

Pharmacogenomics in schizophrenia: the quest for individualized therapy

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There is strong evidence to suggest that genetic variation plays an important role in inter-individual differences in medication response and toxicity. The rapidly evolving disciplines of pharmacogenetics and pharmacogenomics seek to uncover this genetic variation in order to predict treatment outcomes. The goal is to be able to select the drugs with the greatest likelihood of benefit and the least likelihood of harm in individual patients, based on their genetic make-up—individualized therapy. Pharmacogenomic studies utilize genomic technologies to identify chromosomal areas of interest and novel putative drug targets, while pharmacogenetic strategies rely on studying sequence variations in candidate genes suspected of affecting drug response or toxicity. The candidate gene variants that affect function of the gene or its protein product have the highest priority for investigation. This review will provide demonstrative examples of functional candidate gene variants studied in a variety of antipsychotic response phenotypes in the treatment of schizophrenia. Serotonin and dopamine receptor gene variants in clozapine response will be examined, and in the process the need for sub-phenotypes will be pointed out. Our recent pharmacogenetic studies of the subphenotype of neurocognitive functioning following clozapine treatment and the dopamine D₁ receptor gene (*DRD1*) will be presented, highlighting our novel neuroimaging data via [¹⁸F]fluoro-2-deoxy-D-glucose (FDG) metabolism position emission tomography (PET) that demonstrates hypofunctioning of several brain regions in patients with specific dopamine D₁ genotype. Preliminary candidate gene studies investigating the side-effect of clozapine-induced weight gain are also presented. The antipsychotic adverse reaction of tardive dyskinesia and its association with the dopamine D₃ receptor will be critically examined, as well as the added influence of antipsychotic metabolism via the cytochrome P450 1A2 gene (*CYP1A2*). Results that delineate the putative gene–gene interaction between *DRD3* and *CYP1A2* are also presented. We have also utilized FDG–PET subphenotyping to demonstrate increased brain region activity in patients who have the dopamine D₃ genotype that confers increased risk for antipsychotic induced tardive dyskinesia. The merits and weaknesses of neuroimaging technologies as applied to pharmacogenetic analyses are discussed. To the extent that the above data become more widely verified and replicated, the field of psychiatry will move closer to clinically meaningful tests that will be useful in deciding the best drug for each individual patient.

Schizophrenia is a paradigmatic disease in which pharmacogenomic and pharmacogenetic research can and has been applied. A devastating psychiatric disorder that affects ~1% of the population, schizophrenia has been treated with an extensive pharmacopeia. Treatment with specific antipsychotic medications often proceeds by trial and error in order to determine the optimal medication and dose that maximize response and minimize toxicity. In spite of the wide array of medicines available, 10–20% of patients do not initially respond to treatment with antipsychotic drug therapy. An additional 20–30% who do respond early on eventually relapse

on their maintenance programs, and some develop serious side-effects that cause them to discontinue the medication. With the introduction of chlorpromazine in 1952, patients suffering from psychosis were able to be de-institutionalized. Chlorpromazine and other ‘typical’ antipsychotics (e.g. haloperidol) demonstrate high *in vitro* binding affinities for the dopamine D₂ receptor. Specifically, their binding potential for D₂ correlates well with their clinical potencies (1). The reintroduction of clozapine, the prototype of ‘atypical’ antipsychotic, in the late 1980s has led to significant advances in the pharmacological management of schizophrenia. The more diverse binding

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profile of clozapine across several central nervous system (CNS) receptors (e.g. serotonergic, dopaminergic, histaminergic, adrenergic and cholinergic) is thought to be responsible for these therapeutic advantages. Since then, there has been a rapid development of novel 'atypical' antipsychotic agents that have been pharmacologically modeled, to a certain extent, after their predecessor clozapine. Although both classes of antipsychotics, typical and atypical, offer some degree of efficacy, it is clear that they do not accommodate all symptoms of the disease. As with all drugs, there is variability among individuals in clinical responses to antipsychotics. The inter-individual variation in antipsychotic drug response creates a clinical dilemma most often addressed by empirical drug trials. Poor response to antipsychotic drug treatment and/or the development of adverse side-effects can lead to patient non-compliance, psychosocial disturbances and poor outcome. Unfortunately, efforts to identify biological or clinical predictors of patient response and adverse side-effect profile during antipsychotic drug treatment have been largely unsuccessful. Pharmacogenetics can provide a novel foundation for understanding this inter-individual variability in antipsychotic response, and may provide an avenue for predicting patient propensity to respond and to develop antipsychotic side-effects *a priori*.

A significant drawback to the treatment of schizophrenia with antipsychotics is the occurrence of adverse reactions. Typical antipsychotics can cause sexual dysfunction and induce movement side-effects, including extrapyramidal symptoms (EPS) and tardive dyskinesia (TD). Novel atypical antipsychotics offer a number of tolerability benefits over the traditional typical antipsychotics, principally regarding EPS. However, the differential binding profile between the two classes, both in terms of the variety of receptors that the antipsychotics have affinity for and in the range of affinities for each receptor, contribute to differences demonstrated with respect to the side-effect profile. Despite an increase in the popularity of atypical use in recent years, typical antipsychotics are commonly prescribed. Although atypical antipsychotics have a lower incidence of motor side-effects, their use is hindered by other adverse events such as weight gain and sedation. A particularly pressing issue has become the prevalent side-effect of weight gain. The significance of this side-effect is often underestimated because it is associated with a common and 'normal' presentation as compared with other antipsychotic side-effects. However, it is clear that weight gain can undermine compliance, inclining patients to relapse, and may also lead to significant psychological distress and medical morbidity and mortality.

Pharmacogenomics is defined as the compilation of comprehensive information about genomic sequences using techniques such as gene mapping, genome scans, sequencing, statistical genetics and expression analysis. This information is then applied to the identification of genomic 'hot spots' and subsequently to the discovery of susceptibility loci and novel drug targets contributing to inter-individual variation in drug response and side-effect profiles. Pharmacogenetics seeks to identify genetic polymorphisms in or near the coding region of genes that encode protein structures with which a drug interacts. The candidate gene variants that affect the function of the gene or its protein product have the highest priority for investigation. The identified genetic polymorphisms are then

assessed for their putative role in the observed inter-individual variability in the clinical profile of the drug (e.g. its pattern of response and/or side-effects). This paradigm can be applied to predict the variable responsiveness to antipsychotics among individuals, thus minimizing the 'trial-and-error' approach that currently exists. The initial pharmacogenetic studies in schizophrenia have focused on determining the role of genetic variation in the antipsychotic efficacy of the atypical antipsychotic agent, clozapine—with an emphasis on genes that code for neurotransmitter receptors such as the serotonergic 5-HT_{2A} and 5-HT_{2C} receptors and the dopaminergic D₃ and D₄ receptors. The results from these studies have been equivocal—most likely secondary to issues surrounding the clinical phenotype of clozapine response and the limited power of individual studies to identify genes of modest effect. A remedy for this may be found in the definition of more quantitative and less subjective psychiatric phenotypes for use in pharmacogenetic association analyses. The combination of neuroimaging technologies such as positron emission tomography (PET) and magnetic resonance imaging (MRI) with molecular genetics can provide more specific and powerful phenotypes that may help to identify genetic predictors of antipsychotic response and side-effects. Here we provide a brief review of the most salient studies in the area of psychiatric pharmacogenetics of antipsychotic medications, with particular emphasis on clozapine response and medication-induced side-effects such as weight gain induced by atypical antipsychotics and tardive dyskinesia induced by typical antipsychotics.

CLOZAPINE RESPONSE AND NEUROPSYCHOLOGICAL MEASURES

Schizophrenia is a complex multifactorial disease with both genetic and environmental influences. Current nosology as defined by the DSM-IV (2) divides the symptoms of schizophrenia into two broad clusters: positive and negative symptoms. The positive symptoms involve an excess or distortion of certain normal functions while the negative symptoms are conversely distinguished by a diminution of other normal functions. The positive symptom cluster can be further subdivided into two dimensions: 'psychotic' and 'disorganized'. The 'psychotic dimension' encompasses distortions or exaggerations of inferential thinking (delusions) and perception (hallucinations). The 'disorganized dimension' includes distortions in language and communication (disorganized speech) and behavioural monitoring (grossly disorganized or catatonic behavior). The negative symptom cluster is characterized primarily by problems in the reduction of range and intensity of emotional expression (affective flattening), fluency and productivity of thought and speech (alogia), and initiation of goal-directed behavior (avolition).

Antipsychotic drugs are the best means available for symptomatically treating individuals suffering from schizophrenia; however, there is significant variability in clinical response to these psychotropic medications. Take, for example, clozapine, the prototype atypical antipsychotic, where only 30–60% of individuals resistant to typical antipsychotics may demonstrate a beneficial clinical response with respect to positive and negative symptomatology (3).

Table 1. Association studies of clozapine response

Gene Studied	Authors/Year (REF.)	Result
Dopamine D ₂ receptor (<i>DRD2</i>)	Arranz <i>et al.</i> (1998) (94)	No significant association
Dopamine D ₃ receptor (<i>DRD3</i>)	Shaikh <i>et al.</i> (1995) (95)	No significant association
	Malhotra <i>et al.</i> (1998) (11)	No significant association
	Scharfetter <i>et al.</i> (1999) (96)	Statistically significant association
Dopamine D ₄ receptor (<i>DRD4</i>)	Rao <i>et al.</i> (1994) (97)	No significant association
	Shaikh <i>et al.</i> (1995) (13)	No significant association
	Rietschel <i>et al.</i> (1996) (98)	No significant association
	Kohn <i>et al.</i> (1997) (99)	No significant association
	Ozdemir <i>et al.</i> (1997) (12)	Statistically significant association
	Kaiser <i>et al.</i> (2000) (100)	No significant association
Serotonin 2A receptor, 5-HT _{2A} (<i>HTR2A</i>)	Arranz <i>et al.</i> (1995) (4)	Statistically significant association
	Masellis <i>et al.</i> (1995) (6)	No significant association
	Nothen <i>et al.</i> (1995) (101)	No significant association
	Arranz <i>et al.</i> (1996) (102)	Non-significant trend
	Malhotra <i>et al.</i> (1996) (9)	No significant association
	Arranz <i>et al.</i> (1998) (5)	No significant association
	Masellis <i>et al.</i> (1998) (7)	No significant association for one polymorphism; borderline significant association for another
Serotonin 2C receptor 5-HT _{2C} (<i>HTR2C</i>)	Lin <i>et al.</i> (1999) (103)	No significant association
	Sodhi <i>et al.</i> (1995) (104)	Statistically significant association
	Malhotra <i>et al.</i> (1996) (10)	No significant association
	Rietschel <i>et al.</i> (1997) (105)	No significant association
	Masellis <i>et al.</i> (1998) (7)	No significant association
Serotonin 6 receptor, 5-HT ₆ (<i>HTR6</i>)	Yu <i>et al.</i> (1999) (106)	Statistically significant association
	Masellis <i>et al.</i> (2001) (8)	No significant association
Serotonin 7 receptor, 5-HT ₇ (<i>HTR7</i>)	Masellis <i>et al.</i> (2001) (8)	No significant association
Serotonin transporter, 5-HTT	Tsai <i>et al.</i> (2000) (107)	No significant association

Pharmacogenetic studies, in attempting to elucidate genetic predictors of global response (e.g. combined measures of positive and negative symptoms), have focused on the impact of genetic polymorphism in serotonin (5-hydroxytryptamine) system receptors such as 5-HT_{2A}, 5-HT_{2C} and 5-HT₆ (4–10), as well as dopaminergic receptors such as D₂, D₃ and D₄ (11–13), as they relate to the clinical efficacy of clozapine. In summary, although there are conflicting results, two studies with sufficient statistical power demonstrate a role for the structural His452Tyr 5-HT_{2A} receptor gene polymorphism in predicting clozapine response (5,7). Table 1 provides a summary of some of the findings regarding the pharmacogenetics of clozapine response. More comprehensive reviews are available, and we direct the reader to these for a detailed discussion (14,15).

Several models have been proposed to explain the development of positive and negative symptoms in schizophrenia, and it is clear from the majority of them that deficits in cognition are involved (16). Neuropsychological research in schizophrenia has shown that there are profound deficits in cognitive processes such as verbal and working memory, attention, and executive function (17). Thus, understanding the nature of cognitive deficits in schizophrenia may help to elucidate the basic neural mechanisms underlying its overall clinical presentation.

There is a body of accumulating evidence suggesting that clozapine may ameliorate the underlying cognitive deficits of schizophrenia (reviewed in 18). As presented at the First Annual Pharmacogenetics in Psychiatry meeting in New York (19), our group has been involved in identifying genetic

predictors of clinical variability in response to clozapine, particularly with respect to cognitive dysfunction. Several lines of converging evidence were presented and represent a novel approach to dissecting out individual genetic components contributing to inter-individual variability in cognitive response to clozapine. The mesocorticolimbic system represents an important anatomical and physiological pathway with respect to cognitive dysfunction in schizophrenia. Dopaminergic projections from the ventral tegmental area in the brainstem ascending to the limbic areas and to the dorsolateral prefrontal cortex (mesocorticolimbic paths) are disrupted (20,21). Specifically, the cognitive deficits observed in schizophrenia are related to reduced dopaminergic innervation of the dorsolateral prefrontal cortex, as suggested by neuroimaging and postmortem studies (22–24).

Dopamine D₁ receptors are located in high concentrations in the dorsolateral prefrontal cortex, and are thought to play an important role in modulating mesocorticolimbic circuitry and thereby cognitive functioning in schizophrenia. Furthermore, clozapine is a potent antagonist of dopamine D₁ receptors, and this is hypothesized to be important in its unique clinical response profile (25). As such, the dopamine D₁ receptor gene is a high-priority candidate gene to assess in predicting response to clozapine with respect to cognition in schizophrenia.

In a pilot study of 35 schizophrenia patients, who were involved in a randomized, prospective clinical trial of clozapine, we observed a significant association between an upstream D₁ receptor gene polymorphism and change in scores

on the Wisconsin Card Sort Test, which measures working memory, attention and executive function, assessed before and after treatment with clozapine ($F_{[2,34]} = 7.929$, $P = 0.002$) (19). Interestingly, we have also found evidence suggesting that this upstream dopamine D₁ receptor polymorphism is associated with modulation of dorsolateral prefrontal cortex metabolic activity, as assessed by [¹⁸F]fluoro-2-deoxy-D-glucose (FDG) PET after clozapine treatment, and that this is predictive of measures of clinical response ($P < 0.1$) (Fig. 1) (26).

CLOZAPINE-INDUCED WEIGHT GAIN

Clozapine, the prototype atypical antipsychotic, remains the most effective agent for the treatment of refractory schizophrenia and over recent years has gained much popularity as a first-line treatment; however, among the atypicals, clozapine appears to have the greatest weight gain liability (27). Some patients may gain as much as 50 kg over a 1-year treatment period. Reviewing the literature, Leadbetter *et al.* (28) found that 13–85% of patients treated with clozapine had an associated increase in weight. Umbricht *et al.* (29) found that the cumulative incidence of all patients reaching $\geq 20\%$ overweight, representing a significant long-term health risk, was $> 50\%$. This side-effect can undermine compliance, leading to relapse, and may also cause significant psychological and medical morbidity. Considerable weight gain may also lead to increases in obesity-related comorbidities and health risks such as type II diabetes mellitus, hypertension, cardiovascular disease, respiratory dysfunction and some types of cancer, which are all associated with significant mortality (30). There appears to be considerable variability among individuals with respect to the ability of an antipsychotic to induce weight gain, i.e. not all patients treated with clozapine gain weight. Thus, the side-effect of weight gain occurs in only a proportion of treated patients who are predisposed to this side-effect. It is likely that this variability in patient propensity to gain weight is determined by a combination of genetic and environmental factors. The genetic factors may include pharmacokinetic (i.e. factors involved in the metabolism and elimination of the drug from the body) as well as pharmacodynamic (i.e. factors at the direct site of action of the drug within the body) elements. Genetic variation in pharmacodynamic factors such as brain receptors may subject some patients to have receptors with higher affinity for the medication and may allow prediction of those patients who are most likely to respond or develop side-effects. Genetic differences in pharmacokinetic factors such as drug-metabolizing enzymes may subject some patients to less active enzymatic forms resulting in higher plasma levels of the medication, and this may also allow prediction of good response and propensity to side-effects. A genetic predisposition to clozapine-induced weight gain has been suggested (29,31), and ample evidence exists demonstrating that body weight and feeding behavior are influenced by genetic factors (32,33).

Weight gain induced by atypical antipsychotics is likely to be due to a combination of disturbances and alterations in satiety control mechanisms, energy expenditure, metabolism and lipogenesis, although there is a limited amount of research

seeking to uncover the precise mechanisms. Figure 2 provides a schematic representation of both the central hypothalamic weight regulation and peripheral thermogenic pathways, highlighting putative areas where clozapine may disrupt these pathways to cause weight gain in predisposed patients (34). Collectively, data from several research paradigms converge and suggest that weight gain induced by atypical antipsychotics and obesity result from multiple neurotransmitter/receptor interactions, with resultant changes in appetite and feeding behavior. Patients treated with clozapine generally complain that they have an inability to control their appetite even after eating a full meal. Satiety signals arise in a variety of areas, including the olfactory and gustatory tracts, esophagus, stomach, liver, and intestines, and are processed in the hypothalamus, which contributes to the regulation and maintenance of an individual's homeostatic body weight. Therefore, it is possible that some antipsychotics may disturb satiety processing in the hypothalamus by binding to receptors involved in weight and satiety regulation. As such, genetic differences in these candidate receptors that have affinity for clozapine and are expressed in the hypothalamus are prime candidates for investigation when trying to uncover genetic determinants of clozapine-induced weight gain.

A large body of evidence supports a role for the serotonin system in regulating feeding behavior (reviewed in 32). Studies in both animals and humans have shown that increasing serotonin results in decreased feeding, and decreasing serotonin increases feeding (35–37). Interestingly, it has been shown that agonists of the 5-HT₁ family of receptors caused hyperphagia, and conversely agonists of the 5-HT₂ family of receptors caused hypophagia (reviewed in 38). More specifically, rat studies have shown that 5-HT_{1A} agonists as well as 5-HT_{2C} antagonists cause a marked increase in feeding (39). It is interesting to note that clozapine is a potent 5-HT_{2C} antagonist and 5-HT_{1A} agonist. Autoradiographic studies have shown that both 5-HT_{2C} and 5-HT_{1A} receptors are localized with high density in the medial hypothalamus, within this established satiety control center (40,41). Perhaps the most compelling evidence supporting a role for the 5-HT_{2C} receptor in feeding behavior is from a study of knockout mice lacking 5-HT_{2C} receptors (42). The knockouts were overweight compared with wild-type mice, and, based on paired feeding analysis, this appeared to be due to increased feeding as opposed to metabolic changes in these animals. For a more comprehensive characterization of the factors to be considered in clozapine-induced weight gain, see Figure 2 and a more detailed description of this figure in our recent review (34). In addition to clozapine, several other atypical antipsychotics induce weight gain. The common factors among these antipsychotics are that they are all 5-HT_{2C} antagonists and 5-HT_{1A} agonists, as well as histamine H₁ receptor antagonists (reviewed in 43). These receptors are therefore again prime candidates for investigation when trying to elucidate genetic determinants of clozapine-induced weight gain.

The peptide that exerts the most significant effects on feeding and weight regulation is leptin. Leptin is secreted by adipocytes in direct proportion to the amount of fat stored within that cell. It is believed to act at the level of the hypothalamus, where it initiates a cascade of events that lead to the regulation of appetite, energy expenditure and satiation. In a recent study by

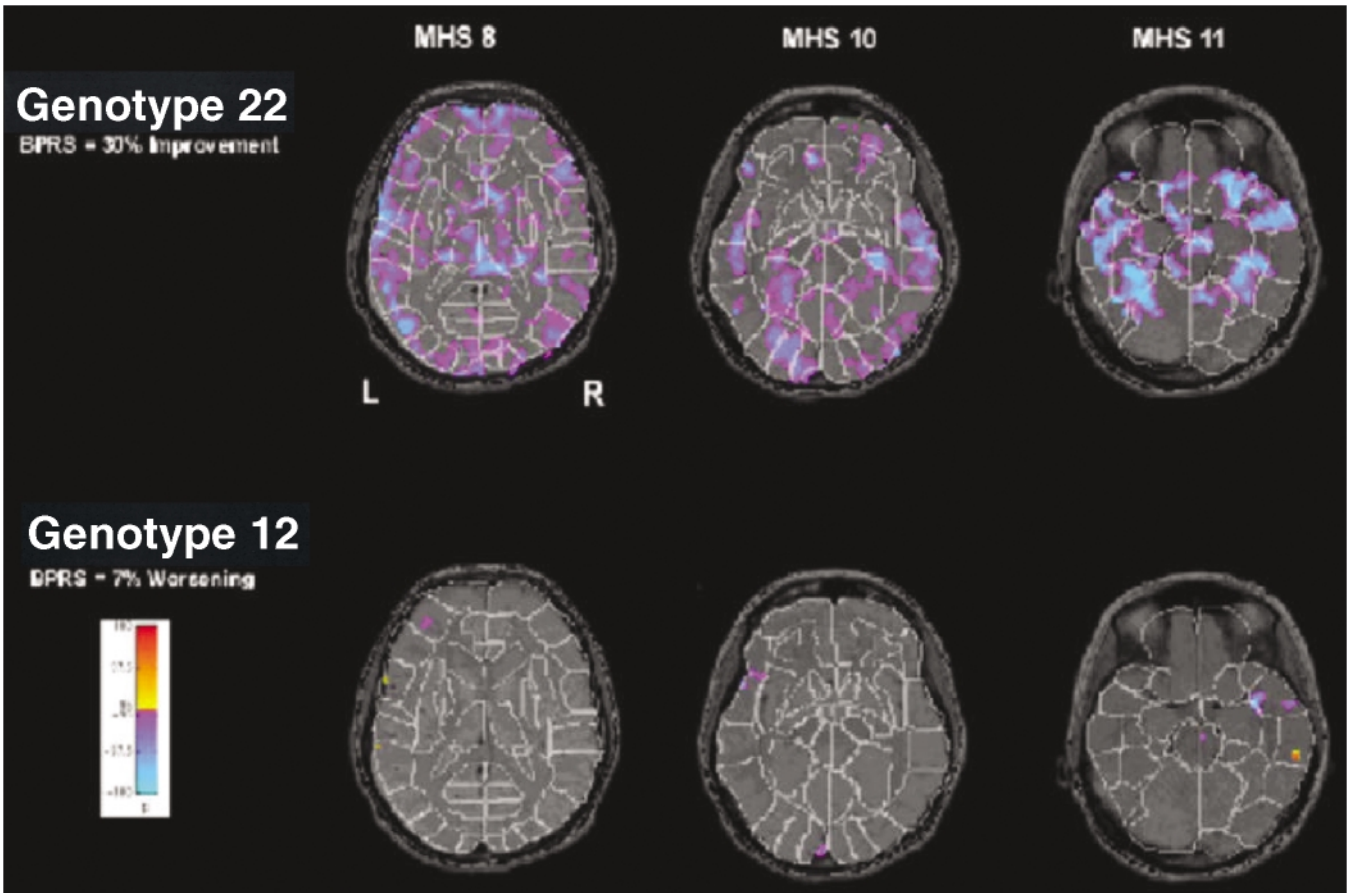


Figure 1. Brain [^{18}F]fluoro-2-deoxy-D-glucose (FDG) metabolism PET following clozapine treatment versus dopamine D_1 receptor genotype ($N = 15$). The figure demonstrates the average metabolic difference before and after clozapine treatment by genotype. Each image is the average of seven individuals with 2,2 genotypes (top row), or eight with 1,2 genotypes (bottom row). Statistically significant metabolic changes are demonstrated on a representative brain slice for each level (each column MHS 8, MHS 10, MHS 11). For the 2,2 genotype group (top row), significant metabolic decreases were observed bilaterally and in all lobules of the neocortices and allocortices in the frontal, temporal, occipital, parietal lobes, cingulate cortex, amygdala and parahippocampal gyrus. Some decreases were also seen in the thalamus, cerebellum, as well as the dorsal caudate and putamen; however, the ventral sectors of the striatum did not exhibit any metabolic changes. In contrast, the 1,2 genotype (bottom row) showed a few significant metabolic decreases limited to left dorsolateral prefrontal cortex and temporal tip and parietal sensory/ideational speech areas bilaterally following treatment with clozapine. In terms of clinical response, the DRD1 2,2 genotype patients with schizophrenia significantly improved with clozapine treatment, demonstrating a 30% decrease in BPRS positive symptoms. In contrast, patients with the 1,2 genotype showed a worsening of 7% for the BPRS positive symptoms ($P < 0.05$). Modified and reprinted with permission from Nature Publishing Group, Potkin *et al.* (26).

Morimoto *et al.* (44), central injection of leptin into mouse brain caused a marked decrease in feeding in wild-type control mice, but not in genetically altered mice lacking the histamine H_1 receptor, suggesting that leptin may operate directly through a histamine H_1 receptor-mediated pathway. It is well established that histamine H_1 receptor antagonism causes increased feeding and weight gain (43,45,46). Autoradiographic studies have shown that histamine H_1 receptors are localized with high density in the ventromedial nucleus and the paraventricular nucleus in the hypothalamus (47). Wirshing *et al.* (48) noted an exponential relationship between the maximum amount of weight gained while being treated with an antipsychotic and that particular antipsychotic's affinity for the histamine H_1 receptor. Those antipsychotics with the maximum weight-gain liabilities (i.e. clozapine and olanzapine) had the greatest affinities for the histamine H_1 receptor. Atypical antipsychotics such as clozapine bind to histamine H_1 receptors as well as to $5\text{-HT}_{2\text{C}}$ and $5\text{-HT}_{1\text{A}}$ receptors, and the subsequent change in

the action of these receptors within the hypothalamus may disrupt satiety control mechanisms, in turn resulting in weight gain. Genetic differences in these central brain receptors may predict patient propensity to gain weight while being treated with clozapine.

It is important to note that clozapine not only may disrupt central hypothalamic weight regulation and satiety control mechanisms, but also may interfere with peripheral thermogenic, lipogenic, lipolytic and adipocyte-regulating pathways to cause weight gain. Agonism at peripheral β_3 and α_1 adrenergic receptors located on white and brown adipocytes, as well as on muscle cells, is known to stimulate intracellular lipolysis and to increase basal metabolic rate by increasing the expression of the mitochondrial uncoupling proteins (UCP1, 2 and 3). In a highly uncoupled state, fuels are oxidized unrelated to the performance of work and the usable potential energy is lost as heat (Fig. 2) (49). Transgenic mice that overexpress UCP3 are lean when compared with wild-type control mice, despite being

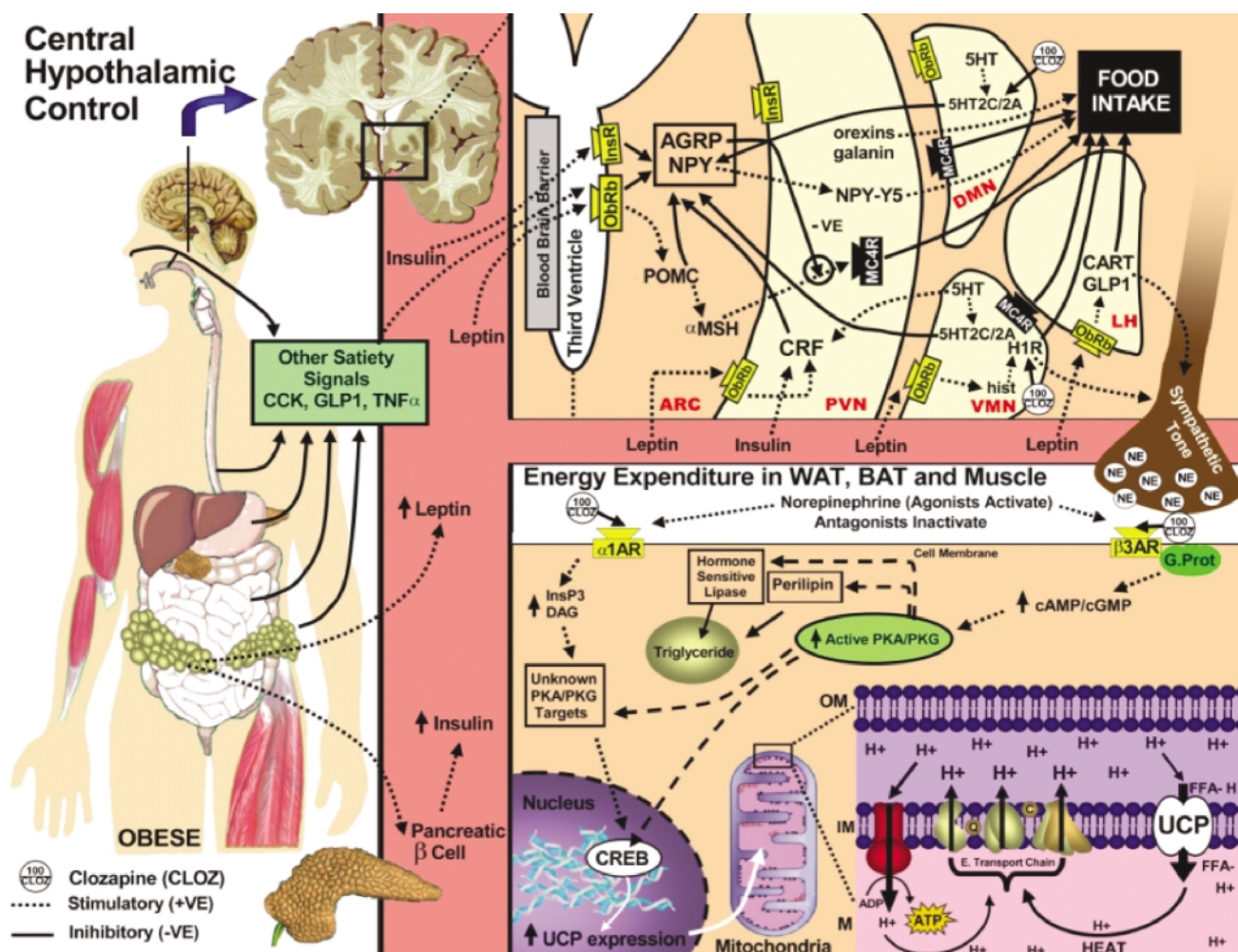


Figure 2. Putative antipsychotic disruption of central and peripheral obesity-related pathways. *Abbreviations:* ADP, adenosine diphosphate; AGRP, agouti-related protein; α MSH, α -melanocyte-stimulating hormone; α 1AR, α 1-adrenergic receptor; ARC, arcuate nucleus; ATP, adenosine triphosphate; BAT, brown adipose tissue; β 3AR, β 3-adrenergic receptor; cAMP, cyclic adenosine monophosphate; C, cytochrome *c*; CART, cocaine- amphetamine-regulated transcript; CCK, cholecystokinin; cGMP, cyclic guanosine monophosphate; CREB, cAMP response element-binding protein transcription factor; CRF, corticotropin-releasing factor; DAG, diacylglycerol; DMN, dorsomedial nucleus; E., electron (transport chain); FFA-H, free fatty acid; FFA-H+, oxidized free fatty acid; 5HT, serotonin; GLP1, glucagon-like peptide; G.Prod, G Protein; hist, histamine; H1R, histamine H_1 receptor; IM, inner mitochondrial membrane; InsP3, inositol triphosphate; InsR, insulin receptor; LH, lateral hypothalamic area; M, mitochondrial matrix; MC4R, melanocortin 4 receptor; NE, norepinephrine (noradrenalin); NPY, neuropeptide Y; ObRb, leptin receptor; OM, outer mitochondrial membrane; POMC, pro-opiomelanocortin; PKA, protein kinase A; PKG, protein kinase G; PVN, paraventricular nucleus; Q, cytochrome Q; TNF α , tumor necrosis factor α ; UCP, uncoupling protein; +VE, stimulatory; -VE, inhibitory; VMN, ventromedial nucleus; WAT, white adipose tissue. Modified from Basile, V.S., Masellis, M., McIntyre, R.S., Meltzer, H.Y., Lieberman, J.A. and Kennedy, J.L. Genetic Dissection of Atypical Anti-psychotic-Induced Weight Gain: Novel Preliminary Data on the Pharmacogenetic Puzzle, *The Journal of Clinical Psychiatry*. **62**, 45–66, 2001. Copyright 2001, Physicians Postgraduate Press. Reprinted by permission (34).

hyperphagic (50). Consequently, individuals with higher levels of UCPs are not as efficient at generating ATP, and as such must consume more energy substrates (e.g. glucose and fat) than would an individual with lower levels of UCPs. As a result, these differences contribute to inter-individual variations in body weight. Clozapine antagonism of peripheral β_3 and α_1 adrenergic receptors may inhibit these mechanisms, making patients more efficient with their energy intake, which can cause significant weight gain in those who are predisposed.

We tested hypotheses for 10 genetic polymorphisms across nine candidate genes from both central hypothalamic weight regulation and peripheral thermogenic pathways in a recent paper (34) that provides a comprehensive review of the current

obesity and weight regulation research, while also speculating on how atypical antipsychotics may disrupt these pathways to cause weight gain in those patients who are predisposed. The candidate genes investigated were the 5-HT $_{2C}$, 5-HT $_{2A}$ and 5-HT $_{1A}$ receptor genes (*HTR2C*, *HTR2A* and *HTR1A*) the histamine H_1 and H_2 receptor genes (*H1R* and *H2R*) the cytochrome P450 1A2 gene (*CYP1A2*), the β_3 and α_{1a} adrenergic receptor genes (*ADRB3* and *ADRA1A*), and the tumor necrosis factor α gene (*TNF- α*). We obtained prospective weight gain data for 80 patients with schizophrenia who had completed a structured clozapine trial. During clozapine treatment, weight in kilograms was assessed at baseline and 6 weeks. ANCOVA analyses correcting for covariates (sex,

ethnicity, baseline weight and response status) were utilized to detect differences among genotypes at candidate gene loci for mean change in weight while on clozapine. Non-significant trends were observed for *ADRB3* ($F=2.29$, $P=0.10$), *ADRA1A* ($F=1.58$, $P=0.22$), *TNF- α* ($F=1.94$, $P=0.15$) and *HTR2C* ($F=0.63$, $P=0.54$); however, replication in larger, independent samples is required (34). Recently, Reynolds *et al.* (51) demonstrated an association between antipsychotic-drug-induced weight gain and a novel promotor region polymorphism (C759T) that may alter 5-HT_{2C} gene expression (52). This finding was not replicated in our prospective sample of clozapine-treated patients (53). Further investigation is required to assess whether this polymorphism may have a predictive role for clozapine induced weight gain that is clinically relevant.

TYPICAL ANTIPSYCHOTIC-INDUCED TARDIVE DYSKINESIA

Tardive dyskinesia is an important side-effect of typical antipsychotics and has been the focus of a number of pharmacogenetic studies. TD is an involuntary movement disorder of the orofacial musculature and may involve the trunk and extremities as well. It occurs in 20–30% of patients either after chronic administration of antipsychotics or after withdrawal of these agents and is potentially irreversible once it arises. The reasons for the development of TD in some patients and not in others are unknown, but there is suggestive evidence that susceptibility has a genetic component. Animal models and family studies indicate that genetic factors importantly influence the risk for TD following treatment (53–56). Although the precise mechanism(s) of TD is not well understood, overactivity of the dopaminergic neurotransmission in the basal ganglia and upregulation of the dopamine D₂-like receptors (D₂, D₃ and D₄) have been postulated to play a role in its pathophysiology (57). Consequently, genetic association studies on the pharmacodynamic component of the TD phenotype have primarily focused on the dopamine system genes. Several risk factors for TD have been identified, such as age, female gender, African-American ethnicity, duration of antipsychotic exposure and organic brain abnormalities (58–61). These factors predict only a minor portion of the variance in the TD phenotype, and therefore a prominent pharmacogenetic component may contribute to this variance and help in predicting those patients who will develop TD. The phenotype of TD has the advantage of being objectively visible and is relatively amenable to scaled scoring in terms of the degree of severity. In contrast to genetic studies of clozapine response, the genetic studies of TD have yielded quite promising and replicable results. Pharmacogenetic studies of TD have investigated both pharmacodynamic and pharmacokinetic aspects of typical antipsychotics. The most interesting and consistent findings regarding candidate gene studies of TD have focused on the dopamine D₃ receptor gene (*DRD3*).

DRD3 mRNA and protein have been localized to the ventral striatum and the ventral putamen in the basal ganglia, a brain region implicated in motor control (62). Pharmacological studies provide evidence that the D₃ receptor exerts an inhibitory effect on locomotor activity. Kling-Petersen *et al.*

(63) found that 7-OH-DPAT, a D₃-selective agonist, inhibits locomotion when injected into the nucleus accumbens of rat brain (63). Conversely, D₃ antagonists increase locomotor activity (63). Consistent with this, *DRD3* knockout mice exhibit hyperactivity (64). A postmortem study in patients with schizophrenia who were previously treated with typical antipsychotics illustrated a 45–56% increase in the number of D₃ receptors in the basal ganglia as compared with controls (65). These data collectively provide evidence that the D₃ receptor may play a role in motor control. The *DRD3* gene exhibits a single-nucleotide polymorphism (SNP) that results in a serine-to-glycine amino acid substitution (Ser9Gly) in the N-terminal extracellular domain of the D₃ receptor (66). A functional study of this Ser9Gly polymorphism in CHO cells revealed allelic differences in affinity for dopamine (67). Specifically, a significantly higher affinity for dopamine was shown for cells homozygous for glycine than heterozygotes and serine/serine homozygotes (67). It is likely that the substitution of a polar serine residue by a non-polar glycine residue might have altered the tertiary structure of the receptor, thus affecting its binding affinity for dopamine.

Several groups, including our own, have independently shown that the Ser9Gly *DRD3* gene polymorphism is associated with risk for TD (68–74). Each group found that either the glycine/glycine genotype or the glycine allele conferred elevated risk for TD. However, this result was not replicated in studies from Inada *et al.* (75), Rietschel *et al.* (76) and Garcia-Barcelo *et al.* (77). The discrepancies among these studies may be due to study population differences and differences in study designs. This finding is promising in that it has been replicated in several independent studies from samples of various ethnic origins. A recent collaborative effort by numerous groups (nine centers), including our own, confirmed the initial finding of association between the Ser9Gly *DRD3* receptor gene polymorphism and TD (78). Another interesting pharmacodynamic candidate is the 5-HT_{2A} receptor gene (*HTA2A*), which was found to be associated with TD in two independent studies (79,80), although we could not replicate this finding in a relatively large prospective study (81). Table 2 provides a summary of the various candidate gene association studies that have been undertaken for the phenotype of TD.

In light of the replicating *DRD3* genotype finding for TD, we have used FDG-PET and MRI in a subset of our patients to determine if there are any differences in regional brain activity/metabolism following haloperidol treatment in patients who are glycine/glycine homozygous when compared with other patients. We found that following haloperidol treatment, patients who were glycine/glycine homozygotes had increased FDG metabolism within the caudate nucleus and the putamen when compared with serine/serine homozygotes and serine/glycine heterozygotes (82). These brain regions are known to mediate the control of movement. Interestingly, those patients that exhibited the increased brain activity in these regions also had the most severe TD (Fig. 3).

Under the assumption of the involvement of multiple genes in the phenotype of TD, our group then examined the role of pharmacokinetic aspects by investigating the cytochrome P450 genes *CYP2D6* and *CYP1A2*, both of which are known to be involved in the metabolism of typical antipsychotics.

Table 2. Association studies of tardive dyskinesia

Gene Studied	Authors/Year (Ref.)	Result
Dopamine D ₂ receptor (<i>DRD2</i>)	Badri <i>et al.</i> (1996) (68) Chen <i>et al.</i> (1997) (108) Inada <i>et al.</i> (1997) (75) Hori <i>et al.</i> (2001) (109)	No significant association Borderline significant association No significant association No significant association
Dopamine D ₃ receptor (<i>DRD3</i>)	Badri <i>et al.</i> (1996) (68) Steen <i>et al.</i> (1997) (69) Inada <i>et al.</i> (1997) (75) Basile <i>et al.</i> (1999) (70) Segman <i>et al.</i> (1999) (71) Rietschel <i>et al.</i> (2000) (76) Lovlie <i>et al.</i> (2000) (73) Liao <i>et al.</i> (2001) (72) Garcia-Barcelo <i>et al.</i> (2001) (77) Woo <i>et al.</i> (2002) (74) Lerer <i>et al.</i> (2002) (78)	Statistically significant association Statistically significant association No significant association Statistically significant association Statistically significant association No significant association Statistically significant association Statistically significant association No significant association Statistically significant association Comprehensive analysis of most of the above-mentioned data sets found a statistically significant association
Serotonin 2A receptor, 5-HT _{2A} (<i>HTR2A</i>)	Segman <i>et al.</i> (2001) (79) Tan <i>et al.</i> (2001) (80) Basile <i>et al.</i> (2001) (81)	Statistically significant association Statistically significant association No significant association
Serotonin 2C receptor, 5-HT _{2C} (<i>HTR2C</i>)	Segman <i>et al.</i> (2000) (110) Basile <i>et al.</i> (unpublished data)	Statistically significant association No significant association
Cytochrome P450 2D6 (<i>CYP2D6</i>)	Arthur <i>et al.</i> (1995) (111) Badri <i>et al.</i> (1996) (68) Armstrong <i>et al.</i> (1997) (112) Andreassen <i>et al.</i> (1997) (113) Kapitany <i>et al.</i> (1998) (114) Ohmori <i>et al.</i> (1998) (115) Ohmori <i>et al.</i> (1999) (116)	No significant association No significant association Non-significant trend Non-significant trend Statistically significant association Statistically significant association No significant association
Cytochrome P450 1A2 (<i>CYP1A2</i>)	Basile <i>et al.</i> (2000) (84) Schulze <i>et al.</i> (2001) (85)	Statistically significant association No significant association
Manganese superoxide dismutase, MnSOD	Hori <i>et al.</i> (2000) (117) Zhang <i>et al.</i> (2002) (118) Basile <i>et al.</i> (unpublished data)	Statistically significant association No significant association No significant association
Serotonin 6 receptor, (5-HT ₆)	Ohmori <i>et al.</i> (2002) (119)	No significant association

Differences in the metabolism and elimination of the antipsychotic could lead to increased risk for TD in those who are genetically poor metabolizers. The *CYP2D6* gene variation investigated did not predict risk for TD; however, the *CYP1A2* polymorphism did show a significant association. Patients who were C-allele homozygotes for *CYP1A2*, which correlates with a less easily inducible form of the enzyme (83), had much more severe TD as measured by mean AIMS scale score (84). However, a recent study in a German sample could not replicate this finding (85).

In view of these two genetic associations with *DRD3* and *CYP1A2*, each contributing to risk for TD, a gene–gene interaction analysis was conducted by our group using methods modified from those of Frankel and Schork (86). First, the various models of gene–gene interaction have been delineated in matrices representing combinations of dominant, recessive, additive, heterogeneity and epistatic effects. The *DRD3* and *CYP1A2* genetic data were then fitted to each of these models. Thus far in the analyses, the best fit is an additive, co-recessive glycine/C-allele model of *DRD3* and *CYP1A2* interaction ($F = 17.36$, $P = 0.00007$). It was found that those patients who exhibited the risk genotype at both *DRD3* (glycine/glycine) and at *CYP1A2* (C/C) had the most severe TD, whereas those who had only one risk genotype (glycine/glycine or CC) demon-

strated intermediate severity of TD. Those patients who did not have any of the risk genotypes at either locus demonstrated the lowest mean TD severity AIMS scale scores (Fig. 4). The overall model now accounts for >50% of the variance in risk for TD in our sample. This promising investigation of gene–gene interaction is thus paving the way, starting with two genes, toward a multigene, demographic and environmental variable model that may account for most of the variance in risk TD. The application of artificial neural network modelling techniques may help decipher the complex interactions among genetic, demographic and environmental variables, to elicit a predictive model or diagnostic kit for TD. If replicated, this model would have significant clinical value in the day-to-day practise of psychiatrists who treat chronically psychotic patients, and may help to predict those patients who are most and least likely to develop TD following treatment with typical antipsychotics.

CONCLUSIONS AND FUTURE DIRECTIONS

Based on our review of the pharmacogenetics of antipsychotic-drug-induced side-effects and response, several recommendations can be made. It is apparent that a great deal of

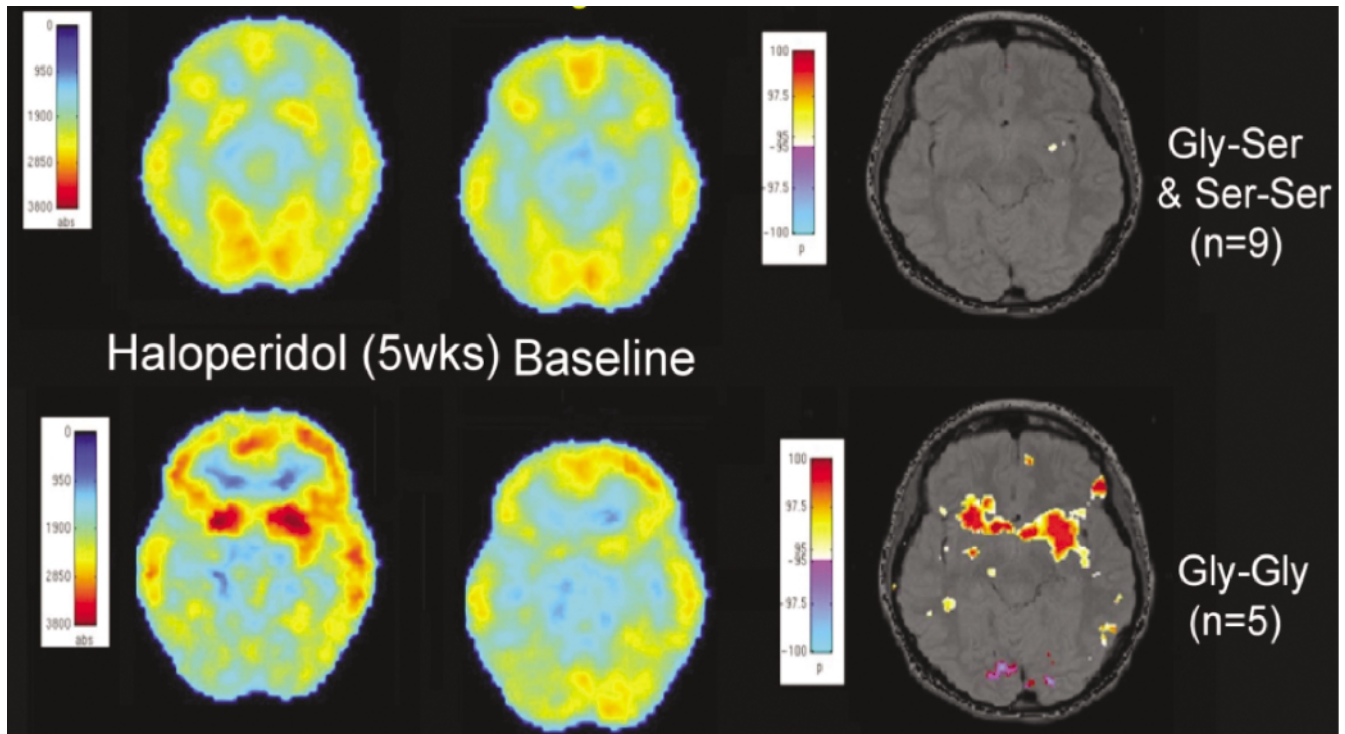


Figure 3. Brain [^{18}F]fluoro-2-deoxy-D-glucose (FDG) metabolism PET following haloperidol treatment versus dopamine D_3 receptor genotype ($N = 14$). The top row presents scans from patients who were either serine/serine homozygotes or serine/glycine heterozygotes at *DRD3* ($N = 9$). Within this row and from left to right, we have the mean FDG-PET following 5 weeks of haloperidol treatment, the mean baseline FDG metabolism and the subtraction of the previous two entities overlaid on MRI to indicate the change in FDG metabolism due to treatment. The bottom row depicts the results of the same methodologies in patients who were glycine/glycine homozygotes ($N = 5$). Note that the subtraction image in these glycine/glycine homozygote patients demonstrates significantly increased metabolic activity in striatal brain regions. Modified from Potkin *et al.* (82). Reprinted with the permission of Cambridge University Press.

methodological heterogeneity exists among these pharmacogenetic studies. This is expected, given the relatively early stage of the field. However, in order for the field to progress, methodological consistency must be achieved not only to form the basis of comparison among studies, but more importantly to allow for collaborative efforts that combine samples. Efforts to combine studies have been very useful, as evidenced by the recent multicenter collaborative study of *DRD3* association with TD (78). Sample-size limitations that decrease the power of analysis can be overcome through these collaborative efforts. Methodological considerations include the establishment of discrete inclusion/exclusion criteria regarding patient diagnosis and sample characterization; consensus regarding the use of particular psychiatric rating instruments should be established *a priori* (87). Furthermore, studies should be designed specifically for the identification of genetic susceptibility to pharmacogenetic traits. To date, studies have used samples obtained from prospective or retrospective clinical trials, with testing of genetic hypotheses in an opportunistic fashion after the trial is completed.

Another critical issue is the definition of the pharmacogenetic phenotype. Regarding response to antipsychotics, groups working in this field need to agree upon a standard definition of response that would include multiple criteria of assessment. Furthermore, categorical non-parametric approaches are limited in power and should be supplemented by

parametric continuous measure designs. For clozapine response, this would entail using the mean change in clinical rating over time (controlling for baseline) in an analysis of variance (ANOVA) with genotype as the grouping variable. Pharmacogenetic studies of TD have begun to move forward in this direction. Further refinement of the TD phenotype has been attempted through the use of an endophenotype that quantifies the degree of involuntary movements by measuring facial muscle activity using standardized electromyographic techniques (88). Techniques such as these should reduce phenotypic heterogeneity, adding to the power of the analysis (89), in addition to removing the problems associated with inter-rater reliability in the primarily subjective assessment of patient symptoms in psychiatry. Another method of refining the pharmacogenetic phenotype of interest is to use multiple rating instruments (e.g. GAS, BPRS and PANSS for clozapine response; AIMS, SARS and Simpson Dyskinesia scale for TD), and conducting factor analysis in order to extract items from each scale that tend to cluster together (90). The use of more narrowly defined phenotypes such as these increases the power of genetic studies.

Neuroimaging may provide an avenue for measuring more narrowly defined endophenotypes, thus limiting some of the heterogeneity inherent in psychiatric genetic studies. The use of structural brain imaging as an endophenotype for genetic studies is beginning to gain popularity, and an association

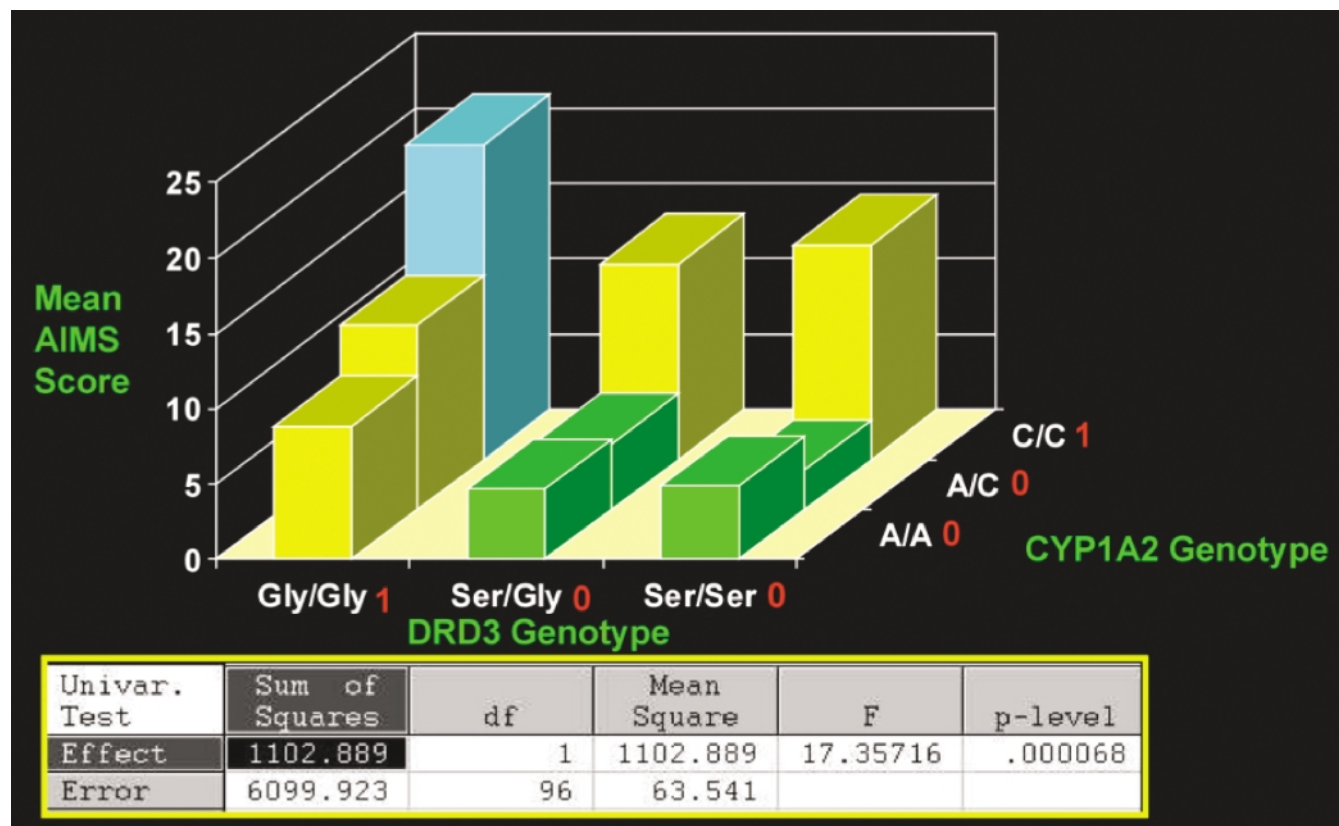


Figure 4. *DRD3* and *CYP1A2* gene–gene interaction model. Our data fit an additive, co-recessive glycine/C-allele model of *DRD3* and *CYP1A2* gene interaction. It was found that those patients who exhibited the risk genotype at both *DRD3* (glycine/glycine) and at *CYP1A2* (C/C) had the most severe tardive dyskinesia (TD)(blue), whereas those who had only one risk genotype (glycine/glycine or C/C) demonstrated intermediate TD severity (yellow). Those patients who did not have any of the risk genotypes at either locus demonstrated the lowest mean TD severity AIMS scale scores (green).

between parietal lobe volume and brain-derived neurotrophic factor (*BDNF*) alleles has been reported (91). Laruelle *et al.* (92) failed to find an association between dopamine D₂ receptor binding and alleles at the *TaqI*-A restriction fragment length polymorphism (RFLP) site in the *DRD2* gene using single-photon emission computed tomography (SPECT) imaging. A recent and seminal study by Hariri *et al.* (93) used functional MRI (fMRI) to assess neuronal activity in subjects genotyped for the serotonin transporter promoter polymorphism. They found that individuals with one or two copies of the short allele exhibit greater amygdala neuronal activity in response to fearful stimuli when compared with individuals homozygous for the long allele.

Despite their small sample sizes, these preliminary studies provide intriguing data regarding the ability of brain imaging to serve as an endophenotype in pharmacogenetic investigations. These studies, however, did not examine the relationship between allelic variation, clinical outcomes to pharmacological treatment (response and side-effects), and the intermediate phenotypes as revealed by brain imaging. One advantage of PET imaging is that specific ligands can be radiolabelled in order to measure specific pharmacological targets in the brain. For example, a radioligand specific for the serotonin transporter has been developed and utilized in studies of patients' response to selective serotonin reuptake inhibitor (SSRI) medications.

The ideal candidate gene to study for this combined neuroimaging plus pharmacogenetic phenotype is the serotonin transporter gene. FDG–PET has the ability to measure regional brain metabolic response while the subject is performing an activation task. PET also has the ability to resolve individual gyri and to distinguish subcortical regions from each other. PET can measure 'brainwork' because of the close coupling between glucose utilization and neuronal activity. Unlike fMRI and SPECT, FDG–PET allows for absolute quantification of metabolic activity. However, fMRI provides a relatively safe and repeatable method of generating brain maps. Each of the imaging techniques may provide differential benefits in defining pharmacogenetic endophenotypes. It may be possible to monitor specific gene expression using neuroimaging, thus quantifying *in vivo* changes as a result of pharmacological challenges. Caveats exist in that neuroimaging endophenotypes may not correlate directly with the behavioral manifestations of pharmacogenetic and neuropsychiatric phenotypes. However, clear strengths exist in using this technology to limit phenotypic heterogeneity and increase the power to detect genetic contributors to pharmacogenetic phenotypes.

Through predictability testing, pharmacogenetic testing kits could break the 'trial-and-error' approach to prescribing antipsychotics. Although in its infancy, pharmacogenetics may in future lead to individualized pharmacotherapy based

on the specific genetic, environmental and demographic characteristics of each patient. The pharmacogenetic goal of providing treatment based on these client-centered characteristics in order to maximize efficacy and minimize the risk of adverse events—getting the right medicine in the right dose to the right patient—will inevitably become common in the not-so-distant future. This results in increased patient comfort in terms of both higher initial response rates and reduced propensity to developing debilitating side-effects.

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