The Pharmacogenetics of Antipsychotic Treatment

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Abstract There is substantial interindividual variability in the effects of treatment with antipsychotic drugs not only in the emergence of adverse effects but also in symptom response. It is becoming increasingly clear that much of this variability is due to genetic factors; pharmacogenetics is the study of those factors, with the eventual goal of identifying genetic predictors of treatment effects. There have been many reported associations of single nucleotide polymorphisms (SNPs) in candidate genes with the consequences of antipsychotic drug treatment. Thus variations in dopaminergic and serotoninergic genes may influence positive and negative symptom outcome, respectively. Among the adverse effects, tardive dyskinesia and weight gain have been the most studied, with some consistent associations of functional SNPs in genes relating to pharmacological mechanisms. Technological advance has permitted large-scale genome-wide association studies (GWAS), but

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as yet there are few reports that replicate prior findings with candidate genes. Nevertheless, GWAS may identify associations which provide new clues relating to underlying mechanisms.

Keywords Schizophrenia • Negative symptoms • Positive symptoms • Adverse effects • Association studies • Candidate gene • Single nucleotide polymorphism • Receptors • Weight gain • Extrapyramidal side effects

1 Introduction

Severe mental illness—schizophrenia, bipolar disorder and major depressive disorder—represents a huge burden to society in general and health care in particular. This fact reflects the limited efficacy of current treatment; pharmacotherapy of depression often achieves response rates of little more than 50%, while even lower proportions of patients with schizophrenia achieve adequate response to their antipsychotic drug treatment.

Antipsychotic drugs are widely prescribed, to over 1% of western populations. Primarily these are patients with schizophrenia, but the drugs are increasingly used in bipolar disorder, and may also be used in treating (often with little in the way of an evidence base) a variety of behavioral problems from autism in childhood to psychosis associated with various neurodegenerative and dementing disorders. While a proportion of people with schizophrenia respond well to antipsychotic drug treatment, a similar proportion (approximately one third) show little amelioration of their symptoms, while the remainder present varying degrees of symptom improvement. Treatment adherence is inevitably one factor that contributes to this substantial individual variability, although patients taking their medication as prescribed can still show profound differences in response. There is little understanding of the underlying reasons for these differences, although accumulating evidence over the past 15 years is pointing to a substantial contribution from genetic factors to the response to drug treatment.

Similar variability is also seen in the occurrence and severity of adverse effects of antipsychotic drug treatment. It remains unclear what underlies the individual differences in the emergence of extrapyramidal side effects such as the chronic and often irreversible tardive dyskinesia (TD), or of drug-induced weight gain and related effects including higher incidence of metabolic syndrome, although again genetic factors appear to play an important role.

Thus pharmacogenetics, the study of the influence of genetic variation on the effects of drug treatment, has much to offer in identifying what may underlie these differences in the consequences of antipsychotic treatment. The pharmacogenetics of antipsychotic drugs has received substantial research effort over the past decade, driven by an awareness of the varied and often limited effectiveness of these drugs both in controlling symptoms of schizophrenia and in inducing adverse effects.

1.1 Concepts and Approaches

Studies of siblings and twin pairs have provided some evidence in support of genetic factors influencing the emergence of certain side effects following antipsychotic drug treatment. A series of first degree relatives concordant for schizophrenia also showed concordance for the presence or absence of TD (Youssef et al. 1989). Weight gain following antipsychotic treatment has been studied in pairs of siblings and monozygotic twins, with greater concordance in the twin pairs being interpreted as evidence for drug-induced weight gain having a strong genetic contribution, estimated at 60–80% (Gebhardt et al. 2010). Treatment responses to clozapine (Vojvoda et al. 1996) and olanzapine (Mata et al. 2001) have also shown strong concordance in monozygotic twin pairs.

Implicit in the search for genetic associations with the outcome of antipsychotic drug treatment is that such associations may enable us to identify genetic predictors of side effects or treatment response. In addition, the results of pharmacogenetic studies can inform, as they are informed by, the pharmacological mechanisms underlying these effects of antipsychotics. Thus, the starting point for pharmacogenetic investigation would usually be a concern over a particular limitation of the drug treatment. Having identified the target problem, a phenotype, early approaches then investigated variations in the DNA (genotype) of one or a small number of "candidate" genes for study. Choice of candidate genes is hypothesis-driven, whereby genes are usually selected on the basis of their coding for a protein that is known to be, or is potentially, involved in pharmacokinetic or pharmacodynamic aspects of drug action. Identification of sites of variation in these genes, primarily single nucleotide polymorphisms ("SNPs") or insertion/deletion sequences provide the factors for association of genotype with phenotype.

Genetic factors could influence drug action at several levels, and I have previously suggested (Reynolds 2007) that pharmacogenetic associations can be considered to be in groups dependent on the mechanism of the drug–gene interaction:

1. genes influencing pharmacokinetic processes, such as the CYP metabolic enzymes, or MDR1 (ABCB1) coding for P-glycoprotein;
2. genes known or thought to be directly involved in the mechanisms of drug action, such as those for the dopamine D_2 receptor and, for most newer antipsychotics, the 5-HT_{2A} receptor;
3. genes that may indirectly modify the primary pharmacological mechanism, such as those involved in second messenger function, such as G-protein subunit beta3, or receptors relating to interacting neurotransmitter systems;
4. genes that are involved in disease pathology and which may therefore determine how responsive the disease may be to pharmacotherapy. These might include genes for disease risk or disease modifying factors such as catechol-O-methyltransferase (COMT) or dysbindin1.

Genetic polymorphisms may have a direct effect on the function of the gene product. Clearly, a SNP in the coding region of the gene leading to a change in the

amino acid sequence (a missense or non-synonymous mutation) is likely to influence gene function through an effect on protein structure. This might, in the case of a receptor for example, affect agonist affinity or the disposition of the protein in the neuronal membrane. SNPs outside the coding region can still affect gene function; thus upstream 5′ SNPs in the promoter sequence of the gene could influence the binding of transcription factors and hence the extent and/or control of gene expression, resulting in changes in, for example, receptor density. Other SNP sites might influence mRNA stability, or affect the binding of miRNA, each of which could result in changes in the expression and availability of gene product.

SNPs that are relatively close to one another tend to be inherited together; these are referred to as being in linkage disequilibrium (LD). Haplotype analysis may then employ multiple SNPs in LD in an attempt to increase genetic association with a clinical phenotype. Other approaches are increasingly being used; gene–gene interaction is studied in recognition of the fact that the effects of polymorphisms in different genes may interact to influence the phenotype, while gene–environment interaction acknowledges the environmental contribution to phenotype and its potential in modifying, or being modified by, the influence of genetic factors. In a sense, of course, pharmacogenetics is the study of gene–environment interactions where the environmental factor is drug treatment.

Technological advance has driven pharmacogenetic approaches beyond the study of single sites of variation, such as SNPs or insertion/deletion sequences, in candidate genes to the application of genome-wide association studies (GWAS). These hypothesis-free approaches investigate many (e.g., one million) SNPs across the whole of the genome and offer great power in identifying novel genetic associations unconstrained by prior hypotheses, which are inevitably founded on a limited understanding of the underlying mechanisms. However, GWAS are not without limitations; they generally employ tagging SNPs, selected on the basis of position in the genome sequence, rather than polymorphisms of known, or potential, functionality that may be chosen in candidate gene studies. They also have their own problems associated with the difficulties of data handling (where a sample of several hundred subjects can produce over 10^8 individual results) and appropriate statistical analysis and interpretation.

2 The Target Phenotypes and Candidate Genes

This section will briefly address the symptoms and side effects that remain a problem with current antipsychotic drugs and identify some of the major hypothesis-driven approaches to understanding their genetic influences. Although our knowledge of the underlying mechanisms is often very limited, what we know of the pharmacological processes involved has provided indications of what genes might be worthy of investigation. These candidate genes will not be comprehensively listed, but the major genes of interest will be briefly mentioned, particularly where they have given rise to further pharmacogenetic study. This will concentrate

on genes particularly related to pharmacodynamic mechanisms, although pharmacokinetic genes are also strong candidates for influencing both symptom response and adverse effects in a drug-specific manner. Functional variants in metabolic enzymes, notably the widely studied cytochrome P450 enzymes, can influence drug concentrations, availability and the ratio of active drug to metabolites (both active and inactive). Similarly, any functional genetic variability in the p-glycoprotein pump, which acts to remove xenobiotics and many drugs from the brain, can also influence drug availability at sites of action. All such effects on drug disposition will inevitably have effects on drug action, whether they are in the relief of symptoms or in the emergence of side effects; influence on the latter is a commonly reported consequence of genetic variability in cytochrome P450 enzymes for several antipsychotic drugs (Arranz and de Leon 2007). To some extent the effects of pharmacokinetic variability can be ameliorated by dose titration, although this may only be true when the pharmacology is uncomplicated by the presence of active metabolites.

2.1 Symptom Response

Clearly the response to drug treatment of the disease symptoms is an important target for pharmacogenetic study, given the high proportion of patients who suffer from residual symptoms of schizophrenia. This inadequate response to treatment is more apparent in subgroups of symptoms; while antipsychotic drugs are often effective at controlling the positive psychotic symptoms, they are less able to ameliorate the negative and cognitive features of schizophrenia. These features include social withdrawal, blunted mood, lack of self-care, and a range of cognitive deficits which, along with depressed mood, are the symptoms that are most problematic in integrating the patient into society.

It is generally considered that the primary antipsychotic mechanism involves antagonist action at the dopamine D_2 receptor. Thus, polymorphisms in this gene (DRD2) have been widely investigated in respect of symptom response, as have the related D_2-like receptor genes DRD3 and DRD4. Similarly, the 5-HT_{2A} receptor is a major drug target proposed to differentiate the atypical antipsychotics from the older drugs. The pharmacological mechanisms underlying antipsychotic drug effects on negative and cognitive symptoms are far from clear, however. It has been suggested that the drug action at 5-HT_{2A} receptors is also responsible for some improved efficacy of the atypical antipsychotics on negative symptoms, although the supporting evidence for this clinical effect is very limited (Lieberman et al. 2005), as is our understanding of the underlying mechanism. Nevertheless, there is some indication that 5-HT systems are involved in models of cognitive dysfunction in schizophrenia (Neill et al. 2010; Meltzer and Massey 2011) as well as in symptom amelioration by newer antipsychotic drugs (Meltzer and Massey 2011), providing candidature for HTR2A and other serotonergic genes such as HTR1A, HTR2C, HTR6, and SLC6A4.

There is, however, increasing evidence of the importance of glutamate neurotransmission in cognitive dysfunction in schizophrenia (Tamminga 2006), and more generally in the pathology of the disease itself (Kantrowitz and Javitt 2010). The cognitive deficits of schizophrenia are modeled by chronic administration of glutamate/NMDA receptor antagonists, and this provides a series of candidate genes, from the NMDA receptor subunit proteins to other glutamate receptors and metabolic enzymes.

The unique efficacy of clozapine in the treatment of otherwise non-responsive patients has resulted in clozapine being a prime target for pharmacogenetic investigation. In addition to its clinical importance, this work has a pragmatic advantage of sample availability and regular patient monitoring in retrospective studies, due to the necessity for blood monitoring for the potentially fatal side effect of agranulocytosis. A pharmacological basis for the clinical efficacy of clozapine remains elusive; among the receptor mechanisms implicated, in addition to the 5-HT_{2A} receptor antagonism common to most atypical antipsychotics, are effects at α_2-adrenoceptors, 5-HT_{1A} receptors and dopamine D_1 receptors, although no single receptor action is likely to explain clozapine's action in full (Reynolds 2004).

2.2 *Adverse Effects*

A consequence of dopamine D_2 receptor antagonism, essential for the antipsychotic effects of current drugs, is an inhibition of dopaminergic function in regions of the brain controlling motor function. This results in the extrapyramidal side effects (EPS), which include the relatively immediate effects of akathisia, dystonia, and parkinsonism, believed to be consequences of acute inhibition of dopaminergic neurotransmission *via* antipsychotic drug antagonism of the D_2 receptor, as well as tardive dyskinesia (TD), a severe problem associated with chronic treatment which may be irreversible. The avoidance of EPS has driven the development of the second generation of antipsychotic drugs; it is proposed that 5-HT_{2A} receptor antagonism may contribute to the lower propensity for EPS shown by some these drugs, although other mechanisms may also be involved. 5-HT_{2C} receptors are also important in the pharmacology and physiology of dyskinesias. Thus, genes associated with dopamine and 5-HT_2 receptors are strong candidates; others, particularly those relating to TD, have been proposed from further theories relating to the possible underlying mechanism(s). These mechanisms include, in addition to receptor-mediated effects, damage associated with oxidative free radicals, implicating genes involved in free radical scavenging such as that for a superoxide dismutase (SOD2).

Dopamine D_2 receptor antagonism has a further consequence of disinhibiting the release of prolactin, resulting in galactorrhoea; much of the work in this area has focused on risperidone, which among the commonly used antipsychotics has the greatest effect on prolactin. These drug effects on the hypothalamic–pituitary–gonadal axis can have further consequences, including amenorrhoea and, potentially,

osteoporosis in some patients, as well as contributing to sexual dysfunction. DRD2, as well as genes involved in the serotonin system and in estrogen function, are among those implicated in these adverse effects seen with several antipsychotic drug treatments. Prolactin secretion occurs following inhibition of dopamine receptors in the pituitary gland; this is accessed directly by drugs in the blood without the restriction of an effective blood–brain barrier. Thus, drugs that are poorly penetrant or substrates for the p-glycoprotein pump, such as risperidone and amisulpride, are likely to affect receptors in the pituitary to a greater extent than in the brain. The major p-glycoprotein gene (ABCB1) is thus a further candidate for effects on prolactin.

Of the other limiting side effects, weight gain and, to a lesser extent, its related metabolic consequences have been investigated in some detail. Here the candidate genes derive from the underlying receptors considered to mediate drug effects on food intake (Reynolds and Kirk 2010), notably but not exclusively the serotonin 5-HT_{2C} and histamine H_1 receptor. In addition, further candidates are provided by the various mechanisms involved in the control of food intake and body weight. These include circulating hormones such as leptin and adiponectin, the hypothalamic neuropeptides, the cannabinoid system and factors involved in glucose and lipid disposition and metabolism (Reynolds and Kirk 2010).

Other problematic side effects include sedation, little studied in pharmacogenetics but considered to relate to antagonism at histamine H_1 receptors, and postural hypotension, for which α_1-adrenoceptor antagonism by many of the antipsychotic drugs is thought to be responsible (Reynolds 2004). QT interval prolongation, involving disturbance of potassium channel function, is a concern with some antipsychotics occasionally, but not inevitably, resulting in the arrhythmia of *torsades de pointes* and, potentially, a sudden cardiac death. Another rare but also potentially fatal side effect is that of agranulocytosis, a particular limitation of treatment with clozapine.

3 Pharmacogenetic Findings

3.1 Scope and Limitations

This chapter reports and comments on the work that reflects progress in, and the current status of, the field of antipsychotic pharmacogenetics. It will not be a comprehensive review of all the various pharmacogenetic results relating to individual differences in the effects of antipsychotic drug treatment, but will provide examples as well as reference to more specific review articles; many single unreplicated findings will not be reported, although some of potential interest will be mentioned. Furthermore, there will be a bias here towards pharmacodynamic rather than pharmacokinetic influences on drug action, driven by the value of pharmacogenetics in informing pharmacological and physiological mechanisms.

Both the casual reader and the systematic reviewer may be struck by the paucity of consistently reproducible findings in the pharmacogenetic studies reported. There are many reasons for this. One particularly important factor is that many studies are underpowered to identify what are often relatively small effects; this factor will inevitably introduce variability of results between studies. Other factors include differences in sample ethnicity, with the inevitable differences in genetic make-up between different ethnic samples. Different drug treatments may be associated with different pharmacogenetic influences, and published literature may give an impression that there are drug-specific pharmacogenetic associations.

A major goal of pharmacogenetics is to inform drug selection, and thus a genetic test that identifies e.g., responders specific to particular drug treatments would be of huge value in guiding prescribing practice. However, there is little evidence for this to be the case in antipsychotic drug treatment, with the possible exception of clozapine. Authors occasionally forget that finding a significant genetic association of the effects of one drug, not reaching significance in patients on another drug, is very different from demonstrating a statistically significant difference between two drugs in the genetic influences on their effects. In fact, as discussed below, some results indicate that several genetic associations with response and with side effects can generalize across drug treatments.

There are other differences between samples that may introduce inconsistencies; a drug effect, whether response to treatment or a side effect, emerging in first-episode and previously drug-naïve patients may well have differences in underlying pharmacological mechanisms, and hence differences in pharmacogenetic influences, from equivalent effects in patients with a chronic treatment history. Furthermore, the clinical phenotypes measured may often be complex and multi-factorial, composed of several physiological responses under different genetic control mechanisms. In the case of symptom response, this problem will be discussed in more detail below.

The important independent CATIE trial of the relative effects of several antipsychotic drugs (Lieberman et al. 2005) has provided a very valuable sample source for pharmacogenetics, given the rigorous and comprehensive assessments undertaken in a large series of people with schizophrenia. Although it is not without limitations, pharmacogenetic studies from this trial are beginning to yield interesting and novel findings, some of which will be discussed here.

3.2 Pharmacogenetic Findings: Symptom Response

Many of the earlier reports assessing genetic associations with antipsychotic treatment response concentrated on the most obvious candidate genes with some replicated, if not totally consistent, findings of polymorphisms in three receptors: dopamine D_2, dopamine D_3, and serotonin 5-HT_{2A}, being associated with response to treatment (reviewed by Reynolds et al. 2006a, b; Malhotra et al. 2004).

The association of DRD2 with response has been confirmed more recently in a systematic review (Zhang et al. 2010), although overall association of DRD3 remains weak and inconsistent (e.g., Hwang et al. 2010; Xuan et al. 2008). Other dopaminergic factors have been investigated in relation to the pharmacogenetics of drug response. The dopamine transporter (DAT) gene has shown both positive (with clozapine) and negative (with risperidone) associations (Xu et al. 2008; Zhang et al. 2007), but there are no convincing results indicating an influence of SNPs in the dopamine D_1 or D_4 receptors on treatment response.

A review of association studies with SNPs in the 5-HT_{2A} receptor gene concluded that results indicate some weak association with antipsychotic response as well as with psychosis itself (Serretti et al. 2007). Some further supporting data for this association with drug response have emerged from several more recent small studies including one employing the methodologically more rigorous transmission disequilibrium test (Benmessaoud et al. 2008). Nevertheless, the effect is a small one and not consistently obtained. The same is true for genes for other markers of serotonergic function. The 5-HT transporter gene (SLC6A4), with what is perhaps the most studied polymorphism in psychiatry, the insertion/deletion (ins/del) sequence in the promoter region (Lesch et al. 1996), is associated with antipsychotic response in some (e.g., Dolzan et al. 2008; Wang et al. 2007) but not all (Lee et al. 2009) studies. A SNP in the 5-HT_{1A} receptor gene has also been shown to have effects on treatment response (Mossner et al. 2009; Reynolds et al. 2006a, b; Wang et al. 2008). Both SLC6A4 and HTR1A genes code for proteins that control presynaptic activity of the serotonin neuron; the major SNPs investigated in each case appear to directly influence gene expression. Thus promoter sequence SLC6A4 SNPs including the ins/del polymorphism of SLC6A4 and the SNP found within the insertion sequence (Hu et al. 2006) influence SLC6A4 expression and activity, while the −1019 C/G promoter SNP in HTR1A affects a transcription factor binding site, again influencing expression of the 5-HT_{1A} receptor and its control, as well as being associated with suicide and diagnosis of depression (Lemonde et al. 2003).

In developing the opportunities for genetic testing, it seems more valuable to differentiate groups of symptoms in terms of their response to treatment. As mentioned above, the negative features of the disease respond poorly to antipsychotic drugs and it is these features, rather than the positive symptoms, that are more important in determining functional recovery in patients. A minority of outcome studies have assessed separately the responses of positive and negative symptoms to drug treatment, despite the established differences in the effects of antipsychotics on these symptom clusters. However, where separate responses have been assessed, it appears that the majority of genes associated with positive symptom response are of dopamine receptors, while effects on negative symptoms are more associated with serotoninergic genes, in particular the 5-HT_{1A} and 5-HT_{2A} receptors. Updating earlier observations (Reynolds 2007), we find that more recent results confirm this impression (Table 1), with notably few anomalies. This is notwithstanding the differences between samples in terms of treatment history (drug-naïve, or previously treated) and ethnicity. These findings may seem

Table 1 Some reported associations differentiating positive and negative symptom response to antipsychotic drugs—influence of dopamine and serotonin genes

	Polymorphism	Association with symptom subgroup:	References
Dopamine D_2 receptor (*DRD2*)	Ser311cys	*Positive*	Lane et al. (2004)
	Taq1A	*Positive*	Suzuki et al. (2000)
Dopamine D_3 receptor (*DRD3*)	Ser9gly	*Negative*	Lane et al. (2005)
	Ser9gly	*Positive*	Reynolds et al. (2005)
	−205A/G, Ser9gly	*Positive*	Staddon et al. (2002)
	Ser9gly and others	*Positive*	Adams et al. (2008)
Norepinephrine transporter (*SLC6A2*)	1287 G/A, −182 T/C	*Positive*	Meary et al. (2008)
5-HT_{2A} receptor (*HTR2A*)	102 T/C	*Negative*	Lane et al. (2002)
	−1438A/G	*Negative*	Hamdani et al. (2005)
	−1438A/G	*Negative*	Ellingrod et al. (2003)
5-HT_{2C} receptor (*HTR2C*)	−759 C/T	*Negative*	Reynolds et al. (2005)
5-HT_{1A} receptor (*HTR1A*)	−1019 C/G	*Negative*	Reynolds et al. (2006a, b)
	−1019 C/G	*Negative*	Mossner et al. (2009)
	−1019 C/G	*Negative*	Wang et al. (2008)
5-HT transporter (*SLC6A4*)	HTTLPR ins/del	*Negative*	Vazquez-Bourgon et al. (2010)

surprising on first sight, given the variety of different genes involved. However this multiplicity of genetic factors points to common mechanistic pathways; for example, changes in the expression and activity of both 5-HT_{1A} receptors and the 5-HT transporter are likely to affect serotonergic activity at the synapse, consequences of which may be mediated by post-synaptic receptors such as 5-HT_{2A}. A similar but unconfirmed observation has been seen for another 5-HT receptor gene, HTR3E (Schuhmacher et al. 2009). However it is notable that the results for catechol-O-methyltransferase (COMT) indicate association solely with negative symptom improvement (discussed below). Nevertheless, the overall results strongly suggest that the dopamine and serotonin neurotransmitter systems are implicated separately in drug response of the two syndromes, while the exact mechanisms of their involvement remain elusive. Certainly, there is evidence that selective serotonin uptake inhibitors may be useful in the relief of negative symptoms in some patients (Silver 2004).

In one study identifying a relatively strong effect of a 5-HT_{1A} gene SNP explaining much of the variance in negative symptom response in first-episode patients (Reynolds et al. 2006a, b), there was also an effect on depressive symptom response, differentiated from that on negative symptoms. This finding is unsurprising, given the established association of this SNP with depression (Lemonde et al. 2003) and its treatment (Lemonde et al. 2004). An association with negative symptoms and depression has been found for the 5-HT transporter gene in patients receiving antipsychotics, although the influence of treatment on this finding was not determined (Goldberg et al. 2009). However it is notable that few pharmacogenetic studies have

investigated separately the depression syndrome in schizophrenia, although it is an important determinant of relapse in patients receiving antipsychotics (Tollefson et al. 1999).

The unique efficacy of clozapine has attracted substantial investigation into the genetic basis of response to treatment with this drug. However, at least 50% of patients not otherwise responding to antipsychotic drug treatment benefit from clozapine; much early work on antipsychotic pharmacogenetics addressed this problem. Arranz et al. (2000) studied a range of candidate genes, primarily chosen on the basis of the known pharmacology of clozapine. They looked for association of response with 19 polymorphisms in ten genes associated with monoamine neurotransmission; six polymorphisms in genes for the 5-HT_{2A} and 5-HT_{2C} receptors, the 5-HT transporter, and the histamine H_2 receptor together gave a (retrospective) sensitivity of 96% in identifying clozapine responders. The strongest components in this profile of polymorphisms are two SNPs in the HTR2A gene: one synonymous (silent) 102 T/C in linkage disequilibrium with a promoter SNP (-1438A/G) with functional activity (Parsons et al. 2004) and one nonsynonymous his452tyr. These findings have not been consistently replicated (Malhotra et al. 2004), but they nevertheless led to the establishment of a pharmacogenetic test for clozapine response. However, this test is no longer available and a confirmatory prospective trial to assess the predictability and value in practice of such pharmacogenetic testing for drug response has yet to be undertaken. Reflecting our incomplete understanding of the unique efficacy of clozapine, a consistent pharmacogenetic finding that might relate selectively to clozapine response still eludes us. Many pharmacogenetic studies, including some cited in this chapter, have been carried out on cohorts of clozapine-treated subjects, but as yet there is no evidence for distinct clozapine-specific pharmacogenetic associations with response.

The positive and replicated findings with SNPs in these dopamine and serotonin genes, reviewed more extensively elsewhere (Zhang and Malhotra 2011), are reassuring in terms of our very limited understanding of pharmacological mechanisms, but are strongly influenced by a research bias towards testing these more obvious hypotheses. Variation in these genes can still only explain a small percentage of the variance in response, and further factors inevitably contribute to antipsychotic-induced improvement in symptoms. Those further factors might include SNPs in a wide variety of other factors potentially influencing neuronal function, including other neurotransmitter receptors, enzymes and transporters, as well as second messenger systems or signaling pathways. This potentially involves many hundreds of further candidate genes, of which just one example is the SNP in the G-protein beta3 subunit gene (GNB3), involved in receptor signal transduction, and which reportedly shows weak association with symptom response (Müller et al. 2005; Anttila et al. 2007; Kohlrausch et al. 2008). However, there are few associations with symptom response outside the genes involving dopamine and serotonin systems that have been consistently replicated.

Concentrating on symptom subgroups, few other pharmacogenetic findings are specifically associated with positive symptom improvement, although many other

genetic associations with undifferentiated symptom response may primarily reflect the (generally relatively greater) improvement in positive symptoms. The latest and strongest single gene risk factor for schizophrenia, ZNF804A, is also interestingly a determinant of positive symptom response (Mossner et al. 2011).

There are some other genetic associations with drug-induced changes in the more problematic negative and cognitive symptoms in schizophrenia. These associations include the val/met COMT polymorphism (Bertolino et al. 2007; Fijal et al. 2009; Weickert et al. 2004), which has a strong effect on enzyme activity and thereby influences dopamine (and norepinephrine) concentrations in the cortex where this enzyme, rather than neuronal transport, is primarily responsible for synaptic removal of catecholamine neurotransmitters. The glutamate metabotropic receptor-3 gene, a further risk factor for schizophrenia, has been reported as having SNPs associated with response (Fijal et al. 2009), particularly of negative symptoms (Bishop et al. 2005), although a following study showed an association not with negative symptom response but with treatment-refractory schizophrenia (Bishop et al. 2011). Dysbindin1 (DTNBP1), another gene with an established association with schizophrenia and implicated in neuronal and synaptic development as well as dopamine receptor function, also shows association with treatment response in refractory schizophrenia (Zuo et al. 2009).

Other genes involved in neuronal development have been implicated in antipsychotic drug response. This is not as specific a statement as it might first seem; a very large number of genes expressed in the brain can potentially influence neuronal development including many related to, for example, serotonin or glutamate neurotransmitter function. However, an interesting model-based approach (Webb et al. 2008) found that several SNPS in the developmental gene EN1 (*engrailed1*) are associated with antipsychotic response in the CATIE trial. This study used datasets for schizophrenia risk genes and for mouse SNPs affecting prepulse inhibition, which is consistently deficient in schizophrenia and reversed by antipsychotic drug treatment, to generate candidates of which only EN1 was significant.

Some similar approaches, using relatively unbiased and independent methods to select candidate genes, have identified other associations. Homer-1, a gene associated with glutamatergic transmission and identified as a candidate from animal studies of gene expression following haloperidol administration, shows SNP associations with response to treatment (Spellmann et al. 2011). A similar approach (Ikeda et al. 2010) with a risperidone mouse administration study coupled with a GWAS for risperidone response identified several novel candidates, of which PDE-7 was found to have association both with disease, internally replicated, and with treatment response. Unfortunately, despite the apparent validity of these approaches, there appears to be little consistency between them. Such criticism, to which much of the pharmacogenetic literature is susceptible, can always be countered by highlighting the differences between study samples in ethnicity, drug treatment and other such factors, but it remains a problem for the generalizability of any findings.

Even within a sample, where the phenotype is identical between studies, different approaches can yield very different results. Thus the CATIE trial has been very

valuable in providing a large set of data on the consequences of antipsychotic treatment of a carefully controlled and rigorously assessed sample. The results of one very focused study have been mentioned above. A further investigation of a large series of 118 candidate genes (Need et al. 2009) identified several significant associations with change in the Positive and Negative Syndrome Scale (PANSS), the numbers of which were roughly in line with the expected false discovery rate (22 of 2,769 SNPs reached significance at $p < 0.01$). Seven of the significant SNPs were in glutamate receptor genes, which might be of more interest were it not for the fact that such genes were represented by over 1,000 of the SNPs studied. Nevertheless, these authors also identified significant association with SNPs on HTR2A, DRD3, the nicotinic receptor alpha7 subunit gene, and the excitatory amino acid transporter 4 gene (SLC1A6) among other candidates.

A GWAS study of the same sample has provided very different results, with the strongest effect on change in PANSS shown with a SNP in an inter-gene sequence on chromosome 4; other novel results close to the significance threshold were in ANKS1B, CNTNAP5, and TRPM1, all of which are potentially involved in neuronal development or neurotransmission (McClay et al. 2011b). How exactly they might be involved in drug response is far from clear; however, certainly replication as candidate genes in other samples is needed. The same group has looked at neurocognition as an outcome measure of response in this series (McClay et al. 2011a), finding significance in several genes of which the top two are EHF (a transcription factor with little evidence for a neuronal role) and SLC26A9 (a chloride ion transporter). Interpretation of these findings is not straightforward, although more reassuring are the findings of (somewhat weaker) association with DRD2 and ANKS1B, the latter also found to be associated with negative symptom response in the previous analysis.

Iloperidone is an antipsychotic that was recently approved (in the USA) and has undergone substantial pharmacogenetic study during its phase III trials. One investigation involved a GWAS that identified six SNPs in six genes contributing to drug treatment response (Lavedan et al. 2009); these data were re-analyzed in a retrospective assessment to identify response-dependent genetic subgroups of patients (Volpi et al. 2009b). How specific these findings are to iloperidone remains unclear; these authors report that the six SNPs did not significantly associate with ziprasidone response, although another group observed that two of the genes (XKR4 and GRIA4) were also associated with risperidone response (Fijal et al. 2011).

3.3 Pharmacogenetic Findings: Adverse Effects

3.3.1 Acute Motor Side Effects

Although they remain a concern with many antipsychotic drug treatments, particularly the earlier typical drugs, parkinsonian and other acute extrapyramidal symptoms have not been widely studied in terms of their genetic risk factors.

This situation may be because they are not considered as limiting effects, being adequately addressed by additional anticholinergic medication, or that more recently developed drugs have rendered them far less common. Nevertheless, several studies have investigated candidate genes such as dopamine and 5-HT_2 receptors. Despite several negative reports indicating no significant association of parkinsonian symptoms with dopamine receptor SNPs (Dolzan et al. 2008; Gunes et al. 2007) one recent study in Afro-Caribbean subjects showed association of polymorphisms in D_2 with rigidity and 5-HT_{2C} with bradykinesia (Al Hadithy et al. 2008). This result certainly emphasizes the value of differentiating the components of EPS that are likely to involve different pathophysiological mechanisms. A small study has shown association of undifferentiated EPS with 5-HT_{2A} and 5-HT_{2C} receptor SNPs (Gunes et al. 2007), confirmed for 5-HT_{2C} (Gunes et al. 2008).

A GWAS using a subgroup from the CATIE cohort failed to identify any SNPs meeting the fairly strict criteria for significant association with parkinsonism, but identified a few possible genes deserving further study (Alkelai et al. 2009). A further study of the full CATIE cohort yielded top associations of parkinsonism with two intergene SNPs and one on ZNF202, a transcription factor controlling PLP, a myelin protein (Aberg et al. 2010a). There was no replication of findings from any of the "promising candidates" from the previous study, indicating the sensitivity of these approaches to subtle differences in methodology and sample.

3.3.2 Tardive Dyskinesia

TD has been the subject of a large number of studies since the initial application of pharmacogenetics to antipsychotic drug effects. It is an important and limiting side effect, although its incidence is less frequent with the newer antipsychotic drugs. But the number of studies may as much reflect the fact that this is a relatively easily assessed side effect, which can be determined on the abnormal involuntary movements scale (AIMS) or as dichotomized categories.

Early studies inevitably focused on the dopamine receptors implicated in the control and modulation of motor function, often the same receptors as are implicated in symptom response. Pharmacogenetic findings have been reviewed comprehensively elsewhere (Zhang and Malhotra 2011; Thelma et al. 2008; Arranz and de Leon 2007) and consistently emphasize the role of dopamine D_2 and D_3 receptors, as well as several enzymes involved in drug metabolism, notably CYP2D6 and CYP1A2. Such pharmacokinetic influences will inevitably be dependent on the drug involved and its related metabolic pathways.

There is also some evidence from inconsistently replicated studies that both 5-HT_{2A} and 5-HT_{2C} receptor SNPs are associated with TD. This reflects the role serotonin systems have in motor function and its disturbances, both directly and in modifying dopaminergic influences. In particular, SNPs in both HTR2A and HTR2C have been, somewhat inconsistently, found to be associated with TD (reviewed in Zhang and Malhotra 2011). Interestingly, there are indications of additive, and perhaps synergistic, gene effects with interactions reported between SNPs in DRD3 and HTR2C (Segman et al. 2000) and DRD3 and SOD2

(Zhang et al. 2003b). The latter study involves the gene for an important enzyme involved in protection from reactive oxygen species, manganese superoxide dismutase (SOD2), which has a reported association with TD although recent meta-analysis could not confirm association with SOD2 or another gene (NQO1) involved in protection from free radical damage (Zai et al. 2010).

Again these candidate gene studies contrast profoundly with the findings from GWAS. The one SNP found to reach the (very conservative) significance for AIMS in the CATIE study was in an intergene region (Aberg et al. 2010a). Another study used the CATIE data to identify "promising SNPs" for further investigation in a second cohort and found association with the GLI2 gene, a transcription factor reportedly involved in dopaminergic embryogenesis (Greenbaum et al. 2010). Two further reports of smaller but internally replicated GWAS from the same group identified separately association of TD with HSPG2 (heparin sulfate proteoglycan 2) (Syu et al. 2010) and with DPP6 (Tanaka et al. 2011), each gene demonstrating possible pathophysiological involvement in animal studies; the first finding has recently been supported, albeit somewhat weakly, by a candidate gene study in two further cohorts (Greenbaum et al. 2011). A different approach, again using the Japanese sample cohorts, was to undertake pathway association analysis which, with multiple genes involved in GABAergic neurotransmission, has provided evidence for this system being involved in the development of TD (Inada et al. 2008).

The inconsistent results are disappointing but may to some extent reflect heterogeneity in the phenotype; there may be different pathophysiological influences on orofacial and limb/trunk dyskinesias, with differing pharmacogenetic influences (e.g., Lerer et al. 2005). The multiplicity of single gene associations with TD strongly indicates an unrealized potential for further investigation of gene–gene interactions and multiple gene effects on TD.

3.3.3 Weight Gain and Metabolic Effects

The first study to demonstrate a clear, and relatively strong, pharmacogenetic association of a candidate gene with antipsychotic drug-induced weight gain investigated a 5-HT_{2C} receptor promoter polymorphism (−759 C/T) in drug-naïve Chinese patients. After 10 weeks treatment there was a highly significant difference in which those patients carrying the minor T allele (22% of the sample) were protected from substantial (>7 %) weight gain caused by risperidone or chlorpromazine with a relative risk of 3.45 (Reynolds et al. 2002). This has, despite some failed replications, also been observed in several further studies including a European first-episode cohort receiving risperidone or olanzapine (Templeman et al. 2005), in chronic patients receiving olanzapine (Ellingrod et al. 2005) and in patients receiving clozapine (Miller et al. 2005; Reynolds et al. 2003). Thus the findings generalize to different drugs, including those with both high (clozapine and olanzapine) or low (risperidone) affinity for the 5-HT_{2C} receptor. The −759 C/T polymorphism, along with other promoter region polymorphisms of the 5-HT2C receptor gene with which it is in linkage disequilibrium, appears to be functional in influencing gene expression (Hill and Reynolds 2007, 2011).

Another candidate gene demonstrating a positive association with antipsychotic drug-induced weight gain is that of leptin. This gene has a promoter region polymorphism influencing the secretion of leptin and which is associated with obesity (Mammes et al. 2000). In two drug-naïve populations also investigated for a 5-HT_{2C} receptor association, antipsychotic weight gain was associated with this −2548A/G polymorphism (Templeman et al. 2005; Zhang et al. 2002), although in each study its influence on weight gain emerges later than that of the HTR2C SNP, which may differentiate effects on initial and longer-term fat deposition. Unpublished calculations from the combined leptin and HTR2C genotype effect reported by Templeman et al. (2005) indicate that, along with baseline measures of BMI, this genetic variability can account for over 25 % of the variance in weight gain. Interestingly, these authors reported that both the HTR2C and leptin SNPs influence leptin secretion, supporting a role for leptin in the mechanism of antipsychotic drug-induced weight gain.

Recent advances in the pharmacogenetics of antipsychotic-induced weight gain have been reviewed comprehensively (Lett et al. 2011); here I shall highlight just some of these findings. While the 5-HT_{2C} receptor and leptin genes have accumulated the most consistent evidence in support of their roles as risk factors for antipsychotic-induced weight gain, a large number of further candidate genes have been investigated, notably those for receptors that may mediate some of the metabolic effects of antipsychotic drugs. Unsurprisingly, there have been many negative findings, including importantly SNPs in genes for the dopamine D_2 (Zhang et al. 2003a) and histamine H_1 receptors (Hong et al. 2002), although both of these also have more recent positive reports (Lencz et al. 2010; Vehof et al. 2011).

Other candidates that have demonstrated replicated positive associations with weight gain on antipsychotic drugs include the α_{2A}-adrenoceptor (Park et al. 2006) and the G protein beta3 subunit genes (Bishop et al. 2006; Wang et al. 2005). Evidence for an effect of HTR2A SNPs on antipsychotic-induced weight gain has been inconsistent, although haplotype study carried out on patients treated with olanzapine showed that HTR2A and HTR2C SNPs, in combination with SNPs in GNB3 and the ß$_3$-adrenoceptor, were significantly associated with olanzapine-induced weight gain, with significant additive effects (Ujike et al. 2008). BDNF has a role in the regulation of food intake and there is a reported association of the functional val66met SNP in males (Zhang et al. 2008). Very recently, SNPs in the melanocortin4 receptor gene, a risk factor for obesity, have been shown to be associated with antipsychotic-induced weight gain in both treatment-naïve and chronic subjects (Lett et al. 2011). Another risk factor for obesity, the FTO gene, is not associated with initial weight gain in first-episode patients (Perez-Iglesias et al. 2010) but in as yet unpublished findings we observed that it is associated with body mass in chronic patients where the effect of the FTO gene appears greatly enhanced after long-term treatment with antipsychotic drugs.

Results from GWAS and other multiple SNP approaches contrast substantially with those from such studies of single candidate genes. The first genome-wide linkage study was successful in identifying a possible genetic indicator underlying antipsychotic drug-induced obesity (Chagnon et al. 2004). These authors identified

linkage in the region of the gene for pro-melanin-concentrating hormone, which is involved in the hypothalamic control of food intake; a subsequent study identified association of obesity in patients treated with olanzapine with a polymorphism in this candidate gene (Chagnon et al. 2007).

Genetic factors in genes that influence serum lipids, such as those for apolipoprotein and lipoprotein lipase, have been studied in one report, with small associations with weight gain being identified (Smith et al. 2008). A DNA microarray candidate-gene approach has led to the identification of further genetic factors that might contribute to antipsychotic-induced hyperlipidemia, with polymorphisms in genes for acetyl-coenzyme A carboxylase α and neuropeptide Y emerging as promising candidates (de Leon et al. 2008). Antipsychotics interact with genes controlled by sterol regulatory binding element protein transcription factors (Ferno et al. 2005), and a strong association has been identified between antipsychotic-induced weight gain and polymorphisms in one of these transcription factors, also a risk gene for obesity, insulin-induced gene 2 (Le Hellard et al. 2009), although this has not been fully replicated (Tiwari et al. 2010).

There has been relatively little investigation into the genetic factors determining the individual differences in liability to antipsychotic drug-induced diabetes. There are at least two different processes here: that associated with the often acute onset, reversible diabetes occurring independent of elevations in body fat mass and underlying the rare occurrences of ketoacidosis, and that which is a long-term consequence of obesity and the development of metabolic syndrome. The first acute effect has not been investigated genetically; the latter has been studied primarily in terms of the emergence of metabolic syndrome. One study reported an association with the leptin SNP, but not with the 5-HT_{2C} receptor (Yevtushenko et al. 2008); however, an interaction between the two polymorphisms was observed. Another group did find, and replicated, association of metabolic syndrome with another 5-HT_{2C} receptor SNP (Risselada et al. 2010a) and with the α_{2A}-adrenoceptor gene (Risselada et al. 2010b).

The CATIE cohort has been studied with respect to a variety of metabolic outcomes (Adkins et al. 2011). Unfortunately, none of the genes associated with the 21 significant SNPs identified have previously been found to associate with metabolic consequences of antipsychotic drug treatment. However two of these genes, MEIS2 and PRKAR2B, respectively, associated with risperdone effects on waist and hip circumference and clozapine effects on triglycerides, have reportedly been previously implicated in metabolic function (Adkins et al. 2011). Here again, more gene–gene interaction analysis as well as further large studies are urgently needed to resolve the inconsistences and replicate novel findings.

3.3.4 Prolactin Secretion and Its Consequences

The main candidate gene for effects on hyperprolactinemia is that for the dopamine D_2 receptor, and several studies have demonstrated an association of DRD2 SNPs with prolactin concentrations following antipsychotic treatment (Young et al. 2004; Zhang et al. 2011; Calarge et al. 2009), albeit with some inconsistencies between

the effects of the various SNPs investigated. Although there have been studies of other candidates including the enzyme CYP2D6, responsible for metabolism of risperidone and some other antipsychotics, and the p-glycoprotein pump (ABCB1), these genes have not shown consistent associations with prolactin concentrations. The associated DRD2 polymorphisms have been shown to be associated with some of the consequences of hyperprolactinemia (Calarge et al. 2009), including the inadequately studied problem of sexual dysfunction (Zhang et al. 2011). However the latter authors indicate that despite the association between a DRD2 SNP and male sexual dysfunction following antipsychotic treatment, dopamine D_2 receptor-mediated hyperprolactinemia does not fully explain the sexual side effects of antipsychotic treatment.

3.3.5 Other Side Effects

Clozapine is unique in its efficacy but is restricted by its liability to cause agranulocytosis. This side effect has been investigated in both GWAS and candidate gene analyses; of the various findings (Opgen-Rhein and Dettling 2008), a very strong (O.R. = 16.9) association with a SNP in HLA-DBQ1 has been identified which is of potential value in prognostic clinical assessment (Athanasiou et al. 2011).

Two further major concerns of antipsychotic drug treatment deserve some mention as target phenotypes in pharmacogenetic studies. One is QT interval prolongation; a GWAS study of iloperidone's effect identified association with SNPs in several genes of relevance to cardiac function (Volpi et al. 2009a), while studies on the CATIE cohort (Aberg et al. 2010b) found association with other genes, including one, SLC22A23, of particular relevance to ion transport.

Sedation has received very little attention despite its importance as a consequence of antipsychotic drug treatment. One study has investigated the α_{1A}-adrenoceptor as a candidate gene and found only weak and non-significant associations with side effects including sedation (Saiz et al. 2008).

4 Concluding Remarks

For more than the past decade much effort has been spent in attempting to determine the genetic predictors of the effects of antipsychotic drugs, not only their positive effects on symptom response but also their many and various adverse effects. These studies have often responded to topical concerns, including the increasing emphasis on the importance of negative and cognitive symptoms in determining outcome, and the recognition of the contribution of metabolic side effects such as weight gain to both treatment adherence and further iatrogenic morbidity. It is clear that, despite this effort, identification of the major genetic contributors to the consequences of antipsychotic drug treatment still eludes us. This is, at least in part, due to the fact that only very rarely will variability in the

consequences of antipsychotic treatment depend on genetic polymorphisms in single genes; most effects will be polygenic in nature. Future work will need to overcome the many limitations and discrepancies between studies that are apparent in the current literature. One problem that is rarely acknowledged in pharmacogenetic studies, particularly of cohorts of subjects with chronic schizophrenia, is that of non-adherence to treatment, making blood monitoring of drug a valuable component of any study. There will also need to be a greater recognition that gene–gene interactions and even, as is increasingly apparent in understanding disease pathogenesis, gene–environment interactions may be important in understanding properly the risk factors contributing to poor response or the emergence of adverse events.

Thus, notwithstanding some past attempts at commercialization and one possible exception for clozapine-induced agranulocytosis mentioned above, we still have some way to go before the application pharmacogenetics to predictive clinical testing becomes a valuable reality. Nevertheless, the pharmacogenetics of antipsychotic drugs has progressed enormously, and new findings are beginning to take us towards a better understanding of the mechanisms underlying the effects of these drugs. As the technology develops and genotyping of large numbers of SNPs in large samples becomes cheaper and more accessible, findings from further GWAS will, we hope, converge to give us consistent results. Industry-sponsored drug trials have already contributed useful GWAS findings (e.g., Lavedan et al. 2009); further such studies can reap the benefit of the well-characterized phenotype data that controlled clinical trials provide, although the often highly restrictive inclusion criteria may limit how easy it is to generalize from such findings. More valuable perhaps are studies of first-episode patients initially naïve to drug treatment; recognition of the importance of effective early intervention in psychosis has identified such cohorts ripe for pharmacogenetic study. Consistent and convergent findings from such studies will open up opportunities for predictive genetic testing, once their validity and, importantly, utility in the clinic are established.

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