Pharmacogenetics and Antipsychotics: Therapeutic Efficacy and Side Effects Prediction

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Abstract

Importance of the field—Antipsychotic drug is the mainstay of treatment for schizophrenia, and there are large inter-individual differences is clinical response and side effects. Pharmacogenetics provides a valuable tool to fulfill the promise of personalized medicine by tailoring treatment based on one's genetic markers.

Areas covered in this review—This article reviews the pharmacogenetic literature from early 1990s to 2010, focusing on two aspects of drug action: pharmacokinetics and pharmacodynamics. Genetic variants in the neurotransmitter receptors including dopamine and serotonin, and metabolic pathways of drugs including CYP2D6 and COMT, were discussed in association with clinical drug response and side effects.

What the reader will gain—Readers are expected to learn the up-to-date evidence in pharmacogenetic research, and to gain familiarity to the issues and challenges facing the field.

Take home message—Pharmacogenetic research of antipsychotic drugs is both promising and challenging. There is consistent evidence that some genetic variants can affect clinical response and side effects. However, more studies that are designed specifically to test pharmacogenetic hypotheses are clearly needed to advance the field.

1. Introduction

Schizophrenia is a chronic and debilitating mental disorder, characterized by both positive and negative symptoms such as hallucinations, delusions, thought disorders, avolition and social withdraw, as well as cognitive and functional impairment[1]. The life-time prevalence of schizophrenia ranges from 0.30% to 0.66% worldwide, up to 2.3% including other psychotic disorders[2]. Schizophrenia carries significant medical co-morbidity and increased mortality, with an average life-span shortened by 10 years. Illness onset typically occurs in late adolescence to young adulthood and its course is commonly chronic and severely disabling, hence life-time treatment is required to maintain social functioning and prevent symptom relapse, causing significant public health and economic burden. The etiology of schizophrenia is considered multifactorial, with both genetic and environmental factors playing important roles.

Antipsychotic drugs are the mainstay of treatment for schizophrenia[1]. Typical or first-generation antipsychotics (FGA) are effective in improving positive symptoms, but often cause extrapymidal motor side effects (EPS) that are disturbing, and even irreversible in the case of tardive dyskinesia (TD). Newer atypical or second-generation antipsychotics (SGA)

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may improve both positive and negative symptoms, and are less frequently accompanied by EPS and TD, compared to FGA, but weight gain, metabolic changes and associated cardiovascular consequences have been a major concern[3]. The mechanism of action of these drugs is mediated mainly by the dopamine neurotransmitter system. Blockage of D2 receptors in the striatum is believed to be "necessary and sufficient" in achieving antipsychotic effects[4], at least for positive symptoms, although D3, D4 receptors, and serotonin as well as the glutamate system may also be involved in drug action[5]. Despite the advances in psychopharmacology, many patients with schizophrenia discontinue or switch antipsychotic drug regimens due to lack of efficacy and/or treatment-emergent side effects, and a large proportion of patients remain symptomatic despite treatment[6, 7]. The factors that influence the variation in response to antipsychotic drug treatment have not been well-elucidated, rendering it difficult to develop effective treatment strategies tailored to individual patients. In clinical practice, it is essentially a trial and error process in deciding the best antipsychotic drug to start or switch to after a failed trial as there is little empirical data available to guide clinicians in drug selection.

Pharmacogenetics provides a promising tool in clinical management of schizophrenia patients. It focuses on the identification of genetic variants that predict who may optimally benefit from antipsychotic treatment. Although schizophrenia has a high heritability of up to 80%, data is scarce regarding the heritability of antipsychotic drug response. Several case series of monozygotic twins that have reported concordant responses to SGAs have suggested a possible role of genetic information in predicting drug response[8]. Since the middle of 1990s, hundred of studies of pharmacogenetics of antipsychotic drugs have been published, making it a rapid growing research area. This article attempts to review this literature that is most relevant to the clinical practice of schizophrenia medication treatment.

2. Antipsychotic Drug Efficacy and Pharmacogenetics

The goal of pharmacogenetics is to predict which patient will benefit from which drug based on genetic information, in order to deliver individually tailored treatment to maximize symptom reduction and minimize drug-induced side effects. Regarding the phenotype of drug efficacy, there are many different ways to gauge clinical response to a drug, ranging from broad clinical impressions to use of highly structured assessment tooles. In antipsychotic clinical trials, the PANSS (Positive and Negative Syndrome Scale) and the BPRS (Brief Psychiatric Rating Scale) are widely used to assess symptoms of schizophrenia. However, different studies use different criteria, different drugs, and varying duration of treatment, rendering comparison across studies difficult.

Pharmacogenetic studies have focused on molecular pathways hypothesized to be the mechanisms of action for antipsychotic drugs. Dysfunction of the dopamine system has been known to underlie the pathophysiology of schizophrenia since 1960s. Dopamine has several receptor subtypes (D1 to D5), but only D2, D3, and D4 have been extensively studied in pharmacogenetics. FGAs, especially high potency drugs such as haloperidol, mainly bind to D2 receptor, where SGAs have more diverse receptor binding profiles including the 5-HT2A and 5-HT2C receptors[5]. Another area of interest is the pharmacokinetics of antipsychotic drugs, especially the cytochrome P450 family of enzymes that metabolize most antipsychotic drugs. Variants in genes coding for these enzymes produce either hypoactive or hyperactive metabolism, which may affect plasma drug levels. In the past 15 years, multiple variants in different genes have been studied in relation to antipsychotic drug response, but with limited replication[8]. Due to space limitations, this article will focus on the evidence of genetic variants affecting antipsychotic drug response in at least two studies (see Table 1).

2.1 DRD2

From a candidate gene perspective, *DRD2* is the ideal gene to study in relation to antipsychotic drug response. Antipsychotic clinical potency is highly correlated with the binding affinity to the dopamine D2 receptor[4, 9], D2 receptor occupancy by antipsychotic agents has been demonstrated to occur with all antipsychotic agents, and drugs targeting other receptor sites without dopamine D2 blockade have not yet been successfully developed as antipsychotics. *DRD2* is located on chromosome 11q22, and consists of eight exons separated by seven introns. It contains a number of SNPs with differing frequencies amongst populations, and several of them have been studied in association with antipsychotic drug response. Among these, −141C Ins/Del (rs1799732), Taq1A (rs1800497), A-241G (rs1799978), Ser311Cys (rs1801028), and Taq1B (rs1079597) have been extensively studied.

−141C Ins/Del **(rs1799732)—**This SNP represents a deletion (versus insertion) of cytosine at position −141, located in the 5′ promoter region of *DRD2*. In vitro data showed that cell lines transfected with the Del allele were less active in a luciferase reporter assay than cell lines transfected with the Ins allele. In vivo data with PET imaging have also suggested that this polymorphism may influence D2 receptor density in the striatum of healthy volunteers unexposed to antipsychotic drug treatment. Del allele carriers had poor response to clozapine in a treatment refractory sample[10], took longer time to respond to olanzapine and risperidone in first episode schizophrenic patients[11], and were less likely to respond to chlorpromazine in Han Chinese patients[12, 13]. However, several studies failed to replicate these findings[13-16]. We recently conducted a meta-analysis of the association between the −141C Ins/Del SNP and antipsychotic drug response in almost 700 patients[17]. Clinical response was defined as 50% reduction in PANSS or BPRS scores from baseline to 8 weeks of treatment, which we considered to be clinically meaningful improvement for acute treatment. Six studies with a total sample size of 687 patients were included in the analysis. There was a significant difference in response rate between the Del carrier vs. Ins/Ins genotypes (pooled odds ratio = 0.65, 95% CI = 0.43 ~ 0.97, p = .03), indicating that patients who carry one or two Del alleles tend to have less favorable antipsychotic drug responses than patients with the Ins/Ins genotype. In other words, patients with the Ins/Ins genotype are 54% more likely to respond to antipsychotic drugs than those with at least one copy of the Del allele.

Taq1A **(rs1800497)—**This SNP involves a C >T substitution, located about 10kb downstream of *DRD2*. The A1 allele is associated with reduced *DRD2* gene expression. Recently, the Taq1A SNP was found to be part of the kinase gene "ankyrin repeat and kinase domain containing 1" (ANKK1). In addition to being the most studied SNP regarding antipsychotic response, it has also been studied in association with substance abuse, alcohol dependence, eating disorder, and smoking cessation. In some studies, the A1 allele carriers were found to be more responsive to antipsychotic drugs[18-20], but the A2/A2 genotype was associated with larger reductions in PANSS or BPRS scores after treatment in other studies[16, 21, 22]. In the above mentioned meta-analysis, eight studies with a total sample size of 748 patients were included in the analysis of Taq1A in association with antipsychotic drug response. Pooled response rates were not significantly different among different genotypes[17].

A-241G **(rs1799978)—**This SNP is also located in the *DRD2* promoter region, and involves substitution of guanine for adenine at position −241. Although the functional consequence of the variant is unknown, the location suggests that it may regulate *DRD2* gene expression. In two Asian samples, the A allele or A/A genotype was associated with better improvement after risperidone treatment[13, 20], but the A/A genotype took long time to

respond to risperidone and olanzapine in a first-episode American sample[11]. It is not clear whether this is a specific marker for Asians in relation to antipsychotic drug response. Larger studies with better design are needed to elucidate this issue.

***Ser311Cys* (rs1801028)**—This SNP is a missense variant resulting in a substitution of serine with cysteine at codon 311 in the exonic region of *DRD2*. Ser311 lies within the third intracellular loop of the *DRD2*, which can modulate the interaction with G-protein. The D2 receptor with the Cys311 variant has half the affinity for dopamine in comparison to its wild type variant, and it is less effective in inhibiting cAMP synthesis. One study found that Han Chinese patients with the Ser/Ser genotype are more likely to respond to risperidone treatment, with larger reduction in negative symptoms, compared to patients of other genotypes[23]. However, another study of Chinese patients using aripiprazole failed to replicate the finding[15].

***Taq1B* (rs1079597)**—This SNP is located in the first intron of *DRD2*. The B1 (C) allele has been associated with reduced D2 density in the striatum in both in-vitro and in-vivo studies. One study found that the B2 (T) allele was associated with a higher response rate to clozapine treatment in Afraican American patients, but in Caucasians[16]. Two other studies yielded negative results[13, 22].

2.2 DRD3

The dopamine D3 receptor is preferentially expressed in limbic and basal ganglia regions associated with cognitive, emotional, and motor functions. The D3 receptor inhibits spontaneous secretion of the neurotransmitter, hence may play an important role in the regulation of neurotransmission. Because many antipsychotic drugs exhibit a high affinity for the D3 receptor, it is reasonable to suspect that *DRD3* genetic variants may affect the clinical efficacy of antipsychotic drugs. *DRD3* gene is located at chromosome 3q13.3 and contains five exons, and has a missense polymorphism in the exon 1 leading to a serine to glycine substitution at amino acid position 9 (Ser9Gly, rs6280) in the N-terminal extracellular domainof the receptor protein. Previous research suggests this SNP is associated with altered dopamine binding affinity and the Gly9 variant may increase DRD3 densities in some brain areas[24].

At least 18 studies have examined the association between the Ser9Gly SNP and antipsychotic drug response, with earlier studies focusing on clozapine and recent studies using risperidone. An early meta-analysis[25] found intriguing results; the Ser allele was associated with better response to FGAs, but it was associated with non-response to clozapine treatment. In a recent meta-analysis specifically targeting clozapine response, Hwang et al[26] showed a non-significant trend that the Ser allele and Ser/Ser genotype were more frequent in non-responders than in responders in 8 cohorts with 758 patients. Examining the *DRD3* studies in Table 1 reveals that most recent studies of SGAs including risperidone and aripiprazole did not produce significant associations with the Ser9Gly SNP. Although it makes theoretical sense that DRD3 may affect antipsychotic drug response, empirical research does not yield consistent data on the hypothesis.

2.3 DRD4

Due to clozapine's superior antipsychotic efficacy and the fact that it potently binds to the dopamine D4 receptor, it has been hypothesized that that the D4 receptor genotype plays a role in mediating clozapine and other SGA's effects. The *DRD4* gene codes for the D4 receptor protein and is located at chromosome 11p15.5. The coding DNA sequence of the *DRD4* is highly polymorphic, resulting in functionally different receptor variants. A well-studied 48-bp variable number tandem repeat (48-bp VNTR) in the third exon, with 2–10

repeats, results in a different length of the third cytoplasmatic loop. The 48-bp VNTR may be functionally important because this region of the D4 receptor is involved in G-protein coupling, and the longer repeat alleles are associated with reduced clozapine binding. Moreover, the potency of dopamine to inhibit cAMP formation was decreased by twofold in the D4,7 variant (i.e., repeating 7 times), when compared with both the D4.4 and the D4.2. Despite several negative studies of clozapine response in early 1990s, Hwu et al[27] found that longer repeat alleles of the 48-bp VNTR were associated with higher response rate using a variety of antipsychotic drugs in 80 Chinese patients. However, this was not replicated in two later studies, one Chinese sample[28] and one Caucasian sample[29]. The inconsistency is yet to be reconciled, but it is likely contributed by different study design, different treatment duration, and various medications used.

2.4 HTR2A

Serotonin system has long been suspected to play a major role in mediating antipsychotic drug action. All SGAs tightly bind to serotonin receptor 2A relative to dopamine D2 receptor, and this was once thought to be one of the defining characteristics of "atypicality" of SGAs. As such, genetic variations in different serotonin receptors have been extensively studied to examine their potential associations with drug response. *HTR2A*, *HTR2C*, *HTR6*, and *5HTT* are reviewed here.

HTR2A is the gene coding for the 5-HT 2A receptor and is located at chromosome 13q14-q21. The 2A receptor is widely distributed in the cortex, and may be associated with negative symptoms of schizophrenia. Neuroimaging studies have suggested that high occupancy of 5-HT2 receptors by SGAs is associated with improvement in negative symptoms and cognition. *HTR2A* is highly polymorphic. One polymorphism that has been investigated in many studies is a synonymous SNP at codon 102 (T102C, rs6313). Although this SNP does not result in an amino acid change, it is in nearly complete linkage disequilibrium (LD) with another functional SNP (A-1438G, rs6311) in the promoter region in Caucasian populations[30]. A recent study suggests the C allele of the T102C SNP and the G allele of the A-1438G SNP may cause lower promoter activities and thus decreased 2A receptor densities in some brain areas, which may lead to a less flexible serotonin system and lower dopaminergic modulation[31]. Conversely, specific methylation of the C allele of the T102C SNP could increase *HTR2A* expression in human temporal cortex[32]. These findings suggest that A-1438G/T102C polymorphisms may influence HTR2A densities in the brain.

At least 15 studies have been published on the association between the T102C SNP and antipsychotic drug response. Early studies focused on clozapine and later studies also examined other SGAs including risperidone, olanzapine, and aripiprazole. A meta-analysis summarized the first six studies of clozapine response in 733 patients revealed that the C allele of T102C was more prevalent among non-responders[33]. However, after excluding the first published study[34], the pooled odds ratio became non-significant. After the meta-analysis was published in 1998, two more studies[35, 36] examined clozapine response, and neither of them found significant association with the T102C SNP. More recently, four studies focused on risperidone response, two of which found a significant association between the C/C genotype and better response, especially in negative symptoms[37, 38]. This is the converse finding of earlier studies of clozapine. It should be noted, however, that earlier clozapine studies were mostly in Caucasians with some African American patients, but more recent studies were mostly from Asian countries. Another recent study of Chinese patients added further complexity by showing that the C/C genotype responded better to aripiprazole treatment with a larger improvement in negative symptoms, compared to other genotypes[39].

Compared to the conflicting findings of the T102C SNP, the A-1438G SNP was more consistently found to be associated with antipsychotic drug response. Three studies[30, 40, 41] showed that the G/G genotype was less likely to respond to clozapine, olanzapine, and aripiprazole, especially in negative symptoms, than other genotypes. However, a recent study of 100 Algerian patients treated with haloperidol reported that the G allele was actually associated with better treatment response[42]. Haloperidol has only minimal effects at the 5-HT 2A receptor, so it is not clear how a genetic variant in HTR2A would mediate clinical response to haloperidol. Although in complete LD with the T102C SNP, the A-1438G SNP has produced more positive findings in fewer studies. Many studies reported one but the other SNP, hence the concordance of the findings between the two SNPs is not clear.

A third SNP in the *HTR2A* gene, His452Tyr, was also examined in several studies. This nonsynonymous SNP is located in exon 3 of the gene and the change from C to T results in a change from histidine to tyrosine at the 452th amino acid. The Tyr variant is associated with reduced calcium release and reduced ability to activate phospholipases. In vitro data indicated that the Tyr variant showed lowered antipsychotic binding affinity and decreased drug potency. Three clinical studies[30, 35, 43] found that the Tyr allele was significantly associated with poor response to clozapine treatment, compared to the His allele. Although other studies failed to replicate the findings[44, 45], an early meta-analysis of five samples showed a clear association of the Tyr/Tyr genotype with poor response to clozapine (OR = 5.55, p = .04)[33]. It should be noted, however, that only 10 out of 676 patients included in the meta-analysis were Tyr/Tyr homozygotes. Intriguingly, all of the studies of this SNP were published before 2002, and publication bias towards significant findings may play an important role.

2.5 HTR2C

Most SGAs except quetiapine tightly bind to serotonin 2C receptors, in addition to the 2A receptors[5]. The 5-HT2C receptors are widely distributed in many areas of the human brain including striatum, prefrontal cortex, and the limbic system, indicating a role in executive functioning, memory, emotional processing, feeding behavior and motor functions. Like the 2A receptors, these postsynaptic receptors are excitatory and positively couple with G-protein. The *HTR2C* gene is located at chromosome Xq24. Several SNPs in the gene have been linked to antipsychotic drug response, but the most studied is the Cys23Ser SNP (rs6318). This non-synonymous SNP is in the coding region with a change from G to C resulting in an amino acid substitution of Cysteine with Serine. Despite a change in receptor protein structure, there has been no evidence of alteration in receptor function. Only the first clinical study[46] found that patients who carry the Ser allele were more likely to respond to clozapine treatment compared to patients who are Cys/Cys homozygotes, but five later studies failed to confirm the finding.

2.6 5HT6 and 5HTT

Genetic variants of other components of the serotonin system have also been linked to antipsychotic drug efficacy, notably the *5HT6* and *5HTT* genes, which code for the serotonin 6 receptor and serotonin transporter. In animal studies, 5-HT6 receptors are associated with the endogenous 5-HT-mediated facilitation of dopamine release, and specific 5-HT6 receptor antagonists produced a favorable outcome for reducing positive symptoms of schizophrenia. HTR6 is located at chromosome 1p36. One SNP, C267T (rs1805054), was examined in four pharmacogenetic studies of clozapine and risperidone. Two studies[47, 48] found a significant association between the T/T genotype and better treatment response, both of which happen to be in Han Chinese patients. Two other studies in Caucasians and Japanese did not yield significant results[20, 49]. It is not clear whether this is a specific

biomarker for antipsychotic response in the Chinese population, and it is not clear what the functional consequences of this variant are, but it is clear that the SNP deserves more research.

5HTT is the gene coding for serotonin transporter (SLC6A4; solute carrier family 6 member 4). It is located at chromosome 17q11.2. The serotonin transporter is an integral membrane protein that transports serotonin from synaptic spaces into presynaptic neurons, thus terminates the action of serotonin and recycles it in a sodium-dependent manner. A repeat length polymorphism, 5-HTTLPR, involves insertion/deletion of a 44-bp segment located upstream of the transcription start site in the promoter region. It has been shown to affect the rate of serotonin uptake and is the most studied genetic variant in psychiatry[50]. Recent meta-analyses of the relationship between the polymorphism and antidepressant response have shown that patients carrying the long allele are about twice as likely to respond to treatment at 4 weeks and reach remission, and less likely to suffer from side effects, than patients with the short/short genotype[51]. Although only a few studies have focused on this polymorphism and response to antipsychotic drugs, three studies showed that the short allele is associated with poor response to clozapine and risperidone treatment[52-54]. Future research should attempt to replicate this finding with other antipsychotic drugs.

2.7 COMT

The catechol-O-methyltransferase (COMT) enzyme is one of the main pathways of dopamine clearance and metabolically terminates dopamine activity, especially in the frontal cortex. It may moderate antipsychotic drug action because all antipsychotics exert their effects on the dopamine system. The *COMT* gene is located at chromosome 22q11.21. A common polymorphism, Val108Met, can causes substantial variations in enzymatic activity. This is due to a G to A transition at codon 158 of the membrane-bound form of COMT, which corresponds to codon 108 of the soluble form of COMT, resulting in a valine to methionine substitution. The met/met genotype results in 3- to 4-fold lower enzyme activity compared with the val/val allele pair, while the met/val heterozygote results in intermediate enzyme activity. In other words, the val allele results in reduced dopamine in synapse due to more rapid degradation. An early case-control study[55] found that patients with the met/met genotype were less likely to respond to treatment with various FGAs. However, a later study of 59 Caucasian first episode schizophrenic patients[56] showed the opposite, that is, patients with the val/val genotype were less likely to respond to 8 weeks of olanzapine treatment, especially in negative symptoms, compared to other patients. This may be due to the fact that schizophrenia is characterized by dopamine hypoactivity in prefrontal cortex and reduced metabolism of dopamine associated with the met allele helps to restore dopamine level. Consistently, another study[57] of clozapine indicated that the met allele carriers were more likely to respond, especially improvement in cognitive functions. This is consistent with the data indicating that the met/met genotype has been associated with higher IQ scores in a meta-analysis[58].

2.8 CYP2D6

The cytochrome P450 enzyme family in the liver is responsible for the metabolism of many psychotropic drugs. Among its subtypes, 2D6 is the main metabolic pathway for several antipsychotics including risperidone, aripiprazole, haloperidole, perphenazine, and chlorpromazine, and a secondary pathway for clozapine, olanzapine, and quetiapine. CYP2D6 is also most relevant to pharmacogenetics because it has more than 100 genetic variants (as catalogued by the website: http://www.cypalleles.ki.se, as of July 20, 2010) and many of them yield non-functional or low-functional enzymes. The CYP2D6 gene is located at chromosome 22q13.1. The polymorphisms in this gene involve various single nucleotide substitutions and insertion/deletion of certain DNA segments. In Caucasians, four

polymorphisms (*3, *4, *5, and *6) are responsible for most inactive alleles (98%). There are four phenotypes of CYP2D6 produced by combinations of various alleles with different degrees of enzymatic activities: poor metabolizer (PM), intermediate Metabolizer (IM), extensive metabolizer (EM), and ultrarapid metabolizer (UM). EMs have normal CYP2D6 enzyme activity, whereas PMs and IMs have no or reduced activity, respectively. Ums have duplicate or multiple copies of the gene which result in increased enzyme activity. Approximately 7-10% of Caucasians and 1-2% of Asians are PMs[8], who tend to accumulate higher drug levels in blood, and theoretically, require lower doses to achieve therapeutic effects. UMs, in contrast, who are rare and consist of only 1% of the population, may require higher doses of an antipsychotic due to faster elimination of the drug. Therefore, CYP2D6 metabolic status could play an important role in determining antipsychotic efficacy for a particular patient.

However, there are few empirical data to support the above hypothesis. None of the six studies investigating the association between CYP2D6 genotypes and antipsychotic response have reported significant findings. Two risperidone studies[59, 60] demonstrated that PMs had higher ratio of blood levels of risperidone to 9-hydroxyrisperidone than other patients, but neither genotypes nor blood levels predicted clinical improvement. Other studies have found significant relationships between PMs and higher rate of drug-induced side effects, which are reviewed in later sections of this article. Although theoretically appealing and clinically meaningful, studies with positive findings are needed to prove the utility of CYP2D6 genotyping in predicting antipsychotic drug response.

In summary, pharmacogenetic research of antipsychotic response has examined a number of genetic variants, from both pharmacodynamic and pharmacokinetic perspectives. Past studies showed promising results for a few polymorphisms including the −141C Ins/Del in *DRD2*, Ser9Gly in *DRD3*, −1438G/A in *HTR2A*, 5-HTTLPR, and Val108Met in *COMT*. Studies with larger samples and better designs are needed to validate these findings.

3. Adverse Drug Reactions of Antipsychotics and Pharmacogenetics

Although antipsychotic efficacy is an important consideration in choosing a particular drug, drug-induced side effects or adverse drug reactions (ADR) are also critical aspects of determining how much a patient may benefit from the drug. Inability to tolerate ADRs is a frequent reason to discontinue antipsychotic treatment[6]. Similar to the fact that it is difficult to predict which patient will respond to a particular drug, it is equally difficult to predict who will develop ADRs and which ADRs. The large inter-individual differences in ADRs prompted researchers to consider what role genetic variability may play. There are many ADRs caused by antipsychotic drugs, but the most severe and troublesome ones include tardive dyskinesia (TD), aganulocytosis, extrapyramidal symptoms (EPS), and weight gain. Below we will review the pharmacogenetic studies that examined genetic variants in association with these four ADRs. Following the same principle as the previous section, only those genetic variants that have been studied multiple times will be reviewed here.

3.1 Tardive Dyskinesia

Tardive dyskinesia (TD) is a chronic involuntary body movement caused by exposure to neuroleptics. It is often irreversible and debilitating. A recent review of 12 clinical trials reported the both FGAs and SGAs can cause TD with a one-year risk of 5.5% and 3.9%, and a prevalence of 32.4% and 13.1%, respectively[61]. Several demographic and clinical factors are known to increase the risk of TD including older age, female gender, African American descents, higher antipsychotic dosage, and early EPS62. Smoking and alcohol abuse may also increase the risk of TD. The etiology of TD is unknown, but the nigrostriatal dopaminergic tract, which is closely involved in the regulation of motor behavior, may play

a key role. Dopamine antagonism of antipsychotic drugs results in up-regulation of D2 receptors post-synaptically, which contributes to nigrostriatal dopaminergic hyperactivity. Genetic factors including variants in dopamine and other neurotransmitters genes may therefore play an important role.

TD is the most studied antipsychotic-induced ADR in pharmacogenetics. Most studies are case-control design in nature which affords larger sample sizes than studies of drug efficacy. Multiple genes of various neurotransmitter systems and many polymorphisms have been examined in association with TD. Among these, Taq1A, −141C Ins/Del, and Ser311Cys in *DRD2*, Ser9Gly in *DRD3*, T102C and −1438G/A in *HTR2A*, Cys23Ser in *HTR2C*, Val108Met in *COMT*, and *CYP2D6* have accumulated sufficient data to warrant discussion below. It is not surprising that many of these genes are the ones that have been studied in association with antipsychotic drug efficacy because they are primary drug targets or metabolic pathways.

Although our recent meta-analysis did not reveal a significant relationship between the *DRD2* Taq1A SNP and antipsychotic drug response[17], it has been associated with TD in two meta-analyses. Despite the fact that only 2 out of 8 studies listed in Table 2 reported significant findings that the A2 allele and the A2/A2 genotype display increased risk of TD, a cumulative sample of 1,256 patients (507 with TD and 749 without TD) from 6 cohorts demonstrated an odds ratio of 1.30 for the risk of TD in the A2 allele[63]. This means that each copy of the A2 allele confers a 30% more risk of developing TD, relative to the A1 allele. Compared to A1/A1 homozygote or A1/A2 heterozygote, patients with the A2/A2 genotype have a 50% increased risk of TD (odds ratio = 1.50). Another meta-analysis[64] of 764 patients (297 with TD and 467 without TD) from 4 studies, which represent a sub-sample of the first meta-analysis, confirmed the previous findings. One mechanistic explanation is that the A1 allele is associated with reduced density of D2 receptors in the striatum, which results in less dopamine antagonism by antipsychotic drugs. Therefore, the A1 allele is protective of TD development. However, a recent report of 710 patients from the CATIE trial (207 with TD and 503 without TD), which was not included in either meta-analyses, did not find any association between the Taq1A SNP and TD, casting some doubts on previous findings. Other SNPs in DRD2, including −141C Ins/Del and Ser311Cys, have not been found to affect TD development[63, 64], despite their promising roles in predicting clinical response to antipsychotic treatment.

The dopamine D3 receptor was initially implicated in TD development because D3 blockade in the basal ganglia produced hyperactivity in animal models[65]. Antipsychotic drugs that have minimal D3 affinity, such as clozapine and quetiapine, tend to have lower liability of causing TD. One of the SNPs in DRD3, Ser9 Gly, has been examined for association with TD in least 20 studies. Interestingly, the Gly allele, previously associated with clinical response to antipsychotics drugs, is also associated with higher risk of TD in at least 8 studies, and this was confirmed in two early meta-analyses with overlapping samples[66, 67]. However, the most recent meta-analysis, with 2,026 patients (928 with TD and 1098 without TD) from 13 cohorts, found only a non-significant trend that the Gly allele carriers may confer a slightly higher risk of TD compared to non-carriers[68]. The odds ratio of 1.16 is modest and there was significant evidence of publication bias and sample heterogeneity. Data from the CATIE trial also did not support any link between the Ser9Gly SNP and antipsychotic-induced TD[69].

The facts that SGAs are less likely to cause TD and that all SGAs bind to serotonin receptors make it plausible that the serotonin system may play an important role in preventing antipsychotic-induced TD[5]. The same SNPs in *HTR2A* and *HTR2C* that have been examined for their association with antipsychotic drug efficacy are also related to TD in a number of

studies. As reviewed earlier, the C allele of the T102C SNP in HTR2A was associated with poor response to antipsychotic drug treatment in several studies[33]. Interestingly, the C allele was also associated with risk of TD in at least three studies[70-72]. A meta-analysis[73] summarized 6 cohorts with 635 patients (256 with TD and 379 without TD) and found that the C allele carriers have a 64% higher risk of developing TD than the non-carriers (T/T homozygotes) (odds ratio = 1.64, p = 0.004), especially in older patients and in patients with limb-truncal TD. However, three later studies in three different populations (Indians, African-Caribbeans, and Americans of mixed ethnicities) were not able to replicate this finding[69, 74, 75]. Another SNP, −1438G/A, that is in complete LD with T102C, was also found to be significantly associated with TD in a couple of studies[70, 76]. The G allele was associated with reduced expression of 5-HT2A receptor. Thus, it is plausible that reduced availability of the receptor in certain brain regions such as basal ganglia may be a risk factor for developing TD. Nevertheless, more data are needed to support this hypothesis.

In addition to dopamine and serotonin receptors that are major targets of antipsychotic drugs, genetic variation in metabolic pathways of the drugs have also been studied in association with TD. Theoretically, if a drug is not cleared fast enough, prolonged stimulation of dopamine receptors may put patients at risk of developing TD. Therefore, the Val108Met SNP of *COMT* is a candidate polymorphism of interest because the Met allele results in lower enzyme activity and slower clearance of synaptic dopamine. A meta-analysis[64] of 5 studies with 1,089 patients (382 with TD and 707 without TD) found that the Met allele was actually protective and the Met allele carriers were less likely to develop TD, with an odds ratio of 0.66. In other words, patients with the Val/Val genotype had a 51% higher risk of TD than others.

CYP2D6 is the other metabolic pathway candidate gene that has been studied extensively. Poor metabolizers of CYP2D6 may have higher blood levels of antipsychotic drugs such as risperidone and haloperidol, which put these patients at risk of developing TD. Interestingly, not only is it found in the liver, *CYP2D6* is also expressed in some brain areas, particularly in those areas rich in the dopamine transporter, and may play an important role in protecting certain susceptible brain regions from toxicants that gain access to the central nervous system[77]. Several studies have demonstrated that patients who are poor or intermediate metabolizers of 2D6 are more likely to have TD[78-80], although there are a few negative studies as well, as shown in Table 2. A meta-analysis[81] of 8 studies with 569 patients (220 with TD and 349 without TD) showed an odds ratio of 1.43 for the PMs compared to EMs. In other words, PMs have 43% higher risk of developing TD, compared to EMs. One issue with this literature is that the PMs account for only 7-10% of Caucasian population and even rarer in some other ethnic groups. Hence, it is difficult to find a large sample of PM patients, of whom TD can be ascertained. Potentially, sample sizes in a range of thousands are needed to robustly test the hypothesis regarding the association between CYP2D6 and TD.

CYP1A2 is another member of the cytochrome P450 enzyme family, and metabolizes many antipsychotics drugs including both FGAs and SGAs such as chlorpromazine, fluphenazine, perphenazine, clozapine, and olanzapine. The *CYP1A2* gene is located on chromosome 15q24.1 and contains a number of non-functional variants, several of which have been associated with the development of TD. CYP1A2 enzyme can be induced by smoking and two SNPs, *1F (−163C>A) and *1C (−3860G>A), affect the inducibility of the enzyme[82, 83]. An early study found that chronically treated patients with the *1F C/C genotype were more likely to have TD symptoms than those *1F A allele carriers, especially among smokers[84]. However, a meta-analysis of seven studies did not find significant association between the *1F SNP and TD frequency[64]. It should be noted that many studies did not report what antipsychotic drugs patients were taking, and it appears that some patients on SGAs were included[85]. The two SGAs metabolized by CYP1A2, clozapine and olanzapine,

have low TD liability. Other SGAs that have relatively high TD liability, such as risperidone, were not metabolized through CYP1A2. As such, inclusion of patients on SGAs might have reduced signal-to-noise ratio.

In addition to the association between TD and genetic variants on the pharmacodynamic and pharmacokinetic pathways of antipsychotic drugs, antipsychotic-inducing oxidative stress and free radicals may cause neuronal injury and contribute to the development of TD. Several studies have examined whether TD is associated with variants of *MnSOD*, the gene encoding manganese superoxide dismutase, a mitochondrial enzyme involved in oxidative metabolism. One SNP, Ala9Val, results in a substitution of alanine with valine and less efficient MnSOD transporter in mitochondria. A meta-analysis of four studies suggested that the Val carriers are less likely to develop TD compared to the Ala/Ala homozygotes[64], although the result of a more recent meta-analysis with ten samples was not significant[86]. Other oxidative enzymes have also been studied, but findings were also mixed[86].

Several studies have focused on EPS instead of TD in association with CYP2D6. Six out of nine studies found that CYP2D6 PMs and IMs were more likely to experience antipsychotic drug-induced EPS[80, 87-91]. In general, pharmacogenetic research of EPS has been less extensive than that of TD, although EPS are much more commonly encountered in clinical practice.

3.2 Weight Gain and Metabolic Syndrome

Weight gain is the most prominent side effect associated with the SGAs, especially clozapine, olanzapine, and quetiapine[92]. Although weight gain is commonly associated with SGAs, patients on FGAs can also gain large amount of weight. In the European Union First Episode Schizophrenia Trial (EUFEST), 53% of patients on haloperidol gained more than 7% of baseline body weight at 1-year follow-up[7]. Due to large inter-individual variation in weight gain, no clear clinical predictors have been identified, and the mechanism remains poorly understood92. Food intake and body weight are regulated by complex interactions between multiple neurotransmitter systems in multiple brain regions. Several studies have examined the possible role genetic variation in the dopamine system may play in drug-induced weight gain93⁻95, but pharmacogenetic research has primarily focused on the serotonin system, especially the 5-HT2C receptor.

The 5-HT2C receptor is involved in the regulation of food intake in rodents. *HTR2C* knockout mice display chronic hyperphagia leading to obesity and hyperinsulinemia. In humans, C-759T (rs3813929), a SNP in the promoter region of the *HTR2C* gene has been related to late-onset diabetes and obesity in a normal population. At least 17 studies have reported on the association between the C-759T SNP in *HTR2C* and antipsychotic drug-induced weight gain. 10 out of 17 studies listed in Table 3 reported significant findings that the C allele was associated with more weight gain than was the T allele after antipsychotic drug treatment, especially clozapine and olanzapine, both of which have high affinity to 5-HT2C. A meta-analysis[96] of 8 studies with 588 patients found that the T allele was significantly protective against antipsychotic drug-induced weight gain. The C allele was associated with more than two fold increase of risk for clinically significant weight gain, i.e., gaining 7-10% or more of baseline body weight. The C allele is the common allele and the T allele is the rare allele with a frequency ranging from 3.3% in African descent to 33.3% in Asians. Of the 9 studies published after the meta-analysis, 5 have also reported positive findings. Although one recent study did not find a significant association between this SNP and iloperidone-induced weight gain[97], iloperidone binds to 5-HT2C only minimally. Overall, the evidence so far suggests that the C-759T SNP in *HTR2C* may play an important role in antipsychotic drug-induced weight gain.

Another gene that has attracted much attention in pharmacogenetics of drug-induced weight gain is *GNB3*, which codes for G-protein β3 subunit. G-proteins are ubiquitous in many intracellular signaling pathways, and relay signals from receptors to effector proteins. The C825T polymorphism of the *GNB3* gene is associated with a GB3 splice variant that results in a deletion of 41 amino acids, although it does not seem to alter protein function. This SNP has been linked to hypertension and obesity, two of the major components of metabolic syndrome, in the general population. A meta-analysis of 3 published and 2 unpublished studies with 402 patients found that the T allele was marginally associated with increased weight gain, but the finding was not statistically significant due to considerable heterogeneity among studies and relatively small sample size[98]. Two recent studies, both from East Asia and with olanzapine, did not provide consistent findings[99, 100].

In summary, a number of antipsychotic drug-induced side effects have been examined in relation to genetic variants. Many genes and polymorphisms were studied, but so far very few have gained consistent support. For TD, the Taq1A in *DRD2*, the Ser9Gly in *DRD3*, the T102C SNP in *HTR2A*, and the loss of functional variants in *CYP2D6* may warrant further research. For weight gain, the only promising variant that has accumulated substantial data is the C759T SNP in *HTR2C*.

4. Genome-Wide Association Studies (GWAS)

With the advances of sequencing technology and bioinformatics, now we can genotype more than a million SNPs covering the whole genome. GWAS has the potential to discover new molecular targets and pathways that elucidate disease mechanisms and drug actions[101]. In the past few years, the number of GWAS application in psychiatry has dramatically increased, but very few GWAS of antipsychotic response and drug-induced side effects have published, partially due to its requirement of large sample size and replication samples. Up to date, there have been six GWAS studies of antipsychotic drugs published, four from the CATIE trial[102-105] and two from Volpi's group[106, 107].

Among the CATIE participants, 738 consented to a blood sample for genetic analysis. Using a mixed model approach to define clinical response, the first GWAS found only one SNP, rs17390445 on chromosome 4p15, above the genome-wide significance after correcting for multiple testing, and predicted the effect of ziprasidone on positive symptoms ($p < 10^{-8}$)[102]. Another SNP in the same area approached the genome-wide significance. However, these two SNPs are located in an intergenic region and the functions of the variants are unknown. In addition, SNPs in Ankyrin Repeat and Sterile Alpha Motif Domain-Containing Protein 1B (*ANKS1B*) and in the Contactin-Associated Protein-Like 5 gene (*CNTNAP5*) also approached genome-wide significance and may mediate the effects of olanzapine and risperidone on negative symptoms. These two genes are involved in regulating neuronal cell proliferation and differentiation as well as interneuron communication in the brain, but how they would affect drug response is unknown.

Two GWAS studies from the CATIE trial focused on EPS as the phenotype, with overlapping samples. The smaller study[103] included 397 patients and used the Simpson-Angus Scale to define antipsychotic-induced parkinsonism. No SNP reached genome-wide significance, but several in *EBF1* (Early B-cell Factor 1), *NOVA1* (Neuro-Oncological Ventral Antigen 1), *FIGN* (Fidgetin) and other genes approached the threshold. The larger study[105] included all 738 patients that contributed blood samples and used three different scales to measure EPS. Three SNPs reached genome-wide significance, with two in intergenic regions and one (rs2126709) in *ZNF202* (zinc finger protein 202) on chromosome 11q24. *ZNF202* is a transcriptional repressor and controls promoter elements of many genes involved in lipid metabolism, critical in neuronal myelination processes. The latest CATIE

GWAS study[104] examined 12 indicators of metabolic side effects of antipsychotic drugs in the same cohort. Multiple SNPs in multiple genes reached genome-wide significance. Notably, rs1568679 in *MEIS2* (Meis homeobox 2) mediated the effect of risperidone on waist and hip circumferences, rs13224682 in *PRKAR2B* (Protein Kinase cAMP-dependent regulatory type II-β) mediated clozapine and olanzapine's effects on triglyceride levels, and two SNPs in *GPR98* (G protein-coupled receptor 98) mediated the effects of olanzapine on hemoglobin A1c levels. It was speculated that these genes may have complex interactions with other genes to influence metabolic side effects of antipsychotic drugs. Interestingly, none of the candidate genes previous reviewed in this article reached or close to reach genome-wide significance in the CATIE GWAS studies. One should note that GWAS is primarily exploratory in nature, and that findings need to be replicated in independent samples.

The other two GWAS studies were based on data from a phase 3 trial of a new antipsychotic drug, iloperidone, recently approved by the Food and Drug Administration in the US. In a GWAS study of 407 patients, a combination of 6 genetic markers predicted treatment response to iloperidone, with an odds ratio of 9.5 for 20% or more improvement on PANSS[107, 108]. These 6 markers come from the neuronal PAS domain protein 3 gene (*NPAS3*), the Kell blood group complex subunit-related faily member 4 gene (*XKR4*), the tenascin-R gene (*TNR*), the AMPA4 glutamate receptor gene (*GRIA4*), the glial cell line-derived neurotrophic factor receptor-α 2 gene (*GFRA2*), and the serotonin receptor 7 gene (*HTR7*). In the same sample, another GWAS found 6 loci associated with drug-induced QT prolongation[106]. These findings need to be validated in other samples.

5. Expert Opinion

Pharmacogenetics promises individualized treatment based on genetic risk factors and hopes to maximize therapeutic outcomes while minimizing drug-induced side effects. In the area of antipsychotic drug treatment, research from the past two decades has provided converging evidence that several genetic polymorphisms are capable of predicting clinical treatment response or drug-induced adverse events and that those findings have been replicated in multiple studies, various ethnic groups, and different medications. However, a number of issues need to be resolved before pharmacogenetic findings can be meaningfully applied to clinical practice.

First, most genetic variants reviewed in this article have small to moderate effect sizes in influencing clinical outcomes, so their clinical significance is unclear. In order to provide a clinically useful genetic test with sufficient sensitivity and specificity to make confident individual predictions, a combination of polymorphisms across multiple loci will be required. To date, most candidate gene studies of antipsychotic drugs have examined single SNP in a single gene. Attempts of combining multiple SNPs across several loci in predicting clinical outcome have not been replicated. For example, a combination of variants in the *HTR2A*, *HTR2C*, and *HTTLPR* genes and genes coding for H2 receptors (Histamine receptor type 2) was found to correctly predict clozapine response in 76% of cases[52]. However, it was not replicated in an independent sample[109]. The previously mentioned GWAS studies[106, 107] on iloperidone treatment response and side effect represent the latest attempt in this effort. Although promising, the findings need to be validated in independent samples.

Second, even if pharmacogenetic research has found a series of genetic markers that can be used to predict antipsychotic drug response or side effects with reasonable sensitivity and specificity, the information has to be available with relatively low cost and obtainable in a timely fashion to justify its use. CYP2D6 metabolic status has been shown to affect drug-induced side effects, and a gene chip, AmpliChip, was developed by Roche Diagnostics to

genotype and classify CYP2D6 metabolic status[110]. Although it is widely available in commercial labs, it is expensive (i.e., more than $600/test) and time-consuming (i.e. about two weeks). These issues limit its clinical value. In addition, there is no prospective study to demonstrate the cost-effective benefit of genotyping patients and selecting and dosing antipsychotic drugs accordingly[111]. In fact, most pharmacogenetic studies of antipsychotic drugs are retrospective in nature in that clinical outcome data was collected for other purposes and genetic variants were tested as an add-on project. Although some studies have been performed with pharmacogenetics as the main aim, none has genotyped patients a priori and then treated them in separate arms of the study.

Third, to truly fulfill the promise of personalized medicine, large pharmacogenetic clinical trials of head-to-head drug comparisons are needed to validate the strategy of selecting and dosing drugs based on genetic testing. CYP2D6 is again a good example. If a patient is a poor metabolizer, the clinician may choose quetiapine or ziprazidone, instead of risperidone or aripiprazole, which are metabolized primarily by CYP2D6. It is more challenging in the case of selecting drugs based on genetic variants of dopamine receptors. The Del allele of −141C Ins/Del in *DRD2* is associated with poor response to antipsychotic drugs[17]. However, all available antipsychotics to date exert their effect by D2 blockade. Even if a patient has the Del allele, there is really no alternative drug treatment. Future research should focus on developing new effective drugs without D2 antagonism, thus provide more options in clinical management when a patient is a poor responder due to variants in the *DRD2* gene.

In summary, pharmacogenetic research of antipsychotic medications is both promising and challenging. There is consistent evidence that some genetic variants in dopamine and serotonin receptors as well as metabolic pathways of drugs including COMT and CYP2D6 can affect clinical response and side effects. Due to many issues reviewed in this article, more studies that are designed specifically to test pharmacogenetic hypotheses with larger sample sizes are clearly needed to advance the field.

Article Highlights

- Pharmacogenetics aims at using genetic information to guide drug selection to maximize therapeutic efficacy and minimize side effects.

- Most pharmacogenetic studies of antipsychotic drugs have used a candidate gene approach, focusing on polymorphisms in genes coding for receptors in the dopamine and serotonin systems, as well as genes coding for enzymes that metabolize drugs, such as COMT and CYP2D6.

- Regarding genetic variants predicting antipsychotic drug efficacy, previous studies have produced promising results for a few polymorphisms including the −141C Ins/Del in *DRD2*, Ser9Gly in *DRD3*, −1438G/A in *HTR2A*, 5-HTTLPR, and Val108Met in *COMT*. Studies with larger samples and better designs are needed to validate these findings.

- Regarding genetic variants predicting antipsychotic drug-induced side effects, different studies have been inconsistent. For tardive dyskinesia, the Taq1A in *DRD2*, the Ser9Gly in *DRD3*, the T102C SNP in *HTR2A*, and the loss of functional variants in *CYP2D6* may warrant further research. For weight gain, the only promising variant that has accumulated substantial data is the C759T SNP in *HTR2C*.

- Pharmacogenetic research of antipsychotic drugs is both promising and challenging. Due to many methodological issues, more studies that are designed

specifically to test pharmacogenetic hypotheses with larger sample sizes are needed to advance the field.

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Table 1

Studies of associations of genetics variants and antipsychotic efficacy

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
DRD2						
−141C Ins/Del (rs1799732)	Arranz, 1998[14]	Caucasian & Chinese (297)	Variable duration of treatment, OL	Clozapine	n.s.	No association
	Malhotra 1999[10]	Caucasian & AA (72)	10 weeks RCT	Clozapine	<.05	Del allele carriers less likely to respond
	Yamanouchi 2003[112] and Ikeda 2008[20]	Japanese (166)	8 weeks OL	Risperidone	n.s.	No association
	Hwang 2005[16]	Caucasian & AA (232)	6 months OL	Clozapine	n.s	No association
	Wu 2005[12]	Chinese (135)	8 weeks RCT	Chlorpromazine	<.05	Del allele carriers less likely to respond
	Lencz 2006[11]	Caucasian & AA (61)	16 weeks RCT	Risperidone Olanzapine	<.05	Del allele carriers took longer time to respond
	Xing 2007[13]	Chinese (125)	8 weeks RCT	Risperidone	n.s.	No association
	Shen 2008[15]	Chinese (128)	4 weeks OL	Aripiprazole	n.s.	No association
Taq1A (rs1800497)	Suzuki 2000[18]	Japanese (25)	3 weeks RCT	Nemonapride	<.05	A1 allele carriers more likely to respond
	Suzuki 2001[113]	Japanese (30)	3 weeks RCT	Bromperidol	n.s.	No association
	Schafer 2001[19]	Caucasian (57)	4 weeks RCT	Haloperidol	<.05	A1 carrier more likely to respond
	Dahmen, 2001[21]	Caucasian (18)	6 weeks RCT	Amisulpride Flupentixol	<.05	A2/A2 had larger reduction in BPRS
	Yamanouchi 2003[112] and Ikeda 2008[20]	Japanese (166)	8 weeks OL	Risperidone	<.05	A1/A1 had larger reduction in PANSS score
	Wu 2005[12]	Chinese (135)	8 weeks RCT	Chlorpromazine	n.s.	No association
	Hwang 2005[16]	Caucasian & AA (232)	6 months OL	Clozapine	<.05	A2 allele was associated with higher response rate in AA, but in Caucasians
	Reynolds 2005[114]	Chinese (117)	10 weeks, OL	Chlorpromazine, Risperidone, Clozapine, Fluphenazine, Sulpride	n.s.	No association

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
	Vijayan 2007[22]	Asian Indian (213)	1 year OL	Clozapine, Haloperidol, Risperidone	<.05	A2/A2 had larger reduction in BPRS
	Xing 2007[13]	Chinese (125)	8 weeks RCT	Risperidone	n.s.	No association
	Shen 2008[15]	Chinese (128)	4 week OL	Aripiprazole	<.05	A1/A1 had larger reduction in PANSS score
	Kwon 2008[115]	Korean (90)	26 weeks RCT	Aripiprazole	<.01	A1/A1 had larger reduction in PANSS score
A-241G (rs1799978)	Hwang 2005[16]	Caucasian & AA (232)	6 months OL	Clozapine	n.s.	No association
	Lencz 2006[11]	Caucasian & AA (61)	16 weeks RCT	Risperidone Olanzapine	<.01	A/A took longer time to respond
	Xing 2007[13]	Chinese (125)	8 weeks RCT	Risperidone	<.05	A allele was associated with higher response rate.
	Ikeda 2008[20]	Japanese (120)	8 weeks OL	risperidone	<.05	A/A had better improvement in PANSS
Ser311Cys	Lane, 2004[23]	Chinese (123)	6 weeks RCT	Risperidone	<.05	Ser/Ser more likely to respond, especially improvement in negative symptoms
	Vijayan 2007[22]	Asian Indian (213)	1 year OL	Clozapine, Haloperidol, Risperidone	n.s.	No association
	Shen 2008[15]	Chinese (128)	4 weeks OL	Aripiprazole	n.s.	No association
Taq1B	Hwang 2005[16]	Caucasian & AA (232)	6 months OL	Clozapine	<.05	T allele was associated with higher response rate in AAs, but not Caucasians.
	Xing 2007[13]	Chinese (125)	8 weeks RCT	Risperidone	n.s.	No association
	Vijayan 2007[22]	Asian Indian (213)	1 year OL	Clozapine, Haloperidol, Risperidone	n.s.	No association
DRD3						
Ser9Gly (rs6280)	Shaikh 1996[116]	Caucasian (133)	3 months OL	Clozapine	<.05	Ser/Ser less likely to respond
Ser9Gly (rs6280)	Gaitonde 1996[117]	Caucasian (84)	Case-control	clozapine	n.s.	No association
(rs6280)						
Ser9Gly (rs6280)	Ebstein 1997[118]	Jews and Caucasians (167)	Case-control	Various AP	<.05	Gly/Gly less likely to respond

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
Ser9Gly (rs6280)	Malhotra 1998[119]	American (68)	10 weeks RCT	Clozapine	n.s.	No association
Ser9Gly (rs6280)	Scharfetter 1999[120]	Pakistani (32)	6 months OL	Clozapine	<.01	Ser9 allele less likely to respond
Ser9Gly (rs6280)	Arranz 2000[52]	Caucasian (200)	Case-control	clozapine	n.s.	No association
Ser9Gly (rs6280)	Joober 2000[121]	Canadian (108)	Case-control	Various AP	n.s.	No association
Ser9Gly (rs6280)	Staddon 2002[122]	Basque (50)	3 months OL	clozapine	n.s.	No association
Ser9Gly (rs6280)	Szekeres 2004[123]	Caucasian (75)	12 weeks	clozapine, olanzapine, quetiapine, risperidone	<.01	Ser/Ser less likely to respond
Ser9Gly (rs6280)	Reynolds 2005[114]	Chinese (117)	10 weeks, OL	Chlorpromazine, Risperidone, Clozapine, Fluphenazine, Sulpride	<.05	Ser/Gly heterozygotes were more likely to respond
Ser9Gly (rs6280)	Lane 2005[124]	Chinese (123)	6 weeks RCT	Risperidone	<.01	Ser allele carriers had more improvement in negative symptoms.
Ser9Gly (rs6280)	Cordeiro 2006[125]	Brazilian (112)	Variable length of treatment, OL	chlorpromazine, thioridazine, haloperidol	n.s.	No association
Ser9Gly (rs6280)	Xuan 2008[126]	Chinese (130)	8 weeks OL	Risperidone	n.s.	No association
Ser9Gly (rs6280)	Kim 2008[38]	Korean (100)	4 weeks OL	risperidone	n.s.	No association
Ser9Gly (rs6280)	Ikeda 2008[20]	Japanese (120)	8 weeks OL	risperidone	n.s.	No association
Ser9Gly (rs6280)	Barlas 2009[127]	Turkish (92)		clozapine	n.s.	No association
Ser9Gly (rs6280)	Chen 2009[41]	Chinese (128)	4 weeks OL	Aripiprazole	n.s.	No association
Ser9Gly (rs6280)	Hwang 2010[26]	Caucasian & AA (232)	6 months OL	Clozapine	n.s.	No association
DRD4						
VNTR 48bp	Shaikh 1993[128]	Caucasian (64)	2 months OL	clozapine	n.s.	No association
VNTR 48bp	Rao 1994[129]	Americans (29)	Case-control	clozapine	n.s.	No association

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
VNTR 48bp	Shaikh 1995[130]	Caucasian and Chinese (189)	2 months, OL	clozapine	n.s.	No association
VNTR 48bp	Rietschel 1996[131]	Caucasian (149)	4 weeks OL	clozapine	n.s.	No association
VNTR 48bp	Kohn 1997[132]	Jews (64)	Case-control	clozapine	n.s.	No association
VNTR 48bp	Hwu 1998[27]	Chinese (80)	Case-control	Various AP	<.05	Longer repeat alleles were associated higher response rate
VNTR 48bp	Cohen 1999[29]	Caucasian (60)	Case-control	Various FGA clozapine	<.05	7 repeat allele carriers less likely to respond
VNTR 48bp	Kaiser 2000[133]	Caucasian (638)	Case-control	Various AP clozapine	n.s.	No association
VNTR 48bp	Zalsman 2003[134]	Jews (24)	8 weeks OL	Risperidone	n.s.	No association
VNTR 48bp	Zhao 2005[28]	Chinese (81)	2 months OL	clozapine	<.05	5 repeat allele was associated with non-responders.
VNTR 48bp	Ikeda 2008[20]	Japanese (120)	8 weeks OL	risperidone	n.s.	No association
5HT2A						
T102C (rs6313)	Arranz 1995[34]	Caucasian (149)	12 weeks OL	clozapine	<.01	C/C less likely to respond
	Nothen 1995[135]	Caucasian (146)	4 weeks OL	clozapine	n.s.	No association
	Masellis 1995[136]	Caucasian and AA (126)	6 months OL	clozapine	n.s.	No association
	Nimgaonkar 1996[137]	Caucasian and AA (174)	Case-control	Various AP clozapine	<.05	C/C less likely to respond
	Malhotra 1996[44]	American (70)	10 weeks RCT	clozapine	n.s.	No association
	Jonsson 1996[138]	Caucasian (118)	Case-control	Various AP	n.s.	No association
	Masellis 1998[35]	Caucasian and AA (185)	6 months OL	clozapine	n.s.	No association
	Lin 1999[36]	Chinese (97)	8 weeks OL	clozapine	n.s.	No association
	Joober 1999[139]	Caucasian (102)	Case-control	FGA	n.s.	No association
	Lane 2002[37]	Chinese (100)	6 weeks OL	risperidone	<.05	C/C had better improvement
	Ellingrod 2002[45]	American (41)	6 weeks OL	olanzapine	.063	T/T had more improvement in negative symptoms
	Yamanouchi 2003[112]	Japanese (73)	8 weeks OL	Risperidone	n.s.	No association

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
	Kim 2008[38]	Korean (100)	4 weeks OL	risperidone	<.05	T/T less likely to respond
	Ikeda 2008[20]	Japanese (120)	8 weeks OL	risperidone	n.s.	No association
	Chen 2009[39]	Chinese (128)	4 weeks OL	Aripiprazole	<.05	C/C had less improvement, especially in negative symptoms
−1438G/A (rs6311)	Arranz 1998[30]	Caucasian (274)	Case-control	clozapine	<.001	G/G less likely to respond
	Yamanouchi 2003[112]	Japanese (73)	8 weeks OL	Risperidone	n.s.	No association
	Ellingrod 2003[40]	American (41)	6 weeks RCT	olanzapine	.054	A/A had larger reduction in negative symptoms
	Hamdani 2005[140]	Caucasian (116)	Case-control	Amisulpride, Clozapine, Olanzapine, risperidone	n.s.	No association
	Benmessaoud 2008[42]	Algerian (100)	Case-control	Haloperidol	<.05	G allele was associated with better response
	Chen 2009[39]	Chinese (128)	4 weeks OL	Aripiprazole		G/G had less improvement, especially in negative symptoms
His452Tyr	Arranz 1996[43]	Caucasian (153)	Case-control	clozapine	<.05	Tyr/Tyr less likely to respond
	Malhotra 1996[44]	American (70)	10 weeks RCT	clozapine	n.s.	No association
	Arranz 1998[30]	Caucasian (274)	Case-control	clozapine	<.05	Tyr allele was associated with poor response
	Masellis 1998[35]	Caucasian and AA (185)	6 months OL	clozapine	<.05	Tyr allele was associated with poor response
	Ellingrod 2002[45]	American (41)	6 weeks OL	olanzapine	n.s.	No association
5HT2C						
C759T (rs3813929)	Reynolds 2005[114]	Chinese (117)	10 weeks, OL	Chlorpromazine, Risperidone, Clozapine, Fluphenazine, Sulpride	<.05	C/C had better improvement, especially negative symptoms
	Ikeda 2008[20]	Japanese (120)	8 weeks OL	risperidone	n.s.	No association
Cys23Ser (rs6318)	Sodhi 1995[46]	Caucasian (162)	Case-control	clozapine	<.01	Ser allele carriers more likely to respond
	Rietschel 1997[141]	Caucasian (152)	4 weeks OL	clozapine	n.s.	No association

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
	Malhotra 1997[142]	American (66)	10 week RCT	clozapine	n.s.	No association
	Masellis 1998[35]	Caucasian and AA (185)	6 months OL	clozapine	n.s.	No association
	Schumacher 2000[109]	Caucasian (163)	4 weeks OL	clozapine	n.s.	No association
	Ellingrod 2002[45]	American (41)	6 weeks OL	olanzapine	n.s.	No association
5HT6						
267-T/C	Yu 1999[47]	Chinese (99)	Case-control	clozapine	<.05	T/T had better response
	Masellis 2001[49]	Caucasian and AA (173)	6 months OL	clozapine	n.s.	No association
	Lane 2004[48]	Chinese (123)	6 weeks OL	risperidone	<.01	T/T had better response
	Ikeda 2008[20]	Japanese (120)	8 weeks OL	risperidone	n.s.	No association
5HTT						
HTTLPR	Arranz 2000[52]	Caucasian (200)	Case-control	clozapine	<.05	Short allele was associated with poor response
	Tsai 2000[143]	Chinese (90)	8 weeks OL	clozapine	n.s.	No association
	Wang 2007[53]	Chinese (129)	8 weeks RCT	risperidone	<.05	Long allele was associated with better response
	Dolzan 2008[54]	Caucasian (56)	4 weeks RCT	Haloperidol, risperidone	<.05	Short allele was associated with poor response
COMT						
Val108Met	Illi 2003[55]	Caucasian (94)	Case-control	FGAs	<.01	Met/Met less likely to respond
	Illi 2007[144]	Caucasian (180)	Case-control	Various AP clozapine	n.s.	No association between genotype and AP maintenance doses
	Woodward 2007[57]	Caucasian and AA (86)	6 month OL	clozapine	<.05	Met carriers had better improvement in cognitive function
	Bertolino 2007[56]	Caucasian (59) frist-episode patients	8 weeks OL	olanzapine	<.01	Val/Val less likely to respond and took longer to respond, especially in negative symptoms
CYP2D6						
*3A and *4A	Arranz 1995[145]	Caucasian (123)	Case-control	clozapine	n.s.	No association
	Aitchison 1999[146]	Caucasian (308)	Case-control	FGAs	n.s.	There were more UMs in non-refractory patients, but not statistically

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
						significant.
	Brockmoller 2002[147]	Caucasian (172)	4 weeks OL	haloperidol	n.s.	Non-significant trend towards lower therapeutic efficacy with increasing number of active CYP2D6 genes
*5 and *10	Kakihara 2005[59]	Japanese (136)	2 weeks OL	risperidone	n.s.	No difference in clinical improvement among genotypes
	Riedel 2005[60]	Caucasian (82)	6 week OL	risperidone	n.s.	CYP2D6 genotypes were associated with drug blood levels, but not clinical response
	Kohlrausch 2008[148]	Braizilian (186)	Case-control	FGA	n.s.	No association
	Laika 2009[91]	Caucasian (365)	Case-control	Various AP	n.s.	IMs on CYP2D6-dependent drugs had lower response rate than IMs on other drugs.

Table 2

Studies of associations of genetics variants and antipsychotic-induced tardive dyskinesia (TD)

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
DRD2 Taq1A (rs1800497)	Chen 1997[149]	93 TD+ and 84 TD− Chinese patients	Case-control	unspecified	<.05	A2/A2 is associated with higher prevalence of TD, especially in women.
	Hori 2001[150]	44 TD+ and 156 TD− Japanese patients	Case-control	unspecified	n.s.	No association
	Segman 2003[151]	59 TD+ and 63 TD− Jewish patients	Case-control	unspecified	n.s.	No association
	Chong 2003[152]	117 TD+ and 200 TD− Chinese patients		unspecified	n.s.	No association
	Lattuada 2004	38 TD+ and 34 TD− Caucasian patients	Case-control	unspecified	n.s.	No association
	Liou 2006[153]	126 TD+ and 127 TD− Chinese patients	Case-control	unspecified	<.05	A2/A2 Is associated with higher risk of TD
	Zai 2007[154]	91 TD+ and 141 TD− Caucasian and AA patients	Case-control	unspecified	n.s.	No association
	Tsai 2010[69]	207 TD+ and 503 TD− American patients	Case-control	unspecified	n.s.	No association
−141C Ins/Del (rs1799732)	Inada 1999[155]	31 TD+ and 108 TD− Japanese patients	Case-control	unspecified	<.05	Del allele is associated with higher risk of TD
	De Leon 2005[156]	162 TD+ and 354 TD− American patients	Case-control	risperidone	n.s.	No association
	Segman 2003[151]	59 TD+ and 63 TD− Jewish patients	Case-control	unspecified	n.s.	No association
	De Leon 2005[156]	162 TD+ and 354 TD− American patients	Case-control	risperidone	n.s.	No association
	Liou 2006[153]	126 TD+ and 127 TD− Chinese patients	Case-control	unspecified	n.s.	No association
	Zai 2007[154]	91 TD+ and 141 TD− Caucasian and AA patients	Case-control	unspecified	n.s.	No association
Ser311Cys	Hori 2001[150]	44 TD+ and 156 TD− Japanese patients	Case-control	unspecified	n.s.	No association
	Chong 2003[152]	117 TD+ and 200 TD− Chinese patients	Case -control	unspecified	n.s.	No association
	De Leon 2005[156]	162 TD+ and 354 TD−	Case-control	risperidone	n.s.	No association

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
		American patients				
	Tsai 2010[69]	207 TD+ and 503 TD− American patients	Case-control	Unspecified	n.s.	No association
DRD3 Ser9Gly (rs6280)	Steen 1997[157]	51 TD+ and 49 TD− Caucasian patients	Cohort study	Unspecified	<.05	Gly/Gly genotype was associated with higher risk of TD
	Inada 1997[158]	49 TD+ and 56 TD− Japanese patients	Cohort study	Unspecified	n.s.	No association
	Basile 1999[159]	112 Caucasian and African American patients	Cohort study	Unspecified	<.001	Gly/Gly genotype was associated with higher AIMS scores
	Segman 1999[160]	53 TD+ and 63 TD− Jewish patients	Case-control	Unspecified	<.05	Gly allele carriers were more likely to have TD
	Lovlie 2000[161]	32 TD+ and 39 TD− Caucasian patients	Cohort study	Unspecified	n.s.	Gly/Gly genotype was associated with more TD, but not significant.
	Rietschel 2000[162]	79 TD+ and 78 TD− Caucasian patients	Case-control	Unspecified	n.s.	No association
	Liao 2001[163]	21 TD+ and 94 TD− Chinese patients	Cohort study	Unspecified	<.01	Ser/Gly genotype was associated with higher risk of TD
	Garcia-Barcelo 2001[164]	65 TD+ and 66 TD− Chinese patients	Cohort study	Unspecified	n.s.	No association
	Mihara 2002[165]	9 TD+ Japanese patients	Cohort study	Unspecified	n.s.	No allele or genotype overrepresentation in the sample
	Woo 2002[166]	59 TD+ and 54 TD− Korean patients	Cohort study	Unspecified	<.05	Gly/Gly genotype was associated with higher risk of TD
	Lerer 2002[66]	317 TD+ and 463 TD− Caucasian patients	Case-control	Unspecified	<.05	Gly allele carriers were associated with higher risk of TD
	Chong 2003[152]	117 TD+ and 200 TD− Chinese patients	Case -control	Unspecified	<.05	Ser/Ser genotype was associated with higher risk of TD
	Zhang 2003[167]	42 TD+ and 52 TD− Chinese patients	Case-control	Unspecified	n.s.	Non-significant trend association between Ser/Gly genotype and risk of TD
	Liou 2004[168]	102 TD+ and 114 TD− Chinese patients	Cohort study	Unspecified	n.s.	No association
	De Leon 2005[156]	162 TD+ and 354 TD− American patients	Case-control	risperidone	<.05	Gly allele was associated with more severe TD
	Srivastava 2006[169]	96 TD+ and 239 TD− Asian Indian patients	Case-control	Unspecified	n.s.	No association
	Al Hadithy 2009[76]	146 Russian Caucasian	Cohort study	Unspecified	<.05	Gly allele carriers were more likely to

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
		patients				have limb-truncal dyskinesia
	Wilffert 2009[75]	114 African-Caribbean patients	Cohort study	Unspecified	n.s.	No difference in AIMS scores among genotypes.
	Zai 2009[170]	70 TD+ and 101 TD– Caucasian patients	Case-control	Unspecified	n.s.	No association
	Tsai 2010[69]	207 TD+ and 503 TD– American patients	Case-control	Unspecified	n.s.	No association
5HT2A T102C (rs6313)	Segman 2001[70]	59 TD+ and 62 TD– Jewish patients	Case-control	Unspecified	<.01	C allele was associated with higher risk of TD
	Basile 2001[171]	54 TD+ and 82 TD– Caucasian and African American patients	Case-control	Unspecified	n.s.	No association
	Tan 2001[71]	87 TD+ and 134- Singaporean patients	Case-control	Unspecified	<.05	C allele was more frequent in patients with TD
	Herken 2003[172]	32 TD+ and 111 TD– Turkish patients	Case-control	Unspecified	n.s.	No association
	Lattuada 2004[72]	38 TD+ and 34 TD– Caucasian patients	Case-control	Unspecified	<.05	C/C genotypes were more frequent in patients with TD
	Deshpande 2005[74]	96 TD+ and 240 TD– Asian Indian patients	Case-control	Unspecified	n.s.	No association
	Wilffert 2009[75]	114 African-Caribbean	Cohort study	Unspecified	n.s.	No difference in AIMS scores among genotypes.
	Tsai 2010[69]	207 TD+ and 503 TD– American patients	Case-control	Unspecified	n.s.	No association
−1438G/A	Segman 2001[70]	59 TD+ and 62 TD– Jewish patients	Case-control	Unspecified	<.01	G allele was associated with higher risk of TD
	Basile 2001[171]	54 TD+ and 82 TD– Caucasian and African American patients	Case-control	Unspecified	n.s.	No association
	Herken 2003[172]	32 TD+ and 111 TD– Turkish patients	Case-control	Unspecified	n.s.	No association
	Deshpande 2005[74]	96 TD+ and 240 TD– Asian Indian patients	Case-control	Unspecified	n.s.	No association
	Al Hadithy 2009[76]	146 Russian Caucasian patients	Cohort study	Unspecified	<.05	A allele carriers were more likely to have orofaciolingual dyskinesia
5HT2C Cys23Ser (rs6318)	Segman 2000[173]	55 TD+ and 60 TD– Jewish patients	Case-control	Unspecified	<.05	Ser allele was more frequent in TD patients
	Segman 2002[174]	147 Jewish patients	Cohort study	Unspecified	<.01	Gly/Gly genotype was associated with higher AIMS scores in older patients

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
	Deshpande 2005[74]	96 TD+ and 240 TD− Asian Indian patients	Case-control	Unspecified	n.s.	No association
	Al Hadithy 2009[76]	146 Russian Caucasian patients	Cohort study	Unspecified	<.05	Ser allele carriers were less likely to have orofaciolingual dyskinesia and lower AIMS scores
	Tsai 2010[69]	207 TD+ and 503 TD− American patients	Case-control	Unspecified	n.s.	No association
COMT Val108Met (rs4680)	Herken 2003[172]	32 TD+ and 111 TD− Turkish patients	Case-control	Unspecified	n.s.	No association
	Matsumoto 2004[188]	43 TD+ and 163 TD− Japanese patients	Case-control	Unspecified	n.s.	No association
	Han 2005	47 TD+ and 67 TD− Korean male patients	Case-control	Unspecified	<.01	Met allele carriers were less likely to have TD
	Lai 2005[189]	166 TD+ and 133 TD− Chinese patients	Case-control	Unspecified	n.s.	No association
	Srivastava 2006[176]	96 TD+ and 239 TD− Asian Indian patients	Case-control	Unspecified	<.05	Met allele carriers were less likely to have TD
	Kang 2008[190]	209 Korean patients	Cohort study	Unspecified	n.s.	No association
CYP2D6	Nikoloff 2002[175]	Korean patients	Cohort study	Unspecified	<.05	Loss of function alleles was associated with higher risk of TD in males, but not in females
	Brockmoller 2002[147]	172 Caucasian patients	4 weeks OL	haloperidol	n.s.	2D6 metabolic status was not associated with AIMS scores
	Lohmann 2003[176]	50 TD+ and 59 TD− Caucasian patients	Case-control	Unspecified	n.s.	No association
	Inada 2003[88]	320 Japanese patients	Cohort study	Unspecified	n.s.	No association
	Liou 2004[78]	113 TD+ and 103 TD− Chinese patients	Case-control	unspecified	<.05	IMs (*10 C188T) were more likely to have TD, especially in males
	Tiwari 2005[177]	96 TD+ and 239 TD− Asian Indian patients	Case-control	Unspecified	n.s.	No association
	de Leon 2005[156]	162 TD+ and 354 TD− American patients	Case-control	Unspecified	n.s.	No association
	Fu 2006[79]	91 TD+ and 91 TD− Chinese patients	Case-control	Unspecified	<.05	T allele (C100T SNP) was more frequent in patients with TD
	Kobylecki 2009[80]	Caucasian (54)	Case-control	Various AP	<.05	EPS and TD were more frequent in PM patients
	Tsai 2010[69]	207 TD+ and 503 TD−	Case-control	Unspecified	n.s.	No association

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
CYP1A2 *1F	Basil 2000[84]	American patients 85 American patients	Cohort study	Various AP (FGAs and SGAs)	<.01	C/C genotype was associated with higher AIMS scores, especially among smokers.
	Tiwari 2005[85]	86 TD+ and 222 TD– Asian Indian patients	Case-control	FGAs and SGAs	n.s.	No association
	Matsumoto 2004[178]	42 TD+ and 157 TD– Japanese patients	Case-control	Unspecified	n.s.	No association
	Chong 2003[179]	43 TD+ and 60 TD– Chinese patients	Case-control	Unspecified	n.s.	No association
	Schulze 2001[180]	56 TD+ and 63 TD– Caucasian patients	Case-control	Unspecified	n.s.	No association
	Fu 2006[79]	73 TD+ and 66 TD– Chinese patients	Case-control	FGAs	<.05	C allele was associated with higher frequency of TD.
EPS						
CYP2D6	Spina 1992[181]	79 Caucasian patients	Case-control	Unspecified	n.s.	No association
	Scordo 2000[182]	119 Caucasian patients	Cohort study	Unspecified	n.s.	PMs had history of EPS
	Schillevoort 2002[87]	531 Caucasian patients	Cohort study	Unspecified	<.05	PM patients taking CYP2D6 dependent APs were more likely to take anti-cholinergic drugs
	Brockmoller 2002[147]	172 Caucasian patients	4 weeks OL	Haloperidol	n.s.	No association
	Inada 2003[88]	320 Japanese patients	Cohort study	Unspecified	<.05	PMs were more likely to have acute EPS
	de Leon 2005[89]	325 American patients	Cohort study	Risperidone	<.01	PMs showed moderate or marked ADRs
	Crescenti 2008[90]	455 Spanish Caucasian patients	Case-control	Various AP	<.05	PM were more frequent in patients with EPS.
	Kobylecki 2009[80]	54 Caucasian patients	Case-control	Various AP	<.05	EPS and TD were more frequent in PM patients
	Laika 2009[91]	365 Caucasian patients	Cohort study	Various psychotropic drugs, not limited to AP	<.05	PMs and IMs were more likely to suffer from side effects

Table 3

Studies of associations of genetics variants and antipsychotic-induced weight gain.

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
5HT2C C759T (rs3813929)	Reynolds 2002[183, 184]	123 Chinese first-episode patients	10 weeks OL	Chlorpromazine Risperidone Clozapine fluphenazine	<.01	C allele was associated with higher weight gain
	Tsai 2002[184]	80 Chinese treatment-resistant patients	4 months OL	clozapine	n.s.	No association
	Basile 2002[185]	73 Caucasian and African American treatment-resistant patients	6 weeks OL	clozapine	n.s.	Non-significant trend towards higher weight gain associated with the T allele
	Reynolds 2003[186]	32 Chinese first-episode patients	6 weeks OL	clozapine	<.05	C allele and C/C genotype were associated with higher weight gain, especially in men
	Miller 2005[187]	41 American treatment-resistant patients	6 months OL	Clozapine	<.01	C allele was associated with higher weight gain
	Ellingrod 2005[188]	42 American acutely psychotic patients	6 weeks OL	Olanzapine	<.001	T allele was associated with less weight gain
	Templeman 2005[189]	73 Spanish Caucasian first-episode patients	10 weeks OL	Various APs	<.05	T allele was associated with less weight gain
	Theisen 2005[190]	97 Caucasian patients	Case-ontrol	clozapine	n.s.	No association
	Lane 2006[191]	123 Chinese acutely psychotic patients	6 weeks OL	risperidone	<.05	T allele was associated with less weight gain
	Ryu 2007[192]	84 Korean patients	4 week OL	Six antipsychotics	<.05	T allele was associated with less weight gain
	Park 2008[193]	79 Korean patients	3 months OL	olanzapine	n.s.	No association
	Ujike 2008[99]	164 Japanese patients	8-24 weeks OL	olanzapine	n.s.	No association
	Kuzman 2008[194]	108 female Croatian Caucasian patients	4 months OL	Olanzapine risperidone	n.s.	No association
	Godlewska 2009[195]	107 Polish patients including 36 first-episode patients	6 weeks OL	olanzapine	<.01	T allele was associated with less weight gain
	Gunes 2009[196]	46 Swedish patients	Case-control	Olanzapine clozapine	<.05	C allele was associated with obesity in clozapine-treated patients
	Opgen-Rhein 2010[197]	128 German Caucasian patients	Case-control	Various AP	<.05	C allele was associated with more weight gain

Gene/SNP	1st Author/year	Sample (n)	Study Design	Antipsychotic	p	Findings
	Thompson 2010[97]	216 American aptients with mixed ethnicities	7 months OL	Iloperidone	n.s.	No association
GNB3 825-C/T	Tsai 2004[198]	87 Chinese patients	4 months OL	Clozapine	n.s.	No association
	Wang 2005[199]	134 Chinese patients	13 months OL	Clozapine	<.01	T/T genotype was associated with more weight gain
	Bishop 2006[200]	42 Caucasian patients	6 weeks OL	Olanzapine	n.s.	Non-significant trend toward TT genotype with more weight gain
	Ujike 2008[99]	164 Japanese patients	8-24 weeks OL	olanzapine	<.05	T allele was associated with more weight gain
	Park 2009[100]	104 Korean patients	3 months OL	olanzapine	n.s.	No association