SYMPOSIUM

The Role of Pharmacogenetics in Treating Central Nervous System Disorders

MEETA PATNAIK,[1] MATTHEW J. RENDA, MARIA C. ATHANASIOU, AND CAROL R. REED
PGxHealth, New Haven, Connecticut 06511

Symptoms of central nervous system (CNS) disorders include abnormalities in both physical and psychological domains. Many drugs indicated for the treatment of CNS disorders are fraught with side effects and/or poor efficacy which impact patients' quality of life and drives non-compliance. Moreover, for many CNS drugs such as antidepressants and antipsychotics, it takes time to determine whether a particular drug is efficacious in an individual patient. To optimize drug treatment for each patient, prescribing physicians often need to raise or lower doses, switch drug classes, or prescribe additional drugs to mitigate side effects, often in a "trial and error" fashion. Pharmacogenetic (PGx) testing, particularly in the realm of CNS therapy, can reduce the unpredictability of this process. By determining a patient's genetic profile, individual therapy parameters may be predicted pre-treatment for drug efficacy, optimal drug dose, and the risk of adverse drug reactions (ADRs). The intent of this review is to highlight the power of PGx testing to predict the likelihood of ADRs and efficacy during the treatment of the following CNS disorders: epilepsy, bipolar disorder, schizophrenia and depression. Exp Biol Med 233:1504–1509, 2008

Key words: pharmacogenetic testing; CNS disorders; predict response; personalized medicine

Two Different CNS Disorders Treated with Carbamazepine

Epilepsy. The World Health Organization estimates that epilepsy, which is characterized by recurrent unprovoked seizures, affects 8.2 per 1000 people, translating to nearly 2.5 million US citizens (WHO website). Carbamazepine (CBZ) is an anticonvulsant and mood stabilizing drug indicated for treatment of epilepsy and trigeminal neuralgia; however, 1 in 1000 to 1 in 10,000 patients suffer from ADRs including severe hypersensitivity reactions which can be fatal (1).

Bipolar Disorder. Also known as manic-depressive illness, bipolar disorder affects 5.7 million US adults and is characterized by mood swings. Other formulations of CBZ are used for the treatment of acute and mixed episodes associated with bipolar disorder.

Carbamazepine and Stevens-Johnson Syndrome

CBZ is associated with cutaneous adverse drug reactions (cADRs) ranging from mild macropapular eruption to the potentially fatal Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) with a mortality rate as high as 40% (2). SJS/TEN is characterized as widespread apoptosis of keratinocytes resulting in extensive blisters. The frequency of CBZ-induced cADRs is between 1 in 1000 and 1 in 10,000 in Caucasians and approximately 10-fold higher in Asians (1). These hypersensitivity reactions to CBZ appear to have an immune etiology. Not only does the timing of sensitization by CBZ suggest immunologic memory, but it has been specifically shown that CBZ-specific human leukocyte antigen (HLA) major histocompatibility complex (MHC) Class I restricted cytotoxicity is involved (3).

Antigen presenting proteins, encoded in the MHC HLA Class 1 locus on chromosome 6, are thought to play a role in a number of disease states including infectious diseases, cancer, graft rejection, auto-immunity and ADRs. Immune mediated drug induced ADRs may occur when antigen presenting proteins on the surface of antigen presenting cells (APC) present drug-derived peptides to T cells, thereby triggering a T cell-mediated allergic response. Drug presentation to the T cell by APCs can occur in one of

[1] To whom correspondence should be addressed at PGxHealth, LLC, A Division of Clinical Data, Inc. (NASDAQ: CLDA), 5 Science Park, New Haven, CT 06511. E-mail: mpatnaik@pgxhealth.com

DOI: 10.3181/0806-S-195
1535-3702/08/23312-1504$15.00

three ways: 1) the drug is directly modified in the APC, such that reactive haptens are presented to T cells, 2) the inert drug is metabolized in the APC to produce reactive prohaptens that are presented to T cells, or 3) the drug can bind directly in a non-covalent manner to the surface of APCs, become stabilized by HLA/peptide interaction, and thereby elicit a T cell response ((4) for review).

In addition to the many modifications a drug can undergo in the antigen presenting process, further variations of antigen presentation are compounded when considering the vast allelic variability of the HLA presentation molecules bound to the drug antigen. It is becoming increasingly more evident that the extensive genetic variability in the HLA locus is an important determinant of specific allergic responses, and importantly, that specific variants are associated with specific ADRs. Indeed, the HLA-B*1502 genotype was shown to be strongly associated with CBZ-induced SJS in 44 Han Chinese patients with an odds ratio of an astounding 2504 (95% confidence interval = 126 – 49,522) when compared with 101 CBZ-tolerant patients (5). This strong association of HLA-B*1502 with CBZ-induced SJS/TEN was confirmed in a larger study by the same research group (91 CBZ-induced SJS/TEN and 144 CBZ-tolerant patients) (6) and in a different Chinese patient population (4 CBZ-induced SJS/TEN patients and 16 CBZ-tolerant controls) (7). Interestingly, the association was phenotype-specific, as it was not associated with the more mild hypersensitivity syndromes such as maculopapular eruption (6). Although these studies are compelling, it can not be assumed that this variant causes SJS especially since the association of HLA-B*1502 with CBZ is not found in patients of European descent (8, 9). Instead, it is possible that the HLA-B*0702 variant may exert a protective effect against developing SJS/TEN in Caucasians (10). Reasons for these differences between the two ethnic groups could be due to the presence of another gene that is in tight linkage disequilibrium in one population and not in another. Alternatively, there may be multiple genetic causes that result in the same observed CBZ-induced SJS/TEN phenotype. Evidence for this possibility lies in the fact that CBZ-SJS is 10-fold more prevalent in Asian populations. The higher prevalence of CBZ-induced SJS in Asians may be due to a distinct mechanism, not found in Caucasians, that is associated with the HLA-B*1502 variant (11).

These CBZ-induced SJS genetic association studies point out the fact that ethnicity can play a key role in identifying biomarkers. Encouragingly, these studies also suggest that strong genetic associations can be identified with a moderate number of patients although the genetic variants associated with SJS differ among ethnic groups; all of the studies confirm the role of the immune system in CBZ-induced ADRs. Most importantly, this work has identified an extremely important predictive tool in the Asian populations for assessing risk for SJS/TEN, since 100% of the patients with CBZ-induced SJS/TEN studied by Chung *et al*. (5) carried the HLA-B*1502 allele. Based on this information, the U.S. Food and Drug Administration added a black box warning to the label of CBZ stating, "Dangerous or even fatal skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions." The HLA-B*1502 variant is found in 8% of Han Chinese, and only 1–2% of Caucasians. More ethnic populations will need to be tested to determine the broader utility of the genetic test.

Schizophrenia

Striking 2.6 million US citizens in a given year, schizophrenia ranks among the top 10 causes of disability (NIMH website). Schizophrenia, characterized by impairments in the perception or expression of reality, is treated using either first generation typical antipsychotics (e.g., haloperidol, perphenazine) or second generation atypical antipsychotics (e.g., clozapine, olanzapine, risperidal). Both drug classes have significant side effects associated with them.

Typical Antipsychotics and Tardive Dyskinesia. Typical antipsychotics are associated with the often irreversible side effect of tardive dyskinesia (TD), an involuntary oral-lingual-buccal movement disorder that resembles a continual chewing motion with grimacing, tongue protrusion, lip smacking and rapid blinking. The intensity of TD varies from mild to severe, with severe cases being marked with additional abnormal movements in limbs, neck, shoulders and hips. This debilitating side effect contributes to a high non-compliance rate (12), and has influenced physician practice trends so that typicals are now prescribed to only 17% of treated schizophrenic patients (2004 Frost & Sullivan report on US Antipsychotics Medication Market), despite their lower cost (Med Letter, 2003) and comparable antipsychotic efficacy (13) when compared to atypicals.

The overall lifetime risk of developing TD is 24% to 32% in patients treated with typical antipsychotics, with an annual incidence of 3.5 to 5.5% per year (14, 15, 16, 17, 18). Both non-genetic and genetic factors are associated with TD. For example, patients over 50 years of age have a 3 to 5 times greater risk of developing TD (19). Smoking is another risk factor for developing TD, with an OR of 2.47 when compared to non-smokers' risk (20–22). Importantly, TD has been shown to have a genetic component, as the

development of TD in relatives tends to correlate with the TD status of the index patient ($P = 0.04$) (23).

A number of studies have been aimed at elucidating genetic associations with the development of TD in patients taking typical antipsychotics. Six genes in particular display small but significant associations with TD in meta-analyses. These genes are: 1) the dopamine receptor D3 (DRD3) (OR = 1.17–1.3) (24, 25), which inhibits adenyl cyclase through inhibitory G-proteins and plays a role in cognitive and emotional functions, 2) the cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) (OR = 1.43) (26), which is integral to the main metabolic pathway for a number of typical antipsychotics, 3) the 5-hydroxytryptamine (serotonin) receptor 2A (5-HT2A) (OR = 1.64) (27), a member of the serotonin receptor signaling pathway, 4) the mitochondrial superoxide dismutase 2 gene (MnSOD) (OR = 0.37) (28), which converts the superoxide byproducts of oxidative phosphorylation to hydrogen peroxide and diatomic oxygen, 5) the dopamine receptor DRD2 gene (OR = 1.30) (28), and 6) the catechol-O-methyl-transferase gene (COMT) (OR = 0.63) (28), which is important in regulating dopamine levels in the brain.

Efforts to collect a well-phenotyped, typical antipsychotic-induced TD cohort for genetic analysis are confounded by the fact that: 1) the onset of TD is often delayed (approximately 3 years); 2) the symptoms of TD vary temporally and clinically 3) schizophrenia is associated with spontaneous abnormal involuntary movements even in treatment-naïve patients (29, 30); and 4) US schizophrenia patients have low compliance rates (31), raising the risk of incorrectly classifying a patient as free from TD when they are in fact non-compliant with medication.

Other Side Effects of Atypical Antipsychotics. Although atypical antipsychotics are less likely to cause extrapyramidal side effects, they are associated with other effects ranging from weight gain, as observed with olanzapine or risperidone, to potentially lethal adverse drug reactions, as seen with clozapine.

Olanzapine and Weight Gain. Olanzapine is an atypical antipsychotic recommended by the American Psychological Association as a first line treatment for schizophrenia. However, body weight gain (BWG) may be a significant side effect in some individuals treated with olanzapine, as well as with other atypical antipsychotics (Baptista *et al*., 2002, for review). BWG, associated with a range of health complications including coronary artery disease and Type II diabetes, is a primary reason for drug non-compliance with many atypicals.

A common biochemical feature of atypical antipsychotics is their stronger affinity for serotonergic receptors than for dopaminergic receptors (32). The mechanisms for olanzapine-induced weight gain may involve the gene for 5-HTR2C, as it has been implicated in the regulation of food intake in mice (33). In humans, Ellingrod *et al*. have shown that the T allele in the –759C/T promoter polymorphism of the HTR2C gene has a protective association against olanzapine-induced weight gain (34). In a meta-analysis of 10 studies, De Lucca *et al*. have shown a modest but significant effect of variation in the HTR2C gene and atypical antipsychotic-induced weight gain (35). It is possible that the association is modified by ethnic differences. For example, this association was not observed in a Korean population (36). Although most of the published studies may be flawed by the inclusion of subjects who were pre-treated with antipsychotics other than olanzapine, the available genetic association studies with 5-HTR2C are intriguing and deserve further study in a well-described, mono-drug cohort. Other promising candidate genes that may be associated with olanzapine-induced BWG include CYP2D6 (37), the synaptosomal-associated protein of 25 kDa (SNAP25) (38), G-protein beta 3 subunit gene (GNB3) (39), the alpha2a-adrenergic receptor (ADRA2A) (40), leptin (LEP) and the leptin receptor (LEPR) (41).

Clozapine and Agranulocytosis. Clozapine, an atypical antipsychotic, is indicated for treatment-refractory schizophrenia, and for reducing recurrent suicidal behavior in schizophrenia or schizoaffective disorders. Clozapine is generally considered to be the most effective antipsychotic (42), as it has been shown to be more effective than typicals (43, 44), and in the CATIE study, to be more effective than other atypicals such as olanzapine, quentiapine, and risperidone in treatment-resistant patients (12, 45). However, clozapine is currently labeled as a third-line treatment option due in part to the potentially lethal risk of clozapine-induced agranulocytosis (CIA), a potentially lethal drop in white blood cells (WBCs).

Due to the frequency and severity of this ADR, clozapine was approved in the United States contingent upon the manufacturer's development and implementation of a blood monitoring system for early identification of patients who may be developing neutropenia or agranulocytosis. Since the risk of CIA rises steeply during the first two months of treatment and is rare after six months of clozapine treatment, WBC counts are measured weekly for the first 6 months, biweekly for the next 6 months, and monthly for the duration of their treatment with clozapine. The implementation of this blood monitoring system has successfully reduced the incidence of CIA to 0.4% from the 1.3% incidence observed in patients treated with clozapine but without mandatory monitoring of WBCs (46). Unfortunately, frequent blood monitoring is not only an added expense to the treatment of an already cost-intensive disease, but is a burdensome requirement that can cause vein damage, limit freedom to travel, and stigmatize patients because of the frequency of clinic visits.

Prediction of the CIA side effect in advance of treatment could significantly change current prescription practices by permitting safer use of clozapine. However, there have been a number of difficulties in identifying a biomarker for CIA. For example, there is no apparent dose-response relationship with this ADR, and genetic studies have been confounded by poor power and the absence of a

thorough 'scan' of the genome. Consistent with suggestions that CIA may be immune mediated (47, 48), risk association studies repeatedly implicate the HLA locus in risk for CIA (31, 49, 50). Through a candidate gene case-control study, PGxHealth utilized a candidate gene approach and has demonstrated that variation in *HLA-DQB1* is associated with CIA. This association has now been confirmed in a second independent cohort of subjects. Data from these and other studies support the possibility that a pharmacogenetic test may be used to identify whether a patient is at higher or lower risk for CIA compared to the untested population.

Depression and Response to Vilazodone

Depression affects more than 20 million people of all races and ages and is characterized by a combination of symptoms that interfere with a person's ability to participate in once-enjoyed activities or function normally in daily life. Unfortunately, first-line treatment options for the treatment of depression are not consistently effective, being accompanied by wide inter-individual variation, delay in response and many side effects. This combination leads to dissatisfaction with treatment, poor compliance, sequential prescriptions or switching among the available medications all resulting in high costs until the best treatment for each patient is identified. As approximately one-half of depressed patients do not achieve satisfactory results with current first-line treatment options (51), PGxHealth is integrating pharmacogenetics into the drug development program for vilazodone. We are currently engaged in Phase III clinical trials for the development of an antidepressant, vilazodone, while simultaneously identifying specific biomarkers that may be used by clinicians to predict the efficacy or safety of vilazodone for their patients.

Vilazodone, a selective serotonin reuptake inhibitor (SSRI) and a partial agonist to the 5-hydoxytryptamine 1A (5-HT1A) receptor, has been shown to have antidepressant-like effects in the well-established forced swimming test model in rats (52). To assess its efficacy in humans, vilazodone was tested in an 8-week, randomized, double-blind, placebo-controlled trial of patients with a diagnosis of major depressive disorder (MDD) according to DSM-IV-TR criteria. The primary endpoint of change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) score measured at 8 weeks was met with a $P = 0.001$.

To identify biomarkers associated with vilazodone efficacy, we employed both a candidate gene and whole genome scan approach. Statistically significant markers were discovered that identify a substantial subset of patients with an increased probability of responding to vilazodone. These markers will be further assessed in a second clinical trial and, have the potential to significantly impact the treatment of depression by aiding physicians in the identification of patients more likely to have a response, leading to better outcomes, less trial-and-error prescribing, and greater patient and physician satisfaction.

The Future of Pharmacogenetics in Drug Development

Pharmacogenetic testing is rapidly becoming the cornerstone of individualized medicine. The field of pharmacogenetics and pharmacogenomics is growing as evidenced by the number of PubMed listings containing these words increasing from 61 references in 1997 to 920 publications in 2007. Not only can pharmacogenetic information be used to predict the optimal dosing of a particular drug for enhanced efficacy in an individual patient, but importantly, it can save lives by identifying patients who are at risk of a lethal adverse drug reaction prior to prescription. To date, most biomarkers of drug safety have been identified post-drug approval, rather than during the drug development phase, placing patients at risk for an ADR that might have been predicted and thereby prevented. Biomarkers for drug efficacy have the potential to assure that patients receive the correct treatment sooner in their disease course with great potential for improved outcomes and reduced health care costs.

Ideally, development programs should be designed not only to develop drugs that are generally safe and efficacious, but simultaneously identify specific biomarkers that affect the efficacy and safety in a subset of individuals. To accomplish this, it is essential to collect appropriate information during pre-approval clinical trials. It is important to 1) create a biobank of isolated DNA and/or tissue samples for each patient, 2) obtain the appropriate informed consent, 3) carefully document ethnicity, 4) anticipate the phenotype of the ADR and collect the appropriate data and 5) consider the development of an anonymized database to facilitate further research.

The cost of pharmacogenetic testing is minimal compared to the overall societal cost of ineffective treatment and ADRs, to the development cost of drug research, and to the cost of withdrawing a compound from the market.

We thank Natalie Coleman for her help in preparing and editing this manuscript. MP, MR, MA, and CR disclose financial interests and are employees of PGxHealth.

1. Kamaliah MD, Zainal D, Mokhtar N, Nazmi N. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in north-eastern Malaysia. Int J Dermatol 37:520–523, 1998.
2. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 331:1272–1285, 1994.
3. Nassif A, Bensussan A, Boumsell L, Deniaud A, Moslehi H, Wolkenstein P, Bagot M, Roujeau JC. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. J Allergy Clin Immunol 114:1209–1215, 2004.
4. Roujeau JC. Immune mechanisms in drug allergy. Allergol Int 55:27–33, 2006.
5. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY,

Chen YT. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 428:486, 2004.

6. Hung SI, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, Hu SL, Wu MT, Chen GS, Wong TW, Hsiao PF, Chen WH, Shih HY, Fang WH, Wei CY, Lou YH, Huang YL, Lin JJ, Chen YT. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics 16:297–306, 2006.
7. Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS, Ng MH. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia 48:1015–1018, 2007.
8. Lonjou C, Thomas L, Borot N, Ledger N, de TC, LeLouet H, Graf E, Schumacher M, Hovnanian A, Mockenhaupt M, Roujeau JC. A marker for Stevens-Johnson syndrome . . . : ethnicity matters. Pharmacogenomics J 6:265–268, 2006.
9. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, Naldi L, Bouwes-Bavinck JN, Sidoroff A, de TC, Schumacher M, Roujeau JC, Hovnanian A, Mockenhaupt M. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics 18:99–107, 2008.
10. Alfirevic A, Jorgensen AL, Williamson PR, Chadwick DW, Park BK, Pirmohamed M. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. Pharmacogenomics 7:813–818, 2006.
11. Chung WH, Hung SI, Chen YT. Human leukocyte antigens and drug hypersensitivity. Curr Opin Allergy Clin Immunol 7:317–323, 2007.
12. McEvoy JP. An overview of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. CNS Spectr 11:4–8, 2006.
13. Meltzer HY, Bobo WV. Interpreting the efficacy findings in the CATIE study: what clinicians should know. CNS Spectr 11:14–24, 2006.
14. Casey DE. Implications of the CATIE trial on treatment: extrapyramidal symptoms. CNS Spectr 11:25–31, 2006.
15. Tarsy D, Baldessarini RJ. Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? Mov Disord 21:589–598, 2006.
16. Remington G. Tardive dyskinesia: eliminated, forgotten, or overshadowed? Curr Opin Psychiatry 20:131–137, 2007.
17. Woerner MG, Kane JM, Lieberman JA, Alvir J, Bergmann KJ, Borenstein M, Schooler NR, Mukherjee S, Rotrosen J, Rubinstein M. The prevalence of tardive dyskinesia. J Clin Psychopharmacol 11:34–42, 1991.
18. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. Curr Opin Psychiatry 21:151–156, 2008.
19. Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. Arch Gen Psychiatry 39:473–481, 1982.
20. Chong SA, Tan EC, Tan CH, Mythily. Smoking and tardive dyskinesia: lack of involvement of the CYP1A2 gene. J Psychiatry Neurosci 28: 185–189, 2003.
21. Yassa R, Lal S, Korpassy A, Ally J. Nicotine exposure and tardive dyskinesia. Biol Psychiatry 22:67–72, 1987.
22. Sacco KA, Termine A, Seyal A, Dudas MM, Vessicchio JC, Krishnan-Sarin S, Jatlow PI, Wexler BE, George TP. Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. Arch Gen Psychiatry 62:649–659, 2005.
23. Muller DJ, Schulze TG, Knapp M, Held T, Krauss H, Weber T, Ahle G, Maroldt A, Alfter D, Maier W, Nothen MM, Rietschel M. Familial occurrence of tardive dyskinesia. Acta Psychiatr Scand 104:375–379, 2001.
24. Bakker PR, van Harten PN, van OJ. Antipsychotic-induced tardive dyskinesia and the Ser9Gly polymorphism in the DRD3 gene: a meta analysis. Schizophr Res 83:185–192, 2006.
25. Lerer B, Segman RH, Fangerau H, Daly AK, Basile VS, Cavallaro R, Aschauer HN, McCreadie RG, Ohlraun S, Ferrier N, Masellis M, Verga M, Scharfetter J, Rietschel M, Lovlie R, Levy UH, Meltzer HY, Kennedy JL, Steen VM, Macciardi F. Pharmacogenetics of tardive dyskinesia: combined analysis of 780 patients supports association with dopamine D3 receptor gene Ser9Gly polymorphism. Neuropsychopharmacology 27:105–119, 2002.
26. Patsopoulos NA, Ntzani EE, Zintzaras E, Ioannidis JP. CYP2D6 polymorphisms and the risk of tardive dyskinesia in schizophrenia: a meta-analysis. Pharmacogenet Genomics 15:151–158, 2005.
27. Lerer B, Segman RH, Tan EC, Basile VS, Cavallaro R, Aschauer HN, Strous R, Chong SA, Heresco-Levy U, Verga M, Scharfetter J, Meltzer HY, Kennedy JL, Macciardi F. 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. Int J Neuropsychopharmacol 8:411–425, 2005.
28. Bakker PR, van Harten PN, van OJ. Antipsychotic-induced tardive dyskinesia and polymorphic variations in COMT, DRD2, CYP1A2 and MnSOD genes: a meta-analysis of pharmacogenetic interactions. Mol Psychiatry 13:544–556, 2008.
29. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. Curr Opin Psychiatry 21:151–156, 2008.
30. Fenton WS. Prevalence of spontaneous dyskinesia in schizophrenia. J Clin Psychiatry 61 Suppl 4:10–14, 2000.
31. Lieberman JA, Yunis J, Egea E, Canoso RT, Kane JM, Yunis EJ. HLA-B38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. Arch Gen Psychiatry 47:945–948, 1990.
32. Meltzer HY, Matsubara S, Lee JC. The ratios of serotonin2 and dopamine2 affinities differentiate atypical and typical antipsychotic drugs. Psychopharmacol Bull 25:390–392, 1989.
33. Tecott LH, Sun LM, Akana SF, Strack AM, Lowenstein DH, Dallman MF, Julius D. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. Nature 374:542–546, 1995.
34. Ellingrod VL, Perry PJ, Ringold JC, Lund BC, Bever-Stille K, Fleming F, Holman TL, Miller D. Weight gain associated with the –759C/T polymorphism of the 5HT2C receptor and olanzapine. Am J Med Genet B Neuropsychiatr Genet 134:76–78, 2005.
35. De Lucca V, Mueller DJ, de BA, Kennedy JL. Association of the HTR2C gene and antipsychotic induced weight gain: a meta-analysis. Int J Neuropsychopharmacol 10:697–704, 2007.
36. Park YM, Cho JH, Kang SG, Choi JE, Lee SH, Kim L, Lee HJ. Lack of association between the –759C/T polymorphism of the 5-HT2C receptor gene and olanzapine-induced weight gain among Korean schizophrenic patients. J Clin Pharm Ther 33:55–60, 2008.
37. Ellingrod VL, Miller D, Schultz SK, Wehring H, Arndt S. CYP2D6 polymorphisms and atypical antipsychotic weight gain. Psychiatr Genet 12:55–58, 2002.
38. Muller DJ, Klempan TA, De Lucca V, Sicard T, Volavka J, Czobor P, Sheitman BB, Lindenmayer JP, Citrome L, McEvoy JP, Lieberman JA, Honer WG, Kennedy JL. The SNAP-25 gene may be associated with clinical response and weight gain in antipsychotic treatment of schizophrenia. Neurosci Lett 379:81–89, 2005.
39. Bishop JR, Ellingrod VL, Moline J, Miller D. 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 12:BR47–BR50, 2006.
40. Park YM, Chung YC, Lee SH, Lee KJ, Kim H, Byun YC, Lim SW, Paik JW, Lee HJ. Weight gain associated with the alpha2a-adrenergic receptor –1,291 C/G polymorphism and olanzapine treatment. Am J Med Genet B Neuropsychiatr Genet 141:394–397, 2006.
41. Ellingrod VL, Bishop JR, Moline J, Lin, YC, Miller del D. Leptin and leptin receptor gene polymorphisms and increases in body mass index (BMI) from olanzapine treatment in persons with schizophrenia. Psychopharmacol Bull 40:57–62, 2007.
42. Claghorn J, Honigfeld G, Abuzzahab FS Sr, Wang R, Steinbook R, Tuason V, Klerman G. The risks and benefits of clozapine versus chlorpromazine. J Clin Psychopharmacol 7:377–384, 1987.
43. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796, 1988.

44. Rosenheck R, Cramer J, Xu W, Thomas J, Henderson W, Frisman L, Fye C, Charney D. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. N Engl J Med 337:809–815, 1997.
45. Volavka J, Czobor P, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, Cooper TB, Chakos M, Lieberman JA. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. Am J Psychiatry 159:255–262, 2002.
46. Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. J Clin Psychiatry 59 Suppl 3:3–7, 1998.
47. Pisciotta AV, Konings SA, Ciesemier LL, Cronkite CE, Lieberman JA. Cytotoxic activity in serum of patients with clozapine-induced agranulocytosis. J Lab Clin Med 119:254–266, 1992.
48. Pisciotta AV, Konings SA, Ciesemier LL, Cronkite CE, Lieberman JA. On the possible mechanisms and predictability of clozapine-induced agranulocytosis. Drug Saf 7 Suppl 1:33–44, 1992.
49. Dettling M, Cascorbi I, Opgen-Rhein C, Schaub R. Clozapine-induced agranulocytosis in schizophrenic Caucasians: confirming clues for associations with human leukocyte class I and II antigens. Pharmacogenomics J 7:325–332, 2007.
50. Lopez-Garcia P, Teresa RJ, De CP, Landecho I, Zapata R. Association between clozapine-induced agranulocytosis and HLA subtyping. J Clin Psychiatry 67:1652–1653, 2006.
51. Demyttenaere K, Mesters P, Boulanger B, Dewe W, Delsemme MH, Gregoire J, Van GE. Adherence to treatment regimen in depressed patients treated with amitriptyline or fluoxetine. J Affect Disord 65: 243–252, 2001.
52. Page ME, Cryan JF, Sullivan A, Dalvi A, Saucy B, Manning DR, Lucki I. Behavioral and neurochemical effects of 5-(4-[4-(5-Cyano-3-indolyl)-butyl)-butyl]-1-piperazinyl)-benzofuran-2-carb oxamide (EMD 68843): a combined selective inhibitor of serotonin reuptake and 5-hydroxytryptamine(1A) receptor partial agonist. J Pharmacol Exp Ther 302:1220–1227, 2002.