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GENETIC MAPPING STUDIES OF SCHIZOPHRENIA AND BIPOLAR DISORDER

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During the last two decades, the search to define medical illnesses by virtue of variations (or mutations) at the level of DNA has ushered in a revolution in our understanding of the origins of many diseases. Although somewhat lagging behind other fields of medicine with regard to actual discoveries of disease genes, psychiatric researchers are now very actively engaged in applying the study of genes and molecular biology to disorders such as schizophrenia, bipolar disorder, and other mental illnesses. Coming roughly 100 years after Emil Kraepelin first defined the major psychotic disorders as "dementia praecox" (currently defined as schizophrenia) and "manic depression" (currently termed bipolar disorder), we are now beginning to see both the utility of these century old diagnostic terms (they have helped us to begin to define gene locations for these discrete illnesses) as well as their limitations. In this paper, we will review the current state of genetic research on schizophrenia and bipolar disorder, with a special emphasis on work that has been done or is currently underway to define predisposition genes for mental illness within the Latin American population.

The promise of genetics: understanding the biologic cause of mental illness

The current dogma of biologically based psychiatry proposes that mental illnesses (some more than others) originate at the level of inherited DNA, and that persons inherit (through their genes) a predisposition for developing any number of illnesses. Variations at the DNA level can result in either different structures of proteins and enzymes (non-conservative mutations) or differences in the rates of expression of proteins (conservative mutations which effect expression at the promoter region of a gene). Since DNA codes for the structures and amounts of all proteins and enzymes in the body, alterations at the DNA (gene) level can result in alterations of structural proteins (such as those which compose cell membranes), neurotransmitters, hormones, or enzymes which catabolize or degrade other proteins. The special promise of gene mapping (also known as reverse genetics), in which genes which cause (or predispose) to an illness are located through the study of families which segregate an illness, is that we can now identify the genes which are the basis of illness without knowing a priori what these genes actually do. This offers the chance to discover the origin of diseases even if the complete anatomy and pathology of an illness is not yet known. Once disease genes are identified, further experiments can define what these genes express and how the alterations in gene product results in pathology. These approaches have worked extremely well for "simple" genetic diseases (those diseases which are caused by alterations in one gene only), such as cystic fibrosis, Huntington's disease, and a large number of rare diseases. Breakthroughs are also beginning to occur for the more complex diseases (those which are caused by multiple genes and, in many cases, interactions of genes and environment); examples of these types of illnesses are Alzheimer's disease, diabetes, breast cancer, and schizophrenia. Specific genes have recently been implicated for all of these disorders (McKusick, 1998).

This article will focus on efforts to map genes, as

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opposed to research which tests already known candidate genes (such as COMT or Dopamine Receptor Genes). As mentioned above, gene mapping offers a chance to identify genes that predispose to mental illnesses without knowing ahead of time what those genes are. Interestingly, in most gene mapping studies done to date, the gene locations identified have not been those which contain some of the more obvious candidates to cause psychopathology. This does not mean that dopamine, serotonin, and other neurotransmitter systems are not altered in psychopathology, but it does mean that the origins of the illnesses (the original biologic causes) lie in other genes which somehow alter these systems. Interestingly, as will be mentioned below, the recent identification of genes (via gene mapping) involved in schizophrenia have pointed strongly to genes within the glutamate system as the possible origin of psychopathology. One other caveat to keep in mind is that the study of genetics of mental illness does not mean precluding the effects of non-genetic factors on these diseases: indeed, all psychiatric illnesses have environmental factors which contribute to the development of illnesses. And not all psychiatric illnesses have a strong genetic component. Gene mapping will be most useful in those psychiatric illnesses, such as schizophrenia and bipolar disorder, which have a major genetic component.

Early attempts to understand mental illness in the context of evolution and inheritance

Before reviewing current research in the genetics of mental disorder, it is useful to review the dilemma faced by our ancestors when they tried to derive an explanation for mental disorders. One hundred years ago, with no knowledge of what the inherited material in humans was, and a limited understanding of gross neurophysiology, explanatory models for mental illness used a combination of evolutionary theory and the study of behavior and mental experience to try to explain psychopathology. Charles Darwin was interested in the study of emotions in man and other animals, and wrote a book on the subject (Darwin, 1872). Freud, profoundly influenced by Darwin's theories, tied all of his theories to an explanatory model that could explain inherited drives or mechanisms of thinking and feeling (Sulloway, 1992). Interestingly, of the early theorists of psychopathology in the 1900's, Carl Jung seemed to have the best understanding of evolutionary theory and how it might apply to human behavior. In particular, Jung postulated inborn character or personality types, which varied within the human species – acknowledging that variation was present due to biologic inheritance (Stevens, 2003). Jung also recognized other aspects of Darwin's theory as being essential to understanding human psychology , such as understanding that emotions, thoughts, and behaviors were present in humans because they had evolved over centuries as adaptive functions of the whole person (Stevens, 1997). Jung alone, of the psychonalytic theorists of the last century, postulated a theory that incorporated three key precepts of Darwin's idea of evolution and behavior: 1. That behaviors (and emotions) are present because they confer survival value, 2. That behaviors are inherited, and 3. That behaviors should vary within the species. Despite the insight of early behavioral theorists such as Darwin, Freud and Jung, all were limited by not knowing in scientific detail what the true mechanism of inheritance was. With the discovery of DNA and the decoding of the entire human genome, behavioral scientists can now begin to study the pathology of mental processes (and mental illness) at a level of detail heretofore unimagined.

The search for genes which cause schizophrenia or bipolar disorder: Kraepelin and the two disease model of major psychoses

When scientists first began to try to identify (or map) genes for psychiatric disease, we used categories of disease that had been defined by a "committee" over the last thirty years. The categories of illnesses studied, such as schizophrenia and bipolar disorder, derive from Kraepelin's early distinction of a chronic, deteriorating psychotic illness (currently re-defined as schizophrenia) and a more cyclical psychotic illness (now defined as bipolar disorder) (Escamilla, 2001a). Kraepelin, whose major work came together in classical textbooks published in the early part of the 20th century, took a non-etiologic approach to classifying the severe mental illnesses – a distinct and less speculative approach to that undertaken by theorists such as Jung and Freud. His classifications were major influences on the researchers who proposed the "Feighner criteria" for defining schizophrenia and bipolar disorder (Feighner et al., 1972) and these criteria in turn formed the basis for our current DSM-IV classifications of these two illnesses (American Psychiatric Association, 1993).

In studies that have tried to define the genetic basis of different illnesses (i.e. how "genetic" various illnesses are), schizophrenia and bipolar disorder are considered two of the most strongly due to genetic inheritance (Escamilla et al., 1997). For example, the concordance of illness in identical twins with bipolar disorder is approximately 4 times the rate seen in non-identical twins (Tsuang and Faraone, 1990). In schizophrenia, the concordance rate is approximately 50%, as

compared to 10% in non-identical twins (Escamilla et al., 1997). Despite some obvious problems with our current categorical definitions of schizophrenia and bipolar disorder (for instance, in the DSM-IV) (American Psychiatric Association, 1993), psychosis can occur in both, mood disorders can occur in both, each has chronic and cyclical forms and we now see both disorders responding to similar medications (Yatham, 2003). Researchers up to the present time have tried to identify genes using these categories and, for the most part, studying families where multiple cases of one or the other of these illnesses cluster. This approach to research led to initially exciting findings of gene localizations for bipolar disorder (Egeland et al., 1987) and schizophrenia (Sherrington et al., 1988), followed by dissapointments when these original findings were not supported by more intensive research (Kelsoe et al., 1989; Detera-Wadleigh et al., 1989). Using more rigorous techniques, narrower definitions of affected cases, and larger sample sizes, family based studies over the last ten years have led to a number of localizations of genes for these two disorders, which are now being replicated (Nurnberger and Faroud, 2000). Some of these localizations have occurred in studies of Latin populations. We will first review studies from Latin America, which have resulted in gene localizations (but no definitive gene identifications), and will then report on findings from outside Latin America, where both gene localizations (for bipolar disorder and schizophrenia) and identification of specific genes (involved in schizophrenia) have occurred.

Genetic mapping studies conducted in Latin America

There has been a paucity of genetic mapping studies conducted in Latin American populations. Indeed, most studies to date have been carried out in European or United States European American populations. Most of the work to identify genes in the Latin American population has been carried out in the Central Valley of Costa Rica. This population has been the focus of gene mapping efforts due to its history as a "genetic isolate" (REF). Although not unique in the Americas, in this regard, Costa Rica does have a history that is especially conducive to gene mapping of complex disorders. The country was "founded" in the 16th and 17th centuries by a relatively small number of Amerindian and Spanish families (Escamilla et al., 1996), and the resulting population expanded to approximately 3 million people by the end of the 1980's. Equally important, admixture into the population due to immigration from surrounding regions or countries was minimal until the last half of the 20th century. This results in a population where many of the current persons can show inheritance back to a small number of ancestors. This type of situation enhances the possibility that persons suffering from a particular "genetic" illness (such as schizophrenia) share the same disease-causing genes, and theoretically, this should make identifying these genes easier than in populations where currently ill people have genetic ancestry from widely disparate sources. In this type of setting (a more homogeneous population such as the Cental Valley of Costa Rica), one can use both classic gene mapping strategies (linkage studies using multiplex families – families with more than one ill member) or association based studies (linkage disequilibrium studies using individual affected cases from the population) (Escamilla, 2001b).

Both of these approaches have been used to identify possible gene locations for bipolar disorder and schizophrenia in the Costa Rican population (Mathews et al., 2004). To date, no specific gene in Costa Rica has been tied to mental illness – although the regions where such genes are located have been identified. Using family based linkage studies, genes for severe bipolar disorder (bipolar disorder Type I in the DSM-III-R), have been localized to regions on chromosome 5, 18p, and 18q (Freimer et al., 1996; Escamilla et al., 1999; Garner et al., 2001). Using linkage disequilibrium studies (individuals with BPI and their parents), the localizations on 18p and 18q have been supported, and additional gene loci have been suggested on chromosome 8p (Escamilla et al., 2001c; Ophoff, 2002). Beginning in 1997, Raventos and colleagues have been conducting a linkage disequilibrium study of schizophrenia in Costa Rica, and have thus far shown evidence of genes being localized to chromosome 8p, as well as chromosomes 18p and 18q (unpublished data). Additionally, in this study of schizophrenia, a locus on chromosome 13, near the G30 and G72 genes (see below) has been identified as likely to harbor a gene variant which is involved in predisposing to schizophrenia (Escamilla et al., 2001d). In a family based study of schizophrenia (Delisi et al., 2002), no loci met criteria for significant linkage, although several areas provided evidence worthy of follow-up in a larger sample. In summary, genetic mapping studies of bipolar disorder and schizophrenia in Costa Rica have resulted pointed to three identical chromosomal regions (8p, 18p and 18q) as carrying genes that are involved in BP and SC, as well as two sites that are linked only to schizophrenia (on chromosomes 13 and 22) and one thus far linked only to bipolar disorder (chromosome 5). It has been interesting, and somewhat unexpected, to find that even in a rather homogeneous population like that of the Central Valley of Costa Rica, multiple genes have been implicated that confer risk for

schizophrenia and bipolar disorder. And, finally, contradicting the dichotomization of psychotic disorders proposed by Kraepelin, some of the loci involved in mental illness are the same for bipolar disorder and schizophrenia. This now makes it likely that mental disorders such as these will be redefined, once the true pathologic origins (genetic) are better understood.

Outside of Costa Rica, there have been no previous genetic mapping studies for psychiatric disorders in Latin America, although the gene which causes one neurologic disorder, Huntington's disease, was mapped by studying families from Venezuela (Gusella et al., 1983). There have been several candidate gene studies, using case-control samples, for various mental disorders including bipolar disorder (Ospina-Duque et al., 2000) and obsessive compulsive disorder (Nicolini et al., 1996), but none of these studies screened the entire genome, and they were testing candidate genes, rather than mapping (identifying genes through linkage analyses or genome wide association analyses). Currently, the National Insititute of Mental Health is sponsoring a large scale gene mapping study to identify genes which predispose to schizophrenia within people of Mexican and Central American origin (Moldin, 2003; Escamilla et al., 2002). This study, led by researchers from Mexico (Humberto Nicolini and Alfonso Ontiveros), the United States (Michael Escamilla, Ricardo Mendoza, Rodrigo Munoz), Costa Rica (Henriette Raventos), and Guatemala (Alvaro Jerez), is based on studying a large number of families who have at least one sibling pair affected with schizophrenia. Currently, over 1000 subjects have been recruited for this study, and a genome screen is being conducted. The study uses standardized diagnostic assessments, using direct interviews of the subjects (Diagnostic Interview for Genetic Studies), their relatives (Family Interview for Diagnostic Studies), and a review of medical records, to accurately diagnose subjects using a best estimate design (Nurnberger et al., 1994). Initial findings from this study are expected to be released in 2004. Of particular interest will be whether gene loci for schizophrenia in the Mexican and Central American populations are similar to (or distinct from) the loci identified in other populations (French Canadian, Irish, Icelandic, and European Americans in the United States).

Current theories of how genes may contribute to schizophrenia and bipolar disorder

The molecular mechanisms that trigger the wide range of symptoms exhibited in neurological disorders such as schizophrenia and bipolar disorder are not clearly understood. Several theories, encompassing both genetic and environmental factors, have been developed in attempts to explain the pathophysiology of these disorders. The neurodevelopmental theory supposes abnormal brain development due to defects in genes involved in neuronal development (Weinberger, 1987; Wolf et al., 1993), along with early insults to the brain, such as prenatal or childhood infections (Brown and Susser, 2002; Koponen et al., 2004), maternal stress and complications during birth (Verdoux and Sutter, 2002; McDonald et al., 2002; Schulze et al., 2003). The neuronal degeneration theory (Berger et al., 2003) proposes failed protection of the neurons, due to defects in genes involved in apoptosis (Jarskog et al., 2004) or oxidative stress regulation (Prabakaran et al., 2004; Rao and Balachandran, 2002), as well as environmental insults such as social stress (Miller et al., 2001; Read and Ross, 2003), infections and/or drug abuse (Howes et al., 2004). Finally, the theory of failed sensitivity or function of neurotransmitters advocates deregulation of neurotransmitter pathways (McGlashan and Hoffman, 2000) due to defective genes, such as the cathecol-O-methyl transferase (COMT) gene (Shifman et al., 2002) as well as environmental factors such as stress and drug abuse. Any (and perhaps all) of these genetic (and environmental) mechanisms may be active in explaining the causes of bipolar disorder and schizophrenia. Indeed, analyses looking at how the degree of relatedness correlates with risk for schizophrenia suggest that there are several genes which are involved in both schizophrenia and bipolar disorder. Only as we unravel the genetic architecture underlying these diseases (through gene mapping studies or studies which analyze the entire genome simultaneously in large samples), will we be able to confirm or reject the above theories. Most likely, we will soon have a complex understanding of these disorders, and will define them less by clinical symptoms (i.e. classical categorical diagnoses like "schizophrenia" and "bipolar disorder"), and more by their etiologic cause.

Current knowledge of the genes involved in SC and BP: Beyond mapping to gene identification

As our knowledge of SC and BP disorders has increased, it has become clear that their pathophysiology does not exclusively fit any one of the proposed theories. Rather, individuals may inherit any number of the aforementioned deviant genetic traits, which can then be further exacerbated by environmental factors (Howes et al., 2004). Accordingly, it is the combination of genetic and environmental insults that puts individuals on the trajectory towards developing schizophrenia or bipolar

disorder. In order to have a complete understanding of the pathophysiology of these disorders, both genetic and environmental factors must be considered. On the genetic side of the coin, great progress has been made in the last two years to identify genes that cause susceptibility to both schizophrenia and bipolar disorder. Following over twenty years of studies reporting weak and non-replicable findings, substantial evidence for putative SC and BP susceptibility loci finally has come from studies that confined themselves to a narrow diagnostic classification, used large study samples and concentrated on one major ethnic group. For SC, susceptibility loci have been identified on chromosomes 1, 6, 8, 13 and 22 (O'Donovan et al., 2003). Further fine mapping on these chromosomal regions has led to identification of 3 putative SC susceptibility genes. Dysbindin, on chromosome 6, was identified in the Irish population (Straub et al., 2002) and confirmed in families from Germany and Israel (Schwab et al., 2003). Neuregulin on chromosome 8, was initially identified in the Icelandic population (Stefansson et al., 2002) and confirmed in a Scottish population (Stefansson et al., 2003). G72, on chromosome 13, was identified in the French-Canadian population (Chumakov et al., 2002). For BP, susceptibility loci have been identified on chromosomes 4, 5, 18, 21 and 22 (Mathews and Reus, 2003; Shink et al., 2002; Kelsoe et al., 2001). Curiously, gene identification in bipolar disorder has been much more difficult, although many laboratories are currently honing in on genes within the above mentioned loci.

Susceptibility loci for both SC and BP have been found to co-localize in several chromosomal regions, 10p13-p12, 13q32, 18p and q, 22q11-q13 (reviewed in Berretini, 2004), which indicate that SC and BP are influenced by some of the same underlying genetic factors. In this respect, it is interesting that the G72 gene, initially identified as a putative SC susceptibility gene, has also been reported to be associated with BP (Hattori et al., 2003; Chen et al., 2004). The original clinical distinctions made by Kraepelin have allowed us to identify many of these genes and loci – however, as the biology unfolds, we may actually see these categories of illness redefined. Interestingly, Kraepelin himself was aware of the tensions suggesting that mental illness did not so easily fit into his proposed divisions (Angst, 2002). In brief, we might look at the field of psychiatry as undergoing a transition similar to that seen in the field of cancer. Original classifications of illnesses based on tools that were at hand (clinical description in psychiatry, histopathology in cancer) have helped to shape studies which now better identify the genetic origins of these illnesses, leading to new nosologies of illness guided by genetics.

Future directions: Genes and psychiatry in the 21st Century

Progress in identifying gene loci for both schizophrenia and bipolar disorder has been promising in the last few years, and it is exciting to see genes localized through gene mapping being identified for schizophrenia. Nevertheless, given that most of these gene mapping studies have occurred in Northern European and United States Caucasian populations, it remains unclear how many of the same genes will be involved in these disorders in the Mexican and Central American populations. Studies in Costa Rica suggest that the "overlap" of schizophrenia and bipolar disorder will be seen in Latin populations, and that some of the identified loci will overlap with non-Latin populations, while other loci will be unique to Latin America. Given the large percentage of United States citizens of Mexican heritage, the time is ripe for collaborative work between researchers from Mexico, the United States and the rest of Latin America, to identify the genetic origins of these illnesses in our people.

The successful identification of genes that are strongly associated with mental disorders provides the first step in the understanding of these disorders at the molecular level. The next step is to characterize the function and expression of these genes at the cellular level, to identify how genetic mutations affect the function of the proteins expressed by the aforementioned genes. These studies may in turn lead to more accurate and timely diagnoses of the illnesses, as well as the development of new medications that treat the real problem and therefore have fewer side effects. At every stage of this work, scientists and doctors who work within the Latino population must be involved, to ensure that this research is applicable to Latinos and the unique genetic origins which we carry.

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