

The Genome Era and Mental Illness

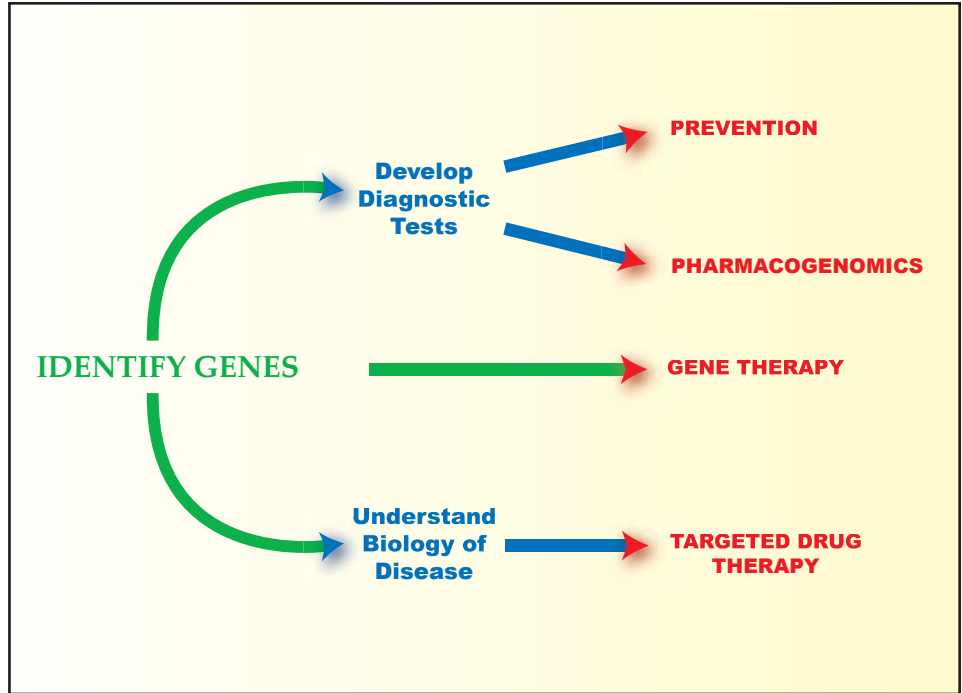
by Francis S. Collins, M.D., Ph.D.

The successful completion of the Human Genome Project on April 14, 2003, marked the end of scientists' monumental effort to sequence the three billion DNA "letters" in the human genetic blueprint. However, for the millions of people suffering from mental illness, April 14, 2003, represents more of a beginning—the dawning of the genome era in medicine.

Just as an architectural blueprint makes it easier for engineers to analyze problems and make repairs to a building, the human genetic blueprint will speed researchers' efforts to understand the biological pathways involved in mental illness and to develop better methods of diagnosis and treatment. Until recently, scientists studying mental illness have concentrated on a few hundred genes, mainly those that encode neurotransmitters and their receptors. However, that focus is now expanding, due in part to a recent analysis of the mouse genome sequence that found that an amazing number of genes—nearly 16,500—are active in the mammalian brain.

Already, the genome era is generating new discoveries. Mapping and sequencing data from the Human Genome Project have accelerated the identification of genes involved in relatively rare, single-gene disorders, some of which are providing new insights into more common conditions. The bad news, however, is that there are no single-gene models for the most common forms of mental illness. Instead, most mental illnesses fall into the category of complex genetic disorders, which includes many other common diseases such as cancer, diabetes, and heart disease. The risk of developing these conditions is thought to be influenced by a mix of factors that may include one or more genes, lifestyle factors, and environmental factors ranging from viral infections to stress.

To identify the genetic roots of complex



Gene discovery provides a range of ways to prevent and treat disease.

disorders, the National Human Genome Research Institute recently tapped into the power of genome data and technology to launch the International HapMap Project. During the next several years, an international consortium plans to build a

Even with this map, piecing together the complicated genetic puzzle of all mental illnesses will likely take many years. Scientists, however, have already begun to uncover genetic clues to some of the more common conditions, including

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catalogue of human genetic variations and determine how these variations are organized into neighborhoods, or haplotypes, along the human chromosomes. This map will serve as a tool for researchers trying to discover the common genetic variations associated with complex diseases, as well as variations responsible for differences in drug response.

schizophrenia, depression, bipolar disorder, and panic disorder. For example, in the past year alone, two teams studying large populations in Iceland and Scotland have linked increased risk of schizophrenia to a certain variant of a gene that carries the instructions for neuregulin 1, a protein involved in brain development.

Of course, it is not enough to discover



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the genes involved in mental illness—our newfound understanding must be moved into the clinic, where it can benefit people struggling with these conditions. The identification of a gene or set of genes involved in disease represents just the first step in what may be a long road toward better diagnostic tests, drug therapies, and prevention strategies (see Figure 1).

For people affected by mental illness, some of the first benefits of the genome era are likely to be in the way drugs are prescribed. Rather than the current trial-and-error method of figuring out which medications work best for a patient, doctors will be able to examine each person's genomic information to predict which drug will be most effective and produce the fewest side effects for that individual. Research in this rapidly emerging field, called pharmacogenomics, has already identified genetic variations that influence responses to antipsychotics and antidepressants. In the long run, genome-based research will play a dominant role in the development of new drugs for mental illnesses, enabling researchers to design more powerful, yet less toxic, compounds targeted at specific biological pathways.

Clearly, the genome era holds tremendous promise for improving the outlook for all those whose lives have been shaken by mental illness. At the same time, our society must take steps to ensure that people are not discriminated against based on their genetic predisposition to mental illness or any other medical condition. Congress is now

considering legislation that will outlaw such discrimination in health insurance and the workplace. With such protections firmly in place, genomic research will help to ease the societal stigma many people still face by providing more precise methods of diagnosing mental illness and by furnishing conclusive evidence of the biological roots of such conditions.

In the same way that antibiotics revolutionized the treatment of infectious diseases in the 20th century, genome research stands ready to revolutionize the treatment of mental illness in the 21st century. But we in the biomedical research community cannot do this alone. We need the support of all those who have fought so hard over the years to raise awareness of mental illness and help the millions struggling with these conditions. Working together, we can build the bridge between today's dreams and tomorrow's reality.

Additional Reading

W. M. Cowan, K.L. Kopkinsky, and S.E. Hyman, "The Human Genome Project and Its Impact on Psychiatry," *Annual Review of Neuroscience* 2002, 25: 1–50.

T.R. Insel and F.S. Collins, "Psychiatry in the Genomics Era," *The American Journal of Psychiatry*, 160: 616–620, 2003.

Francis S. Collins, M.D., Ph.D., is Director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health. He oversees the Human Genome Project, an international, multidisciplinary enterprise that completed mapping of the human genome sequence in April 2003. Building upon that success, Dr. Collins is leading NHGRI's effort to use genomic knowledge to improve human health. His lab is currently searching for genes that contribute to type II diabetes. Dr. Collins' previous research led to the identification of genes responsible for progeria, cystic fibrosis, neurofibromatosis, and Huntington's disease.