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Researchers piece together gene 'network' linked to schizophrenia

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Reporting this week in the Archives of General Psychiatry, researchers at the Johns Hopkins University School of Medicine have uncovered for the first time molecular circuitry associated with schizophrenia that links three previously known, yet unrelated proteins.

"This is very exciting because until now the many known genetic factors implicated in this condition were not connected in any way," says Akira Sawa, M.D., Ph.D., director of the program in molecular psychiatry and associate professor of psychiatry and neuroscience at Hopkins. "Now, through a cross-disciplinary and cross-departmental collaboration, we not only have figured out how these three proteins interact with each other, we also have found patients who carry mutations. These results give us a really good foundation to dig deeper into such an elusive condition."

Sawa's team previously had characterized the DISC1 gene and protein which are required for proper nervous system development, and when disrupted, significantly contribute to schizophrenia. His team also had shown that DISC1 protein binds to PCM1 protein at the centrosome, which coordinates the structure and movement of cells.

Separately, Hopkins geneticist and associate professor of ophthalmology Nicholas Katsanis, Ph.D., and his team were studying an unrelated family of proteins had discovered that one of them, BBS4, also is found near the centrosome and also binds to PCM1. "But we weren't thinking schizophrenia at the time because BBS4 is involved in Bardet-Biedl

Syndrome, which is a wide-ranging condition mainly known for its associated eye and and kidney problems but also does cause behavioral defects in some patients," says Katsanis.

It was Hopkins psychiatrist Nicola Cascella, M.D., co-director of the program in molecular psychiatry and assistant professor of psychiatry who, according to Sawa, "brought it all together" by realizing that the behavioral defects seen in Bardet-Biedl Syndrome patients and the molecular interaction of BBS4 and PCM1 could be related and relevant to schizophrenia.

"Serendipity brought us together from the far corners of campus and allowed us to see the links between these three proteins, centrosomes, and schizophrenia," says Katsanis. So they embarked on a collaboration to see if these coincidental observations would lead to a better understanding of schizophrenia.

First, to show that the three proteins do in fact physically interact with each other in a cell, the research teams attached different tags to each protein and followed the proteins in cells grown in the lab. They found that all three proteins do end up together, at the centrosome. When the researchers removed either DISC1 or BBS4 from cells, PCM1 would not make it to the centrosome, leading the researchers to conclude that DISC1 and BBS4 act together to recruit PCM1.

The researchers then asked if the failure of PCM1 recruitment to the centrosome in mice lacking either DISC1 or BBS4 affects brain development. To do this they reduced the amount of each of the three factors in the brains of developing mice. As a result, nerve cells in the cerebral cortex-the part of the brain responsible for memory and thought-failed to grow properly, suggesting that these three proteins act together synergistically during normal brain development.

The teams' next question was whether PCM1 could contribute to schizophrenia. By examining DNA from families with schizophrenia, the researchers discovered a mutation in PCM1 in one family, but only carried by family members who had been diagnosed with schizophrenia.

"This connection is exactly the sort of daisy chain from gene to disease that psychiatrists pray for," says Cascella. "This is a molecular pathway that we can potentially target for drug therapy."

"We are beginning to sub-stratify psychiatric illness into discrete molecular causes," adds Katsanis. "Now that we know that that a subset of schizophrenia is related to centrosomes and these associated proteins, we can start looking at broader questions of how people get psychiatric illness. We have a hook, now we can start fishing."

Source: Johns Hopkins Medical Institutions