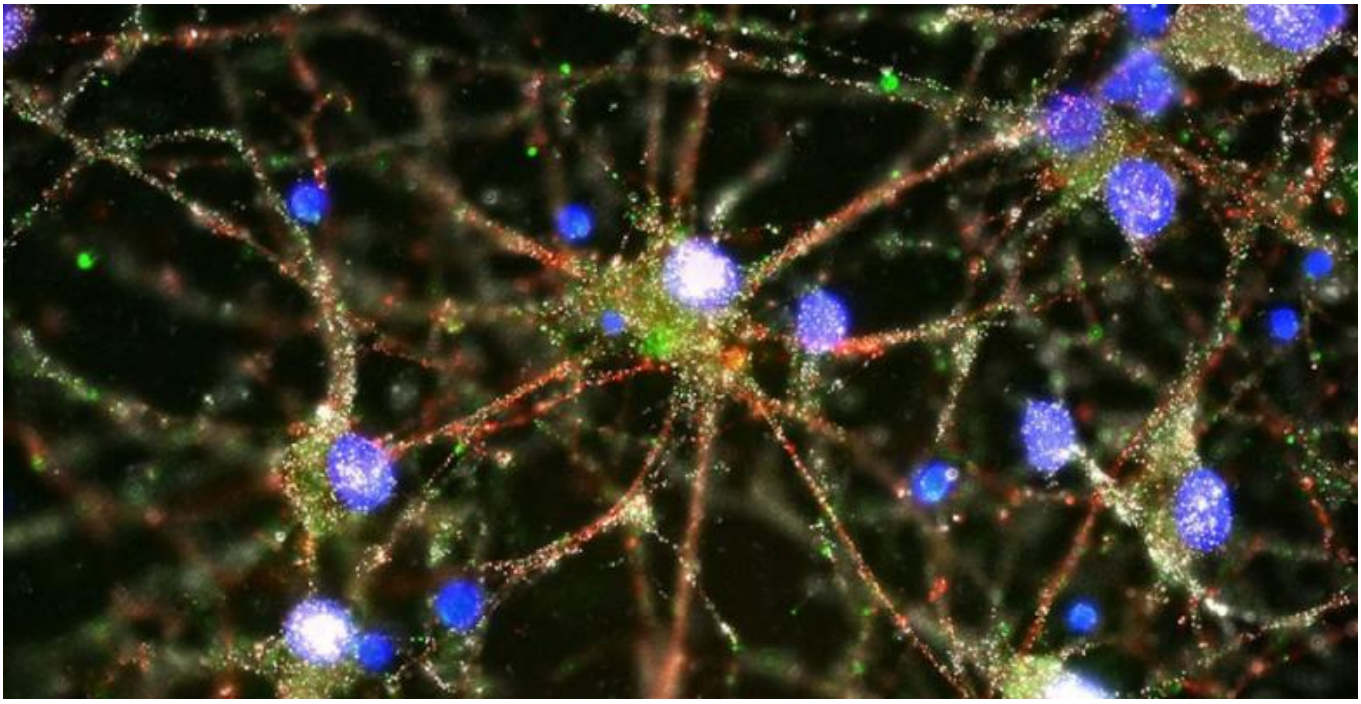
Immune system gene leads to schizophrenia clue

29/01/2016



“It’s not the answer, but it’s an answer,” says psychiatrist and neuroscientist Henry Nasrallah of Saint Louis University School of Medicine. The findings give scientists a clue that may help unravel more insights into how schizophrenia takes hold of the brain, he says.

The study is the first time scientists have been able to move from genetic studies to a biological insight into schizophrenia risk, says geneticist David Goldstein of Columbia University. “Genetics got us there,” he says. “That’s why this is a big deal.”

The research was sparked by genetic studies that identified a mammoth stretch of DNA on chromosome 6 as particularly suspicious. Called the major histocompatibility complex, or MHC, this DNA chunk carries information used by the immune system to help identify invaders. But why these genes were involved in schizophrenia was a mystery. “The MHC association in schizophrenia was considered an almost intractable problem in human genetics,” says study coauthor Steven McCarroll, a geneticist at Harvard Medical School and the Broad Institute.

New ways of analyzing genetic structure yielded an answer. It has to do with the snipping of connections called synapses between brain cells, McCarroll says. This process, called synaptic pruning, is in full swing during adolescence, a time when schizophrenia symptoms often first show up.

By looking at genetic material of more than 60,000 people with or without schizophrenia, McCarroll and colleagues pinpointed versions of a gene within the MHC called *complement component 4*, or *C4,* that elevate the risk of schizophrenia. About 1 percent of people get schizophrenia. For people with a version of the *C4* gene that leads to more C4 protein in the brain, the risk increases to 1.27 percent, the researchers calculate.

C4 protein is found on brain cells, often at synapses. In postmortem brains from people with schizophrenia, there were signs that the *C4* gene had been more active than in people without the disorder, the team found. Further experiments with mice showed that C4 helps control synaptic pruning. Synapses in the brains of mice that didn’t

have C4 weren't pruned effectively, the researchers found. That result hints that the opposite might be going on in people with schizophrenia: Too much C4 might cause excessive pruning. A surplus of synapse trimming, particularly during adolescence, could disrupt elaborate neural connections and lead to the scattered thinking and hallucinations that often come with schizophrenia.

Some scientists had suspected that synaptic pruning goes into overdrive in schizophrenia, Goldstein says. Postmortem brains showed a paucity of synapses, for instance. But this study is the "clearest, strongest evidence we have of synaptic pruning" being implicated in schizophrenia, Goldstein says.

Synaptic pruning may not be the only thing that matters for schizophrenia, Nasrallah cautions. A range of genetic and environmental influences could all contribute to the disorder. "There are so many different ways to become schizophrenic," he says. But studying the link between the gene and synaptic pruning may help pinpoint where and how those influences converge in the brain, he says.

Geneticist Dimitrios Avramopoulos of Johns Hopkins University says that while the evidence for C4-related pruning in schizophrenia is interesting, it's "not undisputable proof at this point." He says more work is needed to be confident that the results are solid.