The Path to New Therapies for Schizophrenia and Bipolar Illness

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ABSTRACT: Schizophrenia and bipolar illness are two of the most serious forms of mental illness. Until relatively recently, almost nothing was known about the molecular pathogenesis of either illness. The single largest risk factor that predisposes people to schizophrenia or bipolar illness is genetic risk. Heritability is high, and the incidence is significantly higher in identical twins than in nonidentical twins. Despite decades of work aimed at identifying the genes involved in these two illnesses, virtually no progress had been made until the past decade. With the knowledge and technologies that have been gained from the Human Genome Project, it has been possible to begin to understand the underlying genetics and to use the new information to begin the effort to discover new and better medicines to treat these illnesses. This article will describe the past decade of work toward this goal and articulate both the promise that now exists and what is still needed to bring dramatic and tangible change to patients.—Scolnick, E. M. The path to new therapies for schizophrenia and bipolar illness. FASEB J. 31, 1254–1259 (2017). www.fasebj.org

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In the fall of 2004, I became an associate member of the Broad Institute, founded on the principle of collaboration among scientists at the Massachusetts Institute of Technology, Harvard, and Harvard-affiliated hospitals. The Broad Institute had been created in 2003 as an outgrowth of the Genome Center at the Whitehead Institute. The Genome Center was overseen by Eric Lander, who soon became director of the new Broad Institute. I had retired from my position as president of research at Merck Research Laboratories at the end of 2002 and then from the company in September 2004. The Broad Institute was interested in expanding its program on the genetics of psychotic illnesses, and I was fortunate to meet and have a partnership with Pamela Sklar, M.D., Ph.D., assistant professor of psychiatry in the Partners Psychiatry Department, as well as an associate member of the Broad Institute. Sklar had been studying the genetics of bipolar illness, and without her help, the new program would not have become a reality.

EPIDEMIOLOGY OF SCHIZOPHRENIA

Research in the field of psychiatry had been trying to gain traction in deciphering the genetics of schizophrenia and bipolar illness for many years. Virtually no reproducible results had been achieved. The Broad Institute had a superb group of scientific experts in human genetics, a field in which I had no particular training. David Altshuler, Mark Daly, and Shaun Purcell were mentors to the program and were essential if the new effort was going to succeed.

A few important facts were known about these two psychotic illnesses, and several epidemiologic observations had been made about variables that conferred risk. Babies born to mothers in populations that had endured famine had a higher incidence of schizophrenia (1, 2). Epidemiology had determined that moving from one country to another also increased risk. But, the single largest risk factor for a person to become ill with one of these illnesses was genetic risk. If a family member had either schizophrenia or bipolar illness, the first-degree relatives of the proband (patient) had a 7- to 10-fold increased risk of having one of these illnesses compared with the average person not related to the patient. This increased risk was true for both schizophrenia and bipolar illness (3).

In addition, if a person had schizophrenia, the first-degree relatives also had an increased risk of bipolar illness. Likewise, if a person had bipolar illness, the person’s first-degree relatives had an increased risk of schizophrenia. The reciprocal overlap in risk was documented in an elegant epidemiologic study by investigators at the Karolinska Institute (Stockholm, Sweden) (4). Despite the fact that the illnesses run in families, many genetic linkage studies in extended families had failed to yield consistent results at finding any genes that predisposed to either illness. Such studies usually involved relatively small
samples of cases. The results were puzzling, because the heritability of each disease is in the range of 50–80%. However, a possible interpretation was that many genes were involved and that no single gene had a strong enough effect to allow that gene to be detected in linkage studies.

I had no training in human population genetics, but I learned from my colleagues, Altshuler, Daly, and Purcell, that new methods were being developed to study the genetic underpinnings of many human diseases that had complex genetics (i.e., where many genes, each with a small effect size contributed to risk for an illness, such illnesses had a polygenic rather than a monogenic risk). The methods were an outgrowth of the sequencing of the human genome project and an ongoing effort to provide a detailed map of the human genome. The map was being constructed by defining and mapping so-called common single-nucleotide polymorphisms (SNPs), that is, single-base changes differing among the human population but shared by a significant percentage of the human population. Although there is no hard and fast definition of common SNPs, it is generally taken to mean those shared by 5% or more of the population.

Why was this mapping important as a tool to study the underlying polygenic architecture of many human diseases? Earlier work by Stacey Gabriel, Altshuler, and Daly had discovered that large blocks of genes in the human genome were in linkage disequilibrium (i.e., their linkage to one another was only rarely interrupted by recombination) (5). Thus, by mapping these common variant SNPs and knowing they provided signposts for other genes in these relatively stable segments, one could then perform a different kind of genetic study—an association study instead of a linkage study. In an association study, one could look for the frequency of association of marker SNPs in control populations without the disease of interest versus the frequency of association of such marker SNPs in the DNA of the population with a given illness.

Although it was not certain that such an approach would yield positive results for schizophrenia or bipolar illness, it was clear that this was a new approach worth trying. Statistical estimates suggested that there was an 80% chance that real associations could be found. The discovery of the multiple genes that were the basis for many common human diseases was a rapidly emerging field, and association studies were begun, not only in schizophrenia and bipolar illness but also in diabetes, macular degeneration, multiple sclerosis, Crohn’s disease, and lipid disorders. Whole exome sequencing methods had not yet been developed. The initial effort would focus on association studies and search for polymorphisms (SNPs) that were relatively common in humans and that associated reliably with either schizophrenia or bipolar illness. The main challenge then was to have access to enough cases and controls to perform such an association study in psychotic mental illnesses.

We set about to try to convince investigators in the field to work together in a consortium and to pool all of their respective cases and controls to attempt to carry out the studies on at least 10,000 cases and controls. Our main collaborators in this initial effort were Dr. Patrick Sullivan (University of North Carolina Medical School, Chapel Hill, NC, USA) and Dr. Michael O’Donovan (Cardiff University, Cardiff, United Kingdom). Sullivan’s major source of cases and controls was from a collection in Sweden with collaborators at the Karolinska Institute, with the guidance of Dr. Christina Hultman. The collection from Sweden was based on identifying thousands of cases, mainly from hospital case records. Validation of this rather simple methodological approach was achieved by detailed study of a small number of cases.

We fully recognized that the identification of cases was based on a collection of symptoms that defined schizophrenia and not on a chemical, biological, or physical test in such patients. It was not at all certain that there would be sufficient homogeneity in the cases, using this approach, to allow a signal to be detected in an association study. This limitation was part of the broader problem in studying schizophrenia and bipolar illness, since the diagnosis of either disease was solely based on symptomatic criteria. We began the effort mainly on patients with schizophrenia, as more cases were available, and initiated efforts to collect sufficient cases of bipolar illness while the initial studies were conducted.

Because of the generous funding from the Stanley Medical Research Institute, in 2007, we were able to begin in earnest the genetic studies. For 2–3 yr as the first data became available, we realized that this was an even more formidable problem than we had thought, and we were not certain that the approach was going to yield positive data. We were buoyed by calculations made by Daly, who showed in several ongoing association studies in other diseases, such as Crohn’s disease, type 2 diabetes, and multiple sclerosis, that the yield of clear associations was a function of the sample size. In each of those studies, his analysis suggested that if we persisted and analyzed enough samples, then positive results would emerge. This was a high-risk strategy; however, it was clear that unless we could begin to identify unambiguously the genes that put people at risk for these diseases, there would not be tangible progress in the field. It was always obvious that it was impossible to carry out biochemistry on living brain tissue, imaging studies did not have the molecular resolution to unravel the abnormal biochemistry, and chemical measurement of peripheral body fluids or tissues would not give information about abnormal brain biochemistry; thus, we had two choices: we could give up our effort, or we could put our faith in Daly’s calculations and persist in the effort. To me, there was no choice but to persist.

Almost a decade later, our faith was rewarded. As the sample size grew to 37,000 cases and 113,000 controls, >100 loci (regions in the genome) were unambiguously identified that are associated with risk of schizophrenia. Dr. Stephan Ripke was instrumental in this analysis. Approximately one third of these loci had only 1 or 2 genes in the region of association (6).

Before discussing the biological findings of the studies, it is important to point out certain limitations to association studies. 1) In identifying a gene within a locus as the risk gene implicated by the statistical association, an assumption is made. The SNP that yields the statistical association...
may not be the SNP that is actually affecting the gene’s biology. 2) Even when a single gene occupies the region detected by the SNP, it is possible that the SNP that yields the association is really a proxy for a more distant gene. 3) The biology of genes associated with risk is known in 95% of cases to be an indicator of an effect on the level of expression of the gene and not an indicator of a coding variant in a coding portion (exome) of the gene.

In studies in other diseases, where expression levels of genes detected in association studies had been examined, very small changes in levels of expression had been found. The expression level change is a result of a promoter or enhancer that affects expression of the gene. With the full realization of these limitations, the association results have still yielded some important information.

Computational analyses have asked whether the genes detected are a random set of the ~20,000 genes in the human genome. Importantly, such analyses have concluded firmly that the detected genes are not a random subset of the 20,000 genes in the human genome. The schizophrenia risk genes are enriched for genes expressed in the brain (6), they are enriched for genes expressed at synapses, especially in the postsynaptic compartment of neurons, and they are enriched for genes whose mRNAs are bound by fragile X mental retardation 1 protein (FMRP), the protein coded for by the gene silenced in fragile X syndrome. FMRP regulates the translation of a number of mRNAs in neurons and in synapses (7). Thus, risk for schizophrenia was proven for the first time to be enhanced by genes involved with synaptic functions of neurons.

A second important observation was made in the earliest positive data from these studies; a strong signal from the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with schizophrenia risk. Of equal importance, in work that is not yet published, this region is not associated with risk for bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness. In a more recent study, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (8) performed fine mapping of the region on chromosome 6 that encompasses the major histocompatibility complex (MHC) locus was strongly associated with risk of bipolar illness.

1. Synaptic calcium homeostasis has been implicated. L-type calcium channels, T-type calcium channels, and neurogranin all are clear association signals (with the caveat above) (11).
2. The dopamine 2 (D2) receptor and a protein, RGS6, that regulates signaling through the D2 receptor have been implicated. It is of interest that all antipsychotic drugs used to treat the positive symptoms of schizophrenia act mainly by blocking the D2 receptor.
3. A gene involved in cation (manganese) transport within cellular compartments and a consequent effect on the biosynthesis of some glycoproteins are clear association signals. This is a rare gene case, where the association has detected a coding change in the transporter. Studies have begun to try to understand the abnormal glycome biochemistry and to determine whether that abnormal biochemistry can lead to a biomarker for some patients with schizophrenia. It is even conceivable that a dietary regimen based on these studies could have efficacy in some cases of schizophrenia.
4. Although we will not discuss the ongoing association studies on bipolar illness, the schizophrenia association studies have been used to detect that some genes that increase risk for schizophrenia also increased risk for bipolar illness (12). These genetic findings seem to be consistent with the earlier epidemiology studies noted above. Importantly, the gene involved in synaptic pruning does not seem to be involved in bipolar illness.

However, major gaps still exist in these ongoing studies. It was noted that the vast majority of association signals affect gene expression. The detection of whether the schizophrenia associations lead to an increase or decrease in expression has lagged dramatically and is holding back biological progress in the field. Secondly, it is important to realize that the increased risk attributable to any 1 gene detected in the association studies is very small, ranging from a 1 to 10% increased risk. Still, the larger number of risk SNPs and therefore, risk genes that a person harbors, the greater the chance that the person will have schizophrenia. Thus, the association studies have been insightful in beginning to indicate areas of abnormal biology but frustrating because of the small effect sizes and the lack of clarity of the directional role that any given gene plays. The 2 clear exceptions are the increased expression of the C4A gene and the decreased function of the manganese transporter SLC39A8.

EXOME SEQUENCING STUDIES

In the past 5 yr, another approach—exome sequencing—has become available to discover the genetic underpinnings of schizophrenia. This method can give much more detailed data about the genes involved in conferring risk. The cost of sequencing the exome portions of genomes has plummeted over the past decade. The protein-coding regions of the genome represent ~1% of the bases in the
genome. The most frequently used method for sequencing these regions involves fragmenting the DNA; capturing the fragments that represent the protein-coding regions by RNA:DNA hybridization, with excess RNA; removing the RNA; and then sequencing the captured DNA using high-capacity DNA sequencing machines. This method has been applied to sequence the DNA from ~7000 cases of schizophrenia and a comparable number of controls.

In addition, a publically available database of exome sequences exists. The database is now called the Genome Aggregation Database (gnomAD) and is the work of Dr. Daniel MacArthur and his colleagues (Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA). This database contains exome sequences from ~150,000 cases of many different patients and controls in the global effort at exome sequencing performed in the past decade. The cases are anonymized, so patient confidentiality can be maintained.

The data garnered from cases of schizophrenia derive from two types of studies: population-based sequencing (i.e., cases and controls from a given population), and trio sequencing (i.e., two parents with no apparent mental illness and one child who has schizophrenia).

To understand the rational and conclusions from the exome sequencing studies, it is important to understand what mutations are being analyzed and the limitations of the analyses. Damaging exome mutations unique to patients with schizophrenia are being explored that include either loss-of-function (LOF) mutations (i.e., cases and controls from a given population), and trio sequencing (i.e., two parents with no apparent mental illness and one child who has schizophrenia).

The rationale behind the trio studies is as follows: on average, each newborn has 1 new exome mutation not found in the parents; this is termed a de novo mutation. Most de novo mutations do not seem to cause disease. It is known that the fecundity of patients with schizophrenia is decreased compared with the fecundity of the general population (i.e., they have fewer offspring) (14, 15). The pathogenic mutations in patients with schizophrenia are being selected against in the population because of the decrease in mating of patients with schizophrenia. Thus, they are not passed on to the next generation. The assumption has been that some genetic contributors to schizophrenia are therefore either a result of de novo exome mutations, since the incidence of schizophrenia remains relatively constant in the human population, or mutations passed on from parents but present for only a few prior generations before being inherited by the proband with schizophrenia. Thus, the trio studies are searching for statistical evidence of an excess of LOF or damaging exome de novo mutations unique to patients with schizophrenia.

In the population studies, an excess of unique mutations has also been analyzed. In this case, the background of mutations is much higher, as each human carries ~40 damaging mutations in the exome portion of his or her genome. Thus, the importance for schizophrenia of any 1 mutation in a patient is difficult to discern. It is easier to detect an excess of unique damaging mutations in a large number of cases versus a large number of controls. gnomAD, which contains such a large number of controls, has been an enormous aid to the statistical efforts, as only ~7000 cases in this 150,000 case database are cases of schizophrenia. Although all of the cases in gnomAD are anonymized, geneticists who know the mutations detected in schizophrenia can discern which cases in gnomAD are the schizophrenia cases and thus, which 143,000 are not. This is an obvious aid in trying to discern mutations unique to schizophrenia.

The major findings from the exome sequencing studies are as follows:

1. There is a small excess of de novo LOF mutations in the trio studies with the number of trios, thus far, analyzed; no one gene has been affected frequently enough to be certain statistically that it is a significant risk, and gene mutations affected seem to be in genes involved with chromatin remodeling (16).

2. In the population exome-sequencing studies, as predicted, there is an increased burden of protein-altering, ultrarare mutations in patients with schizophrenia compared with controls (17). The protein-altering mutations involve both LOF and damaging missense mutations. Again, because of the heterogeneity of genes involved, no one gene has been noted to be mutated frequently enough to yield statistical significance. However, the constellation of genes with the ultrarare protein-altering mutations is not a random set of genes but is enriched for genes involved in synaptic function. It is striking that this enrichment noted in the exome sequencing studies, thus far, is consistent with the enrichment noted from the common variant association studies.

3. Among the individual findings, certain exome data on individual genes seem particularly interesting at this point in the progress of the studies:
   a. The sodium channel gene SCN2a, a gene also implicated in autism and epilepsy, seems also to be implicated in schizophrenia
   b. A particular T-type calcium channel expressed in the thalamic reticular nucleus was found to have a de novo mutation in a trio-based study. This channel is a clear risk gene in the association studies; furthermore, the thalamic reticular nucleus is a way station between the cortex and the thalamus and is involved in integrating the communication in circuits between these two parts of the brain. The detected mutation has a functional consequence in work led by Dr. Jen Pan, along with colleagues (18).
   c. A recurrent mutation has been noted in a gene, Git1, in Swedish cases. This gene is involved in dendrite morphogenesis and also in
presynaptic vesicle release in combination with Piccolo, a gene found in the common variant schizophrenia association studies (19).

The major hypothesis that emerges from both the association studies and the exome studies is that schizophrenia risk is conferred by some combination of changes in expression levels of synaptic genes, each of which causes a small increase in risk and a damaging mutation in the exome of some synaptic gene, with undoubtedly, a larger effect on risk. At this point, the best estimates are that hundreds of genes can be involved, and the goal of the efforts is to identify as many as possible. Enhanced pruning of weakened synapses clearly seems also to contribute to schizophrenia pathogenesis but not bipolar pathogenesis.

Over the next 2–4 yr, exome data will be available on ~40,000 cases of schizophrenia, and association studies will be available on at least 60,000 cases of schizophrenia and 150,000 controls. Cases of bipolar illness are being accumulated, and then, similar size studies will be conducted on those cases.

It is clear that the inscrutable state of what underlies schizophrenia has changed. Unambiguous genetic findings have emerged. Biological and biochemical insights have been made. Many more will be made in a relatively short period of time, and the enormous task of translating the genetic findings into mechanistic biological and chemical insights will be before the field. To harness the most information from this new data set of genetics, many laboratories and new trainees will need to enter the field. Many studies to describe abnormal biochemistry that occurs in specific circuits will be needed. Then, the number of potential proteins that might be new targets for discovery of drugs with new mechanisms of action will be very large.

The original medicines that are used to treat schizophrenia were discovered by serendipity. Later, their main mechanism blockade of the D2 receptor was discovered by Seymour Kety. Clozapine was also discovered by chance, and even today, its unique efficacy for some patients is not understood. As the pharmaceutical industry has tried to make better versions of clozapine, many new medicines have been introduced for the treatment of schizophrenia and bipolar illness. However, there has not been a medicine with a new defined mechanism of action in over 60 yr. A recent issue of The Medical Letter on Drugs and Therapeutics (20) lists all of the approved antipsychotic medicines, and the exploration into their pharmacology will prove that the above statements are true.

The pharmaceutical industry has retreated from the field in the past decade, as nothing was known that was fundamental to the pathogenesis of the diseases, and without such knowledge, it is understandable why new investments have not occurred, and medicines with new mechanisms have not been forthcoming. The clear goal of the genetic studies is to provide the biological basis for the discovering of new and better medicines for schizophrenia and bipolar illness. In fact, data have emerged indicating that, in the near future, industry is likely to re-engage in research in this field. Why? It has become clear in other fields of medicine that genome-wide association (GWA) studies have identified numerous genes that are involved in pathogenesis, and that in several diseases, excellent medicines have been developed, which work by acting through the proteins coded for by the genes identified in the GWA studies. Examples exist in drugs that lower LDL, in drugs that increase insulin sensitivity in type 2 diabetes, in treatments for psoriasis, in several treatments for essential hypertension, and even in schizophrenia (the D2 receptor). Thus, I believe it is a virtual certainty that among the genes identified in schizophrenia in the GWA studies, many new important drug targets exist.

The genetic studies have made clear that schizophrenia is not a single homogeneous category of disease. How many subsets exist is not yet known. The risk for disease is polygenic and complex, yet it is noteworthy that single drugs that block only the D2 receptor have clinical benefit for the positive symptoms of the disease in many patients. Therefore, it is a reasonable assumption that other medicines with new targets can produce clinical benefit in large numbers of patients and that in time, proper combinations of these new drugs can help significant numbers of patients. It is also predictable that some new mechanism drugs will work better in some subsets of patients than in other subsets. Rigorous clinical trials will be necessary to achieve this goal.

Even while more genetic findings are emerging, I believe it is time to organize a new consortium for this next mechanistic phase of the evolution of the field to capitalize on the new genetics. This consortium would focus on the biochemistry and biology that need to be derived from the genetics. If the work is left to a traditional academic model of one laboratory in isolation from other laboratories, then the rate of progress will be much too slow and the rate of progress for patients unacceptably slow. Such a consortium can be organized with private funding and hopefully, with public funding from the National Institute of Mental Health (NIMH). In my opinion, NIMH must focus its resources on this new phase of research so that an optimal rate of progress can occur. The field is not ready for a moonshot but is ready for a reprioritization of available funds and could definitely now benefit from an infusion of new U.S. National Institutes of Health funding.

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