



# Candidate Gene Studies of Antipsychotic Drug Efficacy and Drug-Induced Weight Gain

ANIL K. MALHOTRA\*

Department of Psychiatry Research, Albert Einstein College of Medicine, Zucker Hillside Hospital, 57-59 263rd Street, Glen Oaks, NY 11004, USA. Malhotra@lij.edu

(Received 16 December 2003; Revised 16 February 2004; In final form 16 February 2004)

**Converging data suggest that the identification of the molecular variants that influence antipsychotic drug response may soon be feasible. For the most part, these studies have focused on the new atypical antipsychotic agents, particularly clozapine. Although initial data in this regard has been inconclusive, recent studies have suggested that variation in the gene that codes for the dopamine D<sub>2</sub> receptor (DRD2) may significantly influence the clinical efficacy of a number of typical and atypical antipsychotic drugs, perhaps via a variant that influences messenger RNA (mRNA) stability and translation. Studies of antipsychotic-induced weight gain have been more consistent than studies of antipsychotic drug efficacy, perhaps because weight dysregulation represents a more powerful phenotype for genetic studies, with a specific single nucleotide polymorphism (SNP) in the 5-hydroxytryptamine 2C (5-HT<sub>2C</sub>) receptor being associated with weight gain across diverse samples. Larger, more comprehensive studies are needed to confirm these results, but taken together, they suggest that pharmacogenetic strategies may be critical towards gaining a more precise understanding of the mechanism of action of antipsychotic drugs in the treatment of schizophrenia.**

*Keywords:* Pharmacogenetics; Schizophrenia; Gene; Antipsychotic; Polymorphism; Weight

## INTRODUCTION

The variation in individual clinical response to antipsychotic drug treatment remains a critical problem in the management of schizophrenia. Although a minority of patients may experience complete symptom remission,

a large proportion of patients continue to experience significant psychiatric symptoms (Kane, 1999). Moreover, psychotropic drug efficacy may not occur until weeks after initiation of drug treatment (Conley *et al.*, 1997), and thus the time period before a clinician can determine whether a specific treatment is ineffective and consider alternative pharmacotherapy can be lengthy. During this period, treated patients may experience continuous psychiatric symptoms, employment loss, social dysfunction, medical morbidity and, in the worst case, commit suicide (Kaplan and Sadock, 1994).

Pharmacogenetic approaches provide a novel methodology to dissect the heterogeneity of psychotropic drug response. Pharmacogenetics provides a number of distinct advantages in the search for informative correlates of psychotropic drug response. First, an individual subject's genotype is essentially invariable, and thus collection of the independent measure for analysis versus treatment response can be collected at any time during treatment (or thereafter) and remain unaffected by the treatment itself (Strachan and Read, 1996). Second, current molecular biological techniques provide an accurate assessment of an individual's genotype (Ranade *et al.*, 2001), and measurement error plays little or no role in these analyses. Third, the amount of publicly available genomic information (Lander *et al.*, 2001) now provides the necessary data to conduct comprehensive studies of individual genes and, perhaps, investigations of entire genomes.

## HERITABILITY OF ANTIPSYCHOTIC DRUG RESPONSE

There is limited data on the heritability of antipsychotic drug response. One line of evidence that suggests

\*Corresponding author. Tel.: +1 718 470-8012; Fax: +1 718 343-1659; Email: Malhotra@lij.edu

that genetic factors play a role is derived from studies of treatment response across different ethnic groups. A recent study incorporating data from randomized clinical trials found that black patients displayed greater acute (6 weeks) response to treatment with atypical and typical antipsychotic agents than white patients of European descent (Emsley *et al.*, 2002). In this study, however, there were significant differences in baseline symptoms between groups and no control for potential differences in nutritional status and body mass. Moreover, underlying cultural bias in the treatment and assessment of disparate ethnic groups may play a role in apparent treatment response variation (Kuno and Rothbard, 2002). Other data on heritability of antipsychotic drugs is limited to a study of 28 schizophrenia sibling pairs that found no more concordance for typical antipsychotic agent response than predicted by chance (DeLisi and Dauphinais, 1989) and a single case report (Vojvoda *et al.*, 1996) of a monozygotic twin pair with schizophrenia concordant for clozapine response despite prior non-response to typical antipsychotic agents.

Concordance in twins for behavioral response to a dopamine receptor agonist has been observed. Nurnberger and colleagues (1982) administered 0.3 mg/kg of the dopaminomimetic, dextroamphetamine (DA) to healthy volunteer twin pairs and found that DA-induced alterations in behavioral excitation as well as changes in plasma growth hormone and prolactin levels were highly correlated in 12 MZ twins but not in 3 DZ twin pairs. These results were not accounted for by correlation of plasma amphetamine levels. The small sample of DZ twins was not sufficient to conduct accurate heritability estimates but further research utilizing acute pharmacologic "challenge" paradigms (Malhotra *et al.*, 1998) may be useful to assess heritability of drug responses if appropriate safeguards are in place.

## PHARMACOGENETICS OF ANTIPSYCHOTIC DRUG RESPONSE

Pharmacogenetic studies of antipsychotic drug response have focused on the atypical antipsychotic drug clozapine. The initial clozapine studies were conducted either in the context of clinical trials of clozapine (Malhotra *et al.*, 1996a,b) or were based upon retrospective analyses of clozapine-treated patients (Arranz *et al.*, 1995; Sodhi *et al.*, 1995; Nimgaonkar *et al.*, 1996; Shaikh *et al.*, 1996), in ethnically heterogeneous study groups derived from Western countries

including the U.K, Germany, and the U.S.A.

Clozapine pharmacogenetic studies have primarily included genetic loci within the dopamine and serotonin receptor systems - obvious candidates because of the high affinity of clozapine for these receptor subtypes. Arranz and colleagues (1995) initially attracted interest in the 5-HT<sub>2A</sub> T102C polymorphism with a report of a significant ( $p = 0.02$ ) association between the 102C allele and failure to respond to clozapine in a cohort of 149 chronic schizophrenia patients retrospectively assessed with the Global Assessment Scale (GAS). These data were not replicated in a series of smaller clozapine studies from independent laboratories (Nothen *et al.*, 1995; Malhotra *et al.*, 1996a; Masellis *et al.*, 1998; Lin *et al.*, 1999), as well as in a study that included typical antipsychotic agents (Nimgaonkar *et al.*, 1996). 5-HT<sub>2A</sub> T102C could be considered a relatively weak candidate polymorphism because it does not result in an amino acid substitution at the protein level, and there is little evidence that it produces significant functional effects on 5-HT<sub>2A</sub> receptor function (Burnet and Harrison, 1995). A less common polymorphism within the 5-HT<sub>2A</sub> gene, His452Tyr, which was not found to be in significant linkage disequilibrium (non-random population association) with T102C (Malhotra *et al.*, 1996a), does appear to produce functional effects *in vitro*, however, it has not consistently been found to be associated with clozapine response (Nothen *et al.*, 1995; Malhotra *et al.*, 1996a). Finally, a recent study of 5-HT<sub>2A</sub> T102C and antipsychotic response to the atypical agent, risperidone, in 100 Han Chinese schizophrenia patients also identified an association, but in this case the association was in the opposite direction than previously observed in primarily Caucasian study groups (Lane *et al.*, 2002). Definitive studies with larger sample sizes, prospective clinical data, and comprehensive examination of the gene will be needed to further address the role of this gene in antipsychotic drug response.

Other serotonin-related genes that have been studied in pharmacogenetic studies of clozapine include the 5-HT<sub>2C</sub> (Sodhi *et al.*, 1995; Malhotra *et al.*, 1996b; Reitschel *et al.*, 1997; Masellis *et al.*, 1998), 5-HT<sub>6</sub> (Yu *et al.*, 1999), 5-HT<sub>7</sub> (Masellis *et al.*, 2001) as well as the serotonin transporter (*SLC6A4*) gene (Arranz *et al.*, 2000a; Tsai *et al.*, 2000). Although there have been some positive reports of association, there is little current evidence to suggest that variation within these genes significantly influences clozapine's efficacy.

In addition to significant affinities for serotonin receptor subtypes, clozapine is also a dopamine recep-

tor antagonist. Initial pharmacogenetic studies focused on the relationship between the dopamine D<sub>4</sub> receptor gene (*DRD4*) and clozapine response (Rao *et al.*, 1994; Shaikh *et al.*, 1995). *DRD4* was an attractive candidate gene because of clozapine's affinity for the D<sub>4</sub> receptor (Van Tol *et al.*, 1992) and the identification of a common variable number of tandem repeat (VNTR) polymorphism within the putative third cytoplasmic loop of the receptor with significant effects on the binding affinity of the receptor for clozapine (Van Tol *et al.*, 1992). Most groups, however, have been unable to detect a significant association between this variant and clozapine response (Rao *et al.*, 1994; Shaikh *et al.*, 1995; Reitschel *et al.*, 1996; Kohn *et al.*, 1997). Ozdemir and colleagues (1999) have reported an association between a repeat polymorphism within the first intron of *DRD4* in a preliminary study of 50 patients - however, correction for multiple testing could alter the significance of these results.

Another obvious candidate for pharmacogenetic studies of antipsychotic drug response is the dopamine D<sub>2</sub> receptor gene (*DRD2*). To date, all known antipsychotic drugs have potent affinities for the dopamine D<sub>2</sub> receptor (Creese *et al.*, 1976; Seeman 1992), and functional brain imaging studies have suggested that dopamine D<sub>2</sub> receptor binding by antipsychotic agents may be "necessary and sufficient" for antipsychotic efficacy (Kapur and Seeman, 2001). However, there are few common polymorphisms within the coding regions of *DRD2* (Gejman *et al.*, 1994), and thus fewer studies of *DRD2* and antipsychotic drug response have been conducted as compared with the 5-HT system.

Recently, two preliminary studies have reported evidence that genetic variation within *DRD2* is associated with antipsychotic response (Malhotra *et al.*, 1999; Suzuki *et al.*, 2000). Moreover, Shafer and colleagues (2001) examined the relationship between haloperidol, an antipsychotic drug with greater D<sub>2</sub> affinity than clozapine, and the *DRD2* Taq1A polymorphism and found that subjects with the A2/A2 genotype displayed poorer clinical response than heterozygous patients (no A1/A1 homozygotes were obtained). The distinction between genotypic groups was evident at two weeks of treatment, with 63% of heterozygous subjects meeting response criteria versus 29% of subjects with the A2/A2 genotype. Consistent with these results, recently reported preliminary data has suggested a relationship between the Taq1 A2/A2 genotype and failure to respond to risperidone (Mata *et al.*, 2002), another agent with greater D<sub>2</sub> affinity than clozapine. Finally, Suzuki and colleagues (Suzuki *et al.*, 2001) have

reported a trend for an association between *DRD2* and response to the typical antipsychotic agents, bromperidol and nemonapride. Therefore, many, though not all (Arranz *et al.*, 1998), studies suggest that variation within *DRD2* may significantly influence antipsychotic drug response, particularly with agents with higher affinities for the D<sub>2</sub> receptor. Of note, recent data suggest that both the Taq1A polymorphism and the -141C Ins/Del variant are in linkage disequilibrium with a silent substitution, C957T, that appears to have functional consequences on mRNA stability and dopamine-induced up-regulation of *DRD2* gene expression (Duan *et al.*, 2003), and thus this variant needs to be further assessed in pharmacogenetics studies of *DRD2*.

Finally, examination of multiple genes, and multiple SNPs, in order to identify sensitive and specific "predictor profiles" may be useful. A retrospective analysis of 19 polymorphisms located within genes that code for clozapine targets identified a grouping of 6 variants that provided 76.7% success in predicting clozapine response (Arranz *et al.*, 2000b). As these data have not yet been replicated (Schumacher *et al.*, 2000), it will be critical to conduct prospective studies of this profile before these data can be considered to provide potential clinical utility. Nevertheless, studies that begin to dissect the complex interactions between genetic loci and their effect on clinical phenotypes are likely to be necessary for a greater understanding of the genetic contribution to antipsychotic drug response.

## PHARMACOGENETIC STUDIES OF WEIGHT GAIN

Another phenotype that has attracted interest in pharmacogenetics is antipsychotic-induced weight gain. Several lines of evidence suggest that antipsychotic drug-induced weight gain may represent a powerful phenotype for molecular genetic studies. First, in contrast to clinical symptom ratings, weight gain can be defined more precisely with greater accuracy and reliability. Moreover, related phenotypic measures may be even less likely to be influenced by extrinsic factors unrelated to weight gain and thus provide more statistical power for genetic studies (Comuzzie and Allison 1998). These include assessment of body mass index (BMI) and total fat mass, which can be measured reliably and inexpensively in large samples, as well as other biological correlates of weight gain such as fasting glucose levels, insulin levels and circulating levels of key neuropeptides such as leptin, adiponectin and/or ghrelin. These measures also offer the advantage of

being readily amenable to quantitative trait analyses and thus may be more informative than the arbitrary responder/non-responder criteria commonly used in previous pharmacogenetic studies.

Another factor that suggests weight gain may be a more robust phenotype for pharmacogenetic studies is the large body of evidence on the heritability of weight regulation. Twin, adoption and family studies demonstrate that an individual's risk for obesity is significantly increased if he or she has relatives who are obese (Comuzzie and Allison, 1998). Moreover, 40-70% of the variation in obesity-related phenotypes such as BMI, skin fold thickness, fat mass, and leptin levels is accounted for by genetic factors (Allison *et al.*, 1996). Of note, segregation analyses suggest that there may be several genes that exert relatively large effects, with reports of major genes accounting for as high as 40% of the variation in BMI (Lee *et al.* 1997) and fat mass (Comuzzie *et al.*, 1995). Finally, animals in which single genes are knocked out have been demonstrated to exhibit marked alterations in eating behavior and obesity (Tecott *et al.*, 1995) - indicating that these genes may play critical roles in weight regulation. Taken together, these data suggest that the heritability of weight regulation is relatively high, and thus weight change may represent a more robust phenotype for pharmacogenetic studies than symptom response, for which little to no heritability data exist.

Early pharmacogenetic studies of weight gain have focused on the relationship between a promoter region polymorphism, -759 T/C, in the 5-hydroxytryptamine 2C receptor (5-HT<sub>2C</sub>) gene and antipsychotic-induced weight gain. Reynolds and colleagues (2002) studied 123 drug-naïve Han Chinese schizophrenia patients and reported that this variant significantly influenced weight gain following antipsychotic drug treatment. Subjects with the T allele at this locus gained significantly less weight than subjects with the C allele at 6 weeks ( $p < 0.0001$ ) and at ten weeks ( $p = 0.0003$ ) of treatment. This effect was observed in patients on risperidone ( $n = 46$ ) or chlorpromazine ( $n = 69$ ), in males ( $n = 61$ ) and in females ( $n = 62$ ), and with exclusion of subjects who were either underweight or obese at baseline. None of the 27 subjects with the T allele met criteria for severe weight gain (>7% increase from baseline body weight) after six weeks of treatment, as compared to 28% of the 96 subjects without the T allele. Reynolds *et al.* (2003) extended this work and reported an association between -759 T/C and weight gain in a smaller group of clozapine-treated patients, although this effect was only significant in males (Reynolds *et al.*, 2003). In contrast, two smaller studies

were unable to detect an association between 5-HT<sub>2C</sub> -759 T/C and clozapine-induced weight gain (Basile *et al.*, 2002; Tsai *et al.*, 2002). However, these studies were restricted to chronic patients with far more extensive prior antipsychotic drug treatment histories. More data with larger data sets derived from more ethnically heterogeneous populations (at least as compared to the Han Chinese subjects used by Reynolds and colleagues) are needed to confirm the role of this variant in antipsychotic drug-induced weight gain.

## CONCLUSIONS

Converging data suggest that the identification of molecular variants that influence antipsychotic drug response may soon be feasible. Several studies have suggested that variation in the dopamine D<sub>2</sub> receptor may influence clinical efficacy of antipsychotic drugs, perhaps via a variant that influences mRNA stability and translation. Moreover, variation in the 5-HT<sub>2C</sub> receptor has recently been demonstrated to influence antipsychotic-induced weight gain. Larger, more comprehensive studies are needed to confirm these results but taken together; they suggest that pharmacogenetic strategies may be critical towards gaining a more precise understanding of the mechanism of action of antipsychotic drugs in the treatment of schizophrenia.

## References

- Allison DB, J Kaprio, M Korkeila, M Koskenvuo, MC Neale and K Hayakawa (1996) The heritability of body mass index among an international sample of monozygotic twins reared apart. *Int. J. Obes. Relat. Metab. Disord.* **20**, 501-506.
- Arranz M, D Collier, M Sodhi, D Ball, G Roberts, J Price, P Sham and R Kerwin (1995) Association between clozapine response and allelic variation in 5-HT<sub>2A</sub> receptor gene. *Lancet* **346**, 281-282.
- Arranz MJ, T Li, J Munro, X Liu, R Murray, DA Collier and RW Kerwin (1998) Lack of association between a polymorphism in the promoter region of the dopamine-2 receptor gene and clozapine response. *Pharmacogenetics* **8**, 481-484.
- Arranz MJ, AA Bolonna, J Munro, CJ Curtis, DA Collier and RW Kerwin (2000a) The serotonin transporter and clozapine response. *Mol. Psychiatry* **5**, 124-125.
- Arranz MJ, J Munro, J Birkett, A Bolonna, D Mancama, M Sodhi, KP Lesch, JF Meyer, PSham, DA Collier, RM Murray and RW Kerwin (2000b) Pharmacogenetic prediction of clozapine response. *Lancet* **355**, 1615-1616.
- Basile VS, M Masellis, V De Luca, HY Meltzer and JL Kennedy (2002) 759C/T genetic variation of 5HT(2C) receptor and clozapine-induced weight gain. *Lancet* **360**, 1790-1791.
- Burnet PW and PJ Harrison (1995) Genetic variation of the 5-HT<sub>2A</sub> receptor and response to clozapine. *Lancet* **346**, 909.

- Commuzzie AG and DB Allison (1998) The search for human obesity genes. *Science* **280**, 1374-1377.
- Comuzzie AG, J Blangero, MC Mahaney, BD Mitchell, JE Hixson, PB Samollow, MP Stern and JW MacCluer (1995) Major gene with sex-specific effects influences fat mass in Mexican Americans. *Genet. Epidemiol.* **12**, 475-488.
- Conley RR, WT Carpenter Jr and CA Tamminga (1997) Time to clozapine response in a standardized trial. *Am. J. Psychiatry* **154**, 1243-1247.
- Creese I, DR Burt and SH Snyder (1976) Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* **192**, 481-483.
- DeLisi LE and D Dauphinais (1989) Neuroleptic responsiveness in siblings concordant for schizophrenia. *Arch. Gen. Psychiatry* **46**, 477.
- Duan J, MS Wainwright, JM Cameron, N Saitou, AR Sanders, J Gelernter and PV Gefman (2003) Synonymous mutations in the human dopamine receptor D<sub>2</sub> (DRD2) affect mRNA stability and synthesis of the receptor. *Hum. Mol. Genet.* **12**, 205-216.
- Emsley RA, MC Roberts, S Rataemane, J Pretorius, PP Oosthuizen, J Turner, DJ Niehaus, N Keyter and DJ Stein (2002) Ethnicity and treatment response in schizophrenia, a comparison of 3 ethnic groups. *J. Clin. Psychiatry* **63**, 9-14.
- Gejman PV, A Ram, J Gelernter, E Friedman, Q Cao, D Pickar, K Blum, EP Noble, HR Kranzler and S O'Malley (1994) No structural mutation in the dopamine D<sub>2</sub> receptor gene in alcoholism or schizophrenia. Analysis using denaturing gradient gel electrophoresis. *JAMA* **271**, 204-208.
- Kane JM (1999) Pharmacological treatment of schizophrenia. *Biol. Psychiatry* **46**, 1396-1408.
- Kaplan HI and BJ Sadock (1994) *Kaplan and Sadock's Synopsis of Psychiatry, Behavioral Sciences Clinical Psychiatry*, 7th Edition (Williams & Wilkins, Baltimore, MD).
- Kapur S and P Seeman (2001) Does fast dissociation from the dopamine D<sub>2</sub> receptor explain the action of atypical antipsychotics? A new hypothesis. *Am. J. Psychiatry* **158**, 360-369.
- Kohn Y, RP Ebstein, U Heresco-Levy, B Shapira, L Nemanov, I Gritsenko, M Avnon and B Lerer (1997) Dopamine D<sub>4</sub> receptor gene polymorphisms, relation to ethnicity, no association with schizophrenia and response to clozapine in Israeli subjects. *Eur. Neuropsychopharmacol.* **1**, 39-43.
- Kuno E and AB Rothbard (2002) Racial disparities in antipsychotic prescription patterns for patients with schizophrenia. *Am. J. Psychiatry* **159**, 567-572.
- Lander ES, LM Linton, B Birren, C Nusbaum, MC Zody, J Baldwin, K Devon, K Dewar, M Doyle, W FitzHugh *et al.* (2001) Initial sequencing and analysis of the human genome. *Nature* **409**, 860-921.
- Lane HY, YC Chang, CC Chiu, ML Chen, MH Hsieh and WH Chang (2002) Association of risperidone treatment response with a polymorphism in the 5-HT<sub>2A</sub> receptor gene. *Am. J. Psychiatry* **159**, 1593-1595.
- Lee JH, DR Reed and RA Price (1997) Familial risk ratios for extreme obesity, implications for mapping human obesity genes. *Int. J. Obes. Relat. Metab. Disord.* **21**, 935-940.
- Lin CH, SJ Tsai, YW Yu, HL Song, PC Tu, CB Sim, CP Hsu, KH Yang and CJ Hong (1999) No evidence for association of serotonin-2A receptor variant (102T/C) with schizophrenia or clozapine response in a Chinese population. *NeuroReport* **10**, 57-60.
- Malhotra AK, D Goldman, N Ozaki, A Breier, R Buchanan and D Pickar (1996a) Lack of association between polymorphisms in the 5-HT<sub>2A</sub> receptor gene and the antipsychotic response to clozapine. *Am. J. Psychiatry* **153**, 1092-1094.
- Malhotra AK, D Goldman, N Ozaki, W Rooney, A Clifton, RW Buchanan, A Breier and D Pickar (1996b) Clozapine response and the 5HT<sub>2C</sub> Cys23Ser polymorphism. *NeuroReport* **7**, 2100-2102.
- Malhotra AK, A Breier, D Goldman, L Picken and D Pickar (1998) The apolipoprotein E E4 allele is associated with blunting of ketamine-induced psychosis in schizophrenia. *Neuropsychopharmacology* **19**, 445-448.
- Malhotra AK, RW Buchanan, S Kim, L Kestler, A Breier, D Pickar and D Goldman (1999) Allelic variation in the promoter region of the dopamine D<sub>2</sub> receptor gene and clozapine response. *Schizophr. Res.* **36**, 92-93.
- Masellis M, V Basile, HY Meltzer, JA Lieberman, S Sevy, FM Macciardi, P Cola, A Howard, F Badri, MM Nothen, W Kalow and JL Kennedy (1998) Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. *Neuropsychopharmacology* **19**, 123-132.
- Masellis M, VS Basile, HY Meltzer, JA Lieberman, S Sevy, DA Goldman, MW Hamblin, FM Macciardi and JL Kennedy (2001) Lack of association between the T C 267 serotonin 5-HT<sub>6</sub> receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. *Schizophr. Res.* **47**, 49-58.
- Mata I, MJ Arranz, T Lai, D Mancama, J Arrondo, M Beperet, R Villavicencio, J Munro, S Osborne and RW Kerwin (2002) The serotonergic system influences individual's response to risperidone. *Am. J. Med. Genetics* **114**, 728.
- Nimgaonkar VL, XR Zhang, JS Brar, M DeLeo and R Ganguli (1996) 5-HT<sub>2</sub> receptor gene locus, association with schizophrenia or treatment response not detected. *Psychiatr. Genet.* **6**, 23-27.
- Nothen MM, M Rietschel, J Erdmann, H Oberlander, HJ Moller, D Nöber and P Propping (1995) Genetic variation of the 5-HT<sub>2A</sub> receptor and response to clozapine. *Lancet* **346**, 908-909.
- Nurnberger Jr, ES Gershon, S Simmons, M Ebert, LR Kessler, ED Dibble, SS Jimerson, GM Brown, P Gold, DC Jimerson, GM Brown, P Gold, DC Jimerson, JJ Guroff and FI Storch (1982) Behavioral, biochemical and neuroendocrine responses to amphetamine in normal twins and "well state" bipolar patients. *Psychoneuroendocrinology* **7**, 163-176.
- Ozdemir V, M Masellis, VS Basile, W Kalow, HY Meltzer, JA Lieberman and JL Kennedy (1999) Variability in response to clozapine, potential role of cytochrome P450 1A2 and the dopamine D<sub>4</sub> receptor gene. *CNS Spectrums* **4**, 30-56.
- Ranade K, MS Chang, CT Ting, D Pei, CF Hsiao, M Olivier, R Pesich, J Herbert, YD Chen, VJ Dzau, D Curb, R Olshen, N Risch, DR Cox and D Botstein (2001) High-throughput genotyping with single nucleotide polymorphisms. *Genome Res.* **11**, 1262-1268.
- Rao PA, D Pickar, PV Gejman, A Ram, ES Gershon and J Gelernter (1994) Allelic variation in the D<sub>4</sub> dopamine receptor (DRD4) gene does not predict response to clozapine. *Arch. Gen. Psychiatry* **51**, 912-917.
- Reitschel M, D Naber, H Oberlander, R Holzbach, R Fimmers, K Eggermann, HJ Moller, P Propping and MM Nothen (1996) Efficacy and side-effects of clozapine, testing for association with allelic variation in the dopamine D<sub>4</sub> receptor gene. *Neuropsychopharmacology* **15**, 491-496.
- Reitschel M, D Naber, R Fimmers, HJ Moller, P Propping and MM Nothen (1997) Efficacy and side-effects of clozapine not associated with variation in the 5-HT<sub>2C</sub> receptor. *NeuroReport* **8**, 1999-2003.
- Reynolds GP, ZJ Zhang and XB Zhang (2002) Association of antipsychotic drug-induced weight gain with a 5-HT<sub>2C</sub> receptor

- gene polymorphism. *Lancet* **359**, 2086-2087.
- Reynolds GP, Z Zhang and X Zhang (2003) Polymorphism of the promoter region of the serotonin 5-HT<sub>2C</sub> receptor gene and clozapine-induced weight gain. *Am. J. Psychiatry* **160**, 677-679.
- Schumacher J, TG Schulze, TF Wienker, M Rietschel and MM Nothen (2000) Pharmacogenetics of the clozapine response. *Lancet* **356**, 506-507.
- Seeman P (1992) Dopamine receptor sequences. Therapeutic levels of neuroleptics occupy D<sub>2</sub> receptors, clozapine occupies D<sub>4</sub>. *Neuropsychopharmacology* **7**, 261-284.
- Shafer M, D Rujescu, I Giegling, A Gunterman, A Erfurth, B Bondy and H Moller (2001) Association of short-term response to haloperidol treatment with a polymorphism in the dopamine D<sub>2</sub> receptor gene. *Am. J. Psychiatry* **158**, 802-804.
- Shaikh S, DA Collier, P Sham, L Pilowsky, T Sharma, LK Lin, MA Crocq, M Gill and R Kerwin (1995) Analysis of clozapine response and polymorphisms of the dopamine D<sub>4</sub> receptor gene (DRD4) in schizophrenic patients. *Am. J. Med. Genet.* **60**, 541-550.
- Shaikh S, DA Collier, PC Sham, D Ball, K Aitchison, H Vallada, I Smith, M Gill and RW Kerwin (1996) Allelic association between a Ser-9-Gly polymorphism in the dopamine D<sub>3</sub> receptor gene and schizophrenia. *Hum. Genet.* **97**, 714-719.
- Sodhi MS, MJ Arranz, D Curtis, DM Ball, P Sham, GW Roberts, J Price, DA Collier and RW Kerwin (1995) Association between clozapine response and allelic variation in the 5-HT<sub>2C</sub> receptor gene. *NeuroReport* **7**, 169-172.
- Strachan T and AP Read (1996) Mutation and instability of human DNA. *Hum. Mol. Genet.* **10**, 241-273.
- Suzuki A, K Mihara, T Kondo, O Tanaka, U Nagashima, K Otani and S Kaneko (2000) The relationship between dopamine D<sub>2</sub> receptor polymorphism at the Taq1 A locus and therapeutic response to nemonapride, a selective dopamine antagonist, in schizophrenic patients. *Pharmacogenetics* **10**, 335-341.
- Suzuki A, T Kondo, K Mihara, N Yasui-Furukori, M Ishida, H Furukori, S Kaneko, Y Inoue and K Otani (2001) The -141C Ins/Del polymorphism in the dopamine D<sub>2</sub> receptor gene promoter region is associated with anxiolytic and antidepressive effects during treatment with dopamine antagonists in schizophrenic patients. *Pharmacogenetics* **11**, 545-550.
- Tecott LH, LM Sun, SF Akana, AM Strack, DH Lowenstein, MF Dallman and D Julius (1995) Eating disorder and epilepsy in mice lacking 5-HT<sub>2C</sub> serotonin receptors. *Nature* **374**, 542-546.
- Tsai SJ, CJ Hong, YW-Y Yu, C Lin, H Song, H Lai and K Yang (2000) Association study of a functional serotonin transporter gene polymorphism with schizophrenia, psychopathology and clozapine response. *Schizophr. Res.* **44**, 177-181.
- Tsai SJ, CJ Hong, YW Yu and CH Lin (2002) 759C/T genetic variation of 5HT<sub>2C</sub> receptor and clozapine-induced weight gain. *Lancet* **360**, 1790.
- Van Tol HH, CM Wu, HC Guan, K O'Hara, JR Bunzow, O Civelli, J Kennedy, P Seeman, HB Niznik and V Jovanovic (1992) Multiple dopamine D<sub>4</sub> receptor variants in the human population. *Nature* **358**, 149-152.
- Vojvoda D, K Grimmell, M Sernyak and CM Mazure (1996) Monozygotic twins concordant for response to clozapine. *Lancet* **347**, 61.
- Yu YW, SJ Tsai, CH Lin, CP Hsu, KH Yang and CJ Hong (1999) Serotonin-6 receptor variant (C267T) and clinical response to clozapine. *NeuroReport* **10**, 1231-1233.