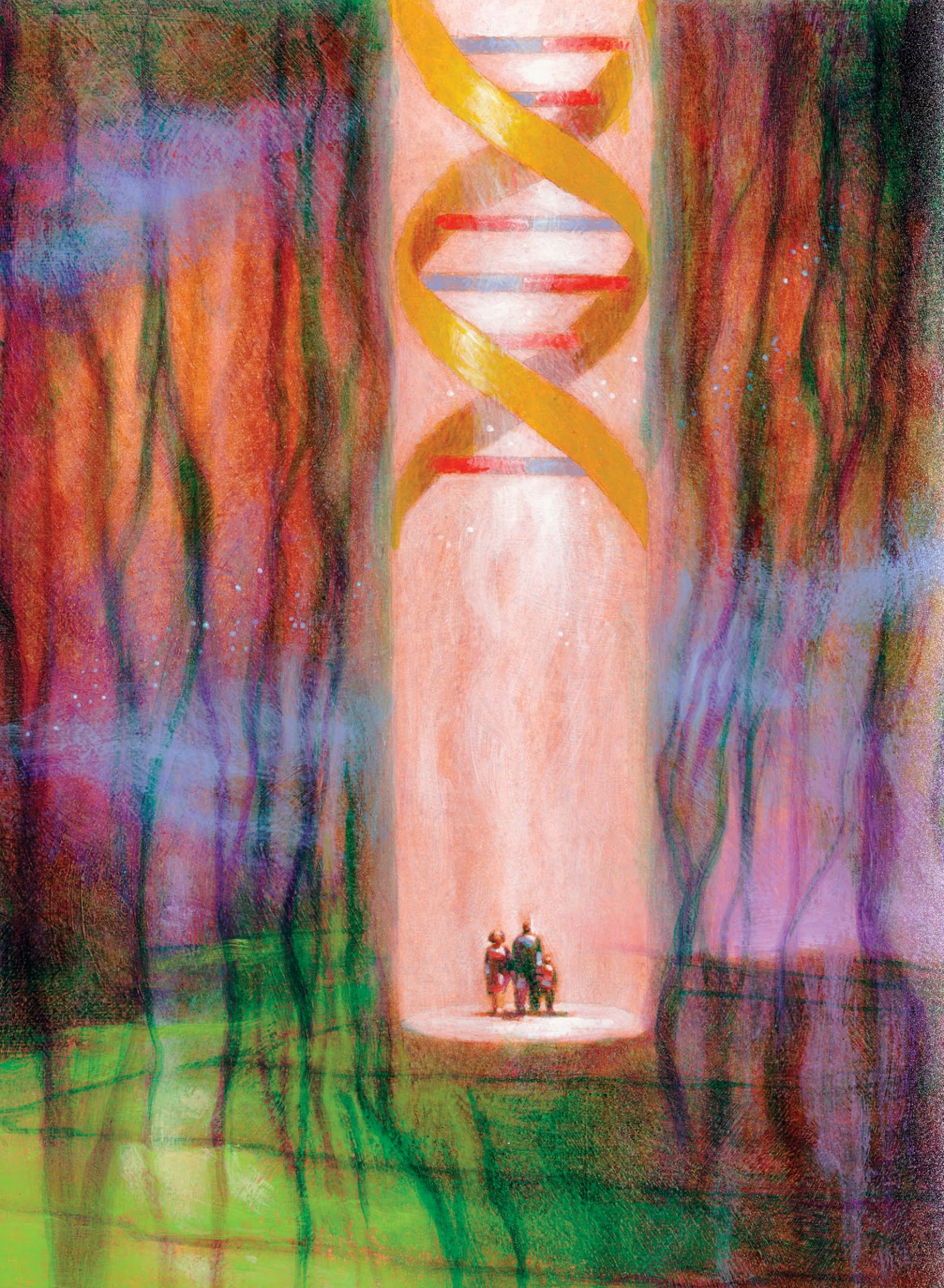

GENETICS OF SCHIZOPHRENIA: WHAT DO WE KNOW?

Researchers are discovering clues to predict susceptibility, improve treatment

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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, ie, 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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Clinical Point

Genome-wide association studies have implicated *ZNF804A*, the MHC region, and *MIR137* in schizophrenia pathophysiology

Table

Select genes and their functions

Gene	Name	Location	Function(s)
CACNA1C	Calcium channel, voltage-dependent, L type, alpha 1C subunit	12p13.3	Calcium channels mediate the influx of calcium ions into the cell upon membrane polarization
COMT	Catechol-O-methyltransferase	22q11.21	Key enzyme in degradation of dopamine and norepinephrine
CSMD1	CUB and Sushi multiple domains 1	8p23.2	One of the proteins that modulate the classical complement pathway, part of the immune system
CYP2D6	Cytochrome P450 2D6	22q13.1	Key enzyme in drug metabolism
C10orf26	Chromosome 10 open reading frame 26	10q24.32	Unknown
DISC1	Disrupted in schizophrenia 1	1q42	Neurite outgrowth, cortical development, synaptic function
DRD1	Dopamine receptor D1	5q35.1	D1 receptors regulate neuronal growth and development, mediate behavioral responses, and modulate D2 receptor-mediated events
DRD2	Dopamine receptor D2	11q23	D2 receptors regulate motor activities and information processing in the brain
DTNBP1	Dystrobrevin binding protein 1	6p22	Neurodevelopment and synaptic transmission
HLA-DQB1	Major histocompatibility complex, class II, DQ beta 1	6p21.3	Plays a central role in the immune system by presenting peptides derived from extracellular proteins
HTR2C	Serotonin receptor 2C	Xq24	Modulate mood, food intake behavior, and feeling of satiety
MC4R	Melanocortin 4 receptor	18q22	Modulate food intake behavior and feeling of satiety
MHC region	Major histocompatibility complex	6p21-22	Immune function; neurodevelopment, synaptic plasticity
MIR137	MicroRNA 137	1p23.3	Post-transcriptional regulation of messenger RNAs; neuron maturation, adult neurogenesis
MTHFR	Methylenetetrahydrofolate reductase	1p36.3	Key enzyme in folate metabolism
TCF4	Transcription factor 4	18q21.2	Neuronal transcriptional factor, neurogenesis
TPH1	Tryptophan hydroxylase 1	11p15.3	Key enzyme in biosynthesis of serotonin
ZNF804A	Zinc finger protein 804A	2q32.1	Transcription factor, neuronal connectivity in the dorsolateral prefrontal cortex

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).[3] 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

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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.[4] 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.[5] 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-D-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.[6,7] 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.

DTNBP1 is another schizophrenia susceptibility gene discovered in linkage studies. Originally found in a large Irish cohort, several SNPs of *DTNBP1* were significantly associated with schizophrenia.[8] A meta-analysis of candidate genes identified *DTNBP1* as one of 4 genes with the strongest evidence for association with schizophrenia (the other 3 are *DRD1*, *MTHFR*, and *TPH1*).[9] *DTNBP1* 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, *DTNBP1* is associated with cognitive functions in schizophrenia patients[10] as well as in control subjects.[11] Cognitive impairment is considered an endophenotype for schizophrenia. Similar to *DISC1* and other candidate genes, *DTNBP1* has not emerged as a significant hit in later, large-scale GWAS studies.

Since the first schizophrenia GWAS in 2007,[12] >15 GWAS have been published, with increasingly larger samples 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 $P < 5\times10^{-8}$) 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,[13] 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 in animal studies.[14] The minor allele of SNP rs1344706 was associated with impaired brain functional connectivity in a human study.[15] More work is needed to understand how this gene increases schizophrenia susceptibility.

continued

Clinical Point

***ZNF804A* is a putative transcription factor, upregulating expression of COMT while downregulating dopamine D2 receptors**

See this article at CurrentPsychiatry.com for a glossary of genetic terms

Clinical Point

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

The MHC region on chromosome 6p22.1,1 also was significant in schizophrenia GWAS,[16,17] and this may be the most replicated schizophrenia GWAS finding. This region is a recombination hotspot and harbors many genetic variants. Many immune-related genes previously were associated with autoimmune and infectious disorders, which may suggest that the immunologic system plays a role in schizophrenia pathogenesis. These genes also may involve neurodevelopment, synaptic plasticity, and other neuronal processes.[18] However, the complex gene composition in the region makes it difficult to pinpoint the exact signal to schizophrenia pathophysiology.

The most recent finding from the largest GWAS is *MIR137*,[19] coding for microRNA 137, which was associated with schizophrenia at $P = 1.6\times10^{-11}$ in 17,836 patients and 33,859 controls. MicroRNAs are small, non-coding RNA fragments that are involved in post-transcriptional regulation of messenger RNAs. *MIR137* plays important roles in neuron maturation and adult neurogenesis by acting at the level of dendritic morphogenesis and spine development.[20] More interestingly, the other 4 loci achieving genome-wide significance in the same GWAS (*TCF4*, *CACNA1C*, *CSMD1*, and *C10orf26*) contain predicted target sites of *MIR137*. This suggests *MIR137*-mediated dysregulation may be an etiologic mechanism in schizophrenia.

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.[21] 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.[22,23]

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

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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[24] and took longer to respond to olanzapine and risperidone among first-episode schizophrenia patients.[25] A 2010 meta-analysis of approximately 700 patients[26] 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.

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Clozapine-induced agranulocytosis may be related to genetic variation in the human leukocyte antigen region

Researchers have studied other genes in relation to antipsychotic efficacy, but have yielded few consistent findings.[27] 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.[28] However, this finding was not replicated in an independent sample.[29] A recent GWAS[30] 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).[31] 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.[32] 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,[33] 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.[34] 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 ($P = 1.6 \times 10^{-7}$).[35] 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.[36] Mutations in this gene are linked with extreme obesity in humans, and *MC4R* knockout mice develop obesity. *MC4R*-expressing neurons in the ventromedial hypothalamus are regulated by circulating levels of leptin via pathways in the arcuate nucleus. In turn, *MC4R* regulates 5-HT2C 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. 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. UMs have duplicate or multiple copies of the gene that result in increased en-

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Clinical Point

A single nucleotide polymorphism in the promoter region of the *HTR2C* gene affects antipsychotic-induced weight gain

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CYP2D6 metabolic status could play an important role in determining patients' antipsychotic response

Related Resource

- National Institute of Mental Health Center for Collaborative Genomic Studies on Mental Disorders. Schizophrenia. www.nimhgenetics.org/available_data/schizophrenia.

Drug Brand Names

Abacavir • Ziagen
Aripiprazole • Abilify
Clozapine • Clozaril
Haloperidol • Haldol
Iloperidone • Fanapt
Lamotrigine • Lamictal
Olanzapine • Zyprexa
Perphenazine • Trilafon
Risperidone • Risperdal

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zyme activity. Approximately 7% to 10% of whites and 1% to 2% of Asians are PMs, who tend to accumulate higher serum drug levels and, theoretically, require lower doses to achieve therapeutic effects. UMs, in contrast, consist of 1% of the population and may require higher doses because of faster drug elimination.[37] Therefore, CYP2D6 metabolic status could play an important role in determining patients' antipsychotic response. So far, no empirical data support the association between CYP2D6 and antipsychotic efficacy, although studies have found significant relationships between PMs and higher rates of drug-induced side effects such as tardive dyskinesia (TD), extrapyramidal symptoms, and weight gain. A meta-analysis[38] of 8 studies showed that PMs had a 43% higher risk of developing TD compared with EMs. An FDA-approved pharmacogenetic test, AmpliChip® CYP450 Test, is available to assess CYP2D6 and CYP2C19 genotypes,[39] but its use is limited, perhaps because of clinician concerns about how to interpret test results, paucity of prospective data suggesting that using the test can improve clinical outcomes, and lack of reimbursement.

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.[40] Researchers hope that new gene discovery will translate to better understanding of the pathophysiological 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,[41] but prospective pharmacogenetic clinical trials are needed to validate the utility and cost-effectiveness of genetic testing-guided treatment algorithms.[42]

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Clinical Point

Prospective pharmacogenetic trials are needed to validate the utility of genetic testing-guided treatment algorithms

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.

Table

Glossary of genetic terms

Allele: One of several variants of a gene, usually referring to a specific site within the gene
Association study: 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)
Candidate gene study: 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.)
Case-control design: 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)
Copy number variation: 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)
Endophenotype: 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)
Genetic association: 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
Genetic marker: A specific genetic variant known to be associated with a recognizable trait or disease
Genome: The entire collection of genetic information (or genes) that an organism possesses
Genome-wide association study: 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
Genotype: The genetic constitution of an individual, either overall or at a specific gene
Heritability (h^2): 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
Linkage disequilibrium (LD): 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
Linkage study: A technique used in genetic epidemiology that focuses on linking a chromosome region to transmission of a particular trait across multiple familial generations
Phenotype: The observable characteristics of a cell or organism, usually being the results of the product coded by a gene (genotype)
Polymorphism: The existence of ≥2 variants of a gene, occurring in a population, with at least 1% frequency of the less common variant
Recombination hotspot: 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)
Single nucleotide polymorphism: A single base pair change in the DNA sequence at a particular point, compared with the "common" or "wild type" sequence
Translocation: A type of chromosomal abnormality resulted by rearrangement of parts between nonhomologous chromosomes, often leading to cancer or developmental abnormalities