Psychiatry in the Genomics Era

"We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest."

—J.D. Watson & F.H.C. Crick

It has now been 50 years since Watson and Crick's landmark paper on the double helical structure of DNA was published in *Nature* (1). This 1-page paper with a single simple figure and six references sparked a revolution in the life sciences that continued through the latter half of the 20th century, yielding the powerful tools of modern molecular biology, the biotechnology revolution, and, in the past 2 years, the sequencing of the human genome. It is probably a safe bet that, until recently, most readers of the *Journal* would have considered this revolution more relevant to their stock portfolios than their clinical practices. As we look beyond the 50th anniversary of the Watson and Crick publication, it is timely to ask whether genomics will become relevant to the practice of psychiatry, and, if so, what the timetable will be. In this commentary we argue that genomics may soon become an important aspect of psychiatry, and we consider what genomics can and cannot do for mental disorders.

Let's start with a few definitions. A gene is simply a sequence of DNA that provides a critical code for messenger RNA, which in turn is translated into protein. How is genomics different from genetics? Genomics and genetics both study the transmission of traits across generations (an interest of Darwin and Freud as well as Mendel). Genetics is the study of single genes and their effects. Genomics is the more ambitious study of all the genes in the genome, including their function, their interaction, and their role in a variety of common disorders that are not due to single genes (2). Advanced draft descriptions of the human genome have now been published (3, 4), and the complete sequence is soon expected in public databases. The number of genes is around 30,000, with these genes spaced unevenly across the 2.9 gigabases of DNA that constitute the human genome.

> *"Will genomics change the way we treat psychiatric patients? Almost certainly."*

While we note a growing tendency to refer to this period following the sequencing effort as the post-genomic era, we want to emphasize that, from a discovery perspective, we are just entering the genomic era. Certainly, there are many mysteries still to be explained. For instance, less than 2% of the DNA in the genome codes for proteins. The >98% that remains consists of vast repetitive stretches of DNA and other sequences that may have regulatory effects or may be a nonfunctional residual of evolution. While this >98% of the genome has been frequently disregarded as "junk DNA," it almost certainly has important functions still to be discovered. As evidence, a recent comparison of the human and mouse genomes (5) revealed that the protein-coding regions account for less than half of the DNA that has been strongly conserved over the 70 million years since humans and rodents diverged. The conservation of millions of base pairs of DNA that do not code for protein suggests that these regions might be functional. It is certain that some of these conserved segments will be found to be involved in regulating gene expression by serving as target sites for protein factors that regulate transcription. Others may act by producing small RNA fragments that interfere with gene expression or may confer other biological functions not yet understood.

The arrangement of genes across the genome is strikingly uneven. Some chromosomes (17, 19, and 22) are gene dense and some (13, 18, and 21) are sufficiently gene poor that trisomy (having a third copy) is nonlethal. We do not understand the importance, if any, of this variation in gene density across chromosomes, although it may have something to do with position in the interphase nucleus. The number of genes is itself a mystery, with humans having essentially the same number as mice (27,000–30,500) (5), less than twice the number of the nematode *C. elegans* (approx. 19,700) (6) and slightly more than twice the number of the fly *Drosophila* (approx. 13,600) (7). But the relatively low number of genes may be misleading, since the original dogma that each gene specifies only a single protein has now been supplanted by the observation that single genes routinely make multiple proteins through the mechanism of alternative splicing (8). By alternative arrangements of RNA follow-

ing transcription of the DNA, 30,000 genes can code for 100,000 proteins. Adding posttranslational modifications (i.e., changes to the protein following translation from RNA) like proteolysis, phosphorylation, and glycosylation may ultimately yield as many as 1,000,000 different human proteins.

Single-Gene Disorders

For nearly 100 years, inherited factors have been recognized in certain families with a Mendelian pattern of transmission. These genetic diseases fall into dominant, recessive, and X-linked modes of inheritance, but all share transmission via a single gene. The online index of the Mendelian Inheritance in Man (OMIM) currently lists mutations in over 1,200 genes that cause single-gene disorders (9). Most of these diseases are uncommon, and many do not have major psychiatric manifestations, but they collectively have taught us three lessons that are important insights for the role of genomics in psychiatry. First, there is genetic heterogeneity: the same syndrome can result from several different mutations in the same gene or even mutations in different genes. As many as 180 different mutations of the vasopressin (V2) receptor gene have been reported to cause nephrogenic diabetes insipidus (10), and familial early onset Alzheimer's disease can arise from mutations in the β-amyloid precursor protein, presenilin-1, or presenilin-2 (11, 12). Conversely, there is variable penetrance: the same mutation in the same gene can result in highly variable phenotypic results. For instance, the gene mutation that results in neurofibromatosis type 1 (von Recklinghausen's disease) can manifest as neurofibromas, malignant peripheral nerve sheath tumors, and bone lesions, but the same exact mutation in blood relatives can manifest as a subclinical phenotype with only a few axillary freckles or café-au-lait spots (13). The extent of pathology, the location of pathology, or the age of onset can be influenced by modifier genes, by environmental factors, or by poorly understood effects that contribute to differences in severity. Finally, a more practical (but less permanent) observation: the discovery of genes for many of these disorders, such as cystic fibrosis or Huntington's chorea, have thus far proven highly informative for investigating the biology of these illnesses but have not yet altered the treatment in any major way. This is an important theoretical as well as practical point. Single-gene diseases are "simple" in terms of the location of the genetic lesion, but they rarely have "simple" or unitary consequences. For instance, a mutation may not only reduce function, it may cause a gain of function of the protein product (as in Huntington's disease, where an abnormal and apparently toxic protein is produced). Moreover, alterations in the function of a single gene almost always exert their effects within a complex cascade of intracellular events (the protein product of the gene mutation seen in neurofibromatosis type 1, for instance, is a negative regulator of *Ras*, an intracellular messenger critical for many kinds of signaling). Successful treatment approaches may therefore ultimately target a downstream mediator (which may be more accessible for drug treatment) and not the abnormal protein product of the gene with the mutation. The point then is that the discovery of a mutation provides an important starting point for understanding the pathophysiology of the disease. Treatment development requires intensive study of these molecular pathways in cultured cells and whole animals to identify the best target for preventing pathology.

Genomics and Psychiatry

We suspect that more than 99% of what has been written about genes and the brain has focused on less than 1% of the genome (about 300 genes). Based on research in the mouse brain, at least 55% of the genes (i.e., roughly 16,500 genes) are expressed in the brain (14). Thus, we have a treasure trove of new genes to explore, including many that may prove more important than the few neurotransmitters and intracellular signaling molecules that have been studied so intensively these past 50 years.

Although these new genes will teach us much about how the brain develops and functions, we are not likely to find many single-gene Mendelian disorders in psychiatry. Even in autism, which has the highest heritability of any psychiatric disorder, as many as 10 genes have been suggested on the basis of modeling the inheritance pattern (15). Rather than looking for rare mutations in genes with big effects, complex genetic disorders involve relatively common variations in multiple genes, each of which has a weak effect. In mental disorders, we are therefore looking at multiple factors that cumulatively make an individual susceptible or vulnerable. Moreover, unlike other complex genetic disorders such as hypertension or diabetes, mental disorders have a complex phenotype for which reliable quantitative traits like blood pressure or blood glucose have been difficult to identify and validate. This shortcoming may be

partly overcome with the identification of endophenotypes, such as eye tracking, sensorimotor gating, or measures of working memory in schizophrenia, which yield stable quantitative traits more reliable than clinical state for characterizing the transmission of mental disorders (16).

Finding genetic factors in mental disorders, whether via linkage or association studies, has proven expensive and, until recently, frustrating. In the past year, several promising candidates have emerged as vulnerability genes for schizophrenia, including neuregulin-1, catechol *O*-methyltransferase, dysbindin, and G72 (17–22). There are promising leads in autism, depression, bipolar disorder, and panic disorder as well (23). Anyone who follows psychiatric genetics has learned to be careful with new reports of genes for mental disorders, since the history of this field is mired in nonreplications and disappointments. We empathize with healthy skepticism, but we caution against unhealthy cynicism. With the evidence of heritability in all of these disorders, there is no question that susceptibility genes for all of these disorders will ultimately be found. In fact, with the recent initiation of an international project to determine a haplotype map of the entire human genome (which will map variation in large stretches of DNA), the era of whole genome association studies is likely to be only a few years away. Such studies are expected to have much greater power than the family-based linkage studies that have until now been the dominant approach to searching for genetic factors in psychiatric disorders.

As with Mendelian disorders, the hope is that these vulnerability genes will provide a starting point for defining the biology of these disorders. We have seen this unfold with hypertension. The discovery of linkage to a novel gene has led to the elaboration of an entire pathway related to hypertension with a new, exquisite understanding of how altered signaling in the kidney contributes to this syndrome (24). Clearly, we need such an anchor to inform the molecular exploration of mental disorders. The promise here is even greater, as genetic variation could be used to redefine the disorders, replacing the current diagnostic system, which has no evident biological basis. In this regard, it is worth noting that the syndromes defined by genotype may have much different boundaries than what we have tried to craft with diagnostic manuals based on presenting symptoms. It is also possible that some genotypes will link to a much broader phenotype than what we have identified diagnostically. For instance, a susceptibility gene for all of the common forms of stroke has been reported on 5q12, suggesting that diverse forms of cerebrovascular disease may paradoxically share a common genetic basis (25). Similarly, we may discover that some of the genes for vulnerability to anorexia nervosa are shared by OCD and depression, with the genotype linked not to a specific disorder but to a perfectionistic, risk-aversive personality style that confers vulnerability to many syndromes.

Although each gene may have weak effects, combining several susceptibility alleles may increase the predictive power. Note, however, that we are talking about predicting susceptibility to mental disorders. Even more than in many other disorders, we expect that the environment will have a powerful effect on the development of mental disorders. A particularly instructive example of this interaction was recently demonstrated for the monoamine oxidase (MAO)-A gene. Children who have been mistreated are at greater risk for violent antisocial behavior. Caspi et al. (26) reported that a genetic variant of the MAO-A gene that increases MAO-A enzyme activity is associated with reduced violent antisocial behavior in male subjects who had been mistreated, but no effect is seen in a nonselected population. The role of vulnerability genes for mental disorders, as with genes for lung cancer or alcoholism, may be to influence the response to environmental factors, including prenatal events. Conversely, we may find genes for resilience or resistance that may have a greater effect than those for vulnerability.

Conclusion

Will genomics change the way we treat psychiatric patients? Almost certainly. It is important to recognize that even a gene with a weak effect may provide a pathway toward new, targeted therapies for schizophrenia or autism, even if the actual targets are downstream from the original gene of interest. This will require considerable research using cell lines and animal models. Equally important, in the very near future we can expect the development of pharmacogenomics, with genetic tests that predict pharmacological treatment response or vulnerability to a particular adverse effect. Such tests could alter psychopharmacology to make drug choice more selective and safer. Indeed, one of the most important consequences of genomics will be to individualize treatment by allowing a clinician to tailor therapy on the basis of the unique genotype of each patient rather than the mean responses of groups of unrelated patients.

Finally, it is important to remember that genomics is a field that is still in its infancy. Having the sequence of the human genome is an important first step, but it is just a beginning. In many ways, it is like having the white pages of the phone directory with all of the numbers and addresses. The white pages are helpful if you know who you are looking for, but useless when something goes wrong and you don't know whom to call. Genomic medicine needs the yellow pages, with the list of all of the mechanics, plumbers, and electricians who can be summoned to fix an abnormal prefrontal cortex or a failing hippocampus. Writing the yellow pages requires an understanding of the function and the interaction of all of the genes in the genome, which may require another 50 years of research. The promise is huge—for psychiatry as much as the rest of medicine. Watson and Crick (1) ended their paper with the prophetic and understated observation, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." It should not escape our notice now, 50 years later, that we have an opportunity to revolutionize the diagnosis and treatment of mental disorders during this genomic era. Students of the history of psychiatry looking back from the Watson and Crick centennial in 2053 may wonder how we could have been so interested in serotonin and dopamine in 2003 when many hundreds of more important factors remained to be found.

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