# Why symptoms of schizophrenia emerge in young adulthood

February 26 2010

In reports of two new studies, researchers led by Johns Hopkins say they have identified the mechanisms rooted in two anatomical brain abnormalities that may explain the onset of schizophrenia and the reason symptoms don't develop until young adulthood. Both types of anatomical glitches are influenced by a gene known as DISC1, whose mutant form was first identified in a Scottish family with a strong history of schizophrenia and related mental disorders. The findings could lead to new ways to treat, prevent or modify the disorder or its symptoms.

In one of the studies, published in the March issue of Nature Neuroscience, researchers examined DISC1's role in forming connections between nerve cells. Numerous studies have suggested that schizophrenia results from abnormal connectivity. The fact that symptoms typically arise soon after adolescence, a time of massive reorganization of connections between nerve cells, supports this idea.

The scientists began their study by surveying rat nerve cells to see where DISC1 was most active. Unsurprisingly, they found the highest DISC1 activity in connections between nerve cells. To determine what DISC1 was doing in this location, the researchers used a technique called RNA interference to partially shut off DISC1 activity. Consequently, they saw a transient increase and eventual reduction in size and number of dendritic spines, spikes on nerve cells' branch-like extensions that receive input from other nerve cells.

To determine how DISC1 regulates dendritic spine formation, the

researchers studied which brain proteins interact with the protein expressed by the DISC1 gene. They identified one, called Kal-7, which earlier studies suggested is critical for proper dendritic spine formation. Further experiments suggested that the DISC1 protein acts as temporary holding place for Kal-7, binding it until it can be released to trigger a molecular cascade that results in dendritic spine formation.

Study leader Akira Sawa, M.D., Ph.D., professor of psychiatry and director of the program in molecular psychiatry at the Johns Hopkins University School of Medicine, says it is becoming clear that having a defective DISC1 gene might lead to an abnormally small number and size of dendritic spines, which could lead nerve cells to maintain weaker connections with unusually low numbers of neighboring neurons. Such abnormal connectivity has long been seen in autopsied brains from schizophrenia patients.

"Connections between neurons are constantly being made and broken throughout life, with a massive amount of broken connections, or 'pruning,' happening in adolescence," Sawa says. "If this pruning doesn't happen correctly, it may be one reason for the pathogenesis of schizophrenia," he adds.

In the second study, published in the Feb. 25 issue of *Neuron*, Sawa's team generated a new animal model of schizophrenia by temporarily shutting off the DISC1 gene in mice in the prefrontal cortex, a brain area known to differ in schizophrenic people. The new model allowed them to study other roles for DISC1 in the brain.

The researchers created their novel model by, again, using RNA interference. They injected short pieces of the nucleic acid RNA engineered to shut off the DISC1 gene into cavities in the developing brains of mouse fetuses two weeks after conception. Tests showed that these snippets of RNA migrated into cells in the prefrontal cortex, part

of the brain located near the forehead.

This shutoff was temporary, with the gene's function fully restored within three weeks, or about a couple of weeks after birth. At various times after the gene was reactivated, the scientists examined the animals' brains and behavior, looking for differences from normal mice.

Sawa's team found that in the DISC1 shutoff group, nerve cells in the prefrontal cortex that produce dopamine, one of the chemical signals that nerve cells use to communicate, were markedly immature as the animals entered adolescence. Furthermore, the animals showed signs of a deficit of interneurons, nerve cells that connect other neurons in neural pathways.

They also found several behavioral differences between these mice compared to normal mice as the animals entered adolescence. For example, those in the shutoff group reacted more strongly to stimulants, displaying more locomotion than normal mice. Interestingly, these effects were somewhat mitigated when the researchers gave the animals clozapine, a drug used to treat schizophrenia.

Taken together, Sawa says, results of both studies suggest that these anatomical differences, which seem to be influenced by the DISC1 gene, cause problems that start before birth but surface only in young adulthood.

"If we can learn more about the cascade of events that lead to these anatomical differences, we may eventually be able to alter the course of schizophrenia. During adolescence, we may be able to intervene to prevent or lessen symptoms," Sawa says.

Provided by Johns Hopkins Medical Institutions