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Pharmacogenetics of antipsychotic treatment response and side effects

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Abstract

Antipsychotic drugs are particularly interesting in pharmacogenetic studies as they are associated with a large interindividual variability in terms of response and side effects and, therefore, frequently need to be discontinued, requiring switches to other antipsychotics. Any information that allows the prediction of outcome to a given antipsychotic in a particular patient will, therefore, be of great help for the clinician to minimize time and find the right drug for the right patient, thus optimizing response and minimizing side effects. This will also have a substantial impact on compliance and doctor–patient relationships. Moreover, antipsychotic drug treatments are often required for life-long treatment and are also frequently prescribed to the more 'vulnerable' populations: children, adolescents and the elderly. This article focuses on some important studies performed with candidate gene variants associated with antipsychotic response. In addition, important findings in pharmacogenetic studies of antipsychotic-induced side effects will be briefly summarized, such as antipsychotic treatment induced tardive dyskinesia and weight gain.

Keywords

antipsychotic; antipsychotic-induced weight gain; pharmacodynamics; pharmacogenetics; pharmacokinetics; psychopharmacology; schizophrenia side effects

Interindividual variability, in terms of response and occurrence of side effects, remains the primary concern in the management of antipsychotic treatment in schizophrenia. It has been estimated that the proportion of treatment-resistant schizophrenia is between 20 and 40%. This statistic remains unchanged, even after the introduction of several new antipsychotic agents [1]. Treatment failure has been due to a lack of efficacy and the occurrence of adverse reactions. Failure to generate a clinical response can be attributed to the inability to reach a sustained therapeutic concentration of plasma levels (pharmacokinetics) or altered receptor binding/coupling (pharmacodynamics). In addition, since schizophrenia is a heterogenous and complex disease, differences in pathophysiology or symptom clusters, may also affect

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response. A better understanding of the etiology of schizophrenia is likely to be achieved through the study of specific pharmacogenetic subtypes that will contribute to the efficacy of the pharmacogenetic prediction of drug response. It is now generally assumed that pharmacogenetic phenotypes are to be considered as complex traits, resulting from the expression of an organism's genes as well as the influence of nongenetic factors and possible interactions between the two.

Cytochrome enzymes, such as cytochrome (CYP)450 and more specifically, CYP3A4, CYP2D6, CYP1A2, CYP2C9 and CYP2C19, play an important role in the metabolism of most antipsychotics, antidepressants and anxiolytic drugs. Substantial genetic variability among individuals is characterized by these enzymes. Genetic polymorphisms consequently induce an altered enzymatic activity – low activity is likely to lead to high-level drug concentrations and the potential to adverse drug reactions, and high enzymatic activity is likely to lead to reduced plasma levels and reduced drug efficacy.

CYP2D6 is highly polymorphic with more than 60 alleles and 130 genetic variations as a combination of single nucleotide polymorphisms (SNPs) and copy number variations. *CYP2D6* is located on chromosome 22 and is one of five major CYP genes that metabolize the majority of prescribed antipsychotics, antidepressants and anxiolytics. Based on genetic polymorphisms, such as those of *CYP2D6*, and thus, the enzymatic activity, individuals can be classified as poor metabolizers (PMs), when both alleles are nonfunctional; intermediate metabolizers (IMs), when one allele is nonfunctional or both the alleles are partially defective; extensive (normal) metabolizers (EMs), when both alleles are functional, or ultrarapid metabolizers, exhibiting the highest activity owing to possession of more than two functional genes. The usefulness of predictive testing for the ultrarapid metabolizer, IM and PM phenotype has been suggested to be particularly valid in antidepressant treatment, bearing strong implications for antipsychotic treatment (AmpliChip® CYP450 Test) (Table 1) [2–4,101].

Most of the pharmacogenetic research to date has been conducted with a limited consideration of environmental influences (e.g., diet and smoking) and demographic or clinical factors (e.g., age, sex, ethnicity and comorbidities). This may partly explain the difficulties encountered in correlating genetic variants with observed treatment variability and in replicating reported findings. Thus, the inclusion of environmental factors is important in future studies. In the last two decades, most pharmacogenetic studies have used candidate gene approaches, selecting genes to be investigated from current pharmacological knowledge, or derived from imaging or animal studies for the identification of response-related genes. In addition to candidate gene studies, a recent expansion of investigations in the areas of genes related to metabolism, transport and neuronal plasticity has advanced our knowledge in pharmacokinetic and pharmacodynamic processes.

Pharmacogenetics of antipsychotic treatment response

Antipsychotics are generally categorized as typical (e.g., chlorpromazine, haloperidol and perphenazine), or atypical (e.g., clozapine, olanzapine, risperidone and quetiapine). Typical antipsychotics are often very effective in treating the positive symptoms of schizophrenia.

Unfortunately, they can also cause undesirable motor side effects, such as tardive dyskinesia (TD). By contrast, atypical antipsychotics possibly treat both positive and negative symptoms of schizophrenia with greater efficacy; however, they can also induce adverse metabolic effects, such as weight gain.

Among the atypical antipsychotics, clozapine has been reported to be effective for 30–60% of schizophrenia subjects that are refractory to typical and atypical antipsychotics [5]. Through binding to dopamine and several serotonin receptor subtypes, clozapine is thought to provide antipsychotic effects, although the actual mechanism of action has not yet been fully elucidated. Pharmacogenetic studies of antipsychotic drug response have largely focused on clozapine. This may be owing to longer treatment periods with these patients. Previous genetic investigations have defined treatment-resistant schizophrenia in two ways. Kane *et al.* defined treatment resistance as: at least three periods of treatment in the preceding 5 years with antipsychotics (from at least two different chemical classes) at doses greater than 1000 mg/day of chlorpromazine equivalents for a period of 6 weeks, each without significant symptomatic relief and no period of good functioning within the preceding 5 years [6]. A second definition of treatment-resistant schizophrenia, based on monotherapy antipsychotic treatment is proposed by Inada *et al.* This definition proposes that schizophrenia patients are treatment resistant when they had been receiving antipsychotic dosages (chlorpromaze equivalents) of 1000 mg/day for more than 1 year and, in addition, had been hospitalized for more than 1 year [7].

Studies from several research groups elucidate the pharmacogenetic mechanisms involved in clozapine response

Using the Kane *et al.* definition of treatment-resistant schizophrenia [6], a significant genotypic association between treatment-resistant schizophrenia and the A2518G variant on the *MCP-1* gene was reported [8], G-allele carriers of the monocyte *MCP-1* were reported to be associated with treatment-resistant schizophrenia [8]. The underlying hypothesis was based on an immunemodulating effect of antipsychotics, which may act on neurotransmitter metabolism by inducing the proinflammatory cytokine system [9].

Using criteria defined by Indala *et al.* [7], three reports published in Asian samples failed to find an association between the Val158Met polymorphism of the *COMT* gene (involved in the degradation of dopamine) with clinical manifestations and response to antipsychotics in schizophrenia patients. However, the daily antipsychotic dosage that patients received during their maintenance therapy was significantly higher in patients with homozygous methionine (Met/Met) genotype than in the other patients, suggesting that this variant may help in the understanding of treatment-resistant features of schizophrenia. Since many atypical antipsychotics do act as serotonin receptor antagonists, several studies have been conducted investigating serotonin receptor polymorphisms. Comparing treatment-resistant and nontreatment-resistant schizophrenia patients, Ji *et al.* found that a 3 bp deletion allele, located in the serotonin receptor *HTR3B* promoter region, was significantly more frequent in their treatment-resistant group than the insertion allele [10]. Patients with the Thr/Thr *HTR3A* genotype, who were taking significantly higher daily dosages of antipsychotic

medication, did not demonstrate significant results in the serotonin receptors and four genes [11].

Using criteria defined by Kane *et al.* [6], clozapine response was associated with the *HTR2A* His452Tyr variant in a Caucasian/ African–American sample, [12]. Other variants, such as *HTR2A* Thr102Cys, *HTR2C* Cys23Ser and *HTR6* Thr267Cys, in the serotonergic system did not reveal any significant association [12–14]. In the same sample, no associations for *DRD1* and *DRD2* gene variants in Caucasians were found [15–17]; however, an association was found with clozapine response in their African–American subsample for *DRD1* rs265976, *DRD2* Taq1A, *DRD2* Taq1B and *DRD2* rs1125394. Based on the findings implicating the *GSK-3*β gene with schizophrenia, no association between *GSK-3*β gene variants and response to schizophrenia was detected in the Caucasian sample [18].

In another study, the *TNF*-α gene was used as a candidate since TNF-α is a cytokine with modulatory effects on the synthesis of neurotransmitters [19]. Significant improvement on the Brief Psychiatric Rating Scale (BPRS) was noted by clozapine-treated patients with the A-allele for the Gly308Ala variant of the *TNF*-α gene compared with patients without allele A [20].

G proteins are involved in the interface between external receptor activation and intracellular signaling and are, therefore, implicated in the mechanism of actions of antipsychotics. An examination of the *GNB3* functional Cys825Thr polymorphism has shown that Caucasians with the Cys/Cys genotype improved significantly in BPRS change scores [21].

Malhotra *et al.* did not find an association between the Thr102Cys and the His452Tyr variants of the *5-HT2A* gene and clozapine response (22). However, by using a larger European sample, Arranz *et al.* have reported a significant association between response in treatment-resistant schizophrenia patients with the *HTR2A* Thr102Cys and *HTR2A* His452Tyr, but not the *HTR2A* Cys516Thr polymorphism [23–25]. *HTR2C* Cys23Ser was also associated with clozapine response [26], although this finding was not supported by others [25]. The dopamine *DRD3* Ser9Gly and histamine H2 Gly1018Ala variants have been significantly associated with clozapine response [27.28]. No significant association with treatment response has been found with other serotonin gene variants [29], dopamine gene variants (*DRD2* and *DRD4*) [30,31], *HTTLPR*, *HTT* VNTR or with cytochrome P450 gene variants (*CYP2D6*) [32]. There have been modest treatment response associations with the *HTR6* Thr267Cys polymorphism [33] and the *BDNF* Val66Met [34] functional variant in a Chinese Han sample. No significant associations were observed for *HTR2A* Thr102Cys [35], *HTTLPR* [36], *APOE*ε4 [37] and *ADRA2A* Cys1291Gly [38] variants. Hong *et al.* have examined clozapine dosage as an alternative phenotype related to response; demonstrating that a marginally higher clozapine dosage is needed for *GRIN2B* C2664C patients than 2664T carriers [39].

A number of studies have evaluated genetic prediction of treatment response in patients treated with an antipsychotic other than clozapine. There have been reports of an association of *DRD2* with haloperidol response [40] and bromperidol response [41]. The P-glycoprotein is coded by the *MDR-1* gene and is located at the blood–brain barrier, potentially

modulating the concentration of various antipsychotics in the brain. Interestingly, *MDR-1* gene variants were also associated with bromperidol response [42]. Risperidone efficacy has been associated with *HTR1A* [43], *HTR2A* [44], *DRD2*, *COMT* [45] and *DRD4* [46] gene polymorphisms. Olanzapine response has been associated with 5-*HTR2AI2C* [47], *GNB-3* [48], choline acetyltransferase [49] and *MDR-1* genes [50].

In contrast to treatment-resistant patients, Lencz *et al.* have analyzed 61 first-episode schizophrenia patients and reported that two promoter polymorphisms (A-241G and −141C insertion/deletion variants) of the *DRD2* gene were associated with timing of clinical response; the G carriers (A-241G) responded faster and the −141C deletion carriers responded slower to antipsychotic treatment [51].

Pharmacokinetic analyses from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, by Feng *et al.* [52] found that poor risperidone clearance was clearly associated with the PM status of CYP2D6 [53]. In this study, risperidone and 9-OH risperidone concentration data distinguished *CYP2D6* polymorphism-related subpopulations. The different proportions of individuals assigned to the PM, IM or EM groups were significantly different. Among these results were differences between African–American and white populations ($p < 0.001$). The results from this study highlight that an adequate understanding of the effects of a drug is contingent upon the characteristics of pharmacokinetic data.

With research on the antipsychotic response being relatively new, it is noticeable that the effect of modulation in pharmacokinetically relevant genes (such as liver enzymes *CYP2D6*) on the drug levels in blood plasma is estimated to be larger than for genes that modulate improvement in psychopathology (see later) [54]. In other words, gene variants associated with response have smaller effect sizes. This is the most likely explanation as to why genetic tests for antipsychotic response are not available even though many studies have reported positive associations and some of these findings have been replicated in independent samples. The most promising findings thus far were in the dopaminergic and serotonergic systems, but these results have not demonstrated enough reliability to be used in routine clinical care and need to be further validated. The minor magnitude is explained by the fact that, functionally, they often modulate their effect cooperatively, so that several variations need to be investigated together for one effect.

To overcome these limitations and to increase the power of the studies on genes with the minor magnitude, a combination approach is employed. For example, the study by Arranz *et al.* examined a relatively large number of candidate gene markers in clozapine response, both alone and in combination. They reported that most of the 19 analyzed variants were not, by themselves, associated with treatment response, that is, no significant associations were found for *ADRA2A* Gly261Ala, *ADRA2A* Cys1291Gly, *ADRA1A* Arg492Cys, *DRD3* Ser9Gly, *H1* Leu449Ser, *H2* Gly1018Ala, *HTR3A* Cys178Thr, *HTR3A* Gly1596Ala, *HTR5A* Ala12Thr, *HTR5A* Gly19Cys and a *HTT* VNTR [25]. However, a combination of six of these variants (*HTR2A* Thr102Cys, *HTR2A* His452Tyr, *HTR2C* Gly330Thr/Cys244Thr, *HTR2C* Cys23Ser, *HTTLPR* and *H2* Gly1018Ala) resulted in 76.7% success in the prediction of clozapine response in a discriminant function type of analysis. However, no

other group has yet been able to complete the full analysis of these six variants, thus, the result remains unreplicated [55]. The British company LGC (Middlesex, UK) is employing this strategy in an effort to develop a predictive test for clozapine efficacy, analyzing the genetic variance in the serotonin system genes, receptors and transporters in combination [56].

In addition, as schizophrenia is a complex disease, probably consisting of several subtypes, pharmacogenetic effects of antipsychotics should ideally be studied in specific, more homogeneous subgroups, as different genes may be involved in the molecular mechanisms of those. The subclasses might be defined by the patients' diversity due to environmental influences or treatment response variability with the risk of side effects. This approach is used in the study by Güzey *et al.*, where the influence of polymorphisms in dopamine and serotonin system genes is investigated on the occurrence of extrapyramidal symptoms during treatment with antipsychotic drugs, and which produced marginally significant p-values for *DRD2* Taq1A ($p = 0.04$) and *DAT1* VNTR ($p = 0.03$) [57]. A study by Shen *et al.* also observed the effect of *DRD2* Taq1A on the response to antipsychotics correlating with clinical factors in acutely schizophrenic patients [58]. More recent studies using larger samples, as in the CATIE study, allow for more robust analyses on sub-phenotypes and reported significant findings with a rare allele in the *RIMS1* gene, discontinuation of quetiapine or a variant in the *GRM-8* gene and improvement in verbal memory [59]. Another interesting finding arising from the CATIE study has been the association between two variants of the *RGS4* gene and treatment response to antipsychotics, considering outcomes in different ethnicities.

Pharmacogenetics of antipsychotic-induced side effects

Antipsychotics can induce a variety of potential side effects that may lead to a discontinuation of a drug despite a good response. The most common, and hence, the most investigated in genetic studies Include antipsychotic-induced TD and induced weight gain. TD is characterized by abnormal involuntary movements and occur relatively frequently (0.5–65%) [60] with the use of older antipsychotic medication. Dyskinetic movements are potentially irreversible and severity is mostly assessed with the Abnormal Involuntary Movement Scale (AIMS). There is compelling evidence for a genetic component in the etiology of TD as suggested by family studies [61]. The most promising pharmacogenetic findings were reported in variants of the *CYP2D6* (*10 allele), *CYP1A2* (*1F allele), *DRD2* (Taq1A or rs1800497 SNP), *DRD3* (Ser9Gly or rs6280 SNP) and the *MnSOD* (Ala9Val or rs4880 SNP) genes (reviewed in Thelma *et al.* [62] and Müller *et al.* [63]).

Weight gain induced by antipsychotics can have dramatic effects in susceptible individuals, leading to medical conditions such as diabetes mellitus, cerebrovascular diseases and other substantial life-shortening comorbidities. Although weight gain can be induced by virtually every antipsychotic, this side effect has become much more prevalent with newer antipsychotics, in particular with clozapine and olanzapine. Clinicians are generally well aware of the risk of weight gain and some counteractive measures appear to reduce or minimize weight gain (such as diet, exercise or pharmacological interventions). However, risk prediction for weight gain would be of great value, and there is support from twin and

family studies that the interindividual variability observed in antipsychotic-induced side effects is related to genetic factors [64]. Over the past years, numerous candidate gene studies have been conducted with this particular side effect and most robust findings (i.e., replicated in at least one independent sample) have been reported for polymorphisms of the *5-HT2C* (−759Cys/Thr), leptin (−2548Ala/Gly), *SNAP-25* (3′UTR polymorphisms) and the *ADRA2A* genes (for review, see Müller and Kennedy [65]). Many other significant associations were reported that will need to be confirmed in other samples, such as with the *INSIG2* gene or the *CB-1* gene [66.67]. Overall, it appears that genetic studies in antipsychotic-induced side effects have resulted in a variety of interesting results. The candidate gene strategy could perhaps be more successful when investigating antipsychotic-induced adverse effects as compared with reponse. However, effect sizes of any single genetic finding are relatively small and therefore a prediction test will need to include a variety of different gene variants to achieve meaningful, and clinically relevant, predictive power.

Future perspective

The advent of chip-based genome-wide investigations has ushered in a new era of genetic research. Pharmacogenetic studies of antipsychotic drugs have begun to identify several genes that may be implicated in diverse phenotypes, such as plasma levels, drug efficacy and development of drug-induced adverse events. These genes require further study, as well as careful functional genomic analyses to identify the specific molecular events that may produce clinical effects in order to contribute to future drug development strategies. Undoubtedly, the introduction of pharmacogenetic tests in the clinical arena will be facilitated if they are robust enough to stand out above the variations among different clinical settings. Clinical genetic tests that are based on the pharmacokinetically involved genes and that aim to predict the response to antipsychotics are making their way through the market of pharmaceuticals. The tests identify *CYP450* alleles, two providers being Roche (NJ, USA) AmpliChip CYP450 Test and Luminex (TX, USA) Tag-It™ Mutation Detection Kit. Such tests that allow detection of non-normal/EMs that help to estimate serum levels for several antipsychotics, are already being used in clinical psychiatry and are likely to become used more often in clinical practice in the near future. An ongoing study by our group is utilizing these tests to investigate the influence of genetic drug-response prediction on patient and physician attitudes towards these technological advances [102], Finally, it is hoped that understanding the genetic variants involved in antipsychotic response and induced side effects will help to illuminate the pathological and etiological mechanisms that underlie the complex syndrome we refer to as schizophrenia.

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Executive summary

Pharmacogenetics of antipsychotic treatment response

- Definitions of treatment response vary.
- Current definitions of treatment response are based on dopamine receptor (DR)D2 antagonism, pharmacological profiles (i.e., typical vs atypical antipsychotics), and ability to effectively treat positive and negative symptoms.
- Pharmacogenetic research on clozapine may improve antipsychotic therapy.
- Clozapine is effective in treating 30–60% of refractory schizophrenia subjects.
- Clozapine is known to affect DRD2 and serotonin receptor binding.
- Ease of access to blood samples from subjects treated with clozapine and its known efficacy may provide novel data on the molecular basis of antipsychotic efficacy.

Treatment resistance

- Two main definitions of treatment resistance in schizophrenia research have been utilized based on periods of treatment without adequate response, drug dosages and periods of poor functioning.
- Treatment resistance can be considered a useful phenotype to examine candidate genes in schizophrenia since research on associations between treatment resistance and gene variants have increased the understanding of treatment-resistant features of schizophrenia.
- Research comparing treatment-resistant versus nontreatment-resistant subjects have shown mixed results.

Treatment-resistant treatment response: recent research findings

- Association studies have examined treatment resistance to clozapine and specific gene variants such as: *HTR2A, HTR2C, HTR6, DRD1, DRD2, GSK-3β, GNB-3, HTR5A, CYP2D6, HTTLPR, APOE, ADRA2A, NMDA* and *GRIN2B*.
- Studies have also shown associations with antipsychotics other than clozapine, such as: haloperidol, brompenidol, risperidone and olanzapine.
- Data from the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE)-SZ study highlight the importance of pharmacokinetics of *CYP2D6* in understanding drug metabolism.

Current challenges in pharmacogenetic research

- Pharmacokinetically relevant genes and modulation on plasma drug levels are easier to measure (major magnitude) relative to the minor magnitude of measurement required in pharmacodynamic analyses.
- Pharmacodynamic analytic challenges have resulted in limited, clinically significant genetic tests.
- Analysis of several variants together ⟨in combination⟩ has resulted in promising research and prediction of clozapine response.
- Heterogeneity of schizophrenia (subtypes) needs to be considered in studies as different genes may be involved.

Future perspective

- Chip-based genome-wide investigations have ushered in a new era of genetic research.
- Functional and structural genomics analyses will make important contirbutions to rational drug design strategies.
- Clinical tests are making their way through the market of pharmaceuticals.

Table 1

CYP2D6 response phenotypes and associated antipsychotic dosing.

Phenotype	Suggested definitions	Prevalence rates	Dosing suggestions	Antipsychotics metabolized by 2D6
Poor metabolizer	No CYP2D6 activity Two nonfunctional alleles	7% Caucasian 1–3% other races	Phenothiazines: may be treated with approximately one half the dose Haloperidol: may be treated with lower doses Risperidone: may be treated with approximately one half the dose (can be identified by therapeutic drug monitoring)	Clozapine Haloperidol Perphenazine Quetiapine Risperidone Thioridazine
Ultrarapid metabolizer	Duplication of an active gene (i.e., two or more active variants)	1 % Sweden 10% South European 29% North African[†] and Middle Eastern 1–2% USA in Caucasian and African–American	Haloperidol: may need increased dose Risperidone: may need higher doses but not been well studied	
Extensive metabolizer	At least one active copy but less than three copies	Most common among normal research subjects Most prevalent among East Asians		
Intermediate metabolizer[‡]	Lower than normal activity only one active copy Less than 0 but greater than one normal active copy			

[†]Published prevalence rates are unreliable since a recent comprehensive, worldwide study suggested that up to 40% in North African and more than 20% in some populations of Oceania are ultra metabolizers.

[‡]The definition for intermediate metabolizers is complicated by race and drug specificity.

Adapted from [51].