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Schizophrenia as Misstep by Giant Gene

By [NICHOLAS WADE](#)

Researchers have made progress in understanding how a variant gene linked to [schizophrenia](#) may exert its influence in the brain. The findings are tentative but, if confirmed, could yield deep insights into the biological basis of the disease.

The gene, called neuregulin-1, was first implicated in schizophrenia in 2002 by DeCode [Genetics](#), a Reykjavik company that looks for the genetic roots of common diseases in the Icelandic population.

But how the variant form of the gene contributed to the disease was far from clear, in part because even the normal gene's function is far from understood. A team led by Amanda J. Law of the University of Oxford in England and Daniel R. Weinberger of the National Institutes of Health has now developed clues as to how the gene may go wrong.

Neuregulin is one of about 10 genes so far linked to schizophrenia. It plays many different roles in the brain, some concerned with synapses, the interconnections between neurons, so derangements of its function are a plausible source of schizophrenia. It is a long road, however, from knowing a variant gene is linked with a disease to understanding the biology of how the disease is caused.

The problem is particularly daunting with neuregulin. It is one of the largest genes in the human genome, sprawling over some 1,125,000 units of DNA, and it generates at least six types of protein through a procedure known as alternative splicing, in which different components of the gene are mixed and matched so that each set specifies a different protein.

Adding to the complexity, the variant stretch of DNA that DeCode linked to schizophrenia does not lie in the neuregulin gene itself but just upstream of it, meaning that it presumably affects not the actual proteins produced by the gene but the way the gene is controlled.

The activity of genes is governed by transcription factors, which bind to specific sequences of DNA units that lie close to the gene. Alteration of these sequences may cause the transcription factors to bind incorrectly and thus impair the proper expression of the gene.

Dr. Weinberger has tested this idea by analyzing the activity of the gene in a large collection of brain samples from schizophrenic patients. The tissue was frozen shortly after the patients died.

Recently he showed that one protein is produced in larger amounts in the prefrontal cortex of schizophrenic patients. But there were reasons for thinking that this protein, the first of neuregulin's six types, might be an effect of schizophrenia rather than its cause.

Dr. Weinberger and Dr. Law have now studied the hippocampus, the region of the brain where initial memories of faces and places are formed and which, like the prefrontal cortex, is affected in schizophrenia. In contrast to their previous analyses, this time they concentrated on Type 4 proteins, which were discovered by DeCode two years ago and seem more likely to play a causative role.

The reason is that the first component of the transcript that makes the Type 4 proteins lies at the very beginning of the neuregulin gene and closest to the upstream genetic segment that is statistically linked to schizophrenia.

The researchers found that people who inherited two versions of the variant segment, one from each parent, were producing 50 percent more of neuregulin's Type 4 protein than those who inherited one or no copies.

This suggests, though does not prove, that the production rate of Type 4 proteins is the mechanism through which the neuregulin gene contributes to schizophrenia.

"This is a wonderful insight into the underlying molecular mechanism of this gene," Dr. Law said. "The field will now move to trying to understand the biology of this change on brain and behavior." She and her colleagues report their findings in today's issue of The Proceedings of the National Academy of Sciences.

The role of neuregulin's Type 4 proteins is unknown, but they may be involved in making neurons migrate, a property of great importance when the brain is being constructed.

Dr. Law said that the variant segment linked to schizophrenia had a single DNA unit change at the center of one of the binding sites recognized by the transcription factors that control the gene. Loss of the binding site presumably upsets the regulation of the gene, causing too much of the Type 4 protein to be generated, she said.

Having slightly more than usual of a single protein may seem a very subtle derangement for so devastating a disease, but subtlety is to be expected, Dr. Weinberger said. "We know that all mental illnesses are about very subtle aspects of the wiring biases. They are about how you process complicated environmental stimuli, not about how you walk down the street."

Dr. Kari Stefansson, a neurologist and DeCode's chief executive, noted it was extremely hard to get enough schizophrenic brain samples for good statistical analysis but, given that constraint, the new finding was promising and "remarkable if true."

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