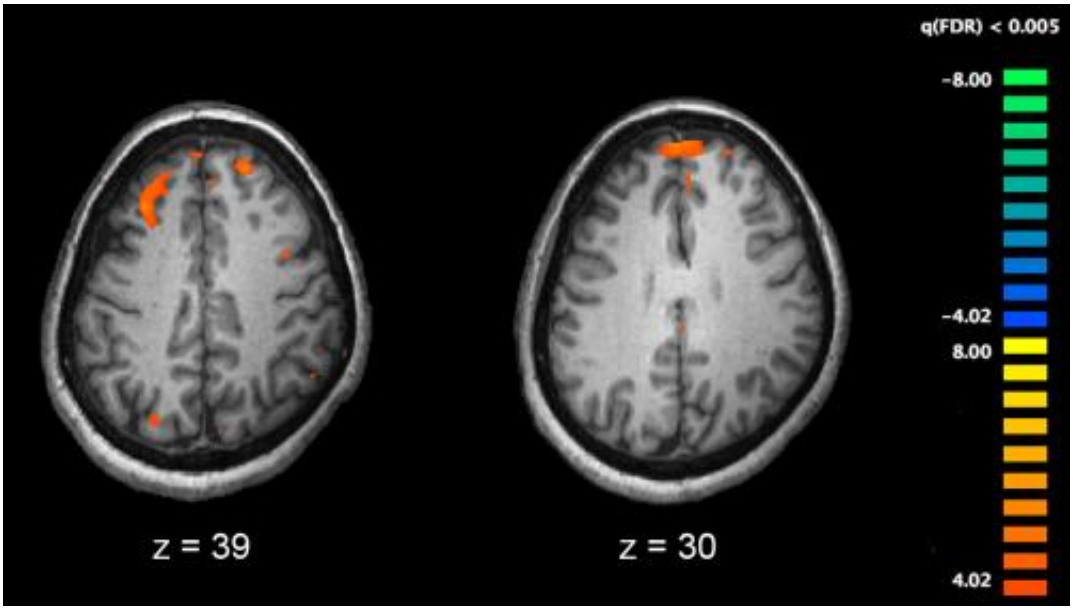
New genetic mutations shed light on schizophrenia

January 22 2014, by Veronica Meade-Kelly



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 from the Broad Institute and several partnering institutions have taken a closer look at the human genome to learn more about the genetic underpinnings of schizophrenia. In two studies published this week in Nature, scientists analyzed the exomes, or protein-coding

regions, of people with schizophrenia and their healthy counterparts, pinpointing the sites of mutations and identifying patterns that reveal clues about the biology underlying the disorder.

One study compared gene sequences from 2,500 people with schizophrenia to 2,500 healthy individuals from the same population. The second study looked for new mutations that might have occurred in protein coding genes by examining gene sequences from more than 600 schizophrenia trios (individuals with the disorder and their unaffected mothers and fathers). Both studies yielded further evidence that the disorder arises from the combined effects of many genes – a condition known as "polygenicity." The studies also suggest that genetic alterations tended to cluster in a few networks of functionally-related genes.

Schizophrenia, a psychiatric disorder often characterized by hallucinations, paranoia, and a breakdown of thought processes, is known to be highly heritable. It affects roughly 1 percent of all adults, and individuals with immediate relatives who suffer from the disorder are at approximately ten times greater risk. While this high rate of heritability has long been recognized, previous genetic studies have struggled to identify specific genes that cause schizophrenia.

The two current studies, which are the largest of their kind to date, looked for mutations that were effectively invisible in previous studies: they detected changes at the scale of single nucleotides – substitutions, insertions, or deletions of individual bases or "letters" in the genetic code.

"Despite the considerable sample sizes, no individual gene could be unambiguously implicated in either study. Taken as a group, however, genes involved in neural function and development showed greater rates of disruptive mutations in patients," explained Broad senior associate member Shaun Purcell, who played key roles in both studies. "That

finding is sobering but also revealing: it suggests that many genes underlie risk for schizophrenia and so any two patients are unlikely to share the same profile of risk genes."

Purcell, who is also a research scientist at Massachusetts General Hospital (MGH) and an associate professor of psychiatry at Mount Sinai's Icahn School of Medicine, served as first author of one of the papers (Purcell et al.), which compared the exomes of individuals with schizophrenia with those from healthy individuals from the same population in Sweden. The researchers involved in the work hailed from nine institutions, including the Broad, Mount Sinai, and MGH.

The second paper (Fromer et al.) reported similar findings. That study, which was conducted by a multi-institutional collaboration that included the Broad Institute's Stanley Center for Psychiatric Research, Mount Sinai, Cardiff University, the Wellcome Trust Sanger Institute, and six other research institutions, looked for de novo mutations – alterations in an offspring's genome that do not exist in the genomes of the parents, and therefore cannot be attributed to heredity. Such mutations account for roughly 5 percent of schizophrenia cases.

Both studies found that mutations were distributed across many genes, and the research teams discovered similar patterns in the distribution of mutations across gene networks. Many of the genes that bore mutations shared common functions: they tended to be part of gene networks that govern synaptic function, including the voltage-gated calcium ion channel, which is involved in signaling between cells in the brain, and the cytoskeletal (ARC) protein complex, which plays a role in synaptic plasticity, a function essential to learning and memory.

"From a scientific standpoint, it's reassuring to see different methods of studying the genetics of schizophrenia converge on the same sets of genes. These varied approaches are pointing toward the same underlying

biology, which can be followed up in future research," said Steven McCarroll, who was an author on both papers. McCarroll is director of genetics for the Broad's Stanley Center for Psychiatric Research and a professor in genetics at Harvard Medical School.

The analysis of de novo mutations also revealed significant overlap between those found in schizophrenia and de novo mutations previously linked to autism and intellectual disability, a finding that may influence the approach researchers take in follow-up studies.

The authors argue that both papers demonstrate that genome sequencing will continue to be a powerful tool in the study of schizophrenia, though many more samples will need to be sequenced before the genetics of this complex disorder can be fully understood.

"Few facts have been firmly established about the molecular or cellular causes of schizophrenia, and that's because many traditional scientific approaches can't be used to study the disorder: you can't grow it in a dish, and there aren't very good animal models for it," McCarroll explained. "We think that genomes are the path out of the darkness, and that these studies and others like them will ultimately provide the molecular clues we will need to map out the pathophysiology of the disorder."

Stanley Center director Steven Hyman and Ed Scolnick, the Stanley Center's chief scientist, thanked the institutions that collaborated on the studies.

"The genetic analysis of schizophrenia is yielding remarkably promising results because scientists around the world have worked collaboratively for years to recruit and study the large number of patients and comparison subjects needed to pick out rare genetic variants associated schizophrenia against the staggeringly complex background genetic

variation that characterizes humanity. Phrases like 'finding needles in haystacks' do not begin to do justice to this shared global effort," Hyman said.

Scolnick emphasized that this collaboration is accelerating research that will ultimately benefit patients.

"The exome sequencing data in these papers together with ongoing whole-genome association studies in patients with schizophrenia are helping to unravel the pathogenesis of this devastating illness," Scolnick said. "This work is building a roadmap which will inexorably lead to better treatments for patients and families."

More information: Purcell et al. "A polygenic burden of rare disruptive mutations in schizophrenia." *Nature* DOI: 10.1038/nature12975 . dx.doi.org/10.1038/nature12975

Fromer et al. "De novo mutations in schizophrenia implicate synaptic networks." *Nature* DOI: 10.1038/nature12929 . dx.doi.org/10.1038/nature12929

Provided by Broad Institute of MIT and Harvard