Introduction

Mental Disorders in the Genomics Era

By Francis J. McMahon, MD

The Genomics Era in medicine began in early 2001 with the publication of a draft of the human genome sequence. We use the label "Genomics Era" since, for the first time, we have a complete roadmap of our entire genome. This roadmap is helping to guide us toward new approaches to the diagnosis and treatment of a host of disorders ranging from Alzheimer's disease to deafness. The finished sequence is still years away and the complete annotation of all functionally relevant stretches of the DNA sequence will take even longer. But we are already beginning to ask the questions: how will the study of psychiatric diseases progress in the Genomics Era? How can we begin to address the complex ways in which genes interact with environment to produce mental illness? When will the fruits of genomic research affect the diagnosis and treatment of mental illnesses such as bipolar disorder? In this month's issue of *CNS Spectrums*, we have assembled a group of papers aimed at addressing these questions.

In the first article, Lange and McInnis review the controversial issue of anticipation in mental illness. Many psychiatric illnesses display the drop in age at onset and an increase in severity of illness across successive generations that are the key features of anticipation. At least eight modern studies in bipolar disorder alone, have addressed the issue of anticipation, and all eight conclude that a significant decrease in age at onset, a significant increase in illness severity (usually measured as frequency of manic and depressive episodes), or both occurs within families containing multiple cases of bipolar disorder. The key question is not whether anticipation occurs, but what it means. Is the observed anticipation merely an artifact of subtle ascertainment biases? We now know that anticipation is not always an illusion, but sometimes reflects an important underlying molecular event, and expansion of repetitive DNA sequences. Anticipation in psychiatric illness is intriguing because it raises the possibility that similar molecular events may be at work, and points to specific molecular genetic strategies that can be applied to answer the question experimentally. Lange and McInnis wisely conclude that no one factor will likely explain anticipation in bipolar disorder, and they suggest that the issue will benefit from a reconsideration once we have some susceptibility genes in hand.

Epigenetics, the study of heritable but dynamic phenomena that regulate gene activity, occupies a spot firmly in the center of the old "nature versus nurture" debate, demonstrating the false dichotomy that debate embodies. Epigenetics encompasses several variables that were traditionally grouped under the set "environment," such as parental origin, as well as many events that occur within the organism, such as imprinting, tissue- and time-dependent variation in gene expression, and related phenomena. Petronis and colleagues apply the concepts of epigenetics to the disparate findings implicating chromosome 22 in psychotic illnesses. They show that the existing data, while at first glance discrepant, become much more coherent when put into an epigenetic context.

Their review persuasively supports the idea that traditional methods of genetic investigation are significantly complemented and enhanced when informed by epigenetic strategies. This makes intuitive sense: the effects of susceptibility genes for mental illness might well be muted or exaggerated depending on the epigenetic context in which they exist.

Next, Kelsoe and colleagues take us into the burgeoning field of functional genomics, which distinguishes itself from traditional genetic approaches by a focus on the dynamic variation in gene expression that occurs in response to nongenetic events, such as drug treatment. They outline a "convergent functional genetics approach" to mapping genes underlying mental illness. This approach considers the results of traditional linkage or association studies, which can be fraught with false positive findings, in the light of gene expression studies that measure changes in gene function in animals following exposure to selected pharmacologic agents. By jointly considering the results of both of these rather independent kinds of studies, it is anticipated that false positive findings will fall away while true positive findings will be enhanced by knowledge about location and function. These kinds of approaches will be increasingly important as we seek to identify all of the genes that play an etiologic role in mental illness or that influence treatment response and toxicity.

The papers gathered here illustrate the ways in which psychiatric genetics continues to develop in the Genomics Era. The core methods of family, twin, linkage, and association studies are increasingly complemented by novel methods based on new concepts of dynamic mutation, epigenetics, and functional genomics. One of my introductory questions (When will the fruits of genomic research affect the diagnosis and treatment of mental illnesses?) must remain unanswered for now. The fruits of the Genomics Era do not necessarily hang low, particularly when it comes to the complex genetics of mental illness, but coherence is beginning to emerge. This month's articles help light the way, even though the destination is uncertain.

In the future, genetic findings may form the basis for many new treatments in psychiatry. For now, we are forced to make the most of the existing pharmacologic armamentarium. This has been enriched in recent years by the addition of atypical antipsychotics and novel anticonvulsants. Finally, Kahn and Chaplan review mood stabilizers currently in use or soon to be released for general use, asking whether any are "good enough" for the task of preventing and treating episodes of mania and depression over time. They conclude that no single ideal mood stabilizer exists, but that the skillful and judicious use of multiple complementary medications often yields the best results. This conclusion highlights a conundrum in psychiatry that genetic findings may ultimately allow us to move beyond: why should several medications with radically different apparent modes of action all possess mood stabilizing properties? CNS

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