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Common gene version optimizes thinking -- but with a possible downside

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Most people inherit a version of a gene that optimizes their brain's thinking circuitry, yet also appears to increase risk for schizophrenia, a severe mental illness marked by impaired thinking, scientists at the National Institutes of Health's (NIH) National Institute of Mental Health (NIMH) have discovered. The seeming paradox emerged from the first study to explore the effects of variation in the human gene for a brain master switch, DARPP-32.

The researchers identified a common version of the gene and showed how it impacts the way two key brain regions exchange information, affecting a range of functions from general intelligence to attention.

Three fourths of subjects studied had at least one copy of the version that results in more efficient filtering of information processed by the brain's executive hub, the prefrontal cortex. However, the same version was also more prevalent among people who developed schizophrenia, a severe mental illness marked by delusions, hallucinations and impaired emotion that affects one percent of the population.

"We have found that DARPP-32 shapes and controls a circuit coursing between the human striatum and prefrontal cortex that affects key brain functions implicated in schizophrenia, such as motivation, working memory and reward related learning," explained Andreas Meyer-Lindenberg, M.D.

"Our results raise the question of whether a gene variant favored by

evolution, that would normally confer advantage, may translate into a disadvantage if the prefrontal cortex is impaired, as in schizophrenia," added Daniel Weinberger, M.D. "Normally, enhanced cortex connectivity with the striatum would provide increased flexibility, working memory capacity and executive control. But if other genes and environmental events conspire to render the cortex incapable of handling such information, it could backfire -- resulting in the neural equivalent of a superhighway to a dead-end."

Meyer-Lindenberg, Weinberger and colleagues in the NIMH Genes, Cognition and Psychosis program report their results in the February 9, 2007 issue of the *Journal of Clinical Investigation*.

Previous studies in animals over two decades, most notably by Nobel Laureate and NIMH grantee Paul Greengard, M.D., Rockefeller University, had established that DARPP-32 in the striatum switches streams of information from multiple brain chemical systems for processing by the cortex. Both the neurotransmitter that it works through, dopamine, and the chromosomal site of its gene have been implicated in schizophrenia.

"Although several groups have looked for possible clinical relevance of DARPP-32, they have not met with great success," noted Greengard. "This study shows a strong connection between this molecule and human cognition -- and perhaps with schizophrenia."

"These first glimpses of DARPP-32 at work in the living human brain build on a quarter century of investigations by Greengard's team that ultimately linked this pivotal protein to depression and substance abuse as well as to schizophrenia," added NIMH Director Thomas Insel, M.D.

To understand DARPP-32's role in the human brain, the NIMH researchers used genetic, structural and functional magnetic resonance

imaging, and post-mortem techniques to identify the human gene's variants and their functional consequences. Seventy five percent of subjects had the most common version of the gene, which boosted circuit activation, structural and functional connectivity and performance on thinking tasks, likely by increasing gene expression. In 257 affected families, people with schizophrenia were more likely to have this common version of the DARPP-32 gene.

Source: NIH/National Institute of Mental Health