Schizophrenia: Small genetic changes pose risk for disease

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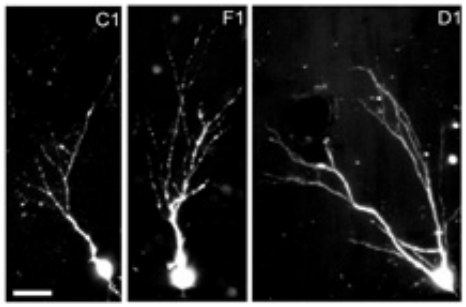

C1: A normal neuron. F1: A neuron with reduced FEZ1 levels. D1: A neuron with reduced DISC1 levels.

(Medical Xpress) -- Carrying single DNA letter changes from two different genes together may increase the risk of developing schizophrenia, Johns Hopkins researchers reported in the November 16 issue of *Neuron*.

Causes for psychiatric diseases like schizophrenia and autism have been difficult to pinpoint, since they may be triggered by many small genetic changes that alone may be insufficient, but in the right combination may cause disease.

Drastic DNA rearrangements in the genetic letters of the DISC1 gene are known to cause schizophrenia and other major mental disorders, however, these large changes are rare and do not apply to the majority of

people with schizophrenia. Nevertheless, DISC1 is thought to be an entry point for study into the cause of the disease, and defects in DISC1 combined with defects in other genes may contribute to disease.

"We studied the function of two proteins known to interact, FEZ1 and DISC1, in cells and animal models, which suggested that these proteins work together in adult brain development" says Guo-li Ming, M.D., Ph.D., professor of neurology and neuroscience and member of the Johns Hopkins Institute for Cell Engineering. "When we looked at the human genetic sequences of DISC1 and FEZ1, we found that a combination of small DNA changes raises risk for schizophrenia."

To determine if FEZ1 and DISC1 work together in adult brain development, the researchers used molecular biology techniques to reduce the amount of FEZ1 in the newborn neurons in mouse adult hippocampus, then examined the cells under a microscope. The neurons with less FEZ1 looked similar to cells with less DISC1; they were larger and had longer feelers that are used to reach out and communicate with other neurons nearby. The researchers proposed that these proteins may be working together in neurons to control cell size and feeler length, and when this process is disrupted, it may lead to psychiatric diseases.

Then, the researchers checked existing cases of schizophrenia to see if combinations of single-letter DNA changes in DISC1 and FEZ1 made people more susceptible to the disease. The researchers examined a large patient database, the Genetic Association Information Network, created by the National Institutes of Health to identify genome associated diseases. Using statistical approaches, the researchers examined four different single-letter DNA changes in the FEZ1 sequence from 1,351 schizophrenia cases and 1,378 healthy people. Single-letter DNA changes in FEZ1 alone did not contribute to schizophrenia risk. However, when the researchers looked at these four different FEZ1 DNA letter changes in combination with a DISC1 single DNA letter

change already known to slightly increase schizophrenia risk, they found that one particular FEZ1 DNA change along with the DISC1 change significantly increased the risk of schizophrenia by two and a half times.

“By continuing to examine interactions of key genes involved with disease in cells and correlating the results with patient databases, we can begin to unravel the genetic contributions of psychiatric disorders that previously were a mystery to us,” says Hongjun Song, Ph.D., professor of neurology and director of the Stem Cell Program at the Institute for Cell Engineering. “Finding sets of proteins, like FEZ1 and DISC1, that synergistically work together to cause disease will also give us new drug targets to develop new therapies.”

Provided by Johns Hopkins University