Published in final edited form as:
Expert Opin Drug Metab Toxicol. 2011 January ; 7(1): 9–37. doi:10.1517/17425255.2011.532787.

Pharmacogenetics and Antipsychotics: Therapeutic Efficacy and Side Effects Prediction

Jian-Ping Zhang, MD, PhD and **Anil K. Malhotra, MD**
Division of Psychiatry Research, Zucker Hillside Hospital, Feinstein Institute of Medical Research, North Shore-Long Island Jewish Health System, Glen Oaks, NY

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)

Corresponding Author: Jian-Ping Zhang, MD, PhD Division of Psychiatry Research Department of Psychiatry The Zucker Hillside Hospital 75-59 263rd Street Glen Oaks, NY 11004 Tel: 718-470-8020 jzhang1@nshs.edu.

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 effects4, at least for positive symptoms, although D3, D4 receptors, and serotonin as well as the glutamate system may also be involved in drug action5. 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 treatment6, [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 replication8. 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 results13، 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 sample28 and one Caucasian sample29. 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 modulation31. 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 genotype51. 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 treatment52–54. 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 allele63. 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-analysis64 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 development63, 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 models65. 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 samples66, 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 TD69.

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 studies33. Interestingly, the C allele was also associated with risk of TD in at least three studies70-72. 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 smokers84. However, a meta-analysis of seven studies did not find significant association between the *1F SNP and TD frequency64. 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 sample109. The previously mentioned GWAS studies106, 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.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1*. van Os J, Kapur S. Schizophreniay. Lancet Aug 22;2009 374(9690):635–45. This is the latest general review of prevelance, etiology, psychopathology, diagnosis and treatment of schizophrenia. [PubMed: 19700006]

2. McGrath J, Saha S, Chant D, et al. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008;30:67–76. [PubMed: 18480098]

3. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet Jan 3;2009 373(9657):31–41. [PubMed: 19058842]

4. Kapur S, Mamo D. Half a century of antipsychotics and still a central role for dopamine D2 receptors. Progress in neuro-psychopharmacology & biological psychiatry Oct;2003 27(7):1081–90. [PubMed: 14642968]

5*. Miyamoto S, Duncan GE, Marx CE, et al. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Molecular psychiatry Jan;2005 10(1):79–104. Comprehensive review of antipsychotic drugs' mechanisms of action with a particular emphasis on receptors and molecular pathways. [PubMed: 15289815]

6*. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. The New England journal of medicine Sep 22;2005 353(12):1209–23. This article reported a large clinical trial of antipsychotic drugs for schizophrenia, and data from the trial formed basis of latest pharmacogenetic findings. [PubMed: 16172203]

7. Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet Mar 29;2008 371(9618):1085–97. [PubMed: 18374841]

8. Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. Molecular psychiatry Aug;2007 12(8):707–47. [PubMed: 17549063]

9. Snyder SH. Dopamine receptors, neuroleptics, and schizophrenia. The American journal of psychiatry Apr;1981 138(4):460–4. [PubMed: 6111227]

10. Malhotra AK, Buchanan RW, Kim S. Allelic variation in the promotor region of the dopamine D2 receptor gene and clozapine response. Schizophr Res 1999;36:92–3.

11. Lencz T, Robinson DG, Xu K, et al. DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients. The American journal of psychiatry Mar;2006 163(3):529–31. [PubMed: 16513877]

12. Wu S, Xing Q, Gao R, et al. Response to chlorpromazine treatment may be associated with polymorphisms of the DRD2 gene in Chinese schizophrenic patients. Neuroscience letters Mar 7;2005 376(1):1–4. [PubMed: 15694263]

13. Xing Q, Qian X, Li H, et al. The relationship between the therapeutic response to risperidone and the dopamine D2 receptor polymorphism in Chinese schizophrenia patients. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) Oct;2007 10(5):631–7. [PubMed: 17105675]

14. Arranz MJ, Li T, Munro J, et al. Lack of association between a polymorphism in the promoter region of the dopamine-2 receptor gene and clozapine response. Pharmacogenetics Dec;1998 8(6): 481–4. [PubMed: 9918131]

15. Shen YC, Chen SF, Chen CH, et al. Effects of DRD2/ANKK1 gene variations and clinical factors on aripiprazole efficacy in schizophrenic patients. Journal of psychiatric research. Oct 14.2008

16. Hwang R, Shinkai T, De Luca V, et al. Association study of 12 polymorphisms spanning the dopamine D(2) receptor gene and clozapine treatment response in two treatment refractory/

intolerant populations. Psychopharmacology (Berl) Aug;2005 181(1):179–87. [PubMed: 15830237]

17**. Zhang JP, Lencz T, Malhotra AK. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. The American journal of psychiatry Jul;2010 167(7):763–72. This meta-analysis examined the association between two SNPs in *DRD2* and antipsychotic drug response, and highlighted the importance of studying patients with first psychotic episode. [PubMed: 20194480]

18. Suzuki A, Mihara K, Kondo T, et al. The relationship between dopamine D2 receptor polymorphism at the Taq1 A locus and therapeutic response to nemonapride, a selective dopamine antagonist, in schizophrenic patients. Pharmacogenetics Jun;2000 10(4):335–41. [PubMed: 10862524]

19. Schafer M, Rujescu D, Giegling I, et al. Association of short-term response to haloperidol treatment with a polymorphism in the dopamine D(2) receptor gene. The American journal of psychiatry May;2001 158(5):802–4. [PubMed: 11329406]

20. Ikeda M, Yamanouchi Y, Kinoshita Y, et al. Variants of dopamine and serotonin candidate genes as predictors of response to risperidone treatment in first-episode schizophrenia. Pharmacogenomics Oct;2008 9(10):1437–43. [PubMed: 18855532]

21. Dahmen N, Muller MJ, Germeyer S, et al. Genetic polymorphisms of the dopamine D2 and D3 receptor and neuroleptic drug effects in schizophrenic patients. Schizophrenia research Apr 15;2001 49(1-2):223–5. [PubMed: 11428346]

22. Vijayan NN, Bhaskaran S, Koshy LV, et al. Association of dopamine receptor polymorphisms with schizophrenia and antipsychotic response in a South Indian population. Behav Brain Funct 2007;3:34. [PubMed: 17651483]

23. Lane HY, Lee CC, Chang YC, et al. Effects of dopamine D2 receptor Ser311Cys polymorphism and clinical factors on risperidone efficacy for positive and negative symptoms and social function. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) Dec;2004 7(4):461–70. [PubMed: 15140279]

24. Jeanneteau F, Funalot B, Jankovic J, et al. A functional variant of the dopamine D3 receptor is associated with risk and age-at-onset of essential tremor. Proceedings of the National Academy of Sciences of the United States of America Jul 11;2006 103(28):10753–8. [PubMed: 16809426]

25. Jonsson EG, Flyckt L, Burgert E, et al. Dopamine D3 receptor gene Ser9Gly variant and schizophrenia: association study and meta-analysis. Psychiatric genetics Mar;2003 13(1):1–12. [PubMed: 12605094]

26**. Hwang R, Zai C, Tiwari A, et al. Effect of dopamine D3 receptor gene polymorphisms and clozapine treatment response: exploratory analysis of nine polymorphisms and meta-analysis of the Ser9Gly variant. The pharmacogenomics journal Jun;2010 10(3):200–18. This meta-analysis examined the association between SNPs in *DRD3* and clozapine treatment response. [PubMed: 20029384]

27. Hwu HG, Hong CJ, Lee YL, et al. Dopamine D4 receptor gene polymorphisms and neuroleptic response in schizophrenia. Biol Psychiatry Sep 15;1998 44(6):483–7. [PubMed: 9777180]

28. Zhao AL, Zhao JP, Zhang YH, et al. Dopamine D4 receptor gene exon III polymorphism and interindividual variation in response to clozapine. Int J Neurosci Nov;2005 115(11):1539–47. [PubMed: 16223700]

29. Cohen BM, Ennulat DJ, Centorrino F, et al. Polymorphisms of the dopamine D4 receptor and response to antipsychotic drugs. Psychopharmacology (Berl) Jan;1999 141(1):6–10. [PubMed: 9952058]

30. Arranz MJ, Munro J, Owen MJ, et al. Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. Molecular psychiatry Jan;1998 3(1):61–6. [PubMed: 9491814]

31. Parsons MJ, D'Souza UM, Arranz MJ, et al. The −1438A/G polymorphism in the 5-hydroxytryptamine type 2A receptor gene affects promoter activity. Biol Psychiatry Sep 15;2004 56(6):406–10. [PubMed: 15364038]

32. Polesskaya OO, Aston C, Sokolov BP. Allele C-specific methylation of the 5-HT2A receptor gene: evidence for correlation with its expression and expression of DNA methylase DNMT1. Journal of neuroscience research Feb 15;2006 83(3):362–73. [PubMed: 16358338]

33**. Arranz MJ, Munro J, Sham P, et al. Meta-analysis of studies on genetic variation in 5-HT2A receptors and clozapine response. Schizophr Res Jul 27;1998 32(2):93–9. This was the first meta-analysis summarizing findings on the association between *HTR2A* variation and clozapine response. [PubMed: 9713904]

34**. Arranz M, Collier D, Sodhi M, et al. Association between clozapine response and allelic variation in 5-HT2A receptor gene. Lancet Jul 29;1995 346(8970):281–2. This was one of the first pharmacogenetic studies of antipsychotic drugs. [PubMed: 7630250]

35. Masellis M, Basile V, Meltzer HY, et al. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology Aug;1998 19(2):123–32. [PubMed: 9629566]

36. Lin CH, Tsai SJ, Yu YW, et al. No evidence for association of serotonin-2A receptor variant (102T/C) with schizophrenia or clozapine response in a Chinese population. Neuroreport Jan 18;1999 10(1):57–60. [PubMed: 10094133]

37. Lane HY, Chang YC, Chiu CC, et al. Association of risperidone treatment response with a polymorphism in the 5-HT(2A) receptor gene. The American journal of psychiatry Sep;2002 159(9):1593–5. [PubMed: 12202283]

38. Kim B, Choi EY, Kim CY, et al. Could HTR2A T102C and DRD3 Ser9Gly predict clinical improvement in patients with acutely exacerbated schizophrenia? Results from treatment responses to risperidone in a naturalistic setting. Human psychopharmacology Jan;2008 23(1):61–7. [PubMed: 17924589]

39. Chen SF, Shen YC, Chen CH. HTR2A A-1438G/T102C polymorphisms predict negative symptoms performance upon aripiprazole treatment in schizophrenic patients. Psychopharmacology (Berl) Aug;2009 205(2):285–92. [PubMed: 19387614]

40. Ellingrod VL, Lund BC, Miller D, et al. 5-HT2A receptor promoter polymorphism, −1438G/A and negative symptom response to olanzapine in schizophrenia. Psychopharmacology bulletin Spring; 2003 37(2):109–12. [PubMed: 14566219]

41. Chen SF, Shen YC, Chen CH. Effects of the DRD3 Ser9Gly polymorphism on aripiprazole efficacy in schizophrenic patients as modified by clinical factors. Progress in neuropsychopharmacology & biological psychiatry Apr 30;2009 33(3):470–4.

42. Benmessaoud D, Hamdani N, Boni C, et al. Excess of transmission of the G allele of the −1438A/G polymorphism of the 5-HT2A receptor gene in patients with schizophrenia responsive to antipsychotics. BMC Psychiatry 2008;8:40. [PubMed: 18513383]

43. Arranz MJ, Collier DA, Munro J, et al. Analysis of a structural polymorphism in the 5-HT2A receptor and clinical response to clozapine. Neuroscience letters Oct 18;1996 217(2-3):177–8. [PubMed: 8916101]

44. Malhotra AK, Goldman D, Ozaki N, et al. Lack of association between polymorphisms in the 5-HT2A receptor gene and the antipsychotic response to clozapine. The American journal of psychiatry Aug;1996 153(8):1092–4. [PubMed: 8678181]

45. Ellingrod VL, Perry PJ, Lund BC, et al. 5HT2A and 5HT2C receptor polymorphisms and predicting clinical response to olanzapine in schizophrenia. Journal of clinical psychopharmacology Dec;2002 22(6):622–4. [PubMed: 12454564]

46. Sodhi MS, Arranz MJ, Curtis D, et al. Association between clozapine response and allelic variation in the 5-HT2C receptor gene. Neuroreport Dec 29;1995 7(1):169–72. [PubMed: 8742444]

47. Yu YW, Tsai SJ, Lin CH, et al. Serotonin-6 receptor variant (C267T) and clinical response to clozapine. Neuroreport Apr 26;1999 10(6):1231–3. [PubMed: 10363930]

48. Lane HY, Lin CC, Huang CH, et al. Risperidone response and 5-HT6 receptor gene variance: genetic association analysis with adjustment for nongenetic confounders. Schizophr Res Mar 1;2004 67(1):63–70. [PubMed: 14741325]

49. Masellis M, Basile VS, Meltzer HY, et al. Lack of association between the T-->C 267 serotonin 5-HT6 receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. Schizophr Res Jan 15;2001 47(1):49–58. [PubMed: 11163544]

50. Serretti A, Calati R, Mandelli L, et al. Serotonin transporter gene variants and behavior: a comprehensive review. Current drug targets Dec;2006 7(12):1659–69. [PubMed: 17168841]

51*. Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. Molecular psychiatry May;2010 15(5):473–500. This is a comprehensive review of pharmacogenetics of antidepressants. [PubMed: 18982004]

52**. Arranz MJ, Munro J, Birkett J, et al. Pharmacogenetic prediction of clozapine response. Lancet May 6;2000 355(9215):1615–6. This study was the first attempt of combining several genetic markers to predict antipsychotic response. [PubMed: 10821369]

53. Wang L, Yu L, He G, et al. Response of risperidone treatment may be associated with polymorphisms of HTT gene in Chinese schizophrenia patients. Neuroscience letters Feb 27;2007 414(1):1–4. [PubMed: 17287080]

54. Dolzan V, Serretti A, Mandelli L, et al. Acute antipyschotic efficacy and side effects in schizophrenia: association with serotonin transporter promoter genotypes. Progress in neuropsychopharmacology & biological psychiatry Aug 1;2008 32(6):1562–6.

55. Illi A, Mattila KM, Kampman O, et al. Catechol-O-methyltransferase and monoamine oxidase A genotypes and drug response to conventional neuroleptics in schizophrenia. Journal of clinical psychopharmacology Oct;2003 23(5):429–34. [PubMed: 14520117]

56. Bertolino A, Caforio G, Blasi G, et al. COMT Val158Met polymorphism predicts negative symptoms response to treatment with olanzapine in schizophrenia. Schizophr Res Sep;2007 95(1-3):253–5. [PubMed: 17644310]

57. Woodward ND, Jayathilake K, Meltzer HY. COMT val108/158met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia. Schizophr Res Feb;2007 90(1-3):86–96. [PubMed: 17123785]

58. Barnett JH, Scoriels L, Munafo MR. Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. Biol Psychiatry Jul 15;2008 64(2):137–44. [PubMed: 18339359]

59. Kakihara S, Yoshimura R, Shinkai K, et al. Prediction of response to risperidone treatment with respect to plasma concencentrations of risperidone, catecholamine metabolites, and polymorphism of cytochrome P450 2D6. International clinical psychopharmacology Mar;2005 20(2):71–8. [PubMed: 15729081]

60. Riedel M, Schwarz MJ, Strassnig M, et al. Risperidone plasma levels, clinical response and side-effects. European archives of psychiatry and clinical neuroscience Aug;2005 255(4):261–8. [PubMed: 15565299]

61. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. Current opinion in psychiatry Mar;2008 21(2):151–6. [PubMed: 18332662]

62. Tenback DE, van Harten PN, van Os J. Non-therapeutic risk factors for onset of tardive dyskinesia in schizophrenia: a meta-analysis. Mov Disord Dec 15;2009 24(16):2309–15. [PubMed: 19645070]

63. Zai CC, De Luca V, Hwang RW, et al. Meta-analysis of two dopamine D2 receptor gene polymorphisms with tardive dyskinesia in schizophrenia patients. Molecular psychiatry Sep;2007 12(9):794–5. [PubMed: 17767146]

64**. Bakker PR, van Harten PN, van Os J. Antipsychotic-induced tardive dyskinesia and polymorphic variations in COMT, DRD2, CYP1A2 and MnSOD genes: a meta-analysis of pharmacogenetic interactions. Molecular psychiatry May;2008 13(5):544–56. This meta-analysis examined the relationships between several genes and risk of TD. [PubMed: 18180754]

65. Accili D, Fishburn CS, Drago J, et al. A targeted mutation of the D3 dopamine receptor gene is associated with hyperactivity in mice. Proceedings of the National Academy of Sciences of the United States of America Mar 5;1996 93(5):1945–9. [PubMed: 8700864]

66. Lerer B, Segman RH, Fangerau H, et al. Pharmacogenetics of tardive dyskinesia: combined analysis of 780 patients supports association with dopamine D3 receptor gene Ser9Gly polymorphism. Neuropsychopharmacology Jul;2002 27(1):105–19. [PubMed: 12062911]

67. Bakker PR, van Harten PN, van Os J. Antipsychotic-induced tardive dyskinesia and the Ser9Gly polymorphism in the DRD3 gene: a meta analysis. Schizophr Res Apr;2006 83(2-3):185–92. [PubMed: 16513329]

68. Tsai HT, North KE, West SL, et al. The DRD3 rs6280 polymorphism and prevalence of tardive dyskinesia: a meta-analysis. Am J Med Genet B Neuropsychiatr Genet Jan 5;2010 153B(1):57–66. [PubMed: 19358223]

69**. Tsai HT, Caroff SN, Miller del D, et al. A candidate gene study of Tardive dyskinesia in the CATIE schizophrenia trial. Am J Med Genet B Neuropsychiatr Genet Jan 5;2010 153B(1):336–40. This CATIE pharmacogenetic study provided data on many candidate genes of TD, but none of the SNPs was statistically significant. [PubMed: 19475583]

70. Segman RH, Heresco-Levy U, Finkel B, et al. Association between the serotonin 2A receptor gene and tardive dyskinesia in chronic schizophrenia. Molecular psychiatry Mar;2001 6(2):225–9. [PubMed: 11317227]

71. Tan EC, Chong SA, Mahendran R, et al. Susceptibility to neuroleptic-induced tardive dyskinesia and the T102C polymorphism in the serotonin type 2A receptor. Biol Psychiatry Jul 15;2001 50(2):144–7. [PubMed: 11526996]

72. Lattuada E, Cavallaro R, Serretti A, et al. Tardive dyskinesia and DRD2, DRD3, DRD4, 5-HT2A variants in schizophrenia: an association study with repeated assessment. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) Dec;2004 7(4):489–93. [PubMed: 15383158]

73. Lerer B, Segman RH, Tan EC, et al. Combined analysis of 635 patients confirms an age-related association of the serotonin 2A receptor gene with tardive dyskinesia and specificity for the non-orofacial subtype. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) Sep;2005 8(3): 411–25. [PubMed: 15857569]

74. Deshpande SN, Varma PG, Semwal P, et al. II. Serotonin receptor gene polymorphisms and their association with tardive dyskinesia among schizophrenia patients from North India. Psychiatric genetics Sep;2005 15(3):157–8. [PubMed: 16094246]

75. Wilffert B, Al Hadithy AF, Sing VJ, et al. The role of dopamine D3, 5-HT2A and 5-HT2C receptor variants as pharmacogenetic determinants in tardive dyskinesia in African-Caribbean patients under chronic antipsychotic treatment: Curacao extrapyramidal syndromes study IX. Journal of psychopharmacology (Oxford, England) Aug;2009 23(6):652–9.

76. Al Hadithy AF, Ivanova SA, Pechlivanoglou P, et al. Tardive dyskinesia and DRD3, HTR2A and HTR2C gene polymorphisms in Russian psychiatric inpatients from Siberia. Progress in neuro-psychopharmacology & biological psychiatry Apr 30;2009 33(3):475–81. [PubMed: 19439249]

77. Britto MR, Wedlund PJ. Cytochrome P-450 in the brain. Potential evolutionary and therapeutic relevance of localization of drug-metabolizing enzymes. Drug metabolism and disposition: the biological fate of chemicals May-Jun;1992 20(3):446–50. [PubMed: 1355722]

78. Liou YJ, Wang YC, Bai YM, et al. Cytochrome P-450 2D6*10 C188T polymorphism is associated with antipsychotic-induced persistent tardive dyskinesia in Chinese schizophrenic patients. Neuropsychobiology 2004;49(4):167–73. [PubMed: 15118351]

79. Fu Y, Fan CH, Deng HH, et al. Association of CYP2D6 and CYP1A2 gene polymorphism with tardive dyskinesia in Chinese schizophrenic patients. Acta pharmacologica Sinica Mar;2006 27(3): 328–32. [PubMed: 16490169]

80. Kobylecki CJ, Jakobsen KD, Hansen T, et al. CYP2D6 genotype predicts antipsychotic side effects in schizophrenia inpatients: a retrospective matched case-control study. Neuropsychobiology 2009;59(4):222–6. [PubMed: 19521114]

81**. Patsopoulos NA, Ntzani EE, Zintzaras E, et al. CYP2D6 polymorphisms and the risk of tardive dyskinesia in schizophrenia: a meta-analysis. Pharmacogenetics and genomics Mar;2005 15(3): 151–8. This meta-analysis summarized studies on *CYP2D6* variants and risks of TD. [PubMed: 15861039]

82. Sachse C, Brockmoller J, Bauer S, et al. Functional significance of a C-->A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. British journal of clinical pharmacology Apr;1999 47(4):445–9. [PubMed: 10233211]

83. Nakajima M, Yokoi T, Mizutani M, et al. Genetic polymorphism in the 5′-flanking region of human CYP1A2 gene: effect on the CYP1A2 inducibility in humans. J Biochem Apr;1999 125(4): 803–8. [PubMed: 10101295]

84. Basile VS, Ozdemir V, Masellis M, et al. A functional polymorphism of the cytochrome P450 1A2 (CYP1A2) gene: association with tardive dyskinesia in schizophrenia. Molecular psychiatry Jul; 2000 5(4):410–7. [PubMed: 10889552]

85. Tiwari AK, Deshpande SN, Rao AR, et al. Genetic susceptibility to tardive dyskinesia in chronic schizophrenia subjects: I. Association of CYP1A2 gene polymorphism. The pharmacogenomics journal 2005;5(1):60–9. [PubMed: 15505641]

86. Zai CC, Tiwari AK, Basile V, et al. Oxidative stress in tardive dyskinesia: genetic association study and meta-analysis of NADPH quinine oxidoreductase 1 (NQO1) and Superoxide dismutase 2 (SOD2, MnSOD) genes. Progress in neuro-psychopharmacology & biological psychiatry Feb 1;2010 34(1):50–6. [PubMed: 19778569]

87. Schillevoort I, de Boer A, van der Weide J, et al. Antipsychotic-induced extrapyramidal syndromes and cytochrome P450 2D6 genotype: a case-control study. Pharmacogenetics Apr;2002 12(3): 235–40. [PubMed: 11927839]

88. Inada T, Senoo H, Iijima Y, et al. Cytochrome P450 II D6 gene polymorphisms and the neuroleptic-induced extrapyramidal symptoms in Japanese schizophrenic patients. Psychiatric genetics Sep;2003 13(3):163–8. [PubMed: 12960748]

89. de Leon J, Susce MT, Pan RM, et al. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. The Journal of clinical psychiatry Jan;2005 66(1):15–27. [PubMed: 15669884]

90. Crescenti A, Mas S, Gasso P, et al. Cyp2d6*3, *4, *5 and *6 polymorphisms and antipsychotic-induced extrapyramidal side-effects in patients receiving antipsychotic therapy. Clinical and experimental pharmacology & physiology Jul;2008 35(7):807–11. [PubMed: 18346175]

91. Laika B, Leucht S, Heres S, et al. Intermediate metabolizer: increased side effects in psychoactive drug therapy. The key to cost-effectiveness of pretreatment CYP2D6 screening? The pharmacogenomics journal. May 19.2009

92. Pramyothin P, Khaodhiar L. Metabolic syndrome with the atypical antipsychotics. Current opinion in endocrinology, diabetes, and obesity. Aug 16.2010

93. Muller DJ, Zai CC, Sicard M, et al. Systematic analysis of dopamine receptor genes (DRD1-DRD5) in antipsychotic-induced weight gain. The pharmacogenomics journal. Aug 17.2010

94. Lencz T, Robinson DG, Napolitano B, et al. DRD2 promoter region variation predicts antipsychotic-induced weight gain in first episode schizophrenia. Pharmacogenetics and genomics Sep;2010 20(9):569–72. [PubMed: 20664489]

95. Hong CJ, Liou YJ, Bai YM, et al. Dopamine receptor D2 gene is associated with weight gain in schizophrenic patients under long-term atypical antipsychotic treatment. Pharmacogenetics and genomics Jun;2010 20(6):359–66. [PubMed: 20375926]

96**. De Luca V, Mueller DJ, de Bartolomeis A, et al. Association of the HTR2C gene and antipsychotic induced weight gain: a meta-analysis. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) Oct;2007 10(5):697–704. This meta-analysis summarized findings on HTR2C genetic variants and antipsychotic drug-induced weight gain. [PubMed: 17291373]

97. Thompson A, Lavedan C, Volpi S. Absence of weight gain association with the HTR2C −759C/T polymorphism in patients with schizophrenia treated with iloperidone. Psychiatry research Feb 28;2010 175(3):271–3. [PubMed: 20045196]

98. Souza RP, De Luca V, Muscettola G, et al. Association of antipsychotic induced weight gain and body mass index with GNB3 gene: a meta-analysis. Progress in neuropsychopharmacology & biological psychiatry Dec 12;2008 32(8):1848–53.

99. Ujike H, Nomura A, Morita Y, et al. Multiple genetic factors in olanzapine-induced weight gain in schizophrenia patients: a cohort study. The Journal of clinical psychiatry Sep;2008 69(9):1416–22. [PubMed: 19193342]

100. Park YM, Chung YC, Lee SH, et al. G-protein beta3 Subunit Gene 825C/T Polymorphism Is Not Associated with Olanzapine-Induced Weight Gain in Korean Schizophrenic Patients. Psychiatry Investig Mar;2009 6(1):39–43.

101**. Cichon S, Craddock N, Daly M, et al. Genomewide association studies: history, rationale, and prospects for psychiatric disorders. The American journal of psychiatry May;2009 166(5):540–56. This paper provides a comprehensive review of genome-wide association studies in psychiatric disorders. [PubMed: 19339359]

102. McClay JL, Adkins DE, Aberg K, et al. Genome-wide pharmacogenomic analysis of response to treatment with antipsychotics. Molecular psychiatry. Sep 1.2009

103. Alkelai A, Greenbaum L, Rigbi A, et al. Genome-wide association study of antipsychotic-induced parkinsonism severity among schizophrenia patients. Psychopharmacology (Berl) Oct;2009 206(3):491–9. [PubMed: 19680635]

104. Adkins DE, Aberg K, McClay JL, et al. Genomewide pharmacogenomic study of metabolic side effects to antipsychotic drugs. Molecular psychiatry. 2010

105. Aberg K, Adkins DE, Bukszar J, et al. Genomewide association study of movement-related adverse antipsychotic effects. Biol Psychiatry Feb 1;2010 67(3):279–82. [PubMed: 19875103]

106. Volpi S, Heaton C, Mack K, et al. Whole genome association study identifies polymorphisms associated with QT prolongation during iloperidone treatment of schizophrenia. Molecular psychiatry Nov;2009 14(11):1024–31. [PubMed: 18521091]

107. Lavedan C, Licamele L, Volpi S, et al. Association of the NPAS3 gene and five other loci with response to the antipsychotic iloperidone identified in a whole genome association study. Molecular psychiatry Aug;2009 14(8):804–19. [PubMed: 18521090]

108. Volpi S, Potkin SG, Malhotra AK, et al. Applicability of a genetic signature for enhanced iloperidone efficacy in the treatment of schizophrenia. The Journal of clinical psychiatry Jun; 2009 70(6):801–9. [PubMed: 19573479]

109. Schumacher J, Schulze TG, Wienker TF, et al. Pharmacogenetics of the clozapine response. Lancet Aug 5;2000 356(9228):506–7. [PubMed: 10981913]

110. de Leon J, Susce MT, Murray-Carmichael E. The AmpliChip CYP450 genotyping test: Integrating a new clinical tool. Mol Diagn Ther 2006;10(3):135–51. [PubMed: 16771600]

111. Perlis RH, Ganz DA, Avorn J, et al. Pharmacogenetic testing in the clinical management of schizophrenia: a decision-analytic model. Journal of clinical psychopharmacology Oct;2005 25(5):427–34. [PubMed: 16160617]

112. Yamanouchi Y, Iwata N, Suzuki T, et al. Effect of DRD2, 5-HT2A, and COMT genes on antipsychotic response to risperidone. The pharmacogenomics journal 2003;3(6):356–61. [PubMed: 14610521]

113. Suzuki A, Kondo T, Mihara K, et al. Association between TaqI A dopamine D2 receptor polymorphism and therapeutic response to bromperidol: a preliminary report. European archives of psychiatry and clinical neuroscience 2001;251(2):57–9. [PubMed: 11407439]

114. Reynolds GP, Yao Z, Zhang X, et al. Pharmacogenetics of treatment in first-episode schizophrenia: D3 and 5-HT2C receptor polymorphisms separately associate with positive and negative symptom response. Eur Neuropsychopharmacol Mar;2005 15(2):143–51. [PubMed: 15695058]

115. Kwon JS, Kim E, Kang DH, et al. Taq1A polymorphism in the dopamine D2 receptor gene as a predictor of clinical response to aripiprazole. Eur Neuropsychopharmacol Dec;2008 18(12):897–907. [PubMed: 18786813]

116. Shaikh S, Collier DA, Sham PC, et al. Allelic association between a Ser-9-Gly polymorphism in the dopamine D3 receptor gene and schizophrenia. Hum Genet Jun;1996 97(6):714–9. [PubMed: 8641685]

117. Gaitonde EJ, Morris A, Sivagnanasundaram S, et al. Assessment of association of D3 dopamine receptor MscI polymorphism with schizophrenia: analysis of symptom ratings, family history, age at onset, and movement disorders. American journal of medical genetics Sep 20;1996 67(5): 455–8. [PubMed: 8886161]

118. Ebstein RP, Macciardi F, Heresco-Levi U, et al. Evidence for an association between the dopamine D3 receptor gene DRD3 and schizophrenia. Human heredity Jan-Feb;1997 47(1):6–16. [PubMed: 9017973]

119. Malhotra AK, Goldman D, Buchanan RW, et al. The dopamine D3 receptor (DRD3) Ser9Gly polymorphism and schizophrenia: a haplotype relative risk study and association with clozapine response. Molecular psychiatry Jan;1998 3(1):72–5. [PubMed: 9491816]
120. Scharfetter J, Chaudhry HR, Hornik K, et al. Dopamine D3 receptor gene polymorphism and response to clozapine in schizophrenic Pakastani patients. Eur Neuropsychopharmacol Dec;1999 10(1):17–20. [PubMed: 10647091]
121. Joober R, Toulouse A, Benkelfat C, et al. DRD3 and DAT1 genes in schizophrenia: an association study. Journal of psychiatric research Jul-Oct;2000 34(4-5):285–91. [PubMed: 11104840]
122. Staddon S, Arranz MJ, Mancama D, et al. Clinical applications of pharmacogenetics in psychiatry. Psychopharmacology (Berl) Jun;2002 162(1):18–23. [PubMed: 12107612]
123. Szekeres G, Keri S, Juhasz A, et al. Role of dopamine D3 receptor (DRD3) and dopamine transporter (DAT) polymorphism in cognitive dysfunctions and therapeutic response to atypical antipsychotics in patients with schizophrenia. Am J Med Genet B Neuropsychiatr Genet Jan 1;2004 124B(1):1–5. [PubMed: 14681904]
124. Lane HY, Hsu SK, Liu YC, et al. Dopamine D3 receptor Ser9Gly polymorphism and risperidone response. Journal of clinical psychopharmacology Feb;2005 25(1):6–11. [PubMed: 15643094]
125. Cordeiro Q, Miguita K, Miracca E, et al. Investigation of possible association between Ser9Gly polymorphism of the D3 dopaminergic receptor gene and response to typical antipsychotics in patients with schizophrenia. Sao Paulo medical journal = Revista paulista de medicina May 4;2006 124(3):165–7. [PubMed: 17119697]
126. Xuan J, Zhao X, He G, et al. Effects of the dopamine D3 receptor (DRD3) gene polymorphisms on risperidone response: a pharmacogenetic study. Neuropsychopharmacology Jan;2008 33(2): 305–11. [PubMed: 17429404]
127. Barlas IO, Cetin M, Erdal ME, et al. Lack of association between DRD3 gene polymorphism and response to clozapine in Turkish schizoprenia patients. Am J Med Genet B Neuropsychiatr Genet Jan 5;2009 150B(1):56–60. [PubMed: 18449897]
128. Shaikh S, Collier D, Kerwin RW, et al. Dopamine D4 receptor subtypes and response to clozapine. Lancet Jan 9.1993 341(8837):116. [PubMed: 8093383]
129. Rao PA, Pickar D, Gejman PV, et al. Allelic variation in the D4 dopamine receptor (DRD4) gene does not predict response to clozapine. Archives of general psychiatry Nov;1994 51(11):912–7. [PubMed: 7944879]
130. Shaikh S, Collier DA, Sham P, et al. Analysis of clozapine response and polymorphisms of the dopamine D4 receptor gene (DRD4) in schizophrenic patients. American journal of medical genetics Dec 18;1995 60(6):541–5. [PubMed: 8825892]
131. Rietschel M, Naber D, Oberlander H, et al. Efficacy and side-effects of clozapine: testing for association with allelic variation in the dopamine D4 receptor gene. Neuropsychopharmacology Nov;1996 15(5):491–6. [PubMed: 8914122]
132. Kohn Y, Ebstein RP, Heresco-Levy U, et al. Dopamine D4 receptor gene polymorphisms: relation to ethnicity, no association with schizophrenia and response to clozapine in Israeli subjects. Eur Neuropsychopharmacol Feb;1997 7(1):39–43. [PubMed: 9088883]
133. Kaiser R, Konneker M, Henneken M, et al. Dopamine D4 receptor 48-bp repeat polymorphism: no association with response to antipsychotic treatment, but association with catatonic schizophrenia. Molecular psychiatry Jul;2000 5(4):418–24. [PubMed: 10889553]
134. Zalsman G, Frisch A, Lev-Ran S, et al. DRD4 exon III polymorphism and response to risperidone in Israeli adolescents with schizophrenia: a pilot pharmacogenetic study. Eur Neuropsychopharmacol May;2003 13(3):183–5. [PubMed: 12729944]
135. Nothen MM, Rietschel M, Erdmann J, et al. Genetic variation of the 5-HT2A receptor and response to clozapine. Lancet Sep 30;1995 346(8979):908–9. [PubMed: 7564704]
136*. Masellis M, Paterson AD, Badri F, et al. Genetic variation of 5-HT2A receptor and response to clozapine. Lancet Oct 21.1995 346(8982):1108. This was one of the first pharmacogenetic studies on HTR2A variants and clozapine response. [PubMed: 7564821]

137. Nimgaonkar VL, Zhang XR, Brar JS, et al. 5-HT2 receptor gene locus: association with schizophrenia or treatment response not detected. Psychiatric genetics Spring;1996 6(1):23–7. [PubMed: 8925254]
138. Jonsson E, Nothen MM, Bunzel R, et al. 5HT 2a receptor T102C polymorphism and schizophrenia. Lancet Jun 29.1996 347(9018):1831. [PubMed: 8667938]
139. Joober R, Benkelfat C, Brisebois K, et al. T102C polymorphism in the 5HT2A gene and schizophrenia: relation to phenotype and drug response variability. J Psychiatry Neurosci Mar; 1999 24(2):141–6. [PubMed: 10212557]
140. Hamdani N, Bonniere M, Ades J, et al. Negative symptoms of schizophrenia could explain discrepant data on the association between the 5-HT2A receptor gene and response to antipsychotics. Neuroscience letters Mar 22;2005 377(1):69–74. [PubMed: 15722190]
141. Rietschel M, Naber D, Fimmers R, et al. Efficacy and side-effects of clozapine not associated with variation in the 5-HT2C receptor. Neuroreport May 27;1997 8(8):1999–2003. [PubMed: 9223092]
142. Malhotra AK, Goldman D, Ozaki N, et al. Clozapine response and the 5HT2C Cys23Ser polymorphism. Neuroreport Sep 2;1996 7(13):2100–2. [PubMed: 8930967]
143. Tsai SJ, Hong CJ, Yu YW, et al. Association study of a functional serotonin transporter gene polymorphism with schizophrenia, psychopathology and clozapine response. Schizophr Res Sep 1;2000 44(3):177–81. [PubMed: 10962219]
144. Illi A, Kampman O, Hanninen K, et al. Catechol-O-methyltransferase val108/158met genotype and response to antipsychotic medication in schizophrenia. Human psychopharmacology Jun; 2007 22(4):211–5. [PubMed: 17526059]
145. Arranz MJ, Dawson E, Shaikh S, et al. Cytochrome P4502D6 genotype does not determine response to clozapine. British journal of clinical pharmacology Apr;1995 39(4):417–20. [PubMed: 7640149]
146. Aitchison KJ, Munro J, Wright P, et al. Failure to respond to treatment with typical antipsychotics is not associated with CYP2D6 ultrarapid hydroxylation. British journal of clinical pharmacology Sep;1999 48(3):388–94. [PubMed: 10510151]
147. Brockmoller J, Kirchheiner J, Schmider J, et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. Clinical pharmacology and therapeutics Oct;2002 72(4):438–52. [PubMed: 12386646]
148. Kohlrausch FB, Gama CS, Lobato MI, et al. Naturalistic pharmacogenetic study of treatment resistance to typical neuroleptics in European-Brazilian schizophrenics. Pharmacogenetics and genomics Jul;2008 18(7):599–609. [PubMed: 18551040]
149. Chen CH, Wei FC, Koong FJ, et al. Association of TaqI A polymorphism of dopamine D2 receptor gene and tardive dyskinesia in schizophrenia. Biol Psychiatry Apr 1;1997 41(7):827–9. [PubMed: 9084902]
150. Hori H, Ohmori O, Shinkai T, et al. Association between three functional polymorphisms of dopamine D2 receptor gene and tardive dyskinesia in schizophrenia. American journal of medical genetics Dec 8;2001 105(8):774–8. [PubMed: 11803529]
151. Segman RH, Goltser T, Heresco-Levy U, et al. Association of dopaminergic and serotonergic genes with tardive dyskinesia in patients with chronic schizophrenia. The pharmacogenomics journal 2003;3(5):277–83. [PubMed: 14583797]
152. Chong SA, Tan EC, Tan CH, et al. Polymorphisms of dopamine receptors and tardive dyskinesia among Chinese patients with schizophrenia. Am J Med Genet B Neuropsychiatr Genet Jan 1;2003 116B(1):51–4. [PubMed: 12497614]
153. Liou YJ, Lai IC, Liao DL, et al. The human dopamine receptor D2 (DRD2) gene is associated with tardive dyskinesia in patients with schizophrenia. Schizophr Res Sep;2006 86(1-3):323–5. [PubMed: 16769201]
154. Zai CC, Hwang RW, De Luca V, et al. Association study of tardive dyskinesia and twelve DRD2 polymorphisms in schizophrenia patients. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) Oct;2007 10(5):639–51. [PubMed: 16959057]

155. Inada T, Arinami T, Yagi G. Association between a polymorphism in the promoter region of the dopamine D2 receptor gene and schizophrenia in Japanese subjects: replication and evaluation for antipsychotic-related features. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) Sep;1999 2(3):181–6. [PubMed: 11281987]

156. de Leon J, Susce MT, Pan RM, et al. Polymorphic variations in GSTM1, GSTT1, PgP, CYP2D6, CYP3A5, and dopamine D2 and D3 receptors and their association with tardive dyskinesia in severe mental illness. Journal of clinical psychopharmacology Oct;2005 25(5):448–56. [PubMed: 16160620]

157. Steen VM, Lovlie R, MacEwan T, et al. Dopamine D3-receptor gene variant and susceptibility to tardive dyskinesia in schizophrenic patients. Molecular psychiatry Mar;1997 2(2):139–45. [PubMed: 9106238]

158. Inada T, Dobashi I, Sugita T, et al. Search for a susceptibility locus to tardive dyskinesia. Hum Psychopharmacol Clin Exp 1997;12(1):35–9.

159. Basile VS, Masellis M, Badri F, et al. Association of the MscI polymorphism of the dopamine D3 receptor gene with tardive dyskinesia in schizophrenia. Neuropsychopharmacology Jul;1999 21(1):17–27. [PubMed: 10379516]

160. Segman R, Neeman T, Heresco-Levy U, et al. Genotypic association between the dopamine D3 receptor and tardive dyskinesia in chronic schizophrenia. Molecular psychiatry May;1999 4(3): 247–53. [PubMed: 10395214]

161. Lovlie R, Daly AK, Blennerhassett R, et al. Homozygosity for the Gly-9 variant of the dopamine D3 receptor and risk for tardive dyskinesia in schizophrenic patients. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) Mar;2000 3(1):61–5. [PubMed: 11343580]

162. Rietschel M, Krauss H, Muller DJ, et al. Dopamine D3 receptor variant and tardive dyskinesia. European archives of psychiatry and clinical neuroscience 2000;250(1):31–5. [PubMed: 10738862]

163. Liao DL, Yeh YC, Chen HM, et al. Association between the Ser9Gly polymorphism of the dopamine D3 receptor gene and tardive dyskinesia in Chinese schizophrenic patients. Neuropsychobiology 2001;44(2):95–8. [PubMed: 11490179]

164. Garcia-Barcelo MM, Lam LC, Ungvari GS, et al. Dopamine D3 receptor gene and tardive dyskinesia in Chinese schizophrenic patients. J Neural Transm 2001;108(6):671–7. [PubMed: 11478419]

165. Mihara K, Kondo T, Higuchi H, et al. Tardive dystonia and genetic polymorphisms of cytochrome P4502D6 and dopamine D2 and D3 receptors: a preliminary finding. American journal of medical genetics Aug 8;2002 114(6):693–5. [PubMed: 12210290]

166. Woo SI, Kim JW, Rha E, et al. Association of the Ser9Gly polymorphism in the dopamine D3 receptor gene with tardive dyskinesia in Korean schizophrenics. Psychiatry and clinical neurosciences Aug;2002 56(4):469–74. [PubMed: 12109967]

167. Zhang ZJ, Zhang XB, Hou G, et al. Interaction between polymorphisms of the dopamine D3 receptor and manganese superoxide dismutase genes in susceptibility to tardive dyskinesia. Psychiatric genetics Sep;2003 13(3):187–92. [PubMed: 12960753]

168. Liou YJ, Liao DL, Chen JY, et al. Association analysis of the dopamine D3 receptor gene ser9gly and brain-derived neurotrophic factor gene val66met polymorphisms with antipsychotic-induced persistent tardive dyskinesia and clinical expression in Chinese schizophrenic patients. Neuromolecular medicine 2004;5(3):243–51. [PubMed: 15626824]

169. Srivastava V, Varma PG, Prasad S, et al. Genetic susceptibility to tardive dyskinesia among schizophrenia subjects: IV. Role of dopaminergic pathway gene polymorphisms. Pharmacogenetics and genomics Feb;2006 16(2):111–7. [PubMed: 16424823]

170**. Zai CC, Tiwari AK, De Luca V, et al. Genetic study of BDNF, DRD3, and their interaction in tardive dyskinesia. Eur Neuropsychopharmacol May;2009 19(5):317–28. This study examined potential gene-gene interactions on risk of TD. [PubMed: 19217756]

171. Basile VS, Ozdemir V, Masellis M, et al. Lack of association between serotonin-2A receptor gene (HTR2A) polymorphisms and tardive dyskinesia in schizophrenia. Molecular psychiatry Mar; 2001 6(2):230–4. [PubMed: 11317228]

172. Herken H, Erdal ME, Boke O, et al. Tardive dyskinesia is not associated with the polymorphisms of 5-HT2A receptor gene, serotonin transporter gene and catechol-o-methyltransferase gene. Eur Psychiatry Mar;2003 18(2):77–81. [PubMed: 12711403]

173. Segman RH, Heresco-Levy U, Finkel B, et al. Association between the serotonin 2C receptor gene and tardive dyskinesia in chronic schizophrenia: additive contribution of 5-HT2Cser and DRD3gly alleles to susceptibility. Psychopharmacology (Berl) Nov;2000 152(4):408–13. [PubMed: 11140333]

174. Segman RH, Lerer B. Age and the relationship of dopamine D3, serotonin 2C and serotonin 2A receptor genes to abnormal involuntary movements in chronic schizophrenia. Molecular psychiatry 2002;7(2):137–9. [PubMed: 11840306]

175. Nikoloff D, Shim JC, Fairchild M, et al. Association between CYP2D6 genotype and tardive dyskinesia in Korean schizophrenics. The pharmacogenomics journal 2002;2(6):400–7. [PubMed: 12629505]

176. Lohmann PL, Bagli M, Krauss H, et al. CYP2D6 polymorphism and tardive dyskinesia in schizophrenic patients. Pharmacopsychiatry Mar-Apr;2003 36(2):73–8. [PubMed: 12734765]

177. Tiwari AK, Deshpande SN, Rao AR, et al. Genetic susceptibility to tardive dyskinesia in chronic schizophrenia subjects: III. Lack of association of CYP3A4 and CYP2D6 gene polymorphisms. Schizophr Res Jun 1;2005 75(1):21–6. [PubMed: 15820320]

178. Matsumoto C, Ohmori O, Shinkai T, et al. Genetic association analysis of functional polymorphisms in the cytochrome P450 1A2 (CYP1A2) gene with tardive dyskinesia in Japanese patients with schizophrenia. Psychiatric genetics Dec;2004 14(4):209–13. [PubMed: 15564895]

179. Chong SA, Tan EC, Tan CH, et al. Smoking and tardive dyskinesia: lack of involvement of the CYP1A2 gene. J Psychiatry Neurosci May;2003 28(3):185–9. [PubMed: 12790158]

180. Schulze TG, Schumacher J, Muller DJ, et al. Lack of association between a functional polymorphism of the cytochrome P450 1A2 (CYP1A2) gene and tardive dyskinesia in schizophrenia. American journal of medical genetics Aug 8;2001 105(6):498–501. [PubMed: 11496364]

181. Spina E, Ancione M, Di Rosa AE, et al. Polymorphic debrisoquine oxidation and acute neuroleptic-induced adverse effects. European journal of clinical pharmacology 1992;42(3):347–8. [PubMed: 1349529]

182. Scordo MG, Spina E, Romeo P, et al. CYP2D6 genotype and antipsychotic-induced extrapyramidal side effects in schizophrenic patients. European journal of clinical pharmacology Dec;2000 56(9-10):679–83. [PubMed: 11214775]

183**. Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. Lancet Jun 15;2002 359(9323):2086–7. This was the first study to demonstrate the association between HTR2C genetic variation and antipsychotic drug-induced weight gain in drug-naïve patients. [PubMed: 12086765]

184. Tsai SJ, Hong CJ, Yu YW, et al. −759C/T genetic variation of 5HT(2C) receptor and clozapine-induced weight gain. Lancet Nov 30.2002 360(9347):1790. [PubMed: 12480466]

185. Basile VS, Masellis M, De Luca V, et al. 759C/T genetic variation of 5HT(2C) receptor and clozapine-induced weight gain. Lancet Nov 30;2002 360(9347):1790–1. [PubMed: 12480467]

186. Reynolds GP, Zhang Z, Zhang X. Polymorphism of the promoter region of the serotonin 5-HT(2C) receptor gene and clozapine-induced weight gain. The American journal of psychiatry Apr;2003 160(4):677–9. [PubMed: 12668355]

187. Miller DD, Ellingrod VL, Holman TL, et al. Clozapine-induced weight gain associated with the 5HT2C receptor −759C/T polymorphism. Am J Med Genet B Neuropsychiatr Genet Feb 5;2005 133B(1):97–100. [PubMed: 15635667]

188. Ellingrod VL, Perry PJ, Ringold JC, et al. Weight gain associated with the −759C/T polymorphism of the 5HT2C receptor and olanzapine. Am J Med Genet B Neuropsychiatr Genet Apr 5;2005 134B(1):76–8. [PubMed: 15666332]

189. Templeman LA, Reynolds GP, Arranz B, et al. Polymorphisms of the 5-HT2C receptor and leptin genes are associated with antipsychotic drug-induced weight gain in Caucasian subjects with a first-episode psychosis. Pharmacogenetics and genomics Apr;2005 15(4):195–200. [PubMed: 15864111]

190*. Theisen FM, Gebhardt S, Haberhausen M, et al. Clozapine-induced weight gain: a study in monozygotic twins and same-sex sib pairs. Psychiatric genetics Dec;2005 15(4):285–9. This is one of the few twin studies in pharmacogenetic research. [PubMed: 16314759]

191. Lane HY, Liu YC, Huang CL, et al. Risperidone-related weight gain: genetic and nongenetic predictors. Journal of clinical psychopharmacology Apr;2006 26(2):128–34. [PubMed: 16633140]

192. Ryu S, Cho EY, Park T, et al. −759 C/T polymorphism of 5-HT2C receptor gene and early phase weight gain associated with antipsychotic drug treatment. Progress in neuropsychopharmacology & biological psychiatry Apr 13;2007 31(3):673–7.

193. Park YM, Cho JH, Kang SG, et al. Lack of association between the −759C/T polymorphism of the 5-HT2C receptor gene and olanzapine-induced weight gain among Korean schizophrenic patients. Journal of clinical pharmacy and therapeutics Feb;2008 33(1):55–60. [PubMed: 18211617]

194. Kuzman MR, Medved V, Bozina N, et al. The influence of 5-HT(2C) and MDR1 genetic polymorphisms on antipsychotic-induced weight gain in female schizophrenic patients. Psychiatry research Sep 30;2008 160(3):308–15. [PubMed: 18718676]

195. Godlewska BR, Olajossy-Hilkesberger L, Ciwoniuk M, et al. Olanzapine-induced weight gain is associated with the −759C/T and −697G/C polymorphisms of the HTR2C gene. The pharmacogenomics journal Aug;2009 9(4):234–41. [PubMed: 19434072]

196. Gunes A, Melkersson KI, Scordo MG, et al. Association between HTR2C and HTR2A polymorphisms and metabolic abnormalities in patients treated with olanzapine or clozapine. Journal of clinical psychopharmacology Feb;2009 29(1):65–8. [PubMed: 19142110]

197. Opgen-Rhein C, Brandl EJ, Muller DJ, et al. Association of HTR2C, but not LEP or INSIG2, genes with antipsychotic-induced weight gain in a German sample. Pharmacogenomics Jun;2010 11(6):773–80. [PubMed: 20504252]

198. Tsai SJ, Yu YW, Lin CH, et al. Association study of adrenergic beta3 receptor (Trp64Arg) and G-protein beta3 subunit gene (C825T) polymorphisms and weight change during clozapine treatment. Neuropsychobiology 2004;50(1):37–40. [PubMed: 15179018]

199. Wang YC, Bai YM, Chen JY, et al. C825T polymorphism in the human G protein beta3 subunit gene is associated with long-term clozapine treatment-induced body weight change in the Chinese population. Pharmacogenetics and genomics Oct;2005 15(10):743–8. [PubMed: 16141801]

200. Bishop JR, Ellingrod VL, Moline J, et al. Pilot study of the G-protein beta3 subunit gene (C825T) polymorphism and clinical response to olanzapine or olanzapine-related weight gain in persons with schizophrenia. Med Sci Monit Feb;2006 12(2):BR47–50. [PubMed: 16449941]

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	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

Expert Opin Drug Metab Toxicol. Author manuscript; available in PMC 2011 March 15.

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

Expert Opin Drug Metab Toxicol. Author manuscript; available in PMC 2011 March 15.

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

Expert Opin Drug Metab Toxicol. Author manuscript; available in PMC 2011 March 15.

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	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
		American patients				
CYP1A2 *1F	Basil 2000[84]	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