Psychiatry and molecular genetics: A paradigm shift

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The late 20th century is witnessing an explosion of biomedical knowledge in the discipline of molecular genetics. In this regard many medical specialties will be transformed in terms of diagnosis and treatment. The technology and the recent clinical research in psychiatry is one of these.

Introduction

A young man, oldest of 2 siblings, was admitted to the hospital at the age of 16 with a history of command hallucinations, paranoid ideation and agitated behavior. Some years later, his sister, who was 19-years-old, was admitted for treatment of hallucinations. One of their parents had been hospitalized with a psychiatric illness. Though their diagnosis of schizoaffective disorder has not been a part of recent genetic studies, in all probability Deoxyribonucleic acid (DNA) technology will be used in the coming century to define this illness.

This article will outline the interface of DNA technologies with psychiatric disorders, review some of the chromosomal findings in specific psychiatric diagnoses and discuss perspectives on organizing the increasing amount of DNA studies directly or indirectly involved in the practice of psychiatry. Numerous authors have noted various aspects of the use of DNA technology in psychiatry[1,2,3,4], but have not emphasized what appears to us to be a marked shift in the paradigm.

Psychiatry has witnessed many shifts in paradigm over the years — from "mind" to "community" and finally to "brain." These changing conceptional models have been well noted by Eisenberg[5], Lipowski[6], and Andreasen[7]. Post World War II psychiatry in the United States was dominated by psychoanalytic theories. Although Grinker[8] noted in 1963 that psychiatry was riding madly in all directions, academic psychiatry was focused on the "mind" and its exploration through psychoanalysis. In the same year, a federal government initiative created "community" psychiatry, which divided the nation into geographical catchment areas, where mental health clinics were established to treat ambulatory psychiatric patients. Around this time, the dopamine hypothesis of schizophrenia appeared. Hence, reflected in the psychiatric literature of the past 3 decades, the paradigms of "troubled mind," "catchment" areas, and a "broken brain" have appeared.

We suggest that the arena of investigation has shifted to "faulty genes." This represents a reconceptualization of the pre-Freudian 19th century focus of psychiatry, the "cell," but at a level of molecular sophistication unimagined before the advent of the electron microscope, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and now the various DNA technologies.

Background

Within the past 45 years, the discoveries in molecular genetics have focused research of disease processes down to the gene level, with the isolation of single factors of inheritance. Molecular genetics emerged in 1953 with the revolutionary discovery by Watson and Crick[9]. They identified the double helical DNA molecule, a sequence of 2 polynucleotide chains responsible for carrying all the genetic information transmitted from generation to generation.

Isolation of specific sequences of DNA was made possible with the discovery of "restriction" endonucleases. These bacterial enzymes recognize and fragment the DNA at specific base sequences, producing specific fragment lengths of DNA. These fragments were first isolated by Gilbert and Sanger in 1975, leading to the probability of the determination of the entire human genome.

Recombinant DNA techniques allow the study of DNA segments on a large scale and with great rapidity. With the recent development of the polymerase chain reaction (PCR) technique (1988), specific segments of DNA can be isolated and replicated to over 1 million copies in a few hours. Resultant DNA segments act as probes, used to isolate complementary fragments of DNA from an individual's entire genetic makeup.

By the method of PCR, the specific sequence of DNA is tagged by short DNA segments of known sequence. These segments act as primers in the process of copying the DNA. The DNA is first heated, denaturing it to form single strands. Then, complementary sequences are added to the primer in the solution, along with DNA polymerase and proper bases for DNA formation. The entire solution is then cooled to the proper temperature which allows the primer to anneal to its complementary sequence. This primer, with the DNA polymerase enzyme, initiates the extension of complementary bases, leading to the formation of the specific DNA of inter-

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est. The result is 2 newly formed DNA segments which are complementary to the 2 original strands of DNA, doubling the total amount of DNA. This process repeats in a cyclical fashion of heating, then cooling the DNA, doubling the total amount of DNA with each cycle.

Edwin Southern in 1975[10] standardized the method of DNA analysis by his "Southern Blot" technique. DNA prepared for analysis was first fragmented by restriction endonucleases, then separated by molecular weight through agarose gel blocks, which allowed no movement of the DNA fragments. The DNA was then denatured to single-strand form. The Southern Blot technique then transferred the DNA from the agarose gel to nitrocellulose paper which held the DNA firmly in place. During the transfer, the nitrocellulose paper lay directly over the gel and was then stacked under layers of blotting paper. Thus, water and DNA were sucked up and lifted from the gel onto the nitrocellulose paper. A radioactively labeled DNA probe exposed to this DNA may now hybridize to its complementary DNA sequence, resulting in the marking of a specific DNA fragment by autoradiography.

Refined techniques and standardization of DNA analysis led to the discovery of consistent abnormalities in the patterns of hybridization. Evidence has shown that, in the DNA of some individuals, use of identical restriction endonucleases and probes generated consistent DNA fragment lengths variable from the norm. This led to the proposal of Restriction Fragment Length Polymorphisms (RFLPs), where alteration to the DNA sequence changed the restriction site and prevented cleavage of the DNA at the usual site. The resultant DNA fragment generated is altered in molecular weight, migrates at a different rate on electrophoresis, and is localized at an alternative position when hybridized with the radioactive probe. The RFLPs have been used more specifically as genetic markers where unique DNA fragments are inherited following simple Mendelian genetic laws. RFLPs may, therefore, represent DNA sequences either adjacent to or specific for a gene linked to a given disorder (character gene).

The formation of linkage studies comes from the theory that RFLPs represent DNA sequences to the character gene. The basis of the study assumes that the closer the approximation of the 2 genes on a chromosome, the more likely those 2 genes will be inherited together. Pedigree studies offer the classical methods of linkage, where the transmission of 2 genes is traced through a minimum of 3 successive generations. By measuring genetic makeup of these 2 genes in each member of the 3 generations, the frequency of recombination between the 2 genes can be calculated, estimating the distance between the 2 genes. In 1955, Morton[11] developed the logarithm of the odds (LOD) score method of linkage analysis. LOD scores can be calculated after 2 generations. It assumes a series of theoretical recombination frequencies.

This revolution in molecular genetics has greatly affected the study of disease. Specific RFLPs have been directly associated with major diseases and have been shown to follow simple Mendelian genetic patterns of inheritance. In 1983 Huntington's disease, an autosomal dominant condition, was linked to an RFLP localized to site G8 on Chromosome 4[12]. RFLP studies in psychiatry have recently included some controversies. There are, however, an estimated 30,000 of the 100,000 human genes that involve the brain. Presently some 500 of these brain genes are known, putting psychiatry in a position to have an exploding base of knowledge as work proceeds on the human genome project in the coming decades.

Findings

The well-established clustering of psychiatric illnesses in families has strongly suggested a genetic transmission for these disorders. The mode of inheritance, however, does not seem to be simple; genetic heterogeneity, incomplete penetrance and variable expression have been proposed as etiology.

In the late 1980s, RFLP studies showing linkage in bipolar disorder and schizophrenia promised an exciting diagnostic future involving the genetics laboratory in psychiatry. Egeland and colleagues[13] studied the old-order Amish population and found linkages between bipolar disorder and chromosome 11 p loci[14]. However, a reanalysis of the same cohort by Kelsoe et al showed a decreased LOD score, and they have recently reported that the original finding was a "false positive" result[15].

Similarly, the exciting finding reported by Sherrington et al in schizophrenia (chromosome 5 q 11 - q 13) has not been replicated. These "false starts" in molecular genetics have provided a degree of caution when it came to the recent announcement of the "alcohol gene"[16,17].

Even though the results of linkage studies are currently uncertain, molecular genetics has moved the psychiatric paradigm into the cell. Numerous studies are being published, using DNA technology, that increase our neuroanatomical, neurophysiologic and neuropathophysiologic understanding of psychiatric illness. The action of psychotropic drugs with side effects on ion channels, receptors and ion pumps in biological membranes are being currently researched[18,19,20,21,22].

Both the diagnostic and therapeutic impacts of the new technology lie in the future, but clearly a correction of the data in the early RFLP studies should argue for some caution in our expectations. Kelsoe suggests that a complete systematic screening of DNA markers in the entire genome may be necessary to find the chromosomal locus of the disease-susceptible gene; the effort is already under way.

Summary

Psychiatric literature includes molecular genetic studies with far reaching implication for diagnosis and treatment. Although this interface is in its infancy, it does require, as we have presented, another paradigm shift for the psychiatry clinician. As neuroscience came to eclipse psychoanalytic views in psychiatry, it appears that the "cell" either in preclinical or clinical studies has become the focus of study as opposed to the "brain." As has occurred in other medical specialties, these molecular genetic studies promise to become more clinically relevant, with the potential of more productive lives for psychiatric patients.

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who are already infected. Physicians should be aware of the many ways in which TB presents a particular threat to them. Hawaii law requires periodic evaluation for TB of health-care providers employed by various institutions such as hospitals and care homes. Although most physicians are not covered by these statutes, physicians should be aware of the recommendations for periodic screening and should assure themselves that they too be screened periodically.

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