ELSEVIER

European Journal of Pharmacology 410 (2000) 227–241

ejp

www.elsevier.nl/locate/ejphar

Pharmacogenomics and schizophrenia

Yoichi Kawanishi, Hirokazu Tachikawa, Toshihito Suzuki *

Department of Psychiatry, Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan

Accepted 20 October 2000

Abstract

Although antipsychotic drugs are effective in alleviating schizophrenic symptoms, individual differences in patient response suggest that genetic components play a major role, and pharmacogenetic studies have indicated the possibility for a more individually based pharmacotherapy. The new field of pharmacogenomics, which focuses on genetic determinants of drug response at the level of the entire human genome, is important for development and prescription of safer and more effective individually tailored drugs. DNA microarray (DNA chip) analysis enables genome-wide scanning, using the high-density single nucleotide polymorphisms map. Pharmacogenomics will aid in understanding how genetics influence disease development and drug response, and contribute to discovery of new treatments. The rate of discovery of those polymorphisms will depend on the quality of the drug response phenotype. Prospective genotyping of schizophrenic patients for the many genes at the level of the drug target, drug metabolism, and disease pathways will contribute to individualized therapy matching the patient's unique genetic make-up with an optimally effective drug.

Keywords: Schizophrenia; Pharmacogenetics; Single nucleotide polymorphism; Pharmacogenomics; Genome-wide scanning; DNA microarray

1. Introduction

Schizophrenia is a psychotic disorder that can greatly limit the patient's ability to function normally and thus impairs the quality of life. For diagnosis of schizophrenia, the fourth Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) (1994) is at present perhaps the most widely used, although the definition in the 10th edition of the International Classification of Disease (ICD-10) (World Health Organization, 1990) provides a similar alternative. In these criterion-based systems, schizophrenia is characterized by symptoms that reflect multiple mental processes, including hallucinations, delusions, disorganized speech, and disorganized behavior (Andreasen, 2000; American Psychiatric Association, 1994). Those four symptoms are the classic positive symptoms of schizophrenia in which normal functions are distorted or exaggerated. The various negative symptoms of schizophrenia, such as alogia, affective blunting, avolition and anhedonia are another important aspect of the illness. Complete remission is probably not common in this disorder (American Psychiatric Association, 1994).

The lifetime prevalence of schizophrenia is approximately 0.5% to 1% worldwide (American Psychiatric Association, 1994). The vast costs associated with schizophrenia are estimated to account for approximately 1.6% to 2.5% of annual total healthcare expenditure in various developed countries, according to data collected from the late 1980s or early to mid-1990s (Foster and Goa, 1999; Hamilton et al., 1999). Of the direct costs of schizophrenia, hospitalization is the greatest contributor, with drug costs representing about 1% to 6% of the total. Therefore, schizophrenia is one of the most important public health problems confronted by society.

Many studies, including twin, family, and adoption studies have consistently revealed that while schizophrenia does not appear to be solely a genetic disorder, genetic factors are involved (Kirov and Murray, 1997; Moldin and Gottesman, 1997; Tsuang, 1998). Furthermore, simple Mendelian inheritance patterns are unlikely and, in this regard, schizophrenia resembles obesity, hypertension, diabetes and many other relatively common yet complex human disorders. It is therefore likely that genetic and environmental risk factors interact in a complex fashion to produce the disorders. Identifying genes that effect an

* Corresponding author. Tel.: +81-298-53-3183; fax: +81-298-53-3180.

E-mail address: psuzukit@md.tsukuba.ac.jp (T. Suzuki).

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00817-7

individual's predisposition to develop schizophrenia could improve diagnosis of the disease, and perhaps lead to improvements in prevention and in pharmacological treatment of the disease. However, it is very disappointing that molecular genetic approaches have yet to yield conclusive evidence.

In the pharmacotherapy of schizophrenia, chlorpromazine was discovered by serendipity and utilized in treating schizophrenia in the 1950s. Neuropsychopharmacological evidence supports the fact that all clinically useful neuroleptics are antidopaminergic (Kaplan and Sadock, 1998; Terenius, 2000). The observation that conventional antipsychotic agents (e.g. haloperidol and chlorpromazine) are primarily dopamine antagonists was first made by Carlsson in 1963 (Carlsson and Lindquist, 1963). Although these antipsychotics are effective in alleviating positive symptoms (for example, delusions and hallucinations) and reducing patient disability (Kaplan and Sadock, 1998), they also possess the ability to cause extrapyramidal and other side effects and may not fully alleviate negative symptoms. In response to these problems, recent years have seen the introduction of a number of so-called atypical antipsychotic agents (e.g. clozapine, risperidone, olanzapine, quetiapine) that target other neurotransmitter receptors, most notably serotonin as well as dopamine (Meltzer, 1995; Jibson and Tandon, 1998; Kaplan and Sadock, 1998; Moore, 1999; Worrel et al., 2000). These agents usually have efficacy against both the positive and negative symptoms of schizophrenia, that demonstrate a superior clinical profile compared with typical antipsychotics, especially in measures of negative symptoms and quality of life (Meltzer, 1995; Jibson and Tandon, 1998; Kaplan and Sadock, 1998; Moore, 1999; Worrel et al., 2000). Furthermore, atypical antipsychotics are associated with a significantly lower incidence and severity of treatment-emergent extrapyramidal symptoms and tardive dyskinesia than conventional agents. However, the response to even these drugs is heterogeneous, and psychiatrists usually prescribe antipsychotics based only on the clinical symptoms since they lack the biological evidence, which would help to make decisions of the appropriate drug for each individual patient. This means that clinical psychiatry is not always a science, but an art.

Then, the observed patient-to-patient differences in the response to drug treatments may be caused by a variety of factors. Among them, genetic components presumably play a major role (Propping and Nöthen, 1995; Evans and Relling, 1999). Clinical observations of such inherited differences in drug effects were first documented in the 1950s (Hughes et al., 1954; Carson et al., 1956; Kalow, 1956; Evance et al., 1960), giving rise to the new field of "pharmacogenetics" which focuses largely on how genetic polymorphisms in drug-metabolizing enzymes translate into inherited differences in drug effects (Vogel, 1959; Nebert, 1997). Such studies have been fundamental in optimizing therapeutic doses in order to minimize toxic effects (Arranz and Kerwin, 2000). However, mutations in metabolizing enzymes cannot fully account for the heterogeneity observed in the response of an individual to drug treatment. The overall pharmacologic effects of medications are typically not monogenetic traits; rather, they are determined by the interplay of several genes encoding proteins involved in multiple pathways of drug effects and disposition in addition to metabolism (Evans and Relling, 1999). Recently, pharmacogenetic research has been extended to include the drug's site of action as a source of variability, independent of metabolism, which could influence treatment response, using methods of DNA analysis that are capable of identifying genetic variations at the level of the drug target (Propping and Nöthen, 1995). Many of these variants are single nucleotide polymorphisms (SNPs) referred to as "snips" (Isaksson et al., 2000; McCarthy and Hilfiker, 2000).

Single nucleotide polymorphisms, the single-base differences in the DNA sequence that can be observed between individuals in a population (Zhao et al., 1998; Brookes, 1999; Hacia et al., 1999b), are present throughout the human genome with an average frequency of approximately 1 per 1000 base pairs (Brookes, 1999). Such frequency means that 3 million single nucleotide polymorphisms exist, since there are 3 billion base pairs in the human genome. The SNP Consortium (a consortium of pharmaceutical and bio-informational companies, five academic centres and a charitable trust) is currently producing an ordered high-density single nucleotide polymorphism map of the human genome (Marshall, 1999). The original target was to produce an single nucleotide polymorphism map with 200,000–300,000 single nucleotide polymorphisms evenly distributed throughout the human genome. In fact, this initiative is ahead of schedule and will probably provide 600,000–800,000 single nucleotide polymorphisms by the end of year 2 (April 2001) with the collaboration of the Human Genome Project, which focuses on a genome-wide map of 100,000 single nucleotide polymorphisms (Brower, 1998). This map will enable disease and drug response phenotypes to be mapped by linkage disequilibrium (Roses, 2000).

On June 26th, 2000, President Clinton, leaders of the Human Genome Project and representatives of the biotechnology company Celera announced the completion of a "working draft" reference DNA sequence of the human genome, which is one of the third plan "U.S. Human Genome Project 5-Year Research Goals 1998–2003". This achievement provides scientists worldwide with a road map to an estimated 90% of genes on every chromosome. The ultimate Human Genome Project goal of generating a high-quality reference genome sequence, expected to be achieved by the year 2003 or sooner, will identify all 100,000 human DNA genes (http://www.ornl.gov/hgmis/resource/media.html).

Knowledge about single nucleotide polymorphisms and genes within the whole genome will speed up the under-

standing of how a person's genetic constitution influences disease development and drug response, and will contribute to the discovery of new treatments. Therefore, the field of pharmacogenetics has entered into a new era when it became recognized as a significant concept for the development and prescription of individually tailored drugs, that are both safer and more effective for each patient (Sadée, 1998, 1999; March, 2000). Applying the large-scale systematic approaches of genomics, the discipline of pharmacogenomics was created. This emerging discipline focuses on genetic determinants of drug response at the level of the entire human genome (Sadée, 1999).

Since the use of single nucleotide polymorphisms is considered to be an excellent tool for pharmacogenetics in schizophrenia and potentially might lead to the discovery of schizophrenia-related genes, many researchers have been engaged in identifying genetic factors that may influence response to and adverse effects of antipsychotic drugs. These investigations have made steady progress (Arranz and Kerwin, 2000; Cichon et al., 2000; Masellis et al., 2000) and our goal is to identify variants relevant to drug response within the whole genome. "Psychopharmacogenetics" (pharmacogenetics in the psychiatric field) will become "psychopharmacogenomics" in the near future through the development of genome science. Although the field of psychopharmacogenomics has a bright future, there are still obstacles to overcome. Therefore, the objectives of this review are two-fold. First, we will review the pharmacogenetic studies of schizophrenia, which have produced evidence that metabolizing enzyme and receptor polymorphisms influence antipsychotic response. Second, we will discuss how this relates to the development of psychopharmacogenomics.

2. Genetic variants of drug-metabolizing enzyme

Most of the drugs acting on the central nervous system are extensively metabolized by cytochrome *P*450 (CYP) enzymes. The CYP enzymes, together with aldehyde and alcohol dehydrogenase and erastases, belong to drug-metabolizing enzymes responsible for functionalization (phase I metabolism) (Evans and Relling, 1999; Nebert, 1997). Among these enzymes, CYP2C9, CYP2C19, CYP1A2, CYP3A4, and CYP2D6 are related to metabolism of drugs used in psychiatry. Pharmacogenetic studies have reported for several decades that CYP phenotypes, which are genetically determined and have large interindividual variations, strongly influence drug sensitivity or response resulting from elimination rates, steady state concentrations, and biotransformation. Thus, adverse effects and efficacy of drugs are strongly influenced by genetic variations of these enzymes. Many of the CYP genes including CYP2C9, CYP2C19, and CYP2D6 gene exhibit genetic polymorphisms, and extensive and poor metabolizers (EM and PM) exist in each enzyme. This means that the PM phenotype consisted of individuals having homozygous or compound heterozygous PM alleles, and the EM phenotype consisted of those having homozygous wild type or heterozygous wild type/PM alleles (Coutts and Urichuk, 1999; Cichon et al., 2000).

CYP2D6 is the most widely studied schizophrenia-related cytochrome, since it plays a major role in metabolism of almost all antipsychotics. Its phenotype is characterized historically by debrisoquine/sparteine metabolism, which is a polymorphic trait following response to the probe drugs. Recent pharmacogenetic studies have revealed that phenotypes of PMs consisted of various alleles (CYP2D6*3, *4, and *9), which decrease or inactivate CYP2D6 activity (Daly et al., 1996). Five to ten percent of Europeans, about 2% of Asians, and 7–8% of Africans are PMs of debrisoquine/sparteine (Marez et al., 1997). Phenotyped panel studies have indicated that the distribution of haloperidol, perphenazine, zuclopenthixol, thioridazine, and risperidone co-segregates with that of debrisoquine (Fang and Gorrod, 1999). PMs of debrisoquine have higher plasma concentrations of and more adverse effects from perphenazine and thioridazine than EMs (Dahl and Bertilsson, 1993). Acute side effects including postural hypotension, excess sedation, or extrapyramidal symptoms have an overrepresentation of PMs (Spina et al., 1992a,b; Vandel et al., 1999). On the other hand, it is not clear whether the development of tardive dyskinesia is associated with a reduced metabolizing capacity of CYP2D6 (Arthur et al., 1995; Armstrong et al., 1997; Andreassen et al., 1997; Kapitany et al., 1998; Ohmori et al., 1998, 1999). All antipsychotics undergo extensive oxidative metabolism in the liver, and many of them have pharmacologically active metabolites. Haloperidol is metabolized by reduction to form reduced haloperidol that is also pharmacologically active and the plasma half life of both was found to be longer in PMs than EMs (Llerena et al., 1996). In summary, these findings suggest that CYP2D6 genotype and phenotype might partially affect response to typical antipsychotics and drug side effects; however, caution must be used because of inter-ethnic differences in the frequency of PM alleles and PM phenotype. The high frequency of a certain CYP2D6 variant in the Chinese population results in a slower average hydroxylation of debrisoquine and of haloperidol in the EM group (Johansson et al., 1994). Several reports suggest that, on the average, Asians develop higher plasma levels than Europeans and thus have an increased sensitivity to antipsychotics including haloperidol (Frackiewicz et al., 1997; Mihara et al., 1999).

Clozapine, an atypical antipsychotic, exhibits large interindividual variations in bioavailability, steady-state plasma concentrations, and clearance. Genetic factors might contribute to the observed variations. Clozapine is metabolized by several CYP enzymes, including CYP1A2, CYP3A4, CYP2D6 and CYP2C19 (Fang and Gorrod, 1999; Prior et al., 1999). In a study by Arranz et al. (1995b),

CYP2D6 was found not to be a major enzyme responsible for metabolizing clozapine. On the contrary, Collier et al. (2000) have indicated that clozapine is metabolized primarily by CYP1A2, since CYP1A2 knock-out mice had a significant decrease in clozapine clearance. These results suggest that CYP1A2 gene polymorphism might be associated with clozapine response. There are only a few reports regarding metabolic pathways of other atypical antipsychotics such as risperidone, olanzapine, and quetiapine (Prior et al., 1999; Scordo et al., 1999). Further research is needed in this area to clarify the relationship between polymorphisms of metabolic enzymes and response to antipsychotic drugs.

3. Genetic variants of drug targets

All receptor genes for neurotransmitters and genes located down stream in the intracellular signaling pathways can be considered candidate genes for pharmacogenetic studies in schizophrenia. These include, among others, dopamine, serotonin, glutamate, γ-aminobutyric acid, and catecholamines. Selecting a good candidate gene is difficult, since it is not always clear which of these systems is responsible for the therapeutic action of the drug. However, the existence of a response-determining variant in a receptor system will indicate its therapeutic relevance, in addition to the discovery of genetic variability related to drug efficacy. To investigate the potential involvement of a specific candidate gene in drug response or occurrence of side effects, association studies have been performed. These studies exemplify the candidate gene approach, which uses biological hypothesis of the disease or a priori knowledge of drug profiles to identify genes relevant to disease or drug response. First, a genetic variation is identified for the potential candidate gene by molecular genetic techniques. Second, the frequencies of gene polymorphisms are compared between responders and nonresponders, or between subjects suffering from adverse effect and subjects showing no adverse reactions. Any significant differences between the two groups will indicate that the drug action is mediated through the receptor studied. Because these studies are time-consuming, from among the large number of potential candidate genes the dopamine and 5-HT (5-hydroxytryptamine; serotonin) receptors have been most extensively studied for the presence of genetic variation, based on dopamine and/or serotonin hypothesis for schizophrenia, and binding profiles of antipsychotics.

3.1. Dopamine receptors

Since almost all antipsychotics are dopamine receptor antagonists, genetic variants in the genes coding the receptors may affect antipsychotic drug responses. Table 1 lists the genetic variants identified in dopamine receptor genes, their functional consequences, and associations with antipsychotic drugs. Dopamine D_2 receptor is a major site of action of conventional antipsychotics, such as chlorpromazine and haloperidol. One functional polymorphism (-141 Ins/Del) in the promoter region (Arinami et al., 1997) and three missense variants (Val96Ala, Pro310Ser, and Ser311Cys) (Gejman et al., 1994; Itokawa et al., 1993) in the coding region of the dopamine D_2 receptor gene have been identified. Although Arinami et al. (1997) reported that -141 Ins/Del polymorphism affected promoter activity and dopamine D_2 receptor expression, no positive results of association studies between this polymorphism and clinical response to clozapine, as well as other typical antipsychotics, have been reported (Ohara et al., 1998; Arranz et al., 1998a; Malhotra et al., 1998). On the other hand, missense variants were reported in relation to genetically determined differences in response to antipsychotics. The Val96Ala mutation was indicated to reduce dopamine, chlorpromazine, and clozapine binding affinities, and increase inhibition of cAMP synthesis, whereas both Pro310Ser and Ser311Cys mutations were shown to decrease inhibition of cAMP synthesis (Cravchik et al., 1996, 1999).

The dopamine D_3 receptor gene has one missense variant (Ser9Gly) (Crocq et al., 1992). Studies in patients treated with classical antipsychotics revealed an association between this polymorphism and response to antipsychotics (Krebs et al., 1998). While Shaikh et al. (1996) reported an association between Ser9 homozygotes and failure to respond to clozapine, Malhotra et al. (1998) could not replicate this result. An in vitro study indicated that this mutation increases dopamine and GR99841 binding affinities (Lundstrom and Turpin, 1996). Recently, three novel nucleotide polymorphisms were identified in the 5′-leader of the dopamine D_3 receptor gene in tight linkage disequilibrium both with each other and with Ser9Gly (Sivagnanasundaram et al., 2000). These polymorphisms were not associated with clozapine response and their functional significance remains unclear.

The dopamine D_4 receptor gene has the characteristic array of genetic polymorphisms that create structural diversity in the receptor. These include 16 amino acids repeat in exon 3 (Van Tol et al., 1991), 4 amino acids repeat in exon 1 (Catalano et al., 1993), a 13-base pairs deletion in exon 1 (Nöthen et al., 1994a,b), Gly11Arg (Cichon et al., 1995), and Val194Gly (Shaikh et al., 1995). In addition, a polymorphism (-521C/T) affecting the transcriptional efficiency in the 5′-promoter region of the dopamine D_4 receptor gene has been recently identified (Okuyama et al., 1999). Among them, the 16 amino acids repeat in exon 3 polymorphism have been the most investigated. A possibility was raised that structural variations of the receptor may be associated with observed variations in individual response to clozapine (Van Tol et al., 1991, 1992). This polymorphism was also shown in an in vitro study to influence sodium chloride sensitivity of clozapine binding and inhibition of cAMP synthesis (Asghari et al., 1994,

Table 1
Genetic variants of dopamine receptors and drug response

Receptor	Variant	Position	Gene frequency (%)	Functional consequence	Association with drug response	Reference
D_1	−2218T/C	Promoter	2			Cichon et al., 1996
	−2102 C/A	Promoter	4			Cichon et al., 1996
	−2030T/C	Promoter	3			Cichon et al., 1996
	−1992G/A	Promoter	<1			Cichon et al., 1996
	−1251G/C	Promoter	13			Cichon et al., 1996
	−800T/C	Promoter	61			Cichon et al., 1996
	−94G/A	5UTR	11			Cichon et al., 1994
	−48G/A	5UTR of exon 2	45			Liu et al., 1995; Kojima et al., 1999
	90A/G	5UTR				Ohara et al., 1993
	Leu66Leu	TMD2	13			Liu et al., 1995
	Ser421Ser	N-term.	2.8			Cichon et al., 1994; Liu et al., 1995
	1403T/C	3UTR	34			Cichon et al., 1994
D_2	−141C Ins/Del	Promoter	11	mRNA Expression ↓		Arinami et al., 1997
	Val96Ala	TMD2	<1	Dopamine, chlorpromazine and clozapine binding ↓, inhibition of cAMP synthesis ↑		Gejman et al., 1994; Cravchik et al., 1996, 1999
	Pro310Ser	ICL3	<1	Inhibition of cAMP synthesis ↓		Gejman et al., 1994; Cravchik et al., 1996, 1999
	Ser311Cys	ICL3	3	Inhibition of cAMP synthesis ↓		Itokawa et al., 1993; Gejman et al., 1994; Cravchik et al., 1996, 1999
D_3	−707C/G	5′-leader	30			Sivagnanasundaram et al., 2000
	−343A/G	5′-leader	30			Sivagnanasundaram et al., 2000
	−204A/G (Lys9Glu)	5′-leader (uORF)	30			Sivagnanasundaram et al., 2000
	Ser9Gly	N-term.	28	Dopamine and GR 99841 binding ↑	clozapine, typical neuroleptics	Crocq et al., 1992; Lundstrom and Turpin, 1996; Shaikh et al., 1996; Scharfetter et al., 1999; Krebs et al., 1998
D_4	−521C/T	Promoter	59	mRNA Expression ↓		Okuyama et al., 1999
	Gly11Arg	N-term.	1			Cichon et al., 1995
	4 aa repeat	N-term.	4 (1 repeat) 96 (two repeats) <1 (three repeats)	Influence on clozapine and quinpirole binding		Catalano et al., 1993; Zenner et al., 1998
	7 aa deletion		<1			Cichon et al., 1995
	13 bp deletion	N-term.	2	Loss of function		Nöthen et al., 1994a
	Val194Gly	TMD2	12.5	Dopamine, clozapine and olanzapine binding ↓, insensitivity to guanine nucleotide suggests non-functional receptor		Seeman et al., 1994; Liu et al., 1996
	16 aa repeat	ICL 3	Highly polymorphic	Influence on sodium chloride sensitivity of clozapine binding and inhibition of cAMP synthesis	clozapine, typical neuroleptics	Van Tol et al., 1991, 1992; Asghari et al., 1994, 1995; Hwu et al., 1998; Cohen et al., 1999
D_5	Leu88Phe	TMD2	<1	Dopamine binding ↑, SCH-23390 and risperidone binding ↓		Feng et al., 1998; Cravchik and Gejman, 1999
	Ala269Val	ICL3	<1	No effect on binding affinities		Sobell et al., 1995; Cravchik and Gejman, 1999
	Pro330Gln	ECL3	10	No effect on binding affinities		Sobell et al., 1995; Cravchik and Gejman, 1999
	Cys355Stop	ECL3	<1	Loss of function		Sobell et al., 1995
	Asn351Asp	TMD7	<1	Dopamine and *R*(+)-SKF-38393 binding ↓		Sobell et al., 1995; Cravchik and Gejman, 1999
	Ser453Cys	N-term.	<1	No effect on binding affinities		Sobell et al., 1995; Cravchik and Gejman, 1999

Table 2
Genetic variants of 5-HT receptors and drug response

Receptor	Variant	Position	Gene frequency (%)	Functional consequence	Association with drug response	Reference
5-HT_{1A}	−1018C/G	Promoter	50			Wu and Comings, 1999
	−581C/A	Promoter	< 1			Kawanishi et al., 1998
	−480delA	Promoter	< 1			Kawanishi et al., 1998
	−321G/C	Promoter	< 1			Kawanishi et al., 1998
	−152C/G	Promoter	< 1			Kawanishi et al., 1998
	−51T/C	Promoter	< 1			Kawanishi et al., 1998
	Pro16Leu	N-term.	4			Kawanishi et al., 1998; Harada et al., 1996
	Gly22Ser	N-term.	1	Agonist-mediated receptor down-regulation ↓ Inhibition of cAMP synthesis ↓		Nakhai et al., 1995; Rotondo et al., 1997
	Ile28Val	N-term.	1	No effect on agonist and antagonist binding and cAMP synthesis		Nakhai et al., 1995; Erdmann et al., 1995; Brüss et al., 1995; Rotondo et al., 1997
	294G/A		5			Xie et al., 1995; Kawanishi et al., 1998
	549C/T		4			Erdmann et al., 1995; Kawanishi et al., 1998
	Arg219Leu	ICL3	< 1			Lam et al., 1996
	Gly272Asp	ICL3	3			Kawanishi et al., 1998
	Asn417Lys	C-term.	1			Lam et al., 1996
5-HT_{1B}	−511G/T	Promoter	1			Nöthen et al., 1994b
	−261T/G	Promoter	49			Nöthen et al., 1994b
	−179/−178del	Promoter	1			Nöthen et al., 1994b
	Phe124Cys	TMD3	1	Dihydroergotamine, sumatriptan and methysergide binding ↑ ketanserin binding ↓		Nöthen et al., 1994b; Bühlen et al., 1996; Brüss et al., 1999
	861G/C		28			Nöthen et al., 1994b
5-HT_{1D}	1350T/C		8			Ozaki et al., 1995
5-HT_{1E}	531C/T		7			Shimron-Abarbanell et al., 1995
5-HT_{1F}	−78C/T	Promoter	< 1			Shimron-Abarbanell et al., 1996
	528C/T		< 1			Shimron-Abarbanell et al., 1996
	783T/A		< 1			Shimron-Abarbanell et al., 1996
5-HT_{2A}	−1438A/G	Promoter	58	No effect on basal activity	clozapine	Spurlock et al., 1998; Arranz et al., 1998b, 2000
	Thr25Asn	N-term.	2			Erdmann et al., 1996a
	102T/C		58		clozapine, typical neuroleptics	Arranz et al., 1995a, 1998c, 2000; Masellis et al., 1998; Joober et al., 1999
	516C/T		2			Erdmann et al., 1996a; Arranz et al., 1995a
	His452Tyr	C-term.	8	Blunting of the shape of the $Ca2^{+}$ mobilization peak	clozapine	Erdmann et al., 1996a; Ozaki et al., 1997; Arranz et al., 1996; Arranz et al., 1998b,c, 2000
5-HT_{2B}						
5-HT_{2C}	−330GT/−244CT	?			clozapine	Arranz et al., 2000
	Cys23Ser	N-term.	13	Serotonin and MCPP binding ↓	clozapine	Lappalainen et al., 1995; Goldman et al., 1995; Sodhi et al., 1995
	2831T/G		10			Song et al., 1999
5-HT_{3A}	178C/T	?				Arranz et al., 2000
	1596G/A	?				Arranz et al., 2000
5-HT_{4}						
5-HT_{5A}	−19G/C	Promoter	37			Shimron-Abarbanell et al., 1997
	−18C/T	Promoter	8			Shimron-Abarbanell et al., 1997
	12A/T		77		clozapine	Shimron-Abarbanell et al., 1997; Birkett et al., 2000

Table 2 (*continued*)

Receptor	Variant	Position	Gene frequency (%)	Functional consequence	Association with drug response	Reference
	Pro15Ser	N-term.	5			Iwata et al., 1998
	789C/T		1			Shimron-Abarbanell et al., 1997
5-HT_{5B}						
5-HT_6	267C/T		31		clozapine	Yu et al., 1999
5-HT_7	Thr92Lys	TMD1	< 1			Erdmann et al., 1996b
	Pro279Leu	ICL3	< 1			Erdmann et al., 1996b
	1233A/G		1			Erdmann et al., 1996b

1995). Therefore, several association studies were carried out and suggested that the polymorphism did not seem to correlate with the degree of response to clozapine (Shaikh et al., 1993; Rao et al., 1994; Rietschel et al., 1996; Kohn et al., 1997). However, it has recently been reported that alleles with homozygous 4 repeats of 16 amino acids were associated with a quick neuroleptic response during typical neuroleptic treatment at the acute sage, and a lower rate of negative symptoms at remission (Hwu et al., 1998). In addition, Cohen et al. (1999) reported differences in allele frequencies between patients showing a good response to typical antipsychotics and those showing a good response to clozapine. These studies suggest that this polymorphism might partially determine the efficacy produced by different classes of antipsychotics. Results from investigations of other polymorphisms were as follows: (1) four amino acids repeat might influence clozapine and quinpirole binding (Zenner et al., 1998), (2) a 13-base pairs deletion might produce the loss of function of dopamine D_4 receptor (Nöthen et al., 1994a,b), and (3) Gly194 might be less sensitive to dopamine, olanzapine, or clozapine than wild type, and produces a non-functional receptor (Liu et al., 1996).

The dopamine D_1 and dopamine D_5 receptor genes have been systematically screened and several polymorphisms have been detected (Ohara et al., 1993; Cichon et al., 1994, 1996; Liu et al., 1995; Sobell et al., 1995; Feng et al., 1998; Kojima et al., 1999). None of the variants in the dopamine D_1 receptor gene were confirmed to correlate with an antipsychotic drug response. Sobell et al. (1995) found a Cys355Stop mutation in the dopamine D_5 receptor gene, producing a non-functional receptor. Cravchik and Gejman (1999) carried out an in vitro study of the dopamine D_5 receptor gene, and showed that Leu88Phe increases dopamine binding affinities and decreases both SCH-23390 (1*H*-3-Benzazepin-7-ol, 8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-, (*R*)) and risperidone binding affinities, whereas Asn351Asp reduces dopamine and *R*(+)-SKF-38393 (*R*(+)-1-Phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol) binding affinities.

3.2. 5-HT receptors

Recent years have seen the introduction of a number of so-called atypical antipsychotic agents (e.g. clozapine, risperidone, olanzapine, quetiapine) that target other neurotransmitter receptors, most notably 5-HT receptors (Meltzer, 1995; Jibson and Tandon, 1998; Kaplan and Sadock, 1998; Moore, 1999; Worrel et al., 2000). Atypical antipsychotic agents usually have efficacy against both the positive and negative symptoms of schizophrenia. This has accelerated the many investigations of 5-HT receptor genes, especially the 5-HT_{2A} gene.

Table 2 lists the genetic variants identified in 5-HT receptor subtype genes. Several genetic variants were identified in most of the receptor subtypes. To date, for variants of the 5-HT_{2A}, 5-HT_{2C}, 5-HT_{5A} and 5-HT_6 receptors, positive findings have been reported in pharmacogenetic studies related to the treatment of schizophrenia. Although strong associations were reported between 102T/C polymorphism in 5-HT_{2A} gene and clozapine response (Arranz et al., 1995a; Masellis et al., 1998), several groups could not replicate the strength of the associations (Masellis et al., 1995; Nöthen et al., 1995; Malhotra et al., 1996a). However, meta-analysis showed that the 102T/C silent polymorphism of the 5-HT_{2A} gene plays a major role in determining clozapine response (Arranz et al., 1998c). Similarly, a-1438G/A polymorphism in the promoter region of the gene was also strongly associated with clozapine response, since it is in an almost complete linkage disequilibrium with the 102T/C polymorphism (Arranz et al., 1998b). Furthermore, the 102T/C polymorphism and the −1438G/A polymorphism by inference have also been associated with the classical neuroleptic response (Joober et al., 1999) and schizophrenia (Williams et al., 1997; Spurlock et al., 1998). With respect to the 5-HT_{2A} gene, positive associations were also reported between a structural His452Tyr variant and clozapine response (Arranz et al., 1996, 1998b,c). Interestingly, the 5-HT_{2A} His452Tyr variant indicates potential functioning significance, based on in vitro studies showing that the function of the receptor protein, as measured by calcium mobilization, is altered (Ozaki et al., 1997). These findings strongly support the involvement of 5-HT_{2A} receptors in the therapeutic activity of both typical and atypical antipsychotics.

Furthermore, an association has also been reported between a Cys23Ser structural change in the 5-HT_{2C} receptor and clozapine response (Sodhi et al., 1995), and this variant showed potential functioning significance, based on

in vitro studies indicating that function of the receptor protein as measured by ligand binding characteristics, is altered (Goldman et al., 1995). However, this association was not replicated by other studies (Malhotra et al., 1996a,b; Rietschel et al., 1997; Masellis et al., 1998).

Other 5-HT receptors investigated for association with an antipsychotic response include the 5-HT_{3A}, 5-HT_5 and 5-HT_6. In vitro studies of the 5-HT_{1A} Gly22Ser and 5-HT_{1B} Phe124Cys variants indicate a potential functioning significance, since results indicate that the function of the receptor protein, as measured by intracellular cAMP production or ligand binding characteristics, is altered, respectively (Bühlen et al., 1996; Rotondo et al., 1997; Brüss et al., 1999). This possibility has yet to be investigated pharmacogenetically due to the rarity of the polymorphisms found. Although two silent polymorphisms were detected in the 5-HT_{3A} receptor gene neither was related to clinical response (Arranz et al., 2000). Investigations of the 5-HT_5 and 5-HT_6 genes produced modest associations. A 12A/T silent polymorphism in the 5-HT_{5A} gene showed a trend toward an association with clozapine response (Birkett et al., 2000). In addition, a silent 267T/C change in the 5-HT_6 gene was marginally associated with clozapine (Yu et al., 1999). Taken together, these results suggest that the 5-HT_{5A} and 5-HT_6 receptors have a minor contributing role in treatment response.

4. Adverse effects of antipsychotics

Previous pharmacogenetic studies concerning adverse effects (side effects) of antipsychotic drugs have targeted the presence of association to CYP enzymes that involve pharmacokinetics of antipsychotics, or dopamine receptors involving their pharmacodynamics. As mentioned in the above section, extrapyramidal symptoms and early stage side effects from initiation of pharmacotherapy, such as postural hypotension and excess sedation, were reported to be associated with overrepresentation of PMs of CYP2D6 (Spina et al., 1992a,b; Vandel et al., 1999).

On the other hand, a correlation between the development of tardive dyskinesia and a reduced metabolizing capacity of CYP2D6 has not been conclusive because of conflicting results (Arthur et al., 1995; Andreassen et al., 1997; Armstrong et al., 1997; Kapitany et al., 1998; Ohmori et al., 1998, 1999; Hamelin et al., 1999). The Ser9Gly polymorphism in the dopamine D_3 receptor gene has also been implicated in the development of tardive dyskinesia, suggesting a protective effect of the Ser9 allele (Steen et al., 1997; Segman et al., 1999; Riestchel et al., 2000). Recently, Basile et al. (1999, 2000) reported a strong significant association both between tardive dyskinesia and dopamine D_3 receptor gene polymorphism and tardive dyskinesia and a functional polymorphism (C/A) in the first intron of the CYP1A2 gene ($P < 0.0005$, and $P < 0.0007$, respectively). Other reports investigating the dopamine D_2 receptor (Chen et al., 1997) and manganese superoxide dismutase genes (Hori et al., 2000) found weak associations with tardive dyskinesia.

Furthermore, other side effects have also been studied for associations with polymorphism of candidwate genes. Acute akathisia, as well as tardive dyskinesia, was reported to associate with dopamine D_3 receptor gene polymorphism (Eichhammer et al., 2000). Neuroleptic-induced hyperprolactinemia might associate with the dopamine D_2 receptor gene Taq1A polymorphism (Mihara et al., 2000). Clozapine-induced agranocytosis was shown to associate with a dominant gene within the major histcompatibility complex region marked by heat shock protein 70-1 and 70-2 variants (Corzo et al., 1995). These findings suggest that, in the near future, single nucleotide polymorphisms might predict potential side effects from psychiatric medications.

5. Further study of pharmacogenetics of schizophrenia

Although the above discussed findings are important, none of the associations reported can fully account for the heterogeneity of response observed in antipsychotic treatment, and thus other genes have been suggested to contribute to antipsychotic response. Association studies performed by Arranz et al. (2000) in multiple candidate genes attempted to find the combination of polymorphisms that gave the best predictive value of response to clozapine in schizophrenic patients. Based on clozapine binding profiles, 19 genetic polymorphisms in eight receptor subtypes and one transporter including the α_{2A}-adrenoceptor, dopamine D_3 receptor, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{3A}, 5-HT_{5A}, histamine H_1 receptor, histamine H_2 receptor, and serotonin transporter were studied. A combination of six polymorphisms showing the strongest association with response ($P < 0.09$; 5-HT_{2A} 102T/C and His452Tyr, 5-HT_{2C}-330GT/−244CT and Cys23Ser, 5-HTTLPR, H_2-1018G/A) gave a level of prediction of 76.86% ($\chi^2 = 35.8$; $P = 0.0001$) and a sensitivity of 95.89 (± 0.04) for the identification of patients who will show a satisfactory improvement with treatment. This finding is the first report on the use of combinations of receptor polymorphisms to predict the response to antipsychotic medication. These data draw attention to possible implications for a more individually based pharmacotherapy, and show great potential for pharmacogenomics of schizophrenia.

6. Genome-wide scanning for pharmacogenomics

6.1. Single nucleotide polymorphisms and linkage disequilibrium

When the high-density single nucleotide polymorphism map of the whole genome is completed, it is possible to

uncover drug response markers through scanning the entire human genome for relevant polymorphisms (Sadée, 1999; McCarthy and Hilfiker, 2000). By broadening the search for genetic polymorphisms that determine drug responses, the new field of pharmacogenomics begins to replace the candidate gene approach typical of pharmacogenetic studies currently performed, because genome-wide scanning using linkage disequilibrium can identify these genes even if the mechanisms by which the drug acts in the body are unknown (McCarthy and Hilfiker, 2000). Through linkage disequilibrium, associations found with these anonymous markers can identify a region of the genome that may harbor a susceptibility gene without any a priori assumptions about what or where the susceptibility gene is. This approach relies on linkage disequilibrium or nonrandom association between single nucleotide polymorphisms in proximity to each other. Tens to hundreds of thousands of anonymous single nucleotide polymorphisms need to be identified and their location in the genome mapped (McCarthy and Hilfiker, 2000), and mapped single nucleotide polymorphisms are being regularly posted on public domain websites http://snp.cshl.org). Although these anonymous single nucleotide polymorphisms may fall within genes and may in fact be considered susceptibility single nucleotide polymorphisms, most are located in the vast amount of non-coding DNA between genes and play no obvious role in drug response. Additional significant efforts using positional cloning are then required to find the gene and single nucleotide polymorphisms within that confer the underlying association. Expanding and selecting the number of single nucleotide polymorphisms, which are functionally relevant single nucleotide polymorphisms in coding or promoter/enhancer regions, currently being investigated would greatly enhance the power of genome-wide scanning (Sadée, 1999).

6.2. Microarray gene chips

One of the major challenges of linkage disequilibrium mapping is the need to genotype each person in the study for every one of the 60,000–500,000 single nucleotide polymorphisms in the map (McCarthy and Hilfiker, 2000). Several genotyping platforms are available today, including nucleic acid hybridization on filter (Saiki et al., 1989) or chips (Chee et al., 1996), single-strand conformational polymorphism (Orita et al., 1989), and primer-extension methods (Syvanen, 1999). Although these genotyping technologies are robust, at the current average price of one dollar per genotype, their use in large-scale single nucleotide polymorphism genotyping studies may be prohibitively expensive (McCarthy and Hilfiker, 2000). However, DNA microarray (DNA chip) analysis is a promising new technology, which potentially may allow rapid and cost-effective screens for all possible mutations and sequence variations in genomic DNA (Hacia, 1999). This technology enables a scan of the entire human genome for relevant polymorphisms (Service, 1998). As applied to genotyping, microarrays usher in the possibility of determining alleles at hundreds of thousands of loci from hundreds of DNA samples, allowing the contemplation of whole genome association studies to determine the genetic contribution to complex polygenetic disorders (Collins, 1999), including schizophrenia and its drug response. Furthermore, when applied to expression analysis this approach facilitates the measurement of RNA levels for the complex set of transcripts of an organism, showing the mechanisms of drug action in a genomic context. It can also clarify interindividual differences in drug response that are downstream of immediate drug effects in the body by sheer force of the massive amount of information emanating from chip technology.

Differential display, which is one of the recent comprehensive transcript expression analyses, can lead to identifying drug-dependent regulation of unknown gene products (messenger RNA). To date, using this technique in an animal model of schizophrenia, both novel and previously described genes have been identified, which could be related to sensitization induced by repeated doses of dopaminergic agonists such as cocaine (Wang et al., 1997; Berke et al., 1998), and might be potential therapeutic targets for treatment of schizophrenia. This technique has also been applied in animals treated with antipsychotics in order to find relevant molecular events underlying the pharmacotherapeutic effects of neuroleptics (Fischer et al., 1998). DNA microarray studies will generate more clues of gene function that can help to identify appropriate targets for therapeutic intervention (Debouck and Goodfellow, 1999) and lead to the discovery of new tailored drugs.

7. Phenotype

To uncover drug response markers and establish individual tailor-made drug treatments for schizophrenic patients by using the strategy of pharmacogenetics and pharmacogenomics, it is important that several phenotypes (e.g. drug response, clinical symptoms, etc.) of schizophrenic patients are taken into account. It should be noted that the rate of discovery of those polymorphisms will depend on the quality of the drug response phenotype, since the polymorphisms relevant to drug response will already exist in the single nucleotide polymorphism maps after the high-density single nucleotide polymorphism map of the whole genome is completed. As mentioned above, pharmacogenetic studies of schizophrenia investigating the same target sometimes report conflicting results. These differences in findings of pharmacogenetic studies may be due to differences of definition of the phenotype including clinical symptoms and drug response, and sample size and ethnicity. In addition, the majority of gene effects in

response to medication might be individually small and statistical error may affect results. Thus, a collection of patient samples with possibly uniform phenotypes, large enough to exclude statistical errors, is required for pharmacogenomic study. Recently, preliminary guidelines in the field of pharmacogenetics have been proposed by the "Consensus Group for Outcome Measures in Psychosis for Pharmacogenetic Studies" (Rietschel et al., 1999).

Rigorous and quantitative definition of phenotype for schizophrenia is difficult, since the disease has neither visible traits nor significant laboratory data. However, as indicated by Cichon et al. (2000), first, patient characteristics including standardized diagnosis such as DSM-IV or ICD-10, subtype criteria, age, gender, ethnicity, the course of the disorder including age at onset, and history of prior treatment response are needed at the start of the investigation. Second, specific symptoms (e.g. presence of negative symptoms, specific hallucinations and delusions) should be followed over the course of investigation. If possible, other quantitative measures of response should be assessed (e.g. neurocognitive functioning, psychophysiologic measures, motor behavior). Finally, assessment of response requires clarification with respect to instruments to be applied, initiation, duration of the study, dose, and co-medication. These considerations for phenotype will accelerate the pharmacogenomic studies in schizophrenia.

8. Prospects

The antipsychotic drug response in schizophrenia might be predicted from a certain pattern of polymorphisms, rather than from a single polymorphism. The development of rapid techniques for mutation screening and genotyping by using DNA array technology will greatly accelerate the discovery of the polymorphisms relevant to drug response. However, it must be noted that the rate of discovery of those polymorphisms will depend on the quality of the drug response phenotype, since the polymorphisms relevant to drug response will already exist in the single nucleotide polymorphism maps after the high-density single nucleotide polymorphism map of the whole genome is completed. The next technical hurdle will be the development of inexpensive high-throughput methods for scoring large numbers of single nucleotide polymorphisms from hundreds of patients. Considerable efforts are now underway within the biotechnical community to establish low-cost, high-throughput, accurate single nucleotide polymorphism scoring technologies (Armstrong et al., 2000; Pastinen et al., 1984). With the use of pharmacogenomics, new antipsychotics that are safer and more effective will be discovered. It might also be possible to salvage useful experimental drugs that would have failed with standard clinical trials, because of an unacceptable incidence of toxicity in a poorly defined patient population. Prospective genotyping of schizophrenic patients for the many genes at the level of the drug target, drug metabolism, and disease pathways, will contribute to individualized therapy matching the patient's unique genetic make up with an optimally effective drug. Perhaps a gene chip that establishes a single nucleotide polymorphism signature involving multiple genes relevant to therapeutic outcome for each individual will be developed in order to select medications and dosages that are optimized for each patient. In addition, psychiatrists may be obliged to order such genetic testing to avoid malpractice litigation. Finally, such optimization will also result in decreasing the overall direct treatment costs of schizophrenia through prescription of the right drug for the right patient, improvement of quality of life and other aspects of day-to-day functioning.

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders. 4th edn. American Psychiatric Association, Washington, DC, pp. 273–315.

Andreasen, N.C., 2000. Schizophrenia: the fundamental questions. Brain Res. Rev. 31, 106–112.

Andreassen, O.A., MacEwan, T., Gulbrandsen, A.K., McCreadie, R.G., Steen, V.M., 1997. Non-functional CYP2D6 alleles and risk for neuroleptic-induced movement disorders in schizophrenic patients. Psychopharmacology (Berlin) 131, 174–179.

Arinami, T., Gao, M., Hamaguchi, H., Toru, M., 1997. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. Hum. Mol. Genet. 6, 577–582.

Armstrong, M., Daly, A.K., Blennerhassett, R., Ferrier, N., Idle, J.R., 1997. Antipsychotic drug-induced movement disorders in schizophrenics in relation to CYP2D6 genotype. Br. J. Psychiatry 170, 23–26.

Armstrong, B., Stewart, M., Mazumder, A., 2000. Suspension arrays for high throughput, multiplexed single nucleotide polymorphism genotyping. Cytometry 40, 102–108.

Arranz, M.J., Kerwin, R.W., 2000. Neurotransmitter-related genes and antipsychotic response: pharmacogenetics meets psychiatric treatment. Ann. Med. 32, 128–133.

Arranz, M., Collier, D., Sodhi, M., Ball, D., Roberts, G., Price, J., Sham, P., Kerwin, R., 1995a. Association between clozapine response and allelic variation in 5-HT_{2A} receptor gene. Lancet 346, 281–282.

Arranz, M., Dawson, E., Shaikh, S., Sham, P., Sharma, T., Aitchison, K., Crocq, M.A., Gill, M., Kerwin, R., Collier, D.A., 1995b. Cytochrome *P*450D6 genotype does not determine response to clozapine. Br. J. Pharmacol. 39, 417–420.

Arranz, M.J., Collier, D.A., Munro, J., Sham, P., Kirov, G., Sodhi, M., Roberts, G., Price, J., Kerwin, R.W., 1996. Analysis of a structural polymorphism in the 5-HT_{2A} receptor and clinical response to clozapine. Neurosci. Lett. 217, 177–178.

Arranz, M.J., Li, T., Munro, J., Liu, X., Murray, R., Collier, D.A., Kerwin, R.W., 1998a. Lack of association between a polymorphism in the promoter region of the dopamine-2 receptor gene and clozapine response. Phrmacogenetics 8, 481–484.

Arranz, M.J., Munro, J., Owen, M.J., Spurlock, G., Sham, P.C., Zhao, J., Kirov, G., Collier, D.A., Kerwin, R.W., 1998b. Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT_{2A} receptor gene and response to clozapine. Mol. Psychiatry 3, 61–66.

Arranz, M.J., Munro, J., Sham, P., Kirov, G., Murray, R.M., Collier,

D.A., Kerwin, R.W., 1998c. Meta-analysis of studies on genetic variation in 5-HT_{2A} receptors and clozapine response. Schizophr. Res. 32, 93–99.

Arranz, M.J., Munro, J., Birkett, J., Bolonna, A., Mancama, D., Sodhi, M., Lesch, K.P., Meyer, J.F., Sham, P., Collier, D.A., Murray, R.M., Kerwin, R.W., 2000. Pharmacogenetic prediction of clozapine response. Lancet 355, 1615–1616.

Arthur, H., Dahl, M.L., Siwers, B., Sjoqvist, F., 1995. Polymorphic drug metabolism in schizophrenic patients with tardive dyskinesia. J. Clin. Psychopharmacol. 15, 211–216.

Asghari, V., Schoots, O., van Kats, S., Ohara, K., Jovanovic, V., Guan, H.C., Bunzow, J.R., Petronis, A., Van Tol, H.H., 1994. Dopamine D4 receptor repeat: analysis of different native and mutant forms of the human and rat genes. Mol. Pharmacol. 46, 364–373.

Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V., Van Tol, H.H., 1995. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J. Neurochem. 65, 1157–1165.

Basile, V.S., Masellis, M., Badri, F., Paterson, A.D., Meltzer, H.Y., Lieberman, J.A., Potkin, S.G., Macciardi, F.M., Kennedy, J.L., 1999. Association of the MscI polymorphism of the dopamine D3 receptor gene with tardive dyskinesia in schizophrenia. Neuropsychopharmacology 21, 17–27.

Basile, V.S., Ozdemir, V., Masellis, M., Walker, M.L., Meltzer, H.Y., Lieberman, J.A., Potkin, S.G., Alva, G., Kalow, M., Macciardi, F.M., Kennedy, J.L., 2000. A functional polymorphism of the cytochrome *P*450 1A2 (CYP1A2) gene: association with tardive dyskinesia in schizophrenia. Mol. Psychiatry 5, 410–417.

Berke, J.D., Paletzki, R.F., Aronson, G.J., Hyman, S.E., Gerfen, C.R., 1998. A complex program of striatal gene expression induced by dopaminergic stimulation. J. Neurosci. 18, 5301–5310.

Birkett, J.T., Arranz, M.J., Munro, J., Osbourn, S., Kerwin, R.W., Collier, D.A., 2000. Association analysis of the 5-HT_{5A} gene in depression, psychosis and antipsychotic response. NeuroReport 11, 2017–2020.

Brookes, A.J., 1999. The essence of SNPs. Gene 234, 177–186.

Brower, V., 1998. Genome II: the next frontier. Nat. Biotechnol. 16, 1004.

Brüss, M., Bühlen, M., Erdmann, J., Göthert, M., Bönisch, H., 1995. Binding properties of the naturally occurring human 5-HT_{1A} receptor variant with the Ile28Val substitution in the extracellular domain. Naunyn-Schmiedeberg's Arch. Pharmacol. 352, 455–458.

Brüss, M., Bönisch, H., Bühlen, M., Nöthen, M.M., Propping, P., Göthert, M., 1999. Modified ligand binding to the naturally occurring Cys-124 variant of the human serotonin 5-HT_{1B} receptor. Pharmacogenetics 9, 95–102.

Bühlen, M., Brüss, M., Bönisch, H., Göthert, M., 1996. Modified ligand binding properties of the naturally occurring Phe-124-Cys variant of the human 5-$HT_{1D\beta¿}$ receptor. Naunyn-Schmiedeberg's Arch. Pharmacol. 353, R91 (Suppl.).

Carlson, A., Lindquist, M., 1963. Effect of chlorpromazine and haloperidol on the formation of 3-methoxytyramine in mouse brain. Acta Pharmacol. 20, 140–144.

Carson, P.E., Flangan, C.L., Ickes, C.E., Alving, A.S., 1956. Enzymatic deficiency in primaquine-sensitive erthrocytes. Science 124, 484–485.

Catalano, M., Nobile, M., Novelli, E., Nothen, M.M., Smeraldi, E., 1993. Distribution of a novel mutation in the first exon of the human dopamine D_4 receptor gene in psychotic patients. Biol. Psychiatry 34, 459–464.

Chee, M., Yang, R., Hubbell, E., Berno, A., Huang, X.C., Stern, D., Winkler, J., Lockhart, D.J., Morris, M.S., Fodor, S.P., 1996. Accessing genetic information with high-density DNA arrays. Science 274, 610–614.

Chen, C.H., Wei, F.C., Koong, F.J., Hsiao, K.J., 1997. Association of TaqI A polymorphism of dopamine D2 receptor gene and tardive dyskinesia in schizophrenia. Biol. Psychiatry 41, 827–829.

Cichon, S., Nothen, M.M., Erdmann, J., Propping, P., 1994. Detection of four polymorphic sites in the human dopamine D1 receptor gene (DRD1). Hum. Mol. Genet. 3, 209.

Cichon, S., Nothen, M.M., Catalano, M., Di Bella, D., Maier, W., Lichtermann, D., Minges, J., Albus, M., Borrmann, M., Franzek, E. et al., 1995. Protein, nucleotide identification of two novel polymorphisms and a rare deletion variant in the human dopamine D4 receptor gene. Psychiatr. Genet. 5, 97–103.

Cichon, S., Nöthen, M.M., Stober, G., Schroers, R., Albus, M., Maier, W., Rietschel, M., Korner, J., Weigelt, B., Franzek, E., Wildenauer, D., Fimmers, R., Propping, P., 1996. Systemic screening for mutations in the 5′-regulatory region of the human dopamine D1 receptor (DRD1) gene in patients with schizophrenia and bipolar affective disorder. Am. J. Med. Genet. 67, 424–428.

Cichon, S., Nöthen, M.M., Rietschel, M., Propping, P., 2000. Pharmacogenetics of schizophrenia. Am. J. Med. Genet. 97, 98–106.

Cohen, B.M., Ennulat, D.J., Centorrino, F., Metthysse, S., Konieczna, H., Chu, H.M., Cherkerzian, S., 1999. Polymorphisms of the dopamine D4 receptor and response to antypsychotic drugs. Psychopharmacology (Berlin) 141, 6–10.

Collins, F.S., 1999. Microarrays and macroconsequences. Nat. Genet. 21 (Suppl. 1), 2.

Corzo, D., Yunis, J.J., Salazar, M., Liebman, J.A., Howard, A., Awdeh, Z., Alper, C.A., Yunis, E.J., 1995. The major histocompatibility complex region marked by HSP70-1 and HSP70-2 variants is associated with clozapine-induced agranulocytosis in two defferent ethnic groups. Blood 86, 3835–3840.

Coutts, R.T., Urichuk, L.J., 1999. Polymorphic cytochrome *P*450 and drugs in psychiatry. Cell. Mol. Neurobiol. 19, 325–354.

Cravchik, A., Gejman, P.V., 1999. Functional analysis of the human D_5 dopamine receptor missense and nonsense variants: differences in dopamine binding affinities. Pharmacogenetics 9, 199–206.

Cravchik, A., Sibley, D.R., Gejman, P.V., 1996. Functional analysis of the human D_2 dopamine receptor missense variants. J. Biol. Chem. 271, 26013–26017.

Cravchik, A., Sibley, D.R., Gejman, P.V., 1999. Analysis of neuroleptic binding affinities and potencies for the different human D_2 dopamine receptor missense variants. Pharmacogenetics 9, 17–23.

Crocq, M.A., Mant, R., Asherson, P., Williams, J., Hode, Y., Mayerova, A., Collier, D., Lannfelt, L., Sokoloff, P., Schwartz, J.C., Gill, M., Macher, J.P., McGuffin, P., Owen, M.J., 1992. Association between schizophrenia and homozygosity at the dopamine D3 receptor gene. J. Med. Genet. 29, 858–860.

Dahl, M.-L., Bertilsson, L., 1993. Genetically variable metabolism of antidepressants and neuroleptic drugs in man. Pharmacogenetics 3, 61–70.

Daly, A.K., Brockmîller, J., Broly, F., Eichbaum, M., Evans, W.E., Gonzalez, F.J., Huang, J.D., 1996. Nomenclature for human CYP2D6 alleles. Pharmacogenetics 6, 193–201.

Debouck, C., Goodfellow, P.N., 1999. DNA microarrays in drug discovery and development. Nat. Genet. 21 (Suppl. 1), 48–50.

Eichhammer, P., Albus, M., Borrmann-Hassenbach, M., Schoeler, A., Putzhammer, A., Frick, U., Klein, H.E., Rohrmeier, T., 2000. Association of dopamine D3-receptor gene variants with neuroleptic induced akathisia in schizophrenic patients: a generalization of Steen's study on DRD3 and tardive dyskinesia. Am. J. Med. Genet. 96, 187–191.

Erdmann, J., Shimron-Abarbanell, D., Cichon, S., Albus, M., Maier, W., Lichtermann, D., Minges, J., Reuner, U., Franzek, E., Ertl, M.A., Hebebrand, J., Remschmidt, H., Lehmkuhl, G., Poustka, F., Schmidt, M., Fimmers, R., Körner, J., Rietschel, M., Propping, P., Nöthen, M.M., 1995. Systematic screening for mutations in the promoter and the coding region of the 5-HT_{1A} gene. Am. J. Med. Genet. 60, 393–399.

Erdmann, J., Shimron-Abarbanell, D., Rietschel, M., Albus, M., Maier, W., Korner, J., Bondy, B., Chen, K., Shih, J.C., Knapp, M., Propping, P., Nöthen, M.M., 1996a. Systematic screening for mutations in the

human serotonin-2A (5-HT_{2A}) receptor gene: identification of two naturally occurring receptor variants and association analysis in schizophrenia. Hum. Genet. 97, 614–619.

Erdmann, J., Nöthen, M.M., Shimron-Abarbanell, D., Rietschel, M., Albus, M., Borrmann, M., Maier, W., Franzek, E., Korner, J., Weigelt, B., Fimmers, R., Propping, P., 1996b. The human serotonin 7 (5-HT_7) receptor gene: genomic organization and systematic mutation screening in schizophrenia and bipolar affective disorder. Mol. Psychiatry 1, 392–397.

Evance, D.A.P., Manley, K.A., McKusick, V.A., 1960. Genetic control of isoniazid metabolism in man. Br. Med. J. 2, 485–491.

Evans, W.E., Relling, M.V., 1999. Pharmacogenomics: translating functional genomics into rational therapeutics. Science 286, 487–491.

Fang, J., Gorrod, J.W., 1999. Metabolism, phaarmacogenetics, and metabolic drug–drug interactions of antipsychotic drugs. Cell. Mol. Neurobiol. 19, 491–510.

Feng, J., Sobell, J.L., Heston, L.L., Cook, E.H.Jr., Goldman, D., Sommer, S.S., 1998. Scanning of the dopamine D1 and D5 receptor genes by REF in neuropsychiatric patients reveals a novel missense change at ahighly conserved amino acid. Am. J. Med. Genet. 81, 172–178.

Fischer, V., Schmitt, U., Weigmann, H., Von Keller, B., Reuss, S., Hiemke, C., Dahmen, N., 1998. Chronical haloperidol and clozapine treatment in rats: differential RNA display analysis, behavioral studies and serum level determination. Prog. Neuropsychopharmacol. Biol. Psychiatry 22, 1129–1139.

Foster, R.H., Goa, K.L., 1999. Olanzapine. A pharmacoeconomic review of its use in schizophrenia. PharmacoEconomics 15, 611–640.

Frackiewicz, E.J., Sramek, J.J., Herrera, J.M., Kurtz, N.M., Cutler, N.R., 1997. Ethnicity and antipsychotic response. Ann. Pharmacother. 31, 1360–1369.

Gejman, P.V., Ram, A., Gelernter, J., Friedman, E., Cao, Q., Pickar, D., Blum, K., Noble, E.P., Kranzler, H.R., O'Malley, S., Hamer, D.H., Whitsitt, F., Rao, P., DeLisi, L.E., Virkkunen, M., Linnoila, M., Goldman, D., Elliot, S., Gershon, E.S., 1994. No structural mutation in the dopamine D2 receptor gene in alcoholism or schizophrenia. Analysis using denaturing gradient gel electrophoresis. JAMA 271, 204–208.

Goldman, D., Lappalainen, J., Ozaki, N., Nakhai, B., Bergen, A., Pesonen, U.-M., Koulu, M., Dean, M., Zhang, L., Weight, F., Eggert, M., Virkkunen, M., Linnolia, M., 1995. Natural structural variants of human serotonin receptors. Psychiatr. Genet. 5 (Suppl. 1), S22.

Hacia, J.G., 1999. Resequencing and mutational analysis using oligonucleotide microarrays. Nat. Genet. 21 (Suppl. 1), 42–47.

Hacia, J.G., Fan, J.B., Ryder, O., Jin, L., Edgemon, K., Ghandour, G., Mayer, R.A., Sun, B., Hsie, L., Robbins, C.M., Brody, L.C., Wang, D., Lander, E.S., Lipshutz, R., Fodor, S.P., Collins, F.S., 1999. Determination of ancestral alleles for human single-nucleotide polymorphisms using high-density oligonucleotide arrays. Nat. Genet. 22, 164–167.

Hamelin, B.A., Dorson, P.G., Pabis, D., Still, D., Bouchard, R.H., Pourcher, E., Rail, J., Turgeon, J., Crismon, M.L., 1999. CYP2D6 mutations and therapeutic outcome in schizophrenic patients. Pharmacotherapy 19, 1057–1063.

Hamilton, S.H., Revicki, D.A., Edgell, E.T., Genduso, L.A., Tollefson, G., 1999. Clinical and economic outcomes of olanzapine compared with haloperidol for schizophrenia. Results from a randomised clinical trial. PharmacoEconomics 15, 469–480.

Harada, S., Okubo, T., Tsutsumi, M., Takase, S., Muramatsu, T., 1996. Investigation of genetic risk factors associated with alcoholism. Alcohol.: Clin. Exp. Res. 20 (Suppl. 9), 93A–296A.

Hori, H., Ohmori, O., Shinkai, T., Kojima, H., Okano, C., Suzuki, T., Nakajima, J., 2000. Maganese superoxide dismutase gene polymorphism and schizophrenia. Relation to tardive dyskinesia. Neuropsychopharmacology 23, 170–177.

Hughes, H.B., Biehl, J.P., Jones, A.P., Schmidt, L.H., 1954. Metabolism of isoniazid in man as related to the occurrence of peripheral neuritis. Am. Rev. Tuberc. 70, 266–273.

Hwu, H.G., Hong, C.J., Lee, Y.L., Lee, P.C., Lee, S.F., 1998. Dopamine D4 receptor gene polymorphisms and neuroleptic response in schizophrenia. Biol. Psychiatry 44, 483–487.

Isaksson, A., Landegren, U., Syvanen, A.C., Bork, P., Stein, C., Ortigao, F., Brookes, A.J., 2000. Discovery, scoring and utilization of human single nucleotide polymorphisms: a multidisciplinary problem. Eur. J. Hum. Genet. 8, 154–156.

Itokawa, M., Arinami, T., Futamura, N., Hamaguchi, H., Toru, M., 1993. A structural polymorphism of human dopamine D2 receptor, D2(Ser311->Cys). Biochem. Biophys. Res. Commun. 196, 1369–1375.

Iwata, N., Virkkunen, M., Linnoila, M., Goldman, D., 1998. Identification of a naturally occurring Pro15–Ser15 substitution in the serotonin5A receptor gene in alcoholics and healthy volunteers. Mol. Brain Res. 58, 217–220.

Jibson, M.D., Tandon, R., 1998. New atypical antipsychotic medications. J. Psychiatr. Res. 32, 215–228.

Johansson, I., Oscarson, M., Yue, Q.Y., Bertilsson, L., Sjoqvist, F., Ingelman-Sundberg, M., 1994. Genetic analysis of the Chinese cytochrome *P*4502D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation. Mol. Pharmacol. 46, 452–459.

Joober, R., Benkelfat, C., Brisebois, K., Toulouse, A., Turecki, G., Lal, S., Bloom, D., Labelle, A., Lalonde, P., Fortin, D., Alda, M., Palmour, R., Rouleau, G.A., 1999. T102C polymorphism in the 5HT_{2A} gene and schizophrenia: relation to phenotype and drug response variability. J. Psychiatry Neurosci. 24, 141–146.

Kalow, W., 1956. Familial incidence of low pseudocholinesterase level. Lancet 211, 576–577.

Kapitany, T., Meszaros, K., Lenzinger, E., Schindler, S.D., Barnas, C., Fuchs, K., Sieghart, W., Aschauer, H.N., Kasper, S., 1998. Genetic polymorphism for drug metabolism (CYP2D6) and tardive dyskinesia in schizophrenia. Schizophr. Res. 27, 101–106.

Kaplan, H.I., Sadock, B.J., 1998. Kaplan and Sadock's synopsis of psychiatry: behavioral sciences, clinical psychiatry. 8th edn. Williams & Wilkins, Maryland, pp. 456–491.

Kawanishi, Y., Harada, S., Tachikawa, H., Okubo, T., Shiraishi, H., 1998. Novel mutations in the promoter and coding region of the human 5-HT_{1A} receptor gene and association analysis in schizophrenia. Am. J. Med. Genet. 81, 434–439.

Kirov, G., Murray, R., 1997. The molecular genetics of schizophrenia: progress so far. Mol. Med. Today 3, 124–130.

Kohn, Y., Ebstein, R.P., Heresco-Levy, U., Shapira, B., Nemanov, L., Gritsenko, I., Avnon, M., Lerer, B., 1997. Dopamine D4 receptor gene polymorphisms: relation to ethnicity, no association with schizophrenia and response to clozapine in Israeli subjects. Eur. Neuropsychopharmacol. 7, 39–43.

Kojima, H., Ohmori, O., Shinkai, T., Terao, T., Suzuki, T., Abe, K., 1999. Dopamine D1 receptor gene polymorphism and schizophrenia. Am. J. Med. Genet. 88, 116–119.

Krebs, M.O., Sautel, F., Bourdel, M.C., Sokoloff, P., Schwartz, J.C., Olie, J.P., Loo, H., Poirier, M.F., 1998. Dopamine D3 receptor gene variants and substance abuse in schizophrenia. Mol. Psychiatry 3, 337–341.

Lam, S., Shen, Y., Nguyen, T., Messier, T.L., Brann, M., Comings, D., George, S.R., O'Dowd, B.F., 1996. A serotonin receptor gene (5HT_{1A}) variant found in a Tourette's syndrome patient. Biochem. Biophys. Res. Commun. 219, 853–858.

Lappalainen, J., Zhang, L., Dean, M., Oz, M., Ozaki, N., Yu, D.H., Virkkunen, M., Weight, F., Linnoila, M., Goldman, D., 1995. Identification, expression, and pharmacology of a Cys23–Ser23 substitution in the human 5-HT_{2c} receptor gene (HTR2C). Genomics 27, 274–279.

Liu, Q., Sobell, J.L., Heston, L.L., Sommer, S.S., 1995. Screening the dopamine D1 receptor gene in 131 schizophrenics and eight alcoholics: identification of polymorphisms but lack of functionally significant sequence changes. Am. J. Med. Genet. 60, 165–171.

Liu, I.S., Seeman, P., Sanyal, S., Ulpian, C., Rodgers-Johnson, P.E.,

Serjeant, G.R., Van Tol, H.H., 1996. Dopamine D4 receptor variant in Africans, D4valine194glycine, is insensitive to dopamine and clozapine: report of a homozygous individual. Am. J. Med. Genet. 61, 277–282.

Llerena, A., Cobaleda, J., Martinez, C., Benitez, J., 1996. Interethnic differences in drug metabolism: influence of genetic and environmental factors on debrisoquine hydroxylation phenotype. Eur. J. Drug Metab. Pharmacokinet. 21, 129–138.

Lundstrom, K., Turpin, M., 1996. Proposed schizophrenia-related gene polymorphism: expression of the Ser9Gly mutant human dopamine D3 receptor with the Semliki Forest virus system. Biochem. Biophys. Res. Commun. 225, 1068–1072.

Malhotra, A.K., Goldman, D., Ozaki, N., Breier, A., Buchanan, R., Pickar, D., 1996a. Lack of association between polymorphisms in the 5-HT_{2A} receptor gene and the antipsychotic response to clozapine. Am. J. Psychiatry 153, 1092–1094.

Malhotra, A.K., Goldman, D., Ozaki, N., Rooney, W., Clifton, A., Buchanan, R.W., Breier, A., Pickar, D., 1996b. Clozapine response and the $5HT_{2C}$ Cys23Ser polymorphism. NeuroReport 7, 2100–2102.

Malhotra, A.K., Goldman, D., Buchanan, R.W., Rooney, W., Clifton, A., Kosmidis, M.H., Breier, A., Pickar, D., 1998. The dopamine D3 receptor (DRD3) Ser9Gly polymorphism and schizophrenia: a haplotype relative risk study and association with clozapine response. Mol. Psychiatry 3, 72–75.

March, R., 2000. Pharmacogenomics: the genomics of drug response. Yeast 17, 16–21.

Marez, D., Legrand, M., Sabbagh, N., Lo Guidice, J.-M., Spire, C., Lafitte, .J.-J., Lundstrom, K., Turpin, M.P., 1997. Polymorphism of the cytochrome *P*450 CYP2D6 gene in a European population: characterization of 48 mutations and 53 alleles, their frequencies and evolution. Pharmacogenetics 7, 193–202.

Marshall, E., 1999. Drug firms to create public database of genetic mutations. Science 284, 406–407.

Masellis, M., Paterson, A.D., Badri, F., Lieberman, J.A., Meltzer, H.Y., Cavazzoni, P., Kennedy, J.L., 1995. Genetic variation of 5-HT_{2A} receptor and response to clozapine. Lancet 346, 1108.

Masellis, M., Basile, V., Meltzer, H.Y., Lieberman, J.A., Sevy, S., Macciardi, F.M., Cola, P., Howard, A., Badri, F., Nöthen, M.M., Kalow, W., Kennedy, J.L., 1998. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology 19, 123–132.

Masellis, M., Basile, V.S., Ozdemir, V., Meltzer, H.Y., Macciardi, F.M., Kennedy, J.L., 2000. Pharmacogenetics of antipsychotic treatment: lessons learned from clozapine. Biol. Psychiatry 47, 252–266.

McCarthy, J.J., Hilfiker, R., 2000. The use of single-nucleotide polymorphism maps in pharmacogenomics. Nat. Biotechnol. 18, 505–508.

Meltzer, H.Y., 1995. Role of serotonin in the action of atypical antipsychotic drugs. Clin. Neurosci. 3, 64–75.

Mihara, K., Suzuki, A., Kondo, T., Yasui, N., Furukori, H., Nagashima, U., Otani, K., Kaneko, S., Inoue, Y., 1999. Effects of the CYP2D6* 10 allele on the steady-state plasma concentrations of haloperidol and reduced haloperidol in japanese patients in schizophrenia. Clin. Pharmacol. 65, 291–294.

Mihara, K., Kondo, T., Suzuki, A., Yasui, N., Nagashima, U., Ono, S., Otani, K., Kaneko, S., 2000. Prolactin response to nemonapride, a selective antagonist for D2 like dopamine receptors, in schizophrenic patients in relation to Taq 1A polymorphism of DRD2 gene. Psychopharmacology 149, 246–250.

Moldin, S.O., Gottesman, I.I., 1997. At issue: genes, experience, and chance in schizophrenia-positioning for the 21st century. Schizophr. Bull. 23, 547–561.

Moore, N.A., 1999. Behavioural pharmacology of the new generation of antipsychotic agents. Br. J. Psychiatry (Suppl. 38), 5–11.

Nakhai, B., Nielsen, D.A., Linnoila, M., Goldman, D., 1995. Two naturally occurring amino acid substitutions in the human 5-HT_{1A} receptor: glycine 22 to serine 22 and isoleucine 28 to valine 28. Biochem. Biophys. Res. Commun. 210, 530–536.

Nebert, D.W., 1997. Polymorphisms in drug-metabolizing enzymes: what is their clinical relevance and why do they exist? Am. J. Hum. Genet. 60, 265–271.

Nöthen, M.M., Cichon, S., Hemmer, S., Hebebrand, J., Remschmidt, H., Lehmkuhl, G., Poustka, F., Schmidt, M., Catalano, M., Fimmers, R. et al., 1994a. Human dopamine D4 receptor gene: frequent occurrence of a null allele and observation of homozygosity. Hum. Mol. Genet. 3, 2207–2212.

Nöthen, M.M., Erdmann, J., Shimron-Abarbanell, D., Propping, P., 1994b. Identification of genetic variation in the human serotonin 1Dβ receptor gene. Biochem. Biophys. Res. Commun. 205, 1194–1200.

Nöthen, M.M., Rietschel, M., Erdmann, J., Oberlander, H., Moller, H.J., Nober, D., Propping, P., 1995. Genetic variation of the 5-HT_{2A} receptor and response to clozapine. Lancet 346, 908–909.

Ohara, K., Ulpian, C., Seeman, P., Sunahara, R.K., Van Tol, H.H., Niznik, H.B., 1993. Schizophrenia: dopamine D1 receptor sequence is normal, but has DNA polymorphisms. Neuropsychopharmacology 8, 131–135.

Ohara, K., Nagai, M., Tani, K., Nakamura, Y., Ino, A., Ohara, K., 1998. Functional polymorphism of −141 C Ins/Del in the dopamine D2 receptor gene promoter and schizophrenia. Psychiatry Res. 81, 117–123.

Ohmori, O., Suzuki, T., Kojima, H., Shinkai, T., Terao, T., Mita, T., Abe, K., 1998. Tardive dyskinesia and debrisoquine 4-hydroxylase (CYP2D6) genotype in Japanese schizophrenics. Schizophr. Res. 32, 107–113.

Ohmori, O., Kojima, H., Shinkai, T., Terao, T., Suzuki, T., Abe, K., 1999. Genetic association in analysis between CYP2D6* 2 allele and tardive dyskinesia in schizophrenic patients. Psychiatry Res. 87, 239–244.

Okuyama, Y., Ishiguro, H., Toru, M., Arinami, T., 1999. A genetic polymorphism in the promoter region of DRD4 associated with expression and schizophrenia. Biochem. Biophys. Res. Commun. 258, 292–295.

Orita, M., Iwahana, H., Kanazawa, H., Hayashi, K., Sekiya, T., 1989. Detection of polymorphisms of human DNA by gel electrophoresis as single-strand conformation polymorphisms. Proc. Natl. Acad. Sci. U. S. A. 86, 2766–2770.

Ozaki, N., Lappalainen, J., Dean, M., Virkkunen, M., Linnoila, M., Goldman, D., 1995. Mapping of the serotonin 5-$HT_{1D\alpha}$ autoreceptor gene (HTR1D) on chromosome 1 using a silent polymorphism in the coding region. Am. J. Med. Genet. 60, 162–164.

Ozaki, N., Manji, H., Lubierman, V., Lu, S.J., Lappalainen, J., Rosenthal, N.E., Goldman, D., 1997. A naturally occurring amino acid substitution of the human serotonin 5-HT_{2A} receptor influences amplitude and timing of intracellular calcium mobilization. J. Neurochem. 68, 2186–2193.

Pastinen, T., Raitio, M., Potkin, S.G., Shen, Y., Pardes, H., Phelps, B.H., Zhou, D., Shu, L., Korpi, E., Wyatt, R.J., 1984. Haloperidol concentrations elevated in Chinese patients. Psychiatry Res. 12, 167–172.

Prior, T.I., Chue, P.S., Tibbo, P., Baker, G.B., 1999. Drug metabolism and atypical antipsychotics. Eur. Neuropsychopharmacol. 9, 301–309.

Propping, P., Nöthen, M.M., 1995. Genetic variation of CNS receptors—a new perspective for pharmacogenetics. Pharmacogenetics 5, 318–325.

Rao, P.A., Pickar, D., Gejman, P.V., Ram, A., Gershon, E.S., Gelernter, J., 1994. Allelic variation in the D4 dopamine receptor (DRD4) gene does not predict response to clozapine. Arch. Gen. Psychiatry 51, 912–917.

Rietschel, M., Naber, D., Oberlander, H., Holzbach, R., Fimmers, R., Eggermann, K., Moller, H.J., Propping, P., Nothen, M.M., 1996. Efficacy and side-effects of clozapine: testing for association with allelic variation in the Dopamine D4 receptor gene. Neuropsychopharmacology 15, 491–496.

Rietschel, M., Naber, D., Fimmers, R., Moller, H.J., Propping, P., Nöthen, M.M., 1997. Efficacy and side-effects of clozapine not associated with variation in the 5-HT_{2C} receptor. NeuroReport 8, 1999–2003.

Rietschel, M., Kennedy, J.L., Macciardi, F., Meltzer, H.Y., 1999. Application of pharmacogenetics to psychotic disorders: the first consensus conference. The Consensus Group for Outcome Measures in Psychoses for Pharmacological Studies. Schizophr. Res. 37, 191–196.

Rietschel, M., Krauss, H., Muller, D.J., Schulze, T.G., Knapp, M., Marwinski, K., Maroldt, A.O., Paus, S., Grunhage, F., Propping, P., Maier, W., Held, T., Nöthen, M.M., 2000. Dopamine D3 receptor variant and tardive dyskinesia. Eur. Arch. Psychiatry Clin. Neurosci. 250, 31–35.

Roses, A.D., 2000. Pharmacogenetics and the practice of medicine. Nature 405, 857–865.

Rotondo, A., Nielsen, D.A., Nakhai, B., Hulihan-Giblin, B., Bolos, A., Goldman, D., 1997. Agonist-promoted down-regulation and functional desensitization in two naturally occurring variants of the human serotonin$_{1A}$ receptor. Neuropsychopharmacology 17, 18–26.

Sadée, W., 1998. Genomics and drugs: finding the optimal drug for the right patient. Pharm. Res. 15, 959–963.

Sadée, W., 1999. Pharmacogenomics. BMJ 319, 1286.

Saiki, R.K., Walsh, P.S., Levenson, C.H., Erlich, H.A., 1989. Genetic analysis of amplified DNA with immobilized sequence-specific oligonucleotide probes. Proc Natl. Acad. Sci. U. S. A. 86, 6230–6234.

Scordo, M.G., Spina, E., Facciola, G., Avenoso, A., Johansson, I., Dahl, M.L., 1999. Cytochrome *P*450 2D6 genotype and steady state plasma levels of risperidone and 9-hydroxyrisperidone. Psychopharmacology (Berlin) 147, 300–305.

Seeman, P., Ulpian, C., Chouinard, G., Van Tol, H.H., Dwosh, H., Lieberman, J.A., Siminovitch, K., Liu, I.S., Waye, J., Voruganti, P., Hudson, C., Serjeant, G.R., Masibay, A.S., Seeman, M.V., 1994. Dopamine D4 receptor variant, D4GLYCINE194, in Africans, but not in Caucasians: no association with schizophrenia. Am. J. Med. Genet. 54, 384–390.

Segman, R., Neeman, T., Heresco-Levy, U., Finkel, B., Karagichev, L., Schlafman, M., Dorevitch, A., Yakir, A., Lerner, A., Shelevoy, A., Lerer, B., 1999. Genotypic association between the dopamine D3 receptor and tardive dyskinesia in chronic schizophrenia. Mol. Psychiatry 4, 247–253.

Service, R.F., 1998. Microchip arrays put DNA on the spot. Science 282, 396–399.

Shaikh, S., Collier, D., Kerwin, R.W., Pilowsky, L.S., Gill, M., Xu, W.M., Thornton, A., 1993. Dopamine D4 receptor subtypes and response to clozapine. Lancet 341, 116.

Shaikh, S., Collier, D.A., Sham, P., Pilowsky, L., Sharma, T., Lin, L.K., Crocq, M.A., Gill, M., Kerwin, R., 1995. Analysis of clozapine response and polymorphisms of the dopamine D4 receptor gene (DRD4) in schizophrenic patients. Am. J. Med. Genet. 60, 541–545.

Shaikh, S., Collier, D.A., Sham, P.C., Ball, D., Aitchinson, K., Vallada, H., Smith, I., Gill, M., Kerwin, R., 1996. Allelic association between a Ser-9-Gly polymorphism in the dopamine D3 receptor gene and schizophrenia. Hum. Genet. 97, 741–749.

Scharfetter, J., Chaudhry, H.R., Hornik, K., Fuchs, K., Sieghart, W., Kasper, S., Aschauer, H.N., 1999. Dopamine D3 receptor gene polymorphism and response to clozapine in schizophrenic Pakastani patients. Eur. Neuropsychopharmacol. 10, 17–20.

Shimron-Abarbanell, D., Nöthen, M.M., Erdmann, J., Propping, P., 1995. Lack of genetically determined structural variants of the human serotonin-1E (5-HT$_{1E}$) receptor protein points to its evolutionary conservation. Mol. Brain Res. 29, 387–390.

Shimron-Abarbanell, D., Harms, H., Erdmann, J., Albus, M., Maier, W., Rietschel, M., Korner, J., Weigelt, B., Franzek, E., Sander, T., Knapp, M., Propping, P., Nöthen, M.M., 1996. Systematic screening for mutations in the human serotonin 1F receptor gene in patients with bipolar affective disorder and schizophrenia. Am. J. Med. Genet. 67, 225–258.

Shimron-Abarbanell, D., Erdmann, J., Vogt, I.R., Bryant, S.P., Spurr, N.K., Knapp, M., Propping, P., Nöthen, M.M., 1997. Human 5-HT$_{5A}$ receptor gene: systematic screening for DNA sequence variation and linkage mapping on chromosome 7q34–q36 using a polymorphism in the 5′ untranslated region. Biochem. Biophys. Res. Commun. 233, 6–9.

Sivagnanasundaram, S., Morris, A.G., Gaitonde, E.J., McKenna, P.J., Mollon, J.D., Hunt, D.M., 2000. A cluster of single nucleotide polymorphism in the 5′-leader of the human dopamine D3 receptor gene (DRD3) and its relationship to schizophrenia. Neurosci. Lett. 279, 13–16.

Sobell, J.L., Lind, T.J., Sigurdson, D.C., Zald, D.H., Snitz, B.E., Grove, W.M., Heston, L.L., Sommer, S.S., 1995. The D5 dopamine receptor gene in schizophrenia: identification of a nonsense change and multiple missense changes but lack of association with disease. Hum. Mol. Genet. 4, 507–514.

Sodhi, M.S., Arranz, M.J., Curtis, D., Ball, D.M., Sham, P., Roberts, G.W., Price, J., Collier, D.A., Kerwin, R.W., 1995. Association between clozapine response and allelic variation in the 5-HT$_{2C}$ receptor gene. NeuroReport 7, 169–172.

Song, H.R., Gu, A., Schanen, N.C., 1999. Identification of a new polymorphism in the 3′-untranslated region of the human serotonin receptor 2C (5-HT$_{2C}$) gene. Mol. Genet. Metab. 66, 224–227.

Spina, E., Ancione, M., Di Rosa, A.E., Meduri, M., Caputi, A.P., 1992a. Polymorphic debrisoquine oxidation and acute neuroleptic-induced adverse effects. Eur. J. Clin. Pharmacol. 42, 347–348.

Spina, E., Sturiale, V., Valvo, S., Ancione, M., Di Rosa, A.E., Meduri, M., Caputi, A.P., 1992b. Debrisoquine oxidation phenotype and neuroleptic-induced dystonic reactions. Acta Psychiatr. Scand. 86, 364–366.

Spurlock, G., Heils, A., Holmans, P., Williams, J., D'Souza, U.M., Cardno, A., Murphy, K.C., Jones, L., Buckland, P.R., McGuffin, P., Lesch, K.P., Owen, M.J., 1998. A family based association study of T102C polymorphism in 5HT$_{2A}$ and schizophrenia plus identification of new polymorphisms in the promoter. Mol. Psychiatry 3, 42–49.

Steen, V.M., Lovlie, R., MacEwan, T., McCreadie, R.G., 1997. Dopamine D3-receptor gene variant and susceptibility to tardive dyskinesia in schizophrenic patients. Mol. Psychiatry 2, 139–145.

Syvanen, A.C., 1999. From gels to chips: "minisequencing" primer extension for analysis of point mutations and single nucleotide polymorphisms. Hum. Mutat. 13, 1–10.

Terenius, L., 2000. Schizophrenia: pathophysiological mechanisms—a synthesis. Brain Res. Rev. 31, 401–404.

Tsuang, M.T., 1998. Recent advances in genetic research on schizophrenia. J. Biomed. Sci. 5, 28–30.

Vandel, P., Haffen, E., Vandel, S., Bonin, B., Nezelof, S., Sechter, D., Broly, F., Bizouard, P., Dalery, J., 1999. Drug extrapyramidal side effects. CYP2D6 genotypes and phenotypes. Eur. J. Clin. Pharmacol. 55, 659–665.

Van Tol, H.H., Bunzow, J.R., Guan, H.C., Sunahara, R.K., Seeman, P., Niznik, H.B., Civelli, O., 1991. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature 350, 610–614.

Van Tol, H.H., Wu, C.M., Guan, H.C., Ohara, K., Bunzow, J.R., Civelli, O., Kennedy, J., Seeman, P., Niznik, H.B., Jovanovic, V., 1992. Multiple dopamine D4 receptor variants in the human population. Nature 358, 149–152.

Vogel, F., 1959. Moderne Probleme der Humangenetik. Ergeb. Inn. Med. Kinderheilkd. 12, 52–125.

Wang, X.B., Funada, M., Imai, Y., Revay, R.S., Ujike, H., Vandenbergh, D.J., Uhl, G.R., 1997. rGβ_1: a psychostimulant-regulated gene essential for establishing cocaine sensitization. J. Neurosci. 17, 5993–6000.

Williams, J., McGuffin, P., Nöthen, M., Owen, M.J., 1997. Meta-analysis of association between the 5-HT2a receptor T102C polymorphism and schizophrenia. EMASS Collaborative Group. European Multicentre Association Study of Schizophrenia. Lancet 349, 1221.

World Health Organization, 1990. Mental and Behavioral Disorders (including disorders of psychological development): Diagnosis Criteria for Research, International Classification of Disease. 10th edn., Chapter V (ICD-10), Geneva.

Worrel, J.A., Marken, P.A., Beckman, S.E., Ruehter, V.L., 2000. Atypi-

cal antipsychotic agents: a critical review. Am. J. Health-Syst. Pharm. 57, 238–255.

Wu, S., Comings, D.E., 1999. A common C-1018G polymorphism in the human 5-HT_{1A} receptor gene. Psychiatr. Genet. 9, 105–106.

Xie, D.W., Deng, Z.L., Ishigaki, T., Nakamura, Y., Suzuki, Y., Miyasato, K., Ohara, K., Ohara, K., 1995. The gene encoding the 5-HT_{1A} receptor is intact in mood disorders. Neuropsychopharmacology 12, 263–268.

Yu, Y.W., Tsai, S.J., Lin, C.H., Hsu, C.P., Yang, K.H., Hong, C.J., 1999. Serotonin-6 receptor variant (C267T) and clinical response to clozapine. NeuroReport 10, 1231–1233.

Zenner, M.T., Nobile, M., Henningsen, R., Smeraldi, E., Civelli, O., Hartman, D.S., Catalano, M., 1998. Expression and characterization of a dopamine D4R variant associated with delusional disorder. FEBS Lett. 422, 146–150.

Zhao, L.P., Aragaki, C., Hsu, L., Quiaoit, F., 1998. Mapping of complex traits by single-nucleotide polymorphisms. Am. J. Hum. Genet. 63, 225–240.