Genomics and the future of pharmacotherapy in psychiatry

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Abstract
Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Preliminary evidence exists for a significant relationship between a promoter region polymorphism in the serotonin transporter gene and antidepressant response, as well as for associations between candidate neurotransmitter receptor genes and second generation antipsychotic drug response. More recent work in schizophrenia has focused on the use of first episode, antipsychotic naïve subjects, which may provide greater study power as suggested by studies examining dopamine receptor genetic variation and clinical response measures. An emerging body of literature suggests that pharmacogenetic strategies may be especially useful in the prediction of drug-induced adverse effects, in particular for the important side effect of antipsychotic-induced weight gain. New developments in genomics, including whole genome genotyping approaches and comprehensive information on genomic variation across populations, coupled with large-scale clinical trials in which DNA collection is routine, now provide the impetus for a next generation of pharmacogenetic studies. These increasingly comprehensive approaches should provide informative data on the genes associated with psychotropic drug response, a critical step towards the ultimate goal of 'personalized' medicine.

Introduction
Individual differences in clinical response to psychotropic drugs have long been recognized as a fundamental problem in the treatment of the seriously mentally ill patient (Kane, 1996). This variability in individual response ranges from patients who experience rapid symptom remission, to a subset of patients often described as 'treatment refractory' (Conley & Kelly, 2001; Leucht, Busch, Hamman, Kissling, & Kane, 2005); there is also marked variability in susceptibility to adverse drug effects and cognitive performance (itself a key predictor of community functioning; e.g. Green, Kern, Braff, & Mintz 2000; Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004). A priori identification of the patients who will respond well to a particular psychotropic drug, or be at a higher risk for development of adverse side effects, has the potential to help clinicians avoid lengthy ineffective medication trials and limit patients’ exposure to drug side effects. Moreover, enhanced predictability of treatment response early in the course of a patient’s illness may result in enhanced medication adherence, a significant predictor of relapse (Robinson et al., 1999).

For the last decade, pharmacogenetics has held out the promise of improved clinical prediction in psychiatry (as in other fields of medicine), with individualized treatment serving as the ultimate goal. Compared to other potential biological assays, genetic approaches to clinical prediction have the advantage of relative lack of burden to the research participant (compared to the invasiveness of lumbar puncture or the time required for brain imaging procedures). Moreover, even early genotyping techniques had relatively low measurement error. Most importantly, pharmacogenetics offers the possibility of insight into molecular mechanisms of drug action, providing guidance for the development of the next generation of antipsychotic medications.

In this paper, we will discuss the theoretical framework and key methods used in pharmacogenetics work, review the prior research in this area, and then
provide an overview of new developments in the field that may influence pharmacogenetics research going forward.

**Genetic factors and psychotropic drug response**

The fundamental hypothesis of pharmacogenetic research is that there are genetic factors that influence the inter-individual variability in psychotropic drug response. Although evidence for this assertion is somewhat limited by the paucity of data on the heritability of psychotropic drug response, primarily due to the difficulties in collecting drug response data from twin pairs discordant for zygosity or from siblings separated at birth, the data that exists does suggest a genetic component to clinical response.

Examples of potential heritability of antidepressant drug response are provided by Angst (1964) who reported that 38 of 41 first-degree relative pairs were concordant for response to the tricyclic antidepressant imipramine, and Pare, Rees and Sainsbury (1962), who found that both members of 12 relative pairs with similar antidepressant treatment had equivalent responses. A more recent study by Franchini, Serretti, Gasperini and Smeraldi (1998), reported that 67% of 45 first-degree relative pairs who were treated with the serotonin reuptake inhibitor fluvoxamine for at least 6 weeks were concordant for response, as compared to the 50% that would be expected by chance. These studies suggest that genetic factors may play a role in antidepressant drug response; however, it is also possible that shared environmental factors may bias relative pairs toward similar response patterns.

The heritability of antipsychotic drug response has been less studied, with a limited number of case reports indicating that monozygotic twin pairs have been observed to be concordant for response to the second generation antipsychotics olanzapine (Mata, Madoz, Arranz, Sham, & Murray, 2001) and clozapine (Vojvoda, Grimmell, Sernyak, & Mazure, 1996). Of note, antipsychotic-induced side effects have also been studied in monozygotic twin pairs, with some evidence for greater than expected concordance for antipsychotic-induced weight gain (Theisen et al., 2005; Wehmeier et al., 2005) as well as for the potentially fatal side effect of clozapine-induced agranulocytosis (Horacek, Libiger, Höschl, Borzová, & Hendrychová, 2001).

Although heritability studies provide evidence that genetic factors play a role in psychotropic drug response, they do not provide information on the specific genes that influence drug response.

To address this, recent research has focused on the identification of specific genes that influence psychotropic drug response.

**Candidate gene approaches to pharmacogenetics of psychotropic drug response**

For the most part, pharmacogenetic studies of psychotropic drug response have utilized a candidate gene approach. In this approach, sequence variants (often single nucleotide polymorphism or SNPs) within a specific gene are genotyped in a group of patients characterized for their drug response, and the data is examined for evidence of a significant relationship between a particular allele, or combination of alleles, and a clinical response parameter (Malhotra Murphy, & Kennedy, 2004). The most striking success with this approach has been studies examining the relationship of a polymorphism in the promoter region of the serotonin transporter gene, 5-HTTLPR, and response to serotonin reuptake inhibitor treatment. Several studies (Pollock et al., 2000; Smeraldi et al., 1998; Zanardi Benedetti, DiBella, Catalano, & Smeraldi, 2000) have reported that the long allele of this polymorphism is associated with better clinical response in Caucasian subjects, although the opposite relationship has been observed in Asian populations. These data are buttressed by the finding of a relationship of this polymorphism to susceptibility to depression, in the context of an interaction with stressful life events (Caspi et al., 2003). A more recent study with a large ($n=1380$) prospectively phenotyped cohort from the National Institute of Health-funded Sequenced Treatment Alternatives for Depression (STAR*D) trial have identified a polymorphism within the 5-HT2A receptor gene that is associated with response to the serotonin reuptake inhibitor, citalopram (McMahon et al., 2006). An important fact to note in this study is the large population examined, which allowed the investigators to pursue a split sample strategy with which to internally replicate results, in contrast to most prior studies of pharmacogenetics of antidepressant response.

Antipsychotic treatment pharmacogenetics have traditionally focused on the antipsychotic agent clozapine, with a flurry of studies in the mid 1990s, primarily investigating single SNPs within the genes coding for key neurotransmitter receptor subtypes in the serotonin and dopamine system (Malhotra et al., 2004), putative sites of clozapine’s action. The interest in clozapine was in part due to its demonstrated superior efficacy in treatment-resistant schizophrenia patients (Kane, Honigfeld, Singer, & Meltzer, 1988),...
as well as the ease of access to blood samples from clozapine treated patients, who required a weekly blood sample collection to minimize risk of the potential fatal side effect of drug-induced agranulocytosis. To date, however, the data from these studies has proved inconclusive and more recent attention has turned to the newer second generation antipsychotics.

Studies of the newer second generation agents have focused on olanzapine and risperidone; similar to the clozapine studies these have usually assessed a limited number of SNPs within single candidate genes; with similarly inconsistent results (Lane, Lee, Liu, & Chang, 2005). A potential important source of heterogeneity in these studies, as well as with the clozapine studies, has been the examination of primarily chronic schizophrenia patients with extensive, yet interindividually variable, prior treatment histories. This interindividual variation, which may be more environmental in nature, may further limit individual study power. Moreover, these studies often derive DNA samples in the context of clinical trials in which the majority of the study subjects have failed prior treatments. These studies may not include sufficient drug responders to detect response-relevant genes.

To offset this, several groups have focused their pharmacogenetic work in first episode schizophrenia patients with limited prior antipsychotic drug exposure. Reynolds, Yao, Zhang, Sun and Zhang (2005) assessed a unique cohort of 117 drug-naive Han Chinese schizophrenia patients who underwent 10 weeks of treatment with risperidone or chlorpromazine, and found that the DRD3 receptor polymorphism Ser9Gly was associated with positive symptom response, while the 5-HT2C receptor promoter region polymorphism –759T/C was associated with negative symptom response. A similar pattern of a specific influence on negative symptom response has also been recently reported in a cohort of drug-naive Spanish subjects, in this case, however, with a putatively functional promoter region polymorphism in the 5-HT-1A receptor gene (Reynolds, Arranz, Templeman, Fertuzinhos, & San, 2006). Finally, Mata and colleagues (2006) have reported that negative symptom improvement was associated with a repeat length polymorphism in the interleukin-1 receptor antagonist gene in a cohort of 154 first episode patients treated with haloperidol, risperidone or olanzapine. An important issue in the consideration of these data is the difficulty in reliably assessing negative symptoms, as well as potential correlations with neuromotor side effects and/or affective symptomatology.

Another potentially informative phenotype for pharmacogenetic analyses of first episode patients is the assessment of the time required to initial response, as the variation in this aspect of treatment response can be quite extensive. Lenz et al. (2006) examined a small cohort of first episode schizophrenia patients and observed a significant effect of two dopamine DRD2 receptor promoter region polymorphisms, –141C Ins/Del and A-241G, on time to clinical response to the second generation antipsychotic agents, olanzapine and risperidone, over the course of a 16-week trial. Of note, the -141C Del allele, which was associated with slower time to response and lower overall response rate in this study, had been previously linked with reduced in vitro activity with a luciferase reporter construct (Arinami, Gao Hamaguchi, & Toru, 1997), and diminished response to clozapine across a ten-week trial in chronic schizophrenia patients (Malhotra et al., 2004). Comprehensive studies of this polymorphism’s role in dopamine receptor function may therefore be warranted.

Pharmacogenetics of drug-induced adverse effects

An emerging area of interest has been the role of genetic variation in the prediction of side effects of psychotropic drug treatment. In a prospective clinical trial of the antidepressants mirtazapine and paroxetine, discontinuations due to paroxetine-induced side effects were strongly associated with the 5-HT2A T102C polymorphism, with a significant linear relationship between C allele ‘dosage’ and the probability of discontinuation. In contrast, 5-HT2A T102C genotype had no effect on side effects associated with mirtazapine treatment (Murphy, Kremer, Rodrigues, & Schatzberg, 2003). These intriguing data provide initial evidence that this single nucleotide polymorphism (SNP) could be utilized to help tailor treatment with specific antidepressant medications for patients based upon a specific genotype, although replication in other samples will be needed.

Similar efforts have been made with antipsychotic drugs, with early studies focusing on prediction of risk for the movement disorder, tardive dyskinesia. Candidate gene studies of the dopamine D3 receptor genes have proved the best evidence for association, but significant methodological issues in the assessment of prior treatment, duration of treatment, type of drug, and cross-sectional assessment of a phenotype known to wax and wane over time, have limited the interpretation of these data (Malhotra et al., 2004). Moreover, as second generation antipsychotic utilization has grown with corresponding diminished utilization of the typical antipsychotic agents, the rationale for these studies may be less compelling, and there may be more difficulty in collecting sufficient sample sizes in homogeneously treated populations of patients.
Pharmacogenetics of antipsychotic-induced weight gain

Although risk for TD may be lower with the second generation antipsychotic agents, their association with significant weight gain has spurred a number of studies seeking to identify the genetic factors underlying antipsychotic-induced weight gain. The number of non-genetic factors influencing weight gain complicates these studies (Figure 1). For example, some studies have demonstrated that age is a significant factor (Ratzoni et al., 2002; Safer, 2004; Sikich, Hamer, Bashford, Sheitman, & Lieberman 2004; Wetterling & Mussigbrodt, 1999; Woods, Martin, Spector, & McGlashan, 2002), with younger patients gaining proportionally more weight than older patients. Similarly, sex may be an important factor, with male patients gaining more weight than females (Ratzoni et al., 2002). There is also marked interindividual variability in psychomotor activity which may predict weight gain and obesity (Levine, Eberhardt, & Jensen, 1999).

It should also be noted that the antipsychotic drugs themselves might influence psychomotor activity, which could influence the amount of weight gain by an indirect mechanism. Similarly, many antipsychotic drugs have sedative properties; increased sedation could result in weight gain, again through a more indirect mechanism. Finally, a patient’s appetite, dietary choices and eating habits will influence weight gain, as well as amount of exercise.

Nevertheless, several lines of evidence suggest that perhaps the largest contributor to the variation in weight gain is genetic. These data include twin, adoption and family studies that demonstrate that an individual’s risk for obesity is significantly increased if he or she has obese relatives (Comuzzie & Allison, 1998). Moreover, 40–70% of the variation in obesity-related phenotypes such as body-mass index (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, Reed, & Price, 1997) and fat mass (Comuzzie et al., 1995). Finally, animals in which single genes are knocked out exhibit marked alterations in eating behaviour and obesity (Tecott et al., 1995) – indicating that these genes may play critical roles in weight regulation.

Drug-induced weight gain may be a particularly powerful phenotype in pharmacogenetic studies (Correll & Malhotra, 2004). First, there are substantial data to suggest that weight regulation is a heritable phenotype. Second, in contrast to clinical symptoms traditionally assessed in pharmacogenetic studies of antipsychotic drug response, weight gain can be defined with greater accuracy and reliability. Moreover, related phenotypic measures such as assessment of BMI and total fat mass, as well as other biological correlates of weight gain such as fasting glucose levels, insulin levels and circulating levels of neuropeptides such as leptin may provide additional power for genetic studies (Comuzzie & Allison, 1998). These measures are also readily amenable to quantitative trait analyses.

Perhaps the best evidence for a specific role of genetic factors in antipsychotic-induced weight gain is provided by studies of the relationship between a promoter region polymorphism, −759 T/C, in the 5-hydroxytryptamine 2C receptor (5-HT2C) gene and antipsychotic-induced weight gain. Reynolds and colleagues (2002) studied 123 adult 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 RIS ($n=46$) 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, Zhang, & Zhang. (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). These data have been replicated in a small study ($n=41$) conducted in Iowa, in which only 2 of 17 subjects with the T allele met criteria for severe weight gain (as compared to 14 of 24 with the C allele) in patients treated with clozapine (Miller, Ellingrod, Holman, Buckley, & Arndt, 2005). Finally, Ellingrod and colleagues (2005) have also reported that the T allele is associated with significantly less weight gain in patients treated with 6 weeks of olanzapine, and Templeman, Reynolds, Arranz and San (2005) reported the same for weight gain associated with a mixed group of antipsychotics, as well as for a smaller subgroup treated with olanzapine over 6 weeks, 3 and 9 months. Other studies, however, have not detected significant associations between −759 T/C and clozapine-induced weight gain (Basile, Masellis, DeLuca, Meltzer, & Kennedy, 2002; Theisen et al., 2004; Tsai, Hong, Yu, & Lin, 2002) but each of these studies was restricted to chronic patients with extensive prior antipsychotic drug treatment histories.

**Future directions**

As noted above, the majority of prior studies have focused on single genes, limited SNPs within these genes, and have often used relatively small prospective samples or retrospective assessments. Recent developments in clinical trials of psychotropic agents and in genomics, however, should lead to marked changes in pharmacogenetic research designs, with potential implications for clinical practice.

An important development is the introduction of routine DNA collection in most industry and many academic clinical trials of psychotropic agents. Prior pharmacogenetic studies have often been limited by small sample sizes secondary to either post hoc collection strategies, or collection from a limited number, or only single sites within multi-site studies. For the past several years however, many industry sponsored clinical trials have offered DNA collection as an option to study participants, enabling industry to collect relatively robust sample sizes for analyses. Strengths of this strategy include the prospective characterization of the sample; often including double-blind assessment methodologies and administration of a placebo control; the relatively comprehensive phenotyping of drug efficacy and drug-related adverse events, and the use of well-validated and reliable assessment measures. A limitation of these cohorts, however, is the potential heterogeneity of the sample as subjects are usually recruited from multiple sites (often >50) thus introducing potential demographic and potential ethnic heterogeneity, subjects are assessed by multiple raters who may not complete formal inter-rater reliability assessments, and the possibility that there are subtle ascertainment biases in industry sponsored studies that may increase response rates, as suggested by the apparent rising placebo response rate
in pivotal trials of the newer antidepressant drugs (Montgomery, 1999).

Academic researchers have also recently completed several large NIH-funded studies of psychotropic drug treatment in schizophrenia, bipolar disorder and major depression (Lieberman et al., 2005). These studies have included much larger cohorts than traditionally assessed in investigator-initiated research, and have all included DNA collection as an option for participants. An important feature of these large trials is the requirement that the DNA samples will be made available to the general research community for investigation, thus ensuring that the data will remain in the public domain and encouraging dissemination of findings. The large sample sizes and resultant multi-site designs of these studies also raise the same concerns as with industry sponsored work, as there may be multiple potential sources of heterogeneity in these samples that cannot be rigorously addressed or controlled for during data analyses.

A second development over the last year is the rapidly developing database on variation within the human genome. The International HAP Map project (2005) has now provided comprehensive information on genetic variability across population, and it is now possible to easily access data concerning: allele frequency, linkage disequilibrium and haplotype structure for millions of SNPs across the entire genome. This not only provides for improved whole genome analyses, but also allows for more comprehensive and more efficient investigation of single genes of interest to pharmacogenetics research.

Finally, the recent application of whole genome association approaches in molecular genetic studies may have considerable impact on pharmacogenetics (Klein et al., 2005). These approaches are predicated on the development of new genotyping methodologies incorporating large numbers of SNPs, including recent products by Affymetrix, that assay 500,000 SNPs, and Illumina that assays 300,000 SNPs. These numbers are subject to rapid change however, as at the time of this writing, both companies have announced the upcoming release of new products with further increases in the SNP density of these products, as well as continued reductions in genotyping costs, increasing the feasibility of conducting large scale whole genome studies. The statistical considerations in analysing whole genome data in pharmacogenetic phenotypes are daunting, but the use of multi-stage strategies; the availability of replication samples; and validation of findings in prospectively genotyped samples should provide additional strategies to ensure confidence in findings made with these rapidly developing approaches.

Clinical utility of pharmacogenetics in psychiatry

Although the clinical utility of the currently available pharmacogenetics data may be limited, it is notable that the Food and Drug Administration has approved a genotyping technology for use in clinical treatment. This chip, called the AmpliChip, is manufactured by Roche Diagnostics, and genotypes multiple variants in the cytochrome P450 system that code for enzymes involved in the oxidative metabolism of many psychotropic drugs (deLeon, Armstrong, Cozza, 2006). Results from the chip provide information on the metabolic status of patients with classifications ranging from poor metabolizer to ultrarapid metabolizer. The aim of this work is to provide clinicians with the ability to better predict the metabolism of a prescribed psychotropic agent, and thus select a drug or titrate dosage based upon empirical data, rather than, at best, by the use of plasma levels of drug. To date, however, the data suggesting that genotyping these variants significantly and cost effectively influences clinical outcome is limited, and prospective trials with this product and related P450 genotyping assays will be worthwhile. Finally, another private biotechnology firm has reported preliminary data suggesting that specific genes may influence risk for clozapine-induced agranulocytosis (Malhotra et al., 2005) and if replication attempts succeed, these data could have significant clinical impact as it could diminish the need for regular venipuncture in clozapine-treated subjects, thus increasing its acceptability and reducing the cost of administration for treatment-resistant schizophrenia patients.

Conclusions

The rapid improvements in genomic technology; the availability of comprehensive information on the genomic variability across populations; and the introduction of routine DNA collection in large scale clinical trials of psychotropic drugs, provides the necessary resources for more comprehensive pharmacogenetic studies of psychotropic drug response. Although early studies have provided intriguing leads, these new data may lead to the development of molecular predictors of drug response, and drug-induced adverse events, as well as potentially result in the identification of new targets for new drug development.

References


