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REVIEW ARTICLE

Pharmacogenetics in schizophrenia: a review of clozapine studies

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Objectives: Clozapine is quite effective to treat schizophrenia, but its use is complicated by several factors. Although many patients respond to antipsychotic therapy, about 50% of them exhibit inadequate response, and ineffective medication trials may entail weeks of unremitted illness, potential adverse drug reactions, and treatment nonadherence. This review of the literature sought to describe the main pharmacogenetic studies of clozapine and the genes that potentially influence response to treatment with this medication in schizophrenics.
Methods: We searched the PubMed database for studies published in English in the last 20 years using keywords related to the topic.
Results and Conclusions: Our search yielded 145 studies that met the search and selection criteria. Of these, 21 review articles were excluded. The 124 studies included for analysis showed controversial results. Therefore, efforts to identify key gene mechanisms that will be useful in predicting clozapine response and side effects have not been fully successful. Further studies with new analysis approaches and larger sample sizes are still required.

Keywords: Schizophrenia; clozapine; polymorphisms; pharmacogenetics; adverse effects

Introduction

Schizophrenia is an oft-devastating neuropsychiatric illness with a lifetime prevalence of 0.8%.[1] Its clinical manifestations usually arise in late adolescence and early adulthood. Schizophrenia is a complex and highly heritable disorder with a significant impact on public health. In Brazil, patients with schizophrenia occupy 30% of psychiatric hospital beds, or about 100,000 beds/day. In addition, 14% of first outpatient psychiatric visits are provided for schizophrenic patients, and schizophrenia is the fifth most common illness leading people to apply for social security disability benefits.[2]

Clozapine is an antipsychotic drug widely used in the treatment of schizophrenia. It is more effective than traditional antipsychotics for patients with poor response or resistance to treatment.[3] The antipsychotic effect of clozapine has been attributed in part to its ability to block stimulation of the serotonin 2A receptor (5-HT2A), particularly when associated with weak dopamine D2 receptor blockade (DRD2).[4] The action of this agent is not limited to 5-HT2 receptors (in particular 5-HT2A and 5-HT2C) and, to a lesser extent, to D2 receptors; it also acts on other dopaminergic (D1, D3, D4), histaminergic, adrenergic and cholinergic receptors.[5]

The variability of response to clozapine treatment in schizophrenia patients has a marked impact on clinical practice. Approximately 50% of patients who do not respond to typical antipsychotics benefit from clozapine.[6] Additionally, clozapine is associated with side effects, including sedation, drowsiness, dizziness, hypersalivation, headache, constipation, generalized seizures, anticholinergic effects, orthostatic hypotension, weight gain, and agranulocytosis.[7]

The effect of psychopharmacological treatment depends on many factors that influence response. The heterogeneity of response is partly attributable to physiological and environmental factors affecting individuals, including age, sex, ethnicity, liver and kidney function, diet, co-medication, severity and type of illness, and alcohol and tobacco use.[8] In some cases, however, response heterogeneity cannot be explained only by these factors, and genetic aspects should be considered as a potential source of variability.

In a study of monozygotic twins, Vojvoda et al.[9] showed the importance of genetic factors in predicting the response to clozapine. Symptom improvement following clozapine treatment showed strong concordance in monozygotic twin pairs. Similarly, the contribution of genetics to antipsychotic-induced weight gain was addressed in studies of monozygotic twins and sib pairs,[10-12] suggesting a genetic contribution of 60-80%. Two case reports of agranulocytosis induced by clozapine in monozygotic twins with schizophrenia provided evidence for a genetic basis of this adverse event.[13,14]

Pharmacogenetics is the study of the influence of genetic variants on response to medications and adverse effects, as well as the consequent understanding of how genes interact to determine individual variability in this response. The goal of pharmacogenetics is to find polymorphisms in

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genes encoding proteins and enzymes involved in the transport, metabolism, and action of drugs, enabling knowledge of the applicability of a particular drug and increasing its effectiveness.[15] Pharmacogenomic studies consider the genome as a whole and do not rely on prior knowledge of candidate genes or specific hypotheses.[16]

The detection of individual genetic differences in the response to clozapine may provide new strategies for the treatment of major psychoses such as schizophrenia. The application of pharmacogenetic data has been analyzed in several studies investigating the impact of genetic polymorphisms on adverse effects and response to treatment with clozapine. The objective of the present literature review was to discuss the main results of these studies.

Methods

We searched the PubMed database for scientific articles published in English in the last 20 years about the use of clozapine to treat schizophrenia. The last search was performed on October 11, 2012. The following keywords were used in the search: antipsychotic or clozapine combined with polymorphism or genetics. Combinations of these keywords with schizophrenia, pharmacogenetic, pharmacogenomic, side effects, adverse effects, genotype, and allele were also used. Further searches were conducted based on the list of references of the selected articles and included in this review when relevant.

The articles were selected according to the following criteria: studies evaluating the impact of genetic polymorphisms on 1) treatment response and/or side effects, and 2) clozapine-treated patients or treatment with no more than three antipsychotics, when clozapine was the main prescribed drug (since findings from studies exploring mixed antipsychotics provided unclear and often contradictory results). Studies containing no information about the type of antipsychotics were not included.

Results

One hundred and forty-five articles met the search and selection criteria. Of these, 21 review articles were excluded. To supplement the data of the 124 remaining studies, six meta-analyses were also assessed.

The articles were divided according to their focus: studies investigating the effect of genetic and pharmacokinetic variation and studies investigating the effect of pharmacodynamic and genetic variability on treatment response and adverse effects. Table 1 summarizes significant results regarding response to treatment. Table 2 shows findings related to adverse effects. Nevertheless, these results are uncertain and should be considered cautiously, since several studies did not report the same associations.

Genetic variants in metabolizing enzymes and response to treatment

Most drugs used in clinical practice that act on the central nervous system (CNS) are extensively metabolized in the liver by enzymes of the cytochrome P450 (CYP) system.[16,85,86] Pharmacogenetic studies report that phenotypes generated by the activity of cytochrome P450 isoenzymes strongly influence the sensitivity or response to medication because of different elimination, concentration, and biotransformation rates.[85] These phenotypes are genetically determined and show great variation between different individuals. Variations in genes coding for CYP enzymes can result in absent, deficient, or increased activity.[87]

Eap et al.,[21] evaluating cytochrome P450, family 1, subfamily A, polypeptide 2 (*CYP1A2*) and plasma levels of clozapine, found that treatment non-responders had low levels of the drug and the *1F/*1F genotype, suggesting that this variation is associated with resistance to treatment. However, van der Weide et al.[88] observed that mean clozapine ratios and daily doses did not vary significantly between patients with different *CYP1A2* genotypes, neither among smokers nor non-smokers.

The cytochrome P450, family 2, subfamily D, polypeptide 6 gene (*CYP2D6*) is highly polymorphic, and more than 90 allelic variants and subvariants have been described.[87] Three studies (one conducted in Brazil) evaluating polymorphisms in *CYP2D6* were unable to find a significant association between *CYP2D6* alleles and response to clozapine.[17,89,90] Dahl et al.[91] evaluated the importance of genetic factors for the metabolism of clozapine and did not find significant differences in the plasma concentrations or any of the pharmacokinetic parameters of clozapine between poor and extensive metabolizers of debrisoquine. Since clozapine is metabolized minimally by this enzyme,[92] more studies on clozapine metabolism would be helpful.

However, variations in metabolizing enzymes cannot be fully responsible for the heterogeneity observed in the response of an individual to treatment. The pharmacological effects of the medication are not typically monogenic traits; moreover, they are determined by the interposition of several genes encoding proteins involved in multiple pathways that determine the disposition and effects of drugs in addition to their metabolism.[85]

Genetic variants in drug target proteins and response to treatment

Since clozapine is a high-affinity antagonist of dopamine receptors, initial studies focused on the relationship between the dopamine D4 receptor gene (*DRD4*) and the response to clozapine. Zhao et al.[29] and Hwang et al.[30] found significant associations between polymorphisms in *DRD4* and response to clozapine. However, most studies were unable to detect this significant association.[93-98]

The dopamine D3 receptor gene (*DRD3*) is important because antipsychotics show high affinity for this receptor, especially in the mesolimbic system.[99] Two studies analyzed the Ser9Gly polymorphism in *DRD3*, and the Ser/Ser genotype was found to be more frequent among non-responders to clozapine,[27,28] but other studies failed to replicate these findings.[100-106] The importance of

Table 1 Reported associations between genetic polymorphisms and clozapine response*

Gene/Polymorphism†	Ethnicity	Sample size	p-value
ABCB1			
3435C>T[17]	Caucasian	75	0.04
3435C>T/2677G>T[18]‡	Caucasian	60	0.028
rs7787082, rs10248420[19]	Korean	96	< 0.001
COMT			
Val158Met[20]	Caucasian and African American	84	< 0.01
CYP1A2			
-163C>A[21]	Caucasian	33	0.01
DRD1			
rs265976[22]	African American	49	0.033
-48A>G[23]	Caucasian	13	0.05
DRD2			
-141C Ins/Del[24]	Caucasian and African American	72	< 0.05
Taq1A/Taq1B/rs1125394c[25]	African American	49	< 0.02
Taq1B/rs1125394[26]‡	African American	31	< 0.02
DRD3			
Ser9Gly[27]	Caucasian	133	0.04
Ser9Gly[28]	Pakistani	32	0.033
DRD4			
VNTR 48 pb[29]	Chinese	81	0.05
VNTR 48 pb[30]	Caucasian	183	0.002
120bp indel[30]	African American	49	0.004
Intron 1 (G)(n)[30]	African American	49	0.014
DTNBP1			
Several[31]‡	Caucasian and African American	88	0.007
GFRA2			
rs1128397/rs13250096/rs4567028[32]‡	mostly Caucasian	140	< 0.04
GNB3			
825C>T[33]	Caucasian	145	0.01
825C>T[34]	Brazilian	121	0.02
HTR2A			
102T>C[35]	Caucasian	149	0.001
102T>C[36]	Chinese	99	0.003
His452Tyr[37]	Caucasian and African American	184	0.01
His452Tyr[38]	Caucasian	153	0.008
-1438G>A[39]	Caucasian	274	0.0006
HTR2C			
Cys23Ser[40]	Caucasian	162	0.005
HTR3A			
rs10622613, rs2276302[41]	Indian	101	0.02
rs1062613[42]	Caucasian	140	0.04
HTR6			
267T>C[43]	Chinese	99	0.04
NRXN1			
rs1045881[44]	Caucasian	302	0.03
OXT			
Several[45]	Caucasian and African American	140	0.04
SLC6A3			
rs2652511/rs2975226/rs2963238[46]‡	Chinese	320	0.01
SLC6A4			
HTTLPR[47]	Caucasian	200	0.04
HTTLPR[48]	Brazilian	116	0.01
TNFA			
-308G>A[49]	Caucasian and African American	190	0.015

* Including only significant association studies. See text for supplementary information about other nonsignificant studies concerning these genes.
† See text for abbreviations.
‡ Haplotype: polymorphisms analyzed as a unique block.

Ser9Gly was confirmed in a meta-analysis, where significant differences were found when the *DRD3* Ser9 allele or the Ser/Ser genotype were compared between responders and non-responders to clozapine in a sample of 233 schizophrenia patients.[107] However, a more recent meta-analysis with a much larger sample size (n=758) reported a negative but consistent trend for the *DRD3* Ser9 allele and poor clozapine response.[108]

Another obvious candidate for pharmacogenetic studies is *DRD2*, because clozapine has an affinity for this receptor.[109] Studies with *DRD2* polymorphisms produced contradictory results. Positive results were found by Malhotra et al.[24] and Hwang et al.,[25,26] not corroborated by Arranz et al.,[110] Reynolds et al.,[111] and Hwang et al.[106] In a meta-analysis including 889 individuals, Zhang et al.[112] concluded that single-nucleotide polymorphisms (SNPs) in the DRD2 promoter region, such as -141C Ins/Del, may be particularly important in predicting clinical response to various antipsychotic drugs.

Recently, Xu et al.[46] found a haplotype combination of genetic variants in the dopamine transporter gene (DAT or *SLC6A3*) significantly associated with response to clozapine, but in a previous study this association was not observed.[113] Two studies analyzed *DRD1* and found a significant association with clozapine response in African Americans[22] and Caucasians,[23] but another study was unable to replicate this association.[106] Hwang et al.[30] evaluated the importance of *DRD5* and found no significant association with clozapine response.

Of the seven subtypes of serotonin receptors (5-HT1-7), 5-HT2 subtypes are the strongest targets of atypical antipsychotic drugs.[114] The 102T>C polymorphism in *HTR2A* was studied by Arranz et al.[35] They found a significant association between the 102C allele and failure to respond to clozapine in schizophrenic patients treated with the drug. These results were subsequently replicated by Yu et al.,[36] but several other studies did not achieve similarly significant results.[37,115-119] Another less common polymorphism is *HTR2A* (His452Tyr), which seems to produce functional effects in vitro, providing both positive[37,38] and negative results.[116,117,118] The -1438A>G polymorphism was significantly associated with clozapine response in one study,[39] whereas another study failed to detect this association.[120] A meta-analysis of association studies on the 102T>C and His452Tyr polymorphisms in 733 clozapine-treated patients found an association between these two polymorphisms and poor response to medication.[121]

The *HTR2C* Cys23Ser polymorphism was associated with response to clozapine by Sodhi et al.,[40] but other studies did not replicate these results.[37,122,123] The serotonin receptor type 6 gene (*HTR6*) was analyzed in two studies; the first study observed a significant association between the *HTR6* and the 267T>C polymorphism,[43] whereas the second study was unable to replicate this result.[124] Individual studies evaluated the influence of *HTR5A*[125] and *HTR3B*,[126] and no significant results were found. Unclear results were observed for *HTR3A*.[41,42,126]

The serotonin transporter gene (HTT or *SLC6A4*) has also been studied. Arranz et al.[47] observed an association between response to clozapine and the HTTLPR (HTT repeat promoter length) polymorphism in the promoter region of the gene. They found that individuals homozygous for the short allele tended to show a poor response to treatment with clozapine. Kohlrausch et al.[48] observed a significant association between the presence of short allele and failure to respond to clozapine in Brazilian schizophrenia patients. Two previous studies did not find a significant relationship.[127,128]

Arranz et al.,[102] analyzing different polymorphisms, found a combination of six polymorphisms in neurotransmitter receptor-related genes predicting clozapine response (*HTR2A* 102T>C and His452Tyr, *HTR2C* -330-GT/244-CT repeat and Cys23Ser, 5HTTLPR, HRH2 -1018G>A). This finding constituted a great potential for pharmacogenetic studies as a key for future improvement and individualization of clinical treatment of patients with schizophrenia. However, these results have not been replicated with the same approach so far, and the pharmacogenetic test designed for use in clinical practice is no longer available on the market.[6]

Genetic variants in other classes of proteins and response to treatment

Since catecholamine receptors are G-protein-coupled (GPCRs) and antipsychotics exert their effects by competitive antagonism of postsynaptic GPCRs, this protein may have an important influence on the function of dopaminergic and serotoninergic systems. Müller et al.[33] found the 825C>T polymorphism in the gene encoding the small Beta-subunit 3 of G proteins (*GNB3*) to be associated with response to clozapine in patients with schizophrenia. This result was corroborated by the study conducted by Kohlrausch et al.[34] in Brazilians, where homozygosity for the 825T allele was more frequent among non-responders to treatment with clozapine.

Studies involving other genes with significant associations include variants in the following genes: ATP-binding cassette sub-family B member 1 (*ABCB1*),[17-19] catechol-*O*-methyltransferase (*COMT*),[20] dystrobrevin binding protein 1 (*DTNBP1*),[31] GDNF family receptor alpha 2 (*GFRA2*),[32] neurexin 1 (*NRXN1*),[44] and oxytocin prepropeptide (*OXT*).[45] In contrast, the adrenoreceptor alpha 2A (*ADRA2A*),[129,130] brain-derived neurotrophic factor (*BDNF*),[131] human glutathione peroxidase (*GPX1*),[132] glutamate receptor ionotropic *N*-methyl D-aspartate 1 (*GRIN1*),[106] 2A (*GRIN2A*)[106] and 2B (*GRIN2B*),[106,133] histamine receptor H1 (*HRH1*),[134] histamine receptor H2 (*HRH2*),[134] and superoxide dismutase 2 mitochondrial (*MNSOD*)[132] were investigated and no significant associations were observed. The tumor necrosis factor gene (*TNF*) showed significant[49] and nonsignificant[135] results. As these studies are mostly unique, confirmation of the results is necessary.

Studies assessing the adverse effects of clozapine

There is strong evidence that the serotonergic (5-HT) system plays a role in the regulation of feeding behavior;

thus, clozapine-induced weight gain could be explained by dysfunction of this neurotransmitter.[16] Several studies linking *HTR2C* (Cys23Ser and -759C>T) polymorphisms to weight gain have been conducted, with significant[57-60] and nonsignificant[136-140] results. A recent meta-analysis of 522 schizophrenia individuals suggested that the -759C allele is associated with weight gain.[141] However, this study detected a relevant publication bias, suggesting preferential publication of significant findings over non-significant observations. A previous meta-analysis of 588 subjects reporting data on -759C>T supported the existence of an association between this individual marker and the side effect only under a fixed model.[142] Both analyses included studies with mixed antipsychotics. Recently, Hill & Reynolds[143] established -759C>T as a functional polymorphism and suggested disruption of DNA-protein interactions as a mechanism whereby *HTR2C* expression is perturbed, leading to an influence on antipsychotic-induced weight gain.

A moderate association between the *GNB3* 825C>T polymorphism and weight gain[56] was not observed in a previous study.[144] Other genes with significant associations include *ADRA2A*,[51,52] *BDNF*,[53] *DRD2*,[54,55] adiponectin, C1Q and collagen domain containing (*ADIPOQ*),[50] melanocortin 4 receptor (*MC4R*),[63] protein kinase beta 2 non-catalytic subunit (*PRKAB2*),[65] protein kinase gamma 2 non-catalytic subunit (*PRKAG2*),[50] and roundabout axon guidance receptor homolog 1 (*ROBO1*).[66] Controversial results were observed for *HTR2A* [57,136] (positive and negative results, respectively), insulin induced gene 2 (*INSIG2*)[60,61,145] (positive results only in the second study), leptin (*LEP*)[60,62] (negative and positive results, respectively), protein kinase alpha 2 catalytic subunit (*PRKAA2*)[50,65] (negative and positive results, respectively), and *TNF*[67,137,146] (positive results only in the second study). No correlation was observed for adrenoreceptor beta 3 (*ADRB3*),[144] cholecystokinin (CCK),[147] cannabinoid receptor 1 (*CNR1*),[148] fatty acid binding protein 3 (*FABP3*),[50] fat mass and obesity associated (*FTO*),[50] peroxisome proliferator-activated receptor gamma (*PPARG*),[149] protein kinase alpha 1 catalytic subunit (*PRKAA1*),[50] protein kinase gamma 1 non-catalytic subunit (*PRKAG1*),[50] protein kinase gamma 3 non-catalytic subunit (*PRKAG3*),[50] *DRD1*,[55] *DRD3*,[55] *DRD4*,[55,150] *DRD5*,[55] *HRH1*,[151] *HTR6*,[136] and *SLC6A4*.[136] Confirmation of these results by other studies is also needed.

Additionally, polymorphisms in the *HTR2C*[68-71] and methylenetetrahydrofolate reductase (*MTHFR*) genes[72,73] were associated with risk of metabolic syndrome induced by clozapine or risperidone/olanzapine. No significant association was found for *ADRA2A*.[152] Polymorphisms in the apolipoprotein A-V (*APOA5*) and C-III (*APOC3*) genes, but not in *LEP*, showed an influence on triglyceride and cholesterol levels in patients treated with clozapine or olanzapine.[74]

Agranulocytosis is a serious adverse effect associated with clozapine. Some studies showed strong associations between polymorphisms in genes of the major histocompatibility complex (*HLA*) and the occurrence of this adverse effect.[76-81] Significant associations were also found with the NAD(P)H dehydrogenase quinone 2 (*NQO2*)[82] and TNF genes.[83] In other studies, no associations were observed with the cytochrome b-245 alpha polypeptide (*CYBA*),[153] P450 family 2 subfamily D polypeptide 6 (*CYP2D6*),[154] and myeloperoxidase (*MPO*).[153,154]

A study conducted with a Brazilian population sample evaluated the influence of *GNB3* polymorphisms and the occurrence of tonic-clonic seizures due to clozapine treatment.[34] The 825T allele of the 825C>T polymorphism was significantly associated with an increased risk of developing seizures.

Ferrari et al.[84] studied the influence of *CYP1A2* polymorphisms and clozapine-induced adverse effects (neurological, cardiovascular, gastroenterological, hematological, behavioral, and musculoskeletal adverse drug reactions, ADRs) and observed that the LA (low activity) phenotype was significantly more frequent in subjects with clozapine-induced ADRs than in those without ADRs.

From candidate genes to genome-wide association studies

Genome-wide association studies (GWASs), a powerful method for the large-scale analysis of genotype-phenotype relationships, are currently the method of choice for dissecting the genetic basis of complex traits.[155] In GWASs, genetic variations associated with response to treatment are detected randomly throughout the genome. Few studies of antipsychotic response and adverse effects have been published, partly due to the need for large samples to achieve truly significant results.[156] Although the few published studies have little statistical power because of insufficient sample size, they may identify new genes for investigation and assist in the elucidation of new metabolic pathways possibly related to efficacy and adverse effects of clozapine.[16]

A few GWASs have been conducted using samples from the CATIE study (Clinical Antipsychotic Trials of Intervention Effectiveness, n=750),[157] where treatment of patients was based on several classes of antipsychotics. One of these studies[75] examined 12 indicators of metabolic side effects of antipsychotics and found a polymorphism in the protein kinase type II beta gene (*PRKAR2B*) mediating effects of clozapine on triglyceride levels.

Malhotra et al.[64] conducted the first GWAS of weight gain in patients undergoing initial exposure to second-generation antipsychotics (SGAs) and also assessing three independent replication cohorts (one treated only with clozapine) to confirm the results. The authors found one polymorphism (rs489693) located approximately 190kb downstream from *MC4R* (previously identified as a candidate for weight-related phenotypes), implicating *MC4R* in extreme SGA-induced weight gain and related metabolic disturbances, including in the clozapine-treated sample.

More intriguing is that most candidate genes that were previously found to be associated with individual

Table 2 Reported associations between genetic polymorphisms and clozapine side effects*

Gene/Polymorphism†	Ethnicity	Sample size	p-value
Weight gain			
ADIPOQ			
Several[50]			
ADRA2A	Caucasian	160	< 0.045
-1291C>G[51]	Taiwanese	394	< 0.05
-1291C>G[52]	Korean	62	0.013
BDNF			
rs6265/rs11030101/rs2291186[53]	Taiwanese	481	0.047
DRD2			
rs4436578[54]	Taiwanese	479	0.001
957C>T, rs1079598, rs1800497[55]	Caucasian and African American	192	< 0.05
GNB3			
825C>T[56]	Chinese	134	0.002
HTR2A			
102T>C/His452Tyr/-1438A>G[57‡]	Caucasian	46	0.034
HTR2C			
-759C>T[58]	Chinese	32	< 0.02
-759C>T[59]	most Caucasian	35	0.003
-759C>T/-697G>C/Cys23Ser[57‡]	Caucasian	46	0.029
rs498207[60]	Caucasian	128	0.019
INSIG2			
rs17587100, rs10490624, rs17047764[61]	Caucasian	160	< 0.05
LEP			
-2548G>A[62]	Chinese	102	0.039
MC4R			
rs8087522[63]	Caucasian	69	0.027
rs489693[64]	Caucasian	73	0.0001
PRKAA2			
rs10789038[65]	Caucasian	208	0.023
PRKAB2			
rs3766522[65]	Caucasian	208	0.022
PRKAG2			
rs17714947, rs7800069[50]	Caucasian	160	< 0.02
ROBO1			
rs1455832[66]	Caucasian	164	0.025
TNF			
-308G>A[67]	Chinese	55	0.008
Metabolic syndrome			
HTR2C			
Several[68]	Caucasian	112	0.01-0.05
rs1414334[69]	Caucasian	164	< 0.05
rs1414334[70]	Caucasian	164	0.015
rs521018/rs498177[71‡]	Chinese	456	0.0108
MTHFR			
1298A>C[72,73]	Caucasian	104,518	0.009, 0.018
Lipid levels			
APOA5			
1131T>C/S19W[74‡]	Caucasian, Hispanic and Black	95	0.049
APOC3			
1100C>T/3238[74‡]	Caucasian, Hispanic and Black	95	0.048
PRKAR2B			
rs13224682[75]	Caucasian	175	< 0.0001
Agranulocytosis			
HLA			
Several[76]	Ashkenazi Jewish and non-Jewish	75	< 0.03
HSP-70 9.0-Ac[77]	Ashkenazi Jewish and non-Jewish	75	0.04
DBQ1*0201[78]	Jewish	18	0.036
B38[79]	Israeli	11	0.001

Continued on next page

Table 2 Continued

Gene/Polymorphism†	Ethnicity	Sample size	p-value
DBQ*0502[80]	Caucasian	103	0.006
6672G>C[81]	N/A	33	< 0.05
NQO2			
1536C>T, 1541G>A, Phe372Leu, 202G>A[82]	Israeli	98	< 0.05
TNF			
TNFb, TNFd[83§]	Ashkenazi Jewish and non-Jewish	33	0.0005
Seizures			
GNB3			
825C>T[34]	Brazilian	108	0.007
General ADRs‖			
CYP1A2			
Low activity[84]	Caucasian	34	0.019

ADR = adverse drug reaction; N/A = not available.
* Including only significant association results. See text for complementary information about other nonsignificant studies concerning these genes.
† See text for abbreviations.
‡ Haplotype: polymorphisms analyzed as a unique block.
§ Microsatellites: short tandem repeat polymorphism.
‖ Neurological, cardiovascular, gastrointestinal, hematological, behavioral, and musculoskeletal adverse reactions.

response to treatment, or adverse effects of clozapine (Tables 1 and 2), did not show statistical significance in these studies. As GWASs are exploratory, they should be replicated in independent samples.

Discussion

The study of pharmacogenetics in schizophrenia had its milestone in the work of Arranz et al.,[102] conducted 12 years ago. This study had a great impact at the time because of its multigene approach and the observation of a strong association between a specific set of six polymorphisms and response to clozapine in schizophrenic patients, with a positive predictive value of 76%. Since then, few studies have been carried out with this approach. Studies with individual candidate genes have been more frequent in recent years, and GWASs are the real promise.[155]

Study limitations

Most of the reviewed articles were individual association studies. This approach has minimal practical value, since most antipsychotics have multiple targets, and it would be unlikely for only one of these targets to be responsible for all variability in treatment response.[114]

Association studies are the most appropriate strategy for pharmacogenetic research.[158] However, determining the practical relevance of pharmacogenetic variants is difficult, partly because of problems with the design and replication of such studies.[159] The results of many studies of response to antipsychotics were not replicated in clinically similar populations, and the implication of the few studies that have been replicated still needs to be established. In addition to type I and II statistical errors, the difficulty lies mainly in the standardization of clinical samples in relation to an appropriate number of individuals and detailed clinical information about symptom improvement and development of adverse effects. The complexity of genetic factors implicated in psychiatric illness and response to medication is also a complicating factor.[159] Polygenic involvement in the etiology of schizophrenia hinders the identification and characterization of many genes that would be relevant as therapeutic targets and how these components interact or combine in the process. Other difficulties include incomplete knowledge of the mechanisms of schizophrenia, the complexity of brain function, and the influence of nongenetic factors, including age, diet, environmental exposures and interactions, comorbidities, and drug interactions. The dynamics of epigenetic events can also be responsible for the variations observed in the clinical response to antipsychotics.[160,161]

In most meta-analyses, the heterogeneity of the antipsychotic drugs used in the analyzed studies limits the possibility of examining the association of candidate genes with any specific drug. In the pharmacogenetics of schizophrenia, meta-analyses support the involvement of *DRD2*[112] and *DRD3*[107] in treatment response and *HTR2C* in weight gain[141,142] but simultaneously indicate that the establishment of pharmacogenetics associations in clinical psychiatry requires much larger sample sizes.

Population stratification in case-control studies causes most false-positive associations,[162] because genetic differences between ethnic groups often lead to differences in treatment response. Additionally, non-publication of negative findings also generates a problem in terms of replication of results.[159] For greater uniformity in studies, some characteristics should be assured, including: 1) large sample sizes, since most genes influencing response have little effect on the phenotype; 2) standardization of clinical data important for the outcome of the phenotype (such as dose, treatment duration, age at start of treatment)[163]; 3) presence of co-medication; 4) standardization of response criteria; 5) disease severity; and 6) prospective studies.

Despite continuous advances toward revealing the genetic basis of many complex traits using GWASs, a major proportion of genetic variance remains unexplained. A large number of disorders have been studied by GWASs, contributing to the detection of many previously undetected loci. For example, Franke et al.[164] conducted a meta-analysis of six Crohn's disease GWASs and 30 new susceptibility loci were identified at genome-wide significance. Jia et al.[165] examined multiple GWAS datasets in schizophrenia through meta-analysis of the related SNPs and identified 205 module genes significantly associated with schizophrenia, including well-studied candidate genes, such as *GRIN2B*, disrupted in schizophrenia 1 (*DISC1*), G protein-coupled receptor 17 (*GPR17*), guanine nucleotide binding protein alpha 12 (*GNA12*) and alpha 13 (*GNA13*), and alpha inhibiting activity polypeptide 1 (*GNAI1*). However, most GWASs have achieved limited success in explaining a considerable proportion of genetic variance of complex traits.[166] The very large number of markers under investigation raises the issue of multiple testing, and the need for correction, which makes it even harder to detect a small association signal.[167] Most of the susceptibility loci that have been discovered so far by GWASs are of small predisposing risk. In addition, detecting such contributions is difficult when the predisposing allele is rare or the sample size is not sufficiently large.[168] Additionally, these studies do not take into account existing biological knowledge about the trait, which could help narrow down datasets and guide the process of extracting biologically meaningful results in a more effective manner.[169] In view of these limitations, new approaches to analyze complex traits would be helpful.

Clinical applications

The CATIE study[157] and a double-blind study investigating dose of antipsychotics,[170] controlled for confounding variables in clinical practice, indicated that variations in metabolizing enzymes play a small role in determining the clinical response to antipsychotics. However, combining assessment of these pharmacokinetic factors with analysis of pharmacodynamic markers, each conferring moderate effects, may be a more valid approach, possibly improving cost-effectiveness in clinical practice.

Substantial advances in knowledge of the gene-response connection have been made, and pharmacogenomics approaches have become increasingly popular. With advances in sequencing technologies and bioinformatics, new dimensions in the search for multiple genes and how their expression affects response to medication are being generated. However, clinical and pharmacogenomic knowledge has not advanced as rapidly as technology, and no application has been developed yet regarding the management of schizophrenia treatment and drug development.[6]

Conclusions

Despite several decades of research, no biological or clinical predictors of response to antipsychotic medication or development of side effects have been identified.[6] To date, efforts to identify key genes that may be useful in predicting response and adverse effects to clozapine treatment have not been fully successful, and additional studies are required. Meta-analysis results have confirmed one of the greatest difficulties of association studies: sample sizes are not large enough to detect positive associations. Therefore, further studies with much larger sample sizes are still needed to detect real associations. Great hope lies in the introduction of GWASs, as the hypothesis that a combination of genes contribute to the effect of the drug is a more likely explanation for the interindividual variability in treatment response.[114]

Pharmacogenetic-driven prescription focused on genotypes might enable optimal selection of medications and their doses in the future. However, in the treatment of multifactorial diseases, pharmacogenetics is only one of several approaches that should be analyzed, such as expression analysis and proteomics. Thus, as noted by Pirmohamed, pharmacogenetics "is coming along, but not for everything."[171] Only time will tell whether prediction of drug efficacy will reduce suffering and improve patient quality of life.

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Disclosure

The author reports no conflicts of interest.

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