This article reviews some of the most recent findings in genetics and pharmacogenetics of schizophrenia—especially those with clinical implications.

Schizophrenia is a complex and debilitating chronic mental illness, and genetic factors play a major role in its etiology and development. Traditional genetic studies estimated the heritability of schizophrenia to be 70% to 90%.\textsuperscript{1} With the rapid advance of genomic technologies, the past decade has seen an explosion of genetic studies in schizophrenia, which opened new doors for our understanding of the molecular mechanisms in this brain disease. Some experts consider these developments to signal the advent of personalized medicine.\textsuperscript{2} With our newfound knowledge of the human genome, treatment may be increasingly tailored to the individual.

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**Risk genes of schizophrenia**

Researchers initially hoped to find just one or a few genes predominantly responsible for schizophrenia. However, recent studies have demonstrated that many genes may be involved in susceptibility to schizophrenia (polygenic), such as the MHC (major histocompatibility complex) region on chromosome 6,\textsuperscript{3} MIR137 (microRNA 137), ZNF804A (zinc finger protein 804A), DISC1 (disrupted in schizophrenia 1), and DTNBP1 (dystrobrevin binding protein 1).

Most recent reports from the Psychiatric Genomics Consortium suggest that the number of genetic loci that attain genome-wide significance in association with schizophrenia is between 50 and 100 and that these loci are distributed across many genes or genomic regions.\textsuperscript{3} In addition, any one particular gene may contribute to the risk of not only schizophrenia but also other psychiatric disorders, such as bipolar disorder (a phenomenon also known as “pleiotropy”).

A recent study found that 4 genomic loci reached genome-wide significance in a sample of 33,000 patients who had 5 psychiatric disorders (autism, schizophrenia, bipolar disorder, MDD, and ADHD) and 27,000 controls, which suggests overlaps in the genetic architecture of different mental illnesses.\textsuperscript{4} Two of these loci are voltage-gated calcium channel genes—\textit{CACNA1C} and \textit{CACNB2}—which supports the idea that calcium channel signaling may be a common pathway for all major mental disorders.

Our understanding of how some genes influence the risks of schizophrenia has evolved in the past decade. An example is the discovery of the \textit{DISC1} gene. Originally found in a linkage study in a Scottish family cohort, a translocation on chromosome 1 was found to be highly correlated with schizophrenia.\textsuperscript{5} This translocation directly disrupts the
DISC1 gene. The protein encoded by DISC1 appears to provide a scaffold to other proteins involved in multiple cellular functions, particularly regulation of brain development and maturation. It is involved in neuronal proliferation, differentiation, and migration via various signaling pathways by interacting with many other proteins.6

Naturally, the disruption of DISC1 results in dysfunction in multiple neurodevelopmental processes and significantly increases susceptibility not only for schizophrenia but also for bipolar disorder and depression. Despite advances in our understanding of the biology of DISC1, however, large case-control studies have not found a consistent association between DISC1 and schizophrenia.7 One possibility is that DISC1 pathology is representative of a subtype of schizophrenia that is not prevalent among the general population, therefore preventing large-scale epidemiological studies from finding evidence to support the role of DISC1 in schizophrenia.

In the past few years, genome-wide association studies have become a useful tool in discovering novel risk genes for schizophrenia. To date, about 20 studies have been published. ZNF804A was the first gene to reach genome-wide significance in a large study, and this finding has since been replicated.8 Although its function is largely unknown, ZNF804A is widely expressed in the brain, especially in the developing hippocampus and the cortex as well as in the adult cerebellum. Recent animal studies found that ZNF804A is a putative transcription factor, up-regulating expression of catechol-O-methyltransferase while down-regulating dopamine D2 receptors, both of which affect dopamine levels in the brain, consistent with the original “dopamine hypothesis” of schizophrenia.9 Variations of the gene were associated with impaired brain functional connectivity.10,11 More research is needed to understand how this gene increases schizophrenia susceptibility. Another significant finding—and perhaps the most replicated finding from genome-wide schizophrenia studies—is the MHC region on chromosome 6p22.1. This region is a recombination hotspot and harbors many genetic variants. Many immune-related genes were previously associated with autoimmune and infectious disorders, which suggests that the immunological system plays a role in schizophrenia pathogenesis. These genes may also involve neurodevelopment, synaptic plasticity, and other neuronal processes.12 Because of the complex gene composition, it is difficult to pinpoint the exact signal to schizophrenia pathophysiology.

Most recently, MIR137 was found to be associated with schizophrenia in a large genome-wide association study in 17,836 patients and 33,859 controls.13 MicroRNAs are small, noncoding RNA fragments involved in posttranscriptional regulation of messenger RNAs. MIR137 affects transcription of genes that play important roles in neuron maturation and adult neurogenesis. The other 4 loci that achieve genome-wide significance (TCF4, CACNA1C, CSMD1, and C10orf26) all contain predicted target sites of MIR137.13 This suggests that MIR137-mediated dysregulation may be an etiological pathway to schizophrenia.

Despite encouraging findings, there are caveats in interpreting these studies. The effect sizes of these genetic variants are small and explain only 1% to 2% of genetic risks for schizophrenia. Multiple genes have to be combined to create a “polygenic score” to explain larger chunks of schizophrenia risk. Sensitivity and specificity of these polygenic scores in predicting schizophrenia or any other mental disorder are quite low, rendering them useless in clinical practice. Future research should focus on gene-environment interactions as well as gene-gene interactions in relation to schizophrenia’s neurodevelopmental processes.

Another issue is that many of the top hits in genome-wide association studies are single nucleotide
polymorphisms that either are not functional or are located in intergenic regions with unknown functions. They may be proxies of variants that play causal roles in pathogenesis of diseases but were not directly genotyped in these studies. Furthermore, although genes such as DISC1 are linked to schizophrenia, they are neither necessary nor sufficient for developing the disorder, and they are equally linked, if not more strongly, to other neuropsychiatric disorders. Thus, they are not schizophrenia genes. In fact, variations in multiple genes likely cause slight deviations in neurodevelopment, which when combined with environmental variables, lead to the development of schizophrenia.

Nevertheless, findings from these schizophrenia genome-wide association studies provide insight into this complex disorder. More work is needed to move from these association signals to understanding the function and regulation of these genes, so that we may turn basic biological knowledge into targets for new medications as well as for other interventions.

**Pharmacogenetics of antipsychotic drug response**

Genetic research of schizophrenia not only has the potential to generate molecular targets for new drugs, but it also contributes to our knowledge of how to best use currently available drugs. Every clinician has experienced the frustration of trying to find an appropriate medication for a schizophrenic patient. Many patients drop out of treatment because the regimen is ineffective and/or because of significant adverse drug reactions. More often than not, medication has to be changed because of lack of efficacy or because of intolerable adverse effects. Clinical predictors for which medications could work for a particular patient are lacking. In this regard, pharmacogenetics may play a role in personalized medicine: pharmacogenetics uses genetic information to guide drug selection to maximize therapeutic efficacy and minimize drug-induced adverse effects.

Clozapine-induced agranulocytosis is a rare but potentially serious adverse effect that limits clinical use of this drug despite its enhanced efficacy in patients with refractory schizophrenia. The burden of weekly blood monitoring might be lifted by the identification of a genetic marker for agranulocytosis. It may be associated with genetic variations of HLA (human leukocyte antigen). A recent pharmacogenetic study replicated the association of an allele at the HLA-DQB1 locus with risk of agranulocytosis in 2 small clozapine-treated cohorts. Effect sizes were extremely high (odds ratio = 16.86); agranulocytosis developed in nearly 90% of allele carriers. Unfortunately, the overall sensitivity of the marker was only 21%, which indicates that a majority of individuals in whom agranulocytosis develops are not carriers of the allele, and presumably they have other genetic risk factors. Thus, a more comprehensive risk profile would be necessary to obviate the need for invasive monitoring.

Weight gain is a common adverse effect of antipsychotic medications. Previous research has found a replicated association between HTR2C and weight gain. Recently, our group has found a strong genetic signal in predicting antipsychotic-induced weight gain. A genome-wide association study of antipsychotic-induced weight gain discovered a single top signal on chromosome 18q21 in a pediatric sample for whom antipsychotic drugs were prescribed for the first time. This was replicated in 3 other independent samples, which confirmed the robustness of the finding.

This locus is approximately 150 kb downstream from MC4R, the melanocortin 4 receptor gene, which has been previously found to be associated with obesity in the general population. Mutations in this gene are linked with extreme obesity in humans. MC4R-expressing neurons in the ventromedial hypothalamus are regulated by circulating levels of leptin via pathways in the arcuate nucleus. These leptin-sensitive pathways are regulated by serotonin (5-HT) 2C receptors, which are implicated in weight gain. In the discovery sample, risk allele homozygotes gained twice as much weight as other patients after 12 weeks of treatment, and the genetic effect was not drug-specific (Figure 1). The consistency of the HTR2C-MC4R findings increases the possibility that a drug may be developed to treat or prevent antipsychotic-induced weight gain.

Another line of pharmacogenetic study of antipsychotic drug response focuses on genes coding for enzymes in drug metabolism. The cytochrome P-450 (CYP) enzymes are responsible for the metabolism of many drugs. Among its subtypes, 2D6 is the main metabolic pathway for several antipsychotics, including risperidone, aripiprazole, haloperidole, and perphenazine.

The CYP2D6 gene contains more than 100 variants, many of which yield nonfunctional or reduced-function enzymes. There are 4 phenotypes of CYP2D6 produced by combinations of various alleles with different degrees of enzymatic activities: poor, intermediate, extensive, and ultrarapid metabolizers. Compared with extensive metabolizers with normal CYP2D6 enzyme activity, poor metabolizers and intermediate metabolizers have minimal or reduced activity, respectively. Approximately 7% to 10% of whites and 1% to 2% of Asians are poor metabolizers, who tend to accumulate higher drug levels in blood and who, theoretically, require lower dosages to achieve
therapeutic effects. In contrast, ultrarapid metabolizers have duplicate or multiple copies of the gene, which results in increased enzyme activity. They account for only 1% of the population and may require higher dosages because of faster elimination of the drug. Therefore, CYP2D6 metabolic status could theoretically play an important role in determining antipsychotic response (Figure 2).

So far, there are no empirical data to support the association between CYP2D6 and antipsychotic efficacy, although studies have found significant relationships between poor metabolizers and a higher rate of drug-induced adverse effects, such as tardive dyskinesia, extrapyramidal symptoms, and weight gain. A meta-analysis of 8 studies demonstrated that poor metabolizers had a 43% higher risk of tardive dyskinesia than extensive metabolizers had. The FDA-approved pharmacogenetic AmpliChip® CYP450 Test is available to assess CYP2D6 and CYP2C19 genotypes. Several other companies also offer pharmacogenetic testing in this regard. However, use has been limited because of clinicians’ concerns about the interpretation of test results and the lack of reimbursement for an expensive test. Most important, there are no prospective data that show that test use influences clinical outcome. We are currently conducting such a prospective clinical trial, and data will soon become available.

**Implications for clinical practice**

Although schizophrenia genetic research has made tremendous progress in the past decade, most of the findings are still at basic science level and clinical applications are limited. It is premature to attempt testing genetic markers to help diagnose schizophrenia or other mental disorders. The hope is that new gene discovery will translate to better understanding of pathophysiological mechanisms that underlie schizophrenia, which, in turn, might lead to novel molecular targets for drug development.

Pharmacogenetics helps clinicians use existing drugs more efficiently by maximizing efficacy and minimizing adverse effects. Several institutions have experimented with genotyping CYP450 in routine clinical practice, but prospective pharmacogenetic clinical trials are needed to validate the utility and cost-effectiveness of genetic testing-guided treatment algorithms. The future is bright, but we are not there yet.

**FIGURE 1: MC4R single nucleotide polymorphisms rs489693 genotype and a...**

**FIGURE 2: Dose adjustments according to CYP2D6 phenotypes. The dose re...**

**Disclosures:**

Dr Zhang is Attending Psychiatrist in the division of psychiatry research at the Zucker Hillside Hospital; Assistant Investigator at the Feinstein Institute of Medical Research, North Shore-Long Island Jewish Health System in Glen Oaks, NY; and Assistant Professor of Psychiatry at the Hofstra North Shore-LIJ School of Medicine in Hempstead, NY. Dr Malhotra is Director, division of psychiatry research at the Zucker Hillside Hospital; Investigator, Center for Psychiatric Neuroscience at the Feinstein Institute for Medical Research in Manhasset, NY; and Professor of Psychiatry and Molecular Medicine at the Hofstra North Shore-LIJ School of Medicine. The authors report no conflicts of interest concerning the subject matter of this article.
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