Scientists identify age-associated defects in schizophrenia

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The underlying causes of the debilitating psychiatric disorder schizophrenia remain poorly understood. In a new study published online in *Genome Research* March 2, 2010, however, scientists report that a powerful gene network analysis has revealed surprising new insights into how gene regulation and age play a role in schizophrenia.

Researchers are actively working to identify the direct cause of schizophrenia, likely rooted in interactions between genes and the environment resulting in abnormal gene expression in the central nervous system. Scientists have been studying expression changes in schizophrenia on an individual gene basis, yet this strategy has explained only a portion of the genetic risk.

In the new work, a team of researchers led by Associate Professor Elizabeth Thomas of The Scripps Research Institute has taken a novel approach to this problem, performing a gene network-based analysis that revealed surprising insight into schizophrenia development.

The group analyzed gene expression data from the prefrontal cortex, a region of the brain associated with schizophrenia, sampled post-mortem from normal individuals and schizophrenia patients ranging from 19 to 81 years old. However, instead of just looking at genes individually, Thomas and colleagues at the Scripps Translational Science Institute, Nicholas Schork and Ali Torkamani, considered interactions between genes, as well as groups of genes that showed similar patterns of expression, to identify dysfunctional cellular pathways in schizophrenia.

"Once gene co-expression networks are identified," said Thomas, "we can then ask how they are affected by factors such as age or drug treatment, or if they are associated with particular cell types in the brain."

The gene network analysis suggested that normal individuals and schizophrenia patients have an unexpectedly similar connectivity between genes, but the most surprising finding was a significant link between aging and gene expression patterns in schizophrenia. The team identified several groups of co-expressed genes that behaved differently in schizophrenia patients compared to normal subjects when age was considered.

A particularly striking age-related difference in co-expression was found in a group of 30 genes related to developmental processes of the nervous system. Normally these genes are turned off as a person ages, but in schizophrenia patients the genes remain active. This critical finding strongly suggests that age-related aberrant regulation of genes important for development can explain at least part of the manifestation of schizophrenia.

Thomas explained that these findings help to refine the developmental hypothesis of schizophrenia, which states that one or more pathogenic "triggers" occur during critical periods of development to increase risk of the disease. Specifically, this work indicates that abnormal gene expression in developmentally related genes might be a significant pathogenic trigger, occurring over a broader time-scale than expected.

"Rather than a pathological trigger occurring at a critical developmental time point," said Thomas, "the trigger is ongoing throughout development and aging."

Furthermore, Thomas noted that the new study supports early intervention and treatment of schizophrenia. Treatment approaches aimed at averting gene expression changes and altering the course of the disease could be specifically tailored to the age of the patient.

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