GENETICS OF SCHIZOPHRENIA: WHAT DO WE KNOW?

Researchers are discovering clues to predict susceptibility, improve treatment

Genetic factors play a major role in the etiology and development of schizophrenia. Genetic linkage studies and twin studies have estimated the heritability of schizophrenia to be 70% to 90%.¹ Research on the genetic underpinnings of schizophrenia has accelerated since the Human Genome Project was completed in 2001, which opened the door to expanding our understanding of molecular mechanisms of human diseases. Experts have hailed the dawn of personalized medicine,² hoping that we will be able to use knowledge of the human genome to tailor individual treatment.

In this article we review some significant recent findings in genetics of schizophrenia. Gene names are italicized and proteins coded by genes are not. The names, functions, and locations of all genes included in this article appear in the Table (page 26). For a glossary of genetic terms, see this article at CurrentPsychiatry.com.

Focusing on single nucleotide polymorphisms

Genetic research of diseases previously relied on linkage studies, which focus on linking a chromosome region to transmission of a particular trait across multiple familial generations. This approach has identified several genomic regions that may be associated with schizophrenia, but most of these regions contain multiple genes and are not specific to schizophrenia.

Today, many genetic studies examine variations of a single nucleotide in the DNA sequence, i.e., a change of 1 letter in a particular location on the DNA chain. Single nucleotide polymorphisms (SNPs)—relatively common DNA variations found in >5% of the population—have

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been a major focus of psychiatric genetics in the past decade. Technology now allows researchers to simultaneously genotype millions of SNPs across the genome, producing tremendous power to investigate the entire genome in relation to a phenotype (a disease or a trait) in genome-wide association studies (GWAS). GWAS do not require an a priori hypothesis regarding which regions or genes may be important, and have yielded many novel genetic variants implicated in schizophrenia.

### Susceptibility genes

Genetic researchers initially hoped to find that one or a few genes are responsible for schizophrenia. However, recent research revealed that many genes may be involved in susceptibility to schizophrenia, and that a particular gene may contribute to the risk of not only schizophrenia but also other psychiatric disorders such as bipolar disorder (BD).

Discovery of the DISC1 gene is an example of how our understanding of the complex genetic architecture in psychiatric illness has advanced with each new genetic variant identified. DISC1 is implicated in both schizophrenia and bipolar disorder, highlighting the potential for this gene to play a role in multiple psychiatric disorders.

### Table

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>Location</th>
<th>Function(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CACNA1C</td>
<td>Calcium channel, voltage-dependent, L type, alpha 1C subunit</td>
<td>12p13.3</td>
<td>Calcium channels mediate the influx of calcium ions into the cell upon membrane polarization</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
<td>22q11.21</td>
<td>Key enzyme in degradation of dopamine and norepinephrine</td>
</tr>
<tr>
<td>CSMD1</td>
<td>CUB and Sushi multiple domains 1</td>
<td>8p23.2</td>
<td>One of the proteins that modulate the classical complement pathway, part of the immune system</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Cytochrome P450 2D6</td>
<td>22q13.1</td>
<td>Key enzyme in drug metabolism</td>
</tr>
<tr>
<td>C10orf26</td>
<td>Chromosome 10 open reading frame 26</td>
<td>10q24.32</td>
<td>Unknown</td>
</tr>
<tr>
<td>DISC1</td>
<td>Disrupted in schizophrenia 1</td>
<td>1q42</td>
<td>Neurite outgrowth, cortical development, synaptic function</td>
</tr>
<tr>
<td>DRD1</td>
<td>Dopamine receptor D1</td>
<td>5q35.1</td>
<td>D1 receptors regulate neuronal growth and development, mediate behavioral responses, and modulate D2 receptor-mediated events</td>
</tr>
<tr>
<td>DRD2</td>
<td>Dopamine receptor D2</td>
<td>11q23</td>
<td>D2 receptors regulate motor activities and information processing in the brain</td>
</tr>
<tr>
<td>DTNBP1</td>
<td>Dystrobevin binding protein 1</td>
<td>6p22</td>
<td>Neurodevelopment and synaptic transmission</td>
</tr>
<tr>
<td>HLA-DQB1</td>
<td>Major histocompatibility complex, class II, DQ beta 1</td>
<td>6p21.3</td>
<td>Plays a central role in the immune system by presenting peptides derived from extracellular proteins</td>
</tr>
<tr>
<td>HTR2C</td>
<td>Serotonin receptor 2C</td>
<td>Xq24</td>
<td>Modulate mood, food intake behavior, and feeling of satiety</td>
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<tr>
<td>MC4R</td>
<td>Melanocortin 4 receptor</td>
<td>18q22</td>
<td>Modulate food intake behavior and feeling of satiety</td>
</tr>
<tr>
<td>MHC region</td>
<td>Major histocompatibility complex</td>
<td>6p21-22</td>
<td>Immune function; neurodevelopment, synaptic plasticity</td>
</tr>
<tr>
<td>MIR137</td>
<td>MicroRNA 137</td>
<td>1p23.3</td>
<td>Post-transcriptional regulation of messenger RNAs; neuron maturation, adult neurogenesis</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Methylenetetrahydrofolate reductase</td>
<td>1p36.3</td>
<td>Key enzyme in folate metabolism</td>
</tr>
<tr>
<td>TCF4</td>
<td>Transcription factor 4</td>
<td>18q21.2</td>
<td>Neuronal transcription factor, neurogenesis</td>
</tr>
<tr>
<td>TPH1</td>
<td>Tryptophan hydroxylase 1</td>
<td>11p15.3</td>
<td>Key enzyme in biosynthesis of serotonin</td>
</tr>
<tr>
<td>ZNF804A</td>
<td>Zinc finger protein 804A</td>
<td>2q32.1</td>
<td>Transcription factor, neuronal connectivity in the dorsolateral prefrontal cortex</td>
</tr>
</tbody>
</table>
disorders has evolved. In 2000, a linkage study in a Scottish family cohort found a translocation on chromosome 1, t(1:11), highly correlated with schizophrenia. Later studies found that this translocation directly disrupts a gene, which researchers named “disrupted in schizophrenia 1.” 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. Disruption of DISC1 results in dysfunction in multiple neurodevelopmental processes, significantly increasing susceptibility not only for schizophrenia but also for BD and depression.

Many common variants of DISC1 slightly alter expression levels of the gene, which may exert subtle but pervasive effects on neural circuitry development. DISC1 knockout mouse models showed close interactions between DISC1 and N-methyl-p-aspartate receptors and dopamine D2 receptors, linking to the glutamate hypothesis of schizophrenia and the common site of action of antipsychotics. Despite advances in understanding the biology of DISC1, large case-control studies have not found a consistent association between DISC1 and schizophrenia. It is possible that DISC1 pathology represents one subtype of schizophrenia that is not prevalent among the general population; therefore, large-scale epidemiologic studies could not find evidence to support DISC1’s role in schizophrenia.

DTNB1 is another schizophrenia susceptibility gene discovered in linkage studies. Originally found in a large Irish cohort, several SNPs of DTNB1 were significantly associated with schizophrenia. A meta-analysis of candidate genes identified DTNB1 as one of 4 genes with the strongest evidence for association with schizophrenia (the other 3 are DRD1, MTHFR, and TPH1). DTNB1 is widely expressed in the brain and is present in presynaptic, postsynaptic, and microtubule locations implicated in a number of brain functions, including synaptic transmission and neurite outgrowth in a developing organism. Furthermore, DTNB1 is associated with cognitive functions in schizophrenia patients as well as in control subjects. Cognitive impairment is considered an endophenotype for schizophrenia. Similar to DISC1 and other candidate genes, DTNB1 has not emerged as a significant hit in later, large-scale GWAS studies.

Since the first schizophrenia GWAS in 2007, >15 GWAS have been published, with increasingly larger sample sizes. GWAS are based on the “common disease/common variant hypothesis” that common disorders such as diabetes, macular degeneration, and schizophrenia are caused by multiple common variants in the genome. Because GWAS can analyze hundreds of thousands of SNPs simultaneously, a stringent criterion (usually \( P < 5 \times 10^{-8} \)) is used to gauge statistical significance to correct for multiple testing. Because most effect sizes associated with genetic markers in psychiatry are fairly small (odds ratios [ORs] are approximately 1.1 to 1.2), large samples are required to detect significant effects. Several international consortia have accumulated large samples. The Psychiatric GWAS Consortium has >17,000 patients with schizophrenia, >11,000 with BD, >16,000 with major depression, and >50,000 healthy controls. This wave of GWAS has implicated several novel genomic regions in schizophrenia pathophysiology, including ZNF804A, the major histocompatibility complex (MHC) region, and MIR137.

ZNF804A was the first gene that reached genome-wide significance in a large GWAS, and this finding has been replicated. The function of this novel gene largely is unknown. ZNF804A is widely expressed in the brain, especially in the developing hippocampus and the cortex as well as in the adult cerebellum. Recent studies found that ZNF804A is a putative transcription factor, upregulating expression of catechol-O-methyltransferase while downregulating dopamine D2 receptors.
The effect of antipsychotic response associated with the DISC1 polymorphism

Clinical Point
The -141C Ins/Del polymorphism of the DRD2 gene is significantly associated with antipsychotic response

Limitations of these findings. The effect sizes of these genetic variants are small, explaining only 1% to 2% of genetic risks of schizophrenia. However, this is not unique to schizophrenia or psychiatry. “Missing heritability” is puzzling in other branches of medicine. Future research will focus on gene-environment interactions as well as gene-gene interactions in relation to schizophrenia’s neurodevelopmental processes.

In addition, many top hits in GWAS are SNPs that are not functional or located in intergenic regions with unknown functions. They may be proxies of causal variants that truly play causal roles in pathogenesis of diseases but were not genotyped in those studies. Recently, researchers have grown increasingly interested in copy number variations (CNVs) in the etiology of complex diseases. Compared with SNPs, CNVs usually are much larger changes in the DNA sequence, including deletions and duplications of a large chunk of DNA segments. Disease-causing CNVs are rare but have large effect sizes. Recent studies have examined the role of CNVs in schizophrenia.

Although genes such as DISC1 and CACNA1C are linked to schizophrenia, they are neither necessary nor sufficient for developing the disorder, and also are linked equally, if not more strongly, to other neuropsychiatric disorders, including BD and autism. Therefore, they are not “schizophrenia genes.” Variations in multiple genes likely cause slight deviations in neurodevelopment that interact with environmental variables and lead to development of schizophrenia.

Nevertheless, these schizophrenia GWAS findings provide insight into this complex disorder. Much work is needed to move from these association signals to understanding the function and regulation of these genes to turn basic biologic knowledge into targets for new drugs or other interventions.

Antipsychotic pharmacogenetics
Genetic research of schizophrenia also contributes to our knowledge of how to best use existing drugs. Medications for treating schizophrenia often need to be changed because patients experience lack of efficacy or intolerable side effects, which may lead them to discontinue treatment. Clinical predictors of which medication would work for an individual patient are lacking. Pharmacogenetics may be able to fulfill the promise of personalized medicine in psychiatry by using genetic information to guide drug selection to maximize therapeutic efficacy and minimize drug-induced side effects.

Researchers first attempted to find genetic predictors of antipsychotic efficacy in the early 1990s. One replicated finding is that DRD2, the gene coding for dopamine receptor D2, is associated with antipsychotic efficacy. This may not be surprising because D2 receptor antagonism is a common and

continued on page 30
necessary drug action mechanism for all antipsychotics. One SNP, -141C Ins/Del (rs1799732), represents a deletion (vs insertion) of cytosine at position -141, located in the 5’ promoter region of DRD2. Pre-clinical studies showed that this SNP might modulate DRD2 gene expression and influence D2 receptor density in the brain. Del allele carriers had poor response to clozapine among a treatment-refractory sample and took longer to respond to olanzapine and risperidone among first-episode schizophrenia patients. A 2010 meta-analysis of approximately 700 patients showed that the -141C Ins/Del polymorphism is significantly associated with antipsychotic response. Patients who carry 1 or 2 Del alleles tend to have a less favorable antipsychotic response than patients with the Ins/Ins genotype. Patients with the Ins/Ins genotype are 54% more likely to respond to antipsychotics than those with ≥1 copy of the Del allele.

Researchers have studied other genes in relation to antipsychotic efficacy, but have yielded few consistent findings. Some have looked at combining multiple SNPs across several genes to predict antipsychotic efficacy, but these findings have not been replicated. For example, a combination of variants in the HTR2A, HTR2C, and 5-HTTLPR genes and genes coding for H2 receptors was found to correctly predict clozapine response in 76% of patients. However, this finding was not replicated in an independent sample.

A recent GWAS found that a combination of 6 genetic markers—NPAS3, XKR4, TNR, GRIA4, GFRA2, and NUDT9P1—predicted treatment response to iloperidone. Although promising, this finding needs to be validated in independent samples.

Predicting adverse drug events
In other branches of medicine, researchers have used pharmacogenetics to successfully identify predictors of drug-induced adverse events. A GWAS found that a specific human leukocyte antigen (HLA) allele markedly increases the risk of liver toxicity from flucloxacillin (OR=80.6). This HLA marker also is related to hypersensitivity reaction to abacavir, a common medication for treating AIDS, and lamotrigine-induced Stevens-Johnson syndrome.

**Clozapine-induced granulocytosis** also may be related to genetic variation in the HLA region. Despite superior efficacy, clozapine remains underutilized in part because it carries the risk of potentially fatal agranulocytosis. Identifying a genetic marker for agranulocytosis would lift the burden of weekly blood monitoring. A recent pharmacogenetic study detected a replicated association of an allele at the HLA-DQB1 locus with risk of agranulocytosis in 2 small groups of clozapine-treated schizophrenia patients. Effect sizes were extremely high (OR=16.86); nearly 90% of allele carriers developed agranulocytosis. Unfortunately, the overall sensitivity of the marker was 21%, indicating that most individuals who develop agranulocytosis are not carriers of the allele and presumably have other genetic risk factors. A more comprehensive risk profile would be necessary to obviate the need for weekly blood monitoring.

**Weight gain** and metabolic syndrome are common side effects of antipsychotics, and no clear clinical predictors have been identified. Researchers have examined potential genetic markers in association with antipsychotic-induced weight gain. One consistent finding has been that a single SNP in the promoter region of the HTR2C gene (serotonin receptor 2C), C-759T (rs3813929), affects antipsychotic-induced weight gain. The 5-HT2C receptor is involved in regulating food intake in rodents and is related to late-onset diabetes and obesity in humans. HTR2C knockout mice display chronic hyperphagia that leads to obesity and hyperinsulinemia. Since the original finding in 2002, at least 17 studies have reported on the association between the C-759T SNP in HTR2C and antipsychotic-induced weight gain. A meta-analysis found that the T allele was significantly protective against antipsychotic-induced weight gain. The C allele was associated with >2-fold increase of risk for clinically significant weight gain (gaining >7% of baseline body weight).
In a GWAS of antipsychotic-induced weight gain in pediatric patients who were prescribed antipsychotics for the first time, researchers discovered a single top signal at a marginally genome-wide significant level \((P = 1.6 \times 10^{-7})\). This was replicated in 3 other independent samples. The peak signal is located on chromosome 18q21, overlapping a peak identified as a predictor of obesity. This locus is approximately 150 kb downstream from \(MC4R\), the melanocortin 4 receptor gene, which has long been suspected as a candidate for weight-related phenotypes, including antipsychotic-induced weight gain.

The consistency of HTR2C-\(MC4R\) findings poses a possibility that a drug may be developed at these targets to treat or prevent antipsychotic-induced weight gain.

**Drug metabolism.** Pharmacogenetic studies of antipsychotic drug response also have focused on genes that code for enzymes in drug metabolism, particularly cytochrome (CYP) 450 enzymes, which are responsible for the metabolism of many drugs. CYP2D6 is the main metabolic pathway for several antipsychotics, including risperidone, aripiprazole, haloperidol, and perphenazine. The \(CYP2D6\) gene contains >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 (PM), intermediate (IM), extensive (EM), and ultrarapid metabolizers (UM). Compared with EMs with normal \(CYP2D6\) enzyme activity, PMs and IMs have minimal or reduced activity, respectively. UMds have duplicate or multiple copies of the gene that result in increased enzyme activity.

**Clinical Point**

A single nucleotide polymorphism in the promoter region of the \(HTR2C\) gene affects antipsychotic-induced weight gain.
CYP2D6 metabolic status could play an important role in determining patients’ antipsychotic response.

Implications for clinical practice

Although schizophrenia genetic research has made tremendous progress in the past decade, most findings are at basic science level and clinical applications are limited. It is premature to attempt to use genetic markers to help diagnose schizophrenia or other psychiatric disorders. Researchers hope that new gene discovery will translate to better understanding of the pathophysiologic mechanisms underlying schizophrenia, which in turn lead to finding novel molecular targets for new drug development. Furthermore, pharmacogenetics helps clinicians use existing drugs more efficiently by maximizing efficacy and minimizing side 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.

References

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22. Walsh T, McClellan JM, McCarthy SE, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science. 2008;320(5875):539-543.


Bottom Line

Variations in multiple genes likely cause slight deviations in neurodevelopment that interact with environmental variables and lead to development of schizophrenia. Genome-wide association studies are allowing researchers to gain insight into which patients may have increased susceptibility to the disorder, identify potential molecular targets for new drugs, and expand their knowledge of how to best use medications.
## Glossary of genetic terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allele</strong></td>
<td>One of several variants of a gene, usually referring to a specific site within the gene</td>
</tr>
<tr>
<td><strong>Association study</strong></td>
<td>Genetic association refers to the association between a particular genotype and a phenotypic trait in the population. Genetic association studies aim to test whether single-locus alleles genotype frequencies or multi-locus haplotype frequencies differ between 2 groups (such as cases and controls)</td>
</tr>
<tr>
<td><strong>Candidate gene study</strong></td>
<td>A study that evaluates association of specific genetic variants with outcomes or traits of interest, selecting variants to be tested according to explicit considerations (known or postulated biology or function, previous studies, etc.)</td>
</tr>
<tr>
<td><strong>Case-control design</strong></td>
<td>An association study design in which the primary comparison is between a group of individuals (cases) ascertained for the phenotype of interest (eg, patients with schizophrenia) and a second group (control) ascertained for not having the phenotype (eg, healthy controls)</td>
</tr>
<tr>
<td><strong>Copy number variation</strong></td>
<td>A class of DNA sequence variant (including deletions and duplications) in which the result is a departure from the expected 2-copy representation of DNA sequence (ie, each person has 2 copies of the same chromosome)</td>
</tr>
<tr>
<td><strong>Endophenotype</strong></td>
<td>Phenotypes that are genetically determined, directly measurable traits as part of a complex illness. This term is used to connect the pathway from genes to a disease (eg, impairment in working memory is an endophenotype of schizophrenia)</td>
</tr>
<tr>
<td><strong>Genetic association</strong></td>
<td>A relationship that is defined by the nonrandom occurrence of a genetic marker with a trait, which suggests an association between the genetic marker (or a marker close to it) and disease pathogenesis</td>
</tr>
<tr>
<td><strong>Genetic marker</strong></td>
<td>A specific genetic variant known to be associated with a recognizable trait or disease</td>
</tr>
<tr>
<td><strong>Genome</strong></td>
<td>The entire collection of genetic information (or genes) that an organism possesses</td>
</tr>
<tr>
<td><strong>Genome-wide association study</strong></td>
<td>A study that evaluates association of genetic variation with outcomes or traits of interest by using 300,000 to 1,000,000 markers across the whole genome. No hypothesis about any particular gene is required for GWAS</td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td>The genetic constitution of an individual, either overall or at a specific gene</td>
</tr>
<tr>
<td><strong>Heritability</strong> (h²)</td>
<td>A measure of the strength of genetic effects on a trait. It is defined as the proportion of the phenotypic variation in a trait that is attributable to genetic effects</td>
</tr>
<tr>
<td><strong>Linkage disequilibrium (LD)</strong></td>
<td>Two polymorphic loci are in LD when they are co-located, and alleles at those loci are distributed non-randomly with respect to each other on chromosomes in the population</td>
</tr>
<tr>
<td><strong>Linkage study</strong></td>
<td>A technique used in genetic epidemiology that focuses on linking a chromosome region to transmission of a particular trait across multiple familial generations</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>The observable characteristics of a cell or organism, usually being the results of the product coded by a gene (genotype)</td>
</tr>
<tr>
<td><strong>Polymorphism</strong></td>
<td>The existence of ≥2 variants of a gene, occurring in a population, with at least 1% frequency of the less common variant</td>
</tr>
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<td><strong>Recombination hotspot</strong></td>
<td>Recombination is breaking and rejoining of DNA strands to form new DNA molecules encoding a novel set of genetic information. Recombination hotspots are individual regions within the genome that have frequent recombination events (eg, the human leukocyte antigen region is a recombination hotspot)</td>
</tr>
<tr>
<td><strong>Single nucleotide polymorphism</strong></td>
<td>A single base pair change in the DNA sequence at a particular point, compared with the “common” or “wild type” sequence</td>
</tr>
<tr>
<td><strong>Translocation</strong></td>
<td>A type of chromosomal abnormality resulted by rearrangement of parts between nonhomologous chromosomes, often leading to cancer or developmental abnormalities</td>
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