Four new genetic diseases defined within schizophrenia

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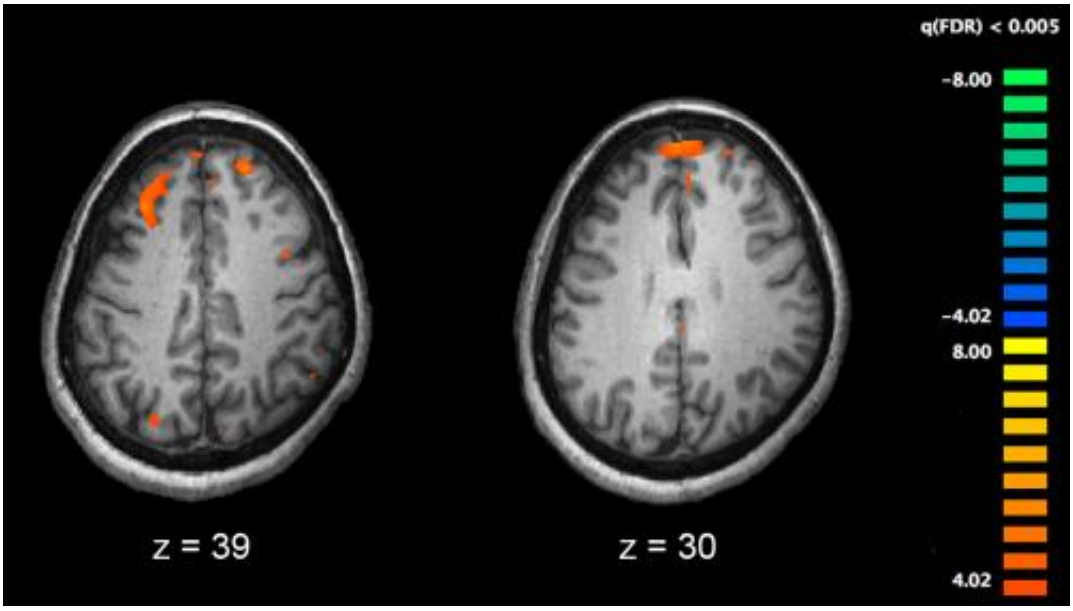

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown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

Changes in key genes clearly define four previously unknown conditions within the umbrella diagnosis of schizophrenia, according to a study led by researchers from NYU Langone Medical Center published online April 28 in *EBioMedicine*, a *Lancet* journal. Cases associated with

changes in each of the four genes were different from each other in terms of symptoms, intelligence level and other disease features.

Unlike "big data" genetic studies, which have loosely linked hundreds of genetic changes to schizophrenia but cannot explain varying symptoms, the new study revealed distinct disease versions that may affect large slices of patients and enable precision treatment design, say the authors.

"A common fallacy is that schizophrenia can be treated as a single disease," says NYU Langone psychiatrist and lead study author Dolores Malaspina, MD. "Our biologically driven study begins to answer longstanding questions in the field about why any two people diagnosed with schizophrenia may have drastically different symptoms. For the first time, we have defined four syndromes mechanistically.

"Perhaps as many as 30 percent of schizophrenic patients may now become candidates for more precise treatment based on the individual characteristics of these four genes, with the remaining cases becoming less mysterious as we pull these groups out of the mix," says Malaspina, the Anita Steckler and Joseph Steckler Professor in the Department of Psychiatry at NYU Langone. "Our approach provides a new framework for finding influential genes across complex genetic diseases associated with paternal age, from schizophrenia to autism."

Patients with schizophrenia struggle to interpret reality, typically suffering from hallucinations, learning disabilities, emotional withdrawal and lack of motivation. In the current study, researchers analyzed 48 ethnically diverse patients diagnosed with schizophrenia, looking at symptom sets in patients found to have rare or previously unknown changes in the DNA code of the four genes that disrupted brain function.

Key Genes Identified

The four influential genes now tied by the study to specific conditions are all involved in the growth or regulation of nerve circuits. They included PTPRG, which encodes a protein that enables nerve cells to connect as they form nerve networks. Patients with rare changes in this gene experienced earlier onset of relatively severe psychosis, and had a history of learning disabilities. Despite the high intelligence in some, they showed cognitive deficits in working memory, the "scratchpad" where the brain stores and processes temporary memories.

A second key gene, SLC39SA13, codes for a zinc transporter that helps nerve cells to "decide" whether or not nerve impulses are amplified of dampened. These cases showed widespread cognitive deficits, low educational attainment and the most severe deficits in emotion and motivation.

A third influential gene was ARMS/KIDINS220, which codes for a protein that regulates the growth of nerve cells. Patients who had changed versions of this gene showed early promise, often attending college, but then experienced cognitive decline consistent with a degenerative disease. The last gene of interest was TGM5, which encodes a protein that stabilizes protein groups. Related proteins have been linked to age-related degenerative conditions like Huntington's disease. TGM5 cases had less severe symptoms, but were more often diagnosed with attention deficit disorder during childhood.

"Our results argue that new treatments should - while addressing core psychoses - also focus on processing speed in TGM5 cases, working memory in PTPRG, zinc augmentation in SLC39A13, and nerve cell protection in patients with ARMS/KIDINS220 mutations," says first study author Thorsten Kranz, a postdoctoral fellow in the lab of NYU Langone neuroscientist Moses Chao, PhD. "Treatments that do not work for all patients may be highly effective in some."

A study published last year by the same team lay the foundation for the current *EBioMedicine* publication by defining the framework for finding influential genes. This study examined the genetic code of affected patients with schizophrenia and their healthy parents to identify newly occurring (sporadic) mutations that disrupted the four influential signaling genes in 31 percent of these patients.

In general, more than 70 percent of schizophrenia cases are sporadic versus familial - so many patients have variants of influential genes that have occurred in them for the first time. Malaspina's team was the first to show in a 2001 paper that the most important source of these rare, sporadic changes was the paternal germline (father's sperm), with advanced paternal age explaining over a quarter of the population risk for schizophrenia in an Israeli cohort. Sperm cells divide and multiply 600 times by the time a father reaches age 50. DNA is copied with each round of cell divisions, and copy errors accumulate as a father ages.

"Our combined findings to date argue that newly occurring mutations introduced via the father's germline in sporadic cases, when compared to healthy parents, represent a powerful tool for defining precise versions of schizophrenia," says Malaspina.

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