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Pharmacogenetics for the Individualization of Psychiatric Treatment

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Contents

Abstract

Drug treatment of psychiatric disorders is troubled by severe adverse effects, low compliance and lack of efficacy in about 30% of patients. Pharmacogenetic research in psychiatry aims to elucidate the reasons for treatment failure and adverse reactions. Genetic variations in cytochrome P450 (CYP) enzymes have the potential to directly influence the efficacy and tolerability of commonly used antipsychotic and antidepressant drugs. The activity of psychiatric drugs can also be influenced by genetic alterations affecting the drug target molecule. These include the dopaminergic and serotonergic receptors, neurotransmitter transporters and other receptors and enzymes involved in psychiatric disorders. Association studies investigating the relation between genetic polymorphisms in metabolic enzymes and neurotransmitter receptors on psychiatric treatment outcome provide a step towards the individualization of psychiatric treatment through enabling the selection of the most beneficial drug according to the individual's genetic background.

1. Drug Therapy in Psychiatric Disorders

Treatment of psychiatric disorders is mainly based on drug therapy. A wide range of classical and new drugs is available for their treatment: antidepressants [including tricyclic compounds, selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline inhibitors (SNRIs), and monoamine-oxidase inhibitors (MAOIs)] and antipsychotic drugs (dopaminergic blockers and multitarget drugs with strong affinity for serotonergic receptors) are widely used. However, treatment failure is poorly understood and medication is selected on a trial and error basis. An average 30 to 40% of treated patients show no improvement after treatment with antipsychotics and 60 to 70% of those who respond present severe adverse effects.[1,2] The newer range of antipsychotic drugs minimise some of the most severe adverse effects. Their superiority in symptom improvement, however, is still under discussion, with the exception of the potent antipsychotic clozapine.[3] Therefore, the growing interest in understanding the mechanisms determining psychiatric treatment response, and in particular of clozapine, is well justified. The purpose of this article is to review the latest advances in discerning the genetic influence on the mechanism of action of psychiatric drugs.

In spite of the lack of epidemiologic studies illustrating their exact contribution to clinical improvement, genes are hypothesized to play an important role in the variability observed in response to psychiatric treatment. The first studies in the field focused on single gene mutations related to toxic responses.[4]

Metabolic mutations directly responsible for altered drug transformation have been identified in cytochrome P450 (CYP) enzymes and are well documented, as discussed in section 3. Genetic variants in metabolic enzymes can cause accumulation or rapid elimination of a drug, leading to a toxic reaction or to lack of effect at therapeutic doses.[5-7] However, the variability observed in response to psychiatric treatment cannot be explained by variation in single genes alone. Furthermore, the therapeutic efficacy of psychiatric drugs may also be affected by alterations in target sites. Recent studies linking mutations in targeted neurotransmitter receptors with clinical outcome suggest that response to psychiatric treatment is determined by a combination of variants in several genes, including metabolic enzymes and/or drug targeted receptors.[8,9] In this review we aim to summarize the existing evidence supporting this hypothesis and give an overview of pharmacogenetic studies on psychiatric drugs.

2. Identifying Genes Related to Treatment Response

Before determining the entire combination of genes which may influence the therapeutic efficacy of a particular drug, studies are performed to single out which individual genes may exhibit DNA alterations affecting response. A variable number of genes may be implicated in determining response, some having a major role and others coding for proteins with minor contributions to response. The preferred strategy to search for such genes is case-control (or nonresponder/responder) association studies.[10] This strategy is more sensitive for the detection of genes with a minor influence in a particular phenotype when compared to other possible strategies such as linkage studies. Linkage studies are more powerful for the detection of genes with a major effect but very unlikely to find genes of weak effect. In the last decade a vast number of association studies have been performed with the goal of correlating polymorphisms in candidate genes with individual's response to treatment.[8] The candidate genes are first screened for mutations using a variety of time-consuming techniques such as single strand conformation polymorphism (SSCP),[11] denaturing high performance liquid chromatography (dHPLC),[12,13] and mismatch cleaving, followed by characterization of DNA change by sequencing.[14,15] This process has been greatly accelerated in recent years with the development of high-throughput automated sequencing and DNA arrays which identify and characterize mutations directly.[16-18] These techniques are generally used for the identification of genes related to particular traits. In pharmacogenetics, the identification of novel polymorphisms in candidate genes is followed by association studies where the distribution of genotype and allele frequencies are compared between patients responding versus those not responding to a particular drug. Any significant difference in the distribution of frequencies between the 2 groups is considered an indication of involvement in the mechanism controlling treatment response.

One of the main limitations of these studies is their susceptibility to producing type I and II errors (false positives or negatives) if the samples are small or not balanced (demographically and/or in terms of patient numbers). In addition, the complexity of the diagnosis and assessment of psychiatric disorders adds to the difficulties in replicating positive associations. Often large interstudy differences are observed, depending on the criteria and assessment tools used to characterise the sample patients, their illness status and their treatment response. Comparison of extreme phenotypes (very good response versus total lack of improvement),[19,20] standardization of response assessment criteria,[10] and collaborative studies involving large and balanced clinical samples will help resolve these difficulties. In spite of these problems, association studies remain useful for the discovery of treatment-related genes.

3. The Influence of Metabolic Enzymes on Response

The first steps in the metabolism of psychiatric drugs are performed by CYP enzymes.[21] Genetic variations affecting the metabolic rate of these enzymes can have direct implications for the biotransformation of drugs.[22] Mutations in the *CYP2D6, CYP2C9* and *CYP2C19* genes have already been shown to cause altered drug metabolism[7] (a full list of polymorphisms in metabolic enzymes with updated nomenclature can be found in http://www.imm.ki.se/CYPalleles[23]). Alterations disrupting the normal functioning of these enzymes have a direct impact in the assimilation of drugs, which can cause severe adverse reactions

Table I. List of common mutations with functional effects in CYP metabolic enzymes

Enzyme	Mutation	Effect
CYP2D6 [21,24-27]	CYP2D6*3A	PM
	CYP2D6*4B	PM
	CYP2D6*5	PM
	CYP2D6*1XN	UM
CYP2C19[28,29]		
	CYP2C19*2B	PM
	CYP2C19*3	PM
	CYP2C19*3	PM
CYP1A2[30-32]		
	CYP1A2*1C	PM
	CYP1A2*1F	UM
CYP2C9[33-35]	CYP2C9*2	PM
	CYP2C9*3	PM

PM = poor metabolisers; **UM** = ultra rapid metabolisers.

(see table I).[9,24] Individuals carrying these mutations may show toxic accumulation (poor metabolisers, PM) or rapid elimination (ultrarapid metabolisers, UM) of various drugs. The frequencies of these mutations vary among populations, being relatively more common in Caucasians [with 7% of individuals showing CYP2D6 (PM) deficient phenotype] than in Asians (1% for the same deficiency).[36,37]

Many psychiatric drugs are metabolized by CYP enzymes (see table II). Most drugs can be metabolized by more than one enzyme, which may dilute the effect of a deficient (PM) CYP subtype. The effect of the rarer UM enzyme variants is unlikely to be compensated for by other enzymes. Those drugs metabolized by only one specific CYP enzyme are at higher risk of producing adverse reactions in patients carrying the deficient variants. In addition, treatment with two or more drugs metabolized by the same subtypes may result in interactions such as competition for the enzyme and decreased rates of metabolism.[6,46,40] Important interactions have been reported between SSRIs and other psychiatric drugs due to the effects of CYP450 enzymes on their metabolism.[51,52] Recent studies have shown that fluvoxamine inhibits its clozapine N-demethylation and causes a pronounced increase in clozapine plasma concentration.[53] However, several studies have failed to find clear association between drug metabolism and therapeutic response.[54-56] More importantly, *CYP2D6* variants have been related to abnormal movements observed during neuroleptic treatment,[57] and *CYP2D6* and *CYP1A2* alleles have been associated with drug induced tardive dyskinesia in schizophrenic patients.[58,59]

In view of the adverse reactions caused by deficient drug metabolism, previous knowledge of a patient's metabolic status and drug pharmacokinetics are vital to avoid such responses. There are a variety of methods for the rapid detection of common metabolic mutations including multiplex PCR,[60,61] allele-specific amplification coupled with allele-specific fluorogenic 5′ nuclease chain reaction (Taqman®) technology[62] and DNA-chip arrays for the identification of CYPs polymorphisms in large samples that have been devised by several companies.[63,64] Pre-treatment characterization of metabolic status will allow the adjustment of therapeutic doses or the selection of alternative medication according to the patient's metabolic rate. The expected result will be a reduction of drug interactions and toxic responses caused by deficient enzymes.

4. Candidate Genes in Target Sites: The Usual Suspects

Aside from the metabolic enzymes responsible for the biotransformation of drugs, therapeutic activity can be affected by alterations on the site of action. In recent years, pharmacogenetic research has investigated genetic variants of receptors targeted by antipsychotic and antidepressant drugs. The candidate genes for these studies are the usual suspects: genes coding for neurotransmitter systems known to be altered in psychiatric disorders, such as dopaminergic and serotonergic receptors, which are strongly targeted by psychiatric drugs. In the last decade numerous association studies have tried to correlate genetic variants in drug targeted receptors with antipsychotic and antidepressant efficacy. In particular, the genes coding for dopaminergic and serotonergic receptors have been thoroughly analyzed for mutations, and the numerous variants detected prompted extensive investigation of their role in psychiatric disorders and psychiatric treatment.

Table II. Commonly used antipsychotic and antidepressant drugs and their metabolic enzymes

Drug	Metabolic enzyme(s)	References
Antipsychotics		
bromperidol	CYP3A4	38
ziprasidone	CYP3A4	39
clozapine	CYP1A2, CYP3A4	22,40-42
olanzapine	CYP1A2, CYP2D6	6,22,43
risperidone	CYP2D6, CYP3A4	6,22,40,42
chlorpromazine	CYP2D6, CYP3A4	22,40,42
haloperidol	CYP1A2, CYP2D6, CYP3A4	22,40,42,44
sertindole	CYP2D6, CYP3A4	22
zotepine	CYP3A4, CYP1A2, CYP2D6	45
Antidepressants		
paroxetine	CYP3A4,CYP2D6, CYP2C19	40
clomipramine	CYP2D6,CYP2C19	46,40
desipramine	CYP2D6	46,40
doxepin	CYP2D6	47
mirtazapine	CYP2D6, CYP3A4	48
trazodone	CYP3A4	40,49
amitriptyline	CYP2C19, CYP3A4, CYP2D6	40,50

4.1 Dopaminergic Receptors

Classical antipsychotic drugs used for the treatment of schizophrenia, the most severe psychiatric disorder, strongly target dopamine D_2 receptors in mesolimbic and striatal areas of the brain. Their action on mesolimbic D_2 receptors is directly related with antipsychotic efficacy. However, their affinity for striatal D_2 receptors is also associated with production of severe extrapyramidal adverse effects (EPS).[2]

Association studies investigating polymorphisms in dopaminergic receptors have thus far produced inconclusive results. Reports of association between D_2 polymorphisms and antipsychotic response[65,66] contradict previous studies which failed to find any

association.[67,68] Association between a D_3 structural polymorphism, Ser9Gly, and response[69-71] was contradicted by Malhotra and collaborators.[72] However, reports of association between this polymorphism and tardive dyskenisia[73-75] suggest that the D_3 receptor may mediate improvement of specific symptoms. Reports of D_4 variants associated with antipsychotic response[76,77] seemed to confirm their potential as therapeutic targets. However, several studies failed to confirm this finding.[78-81]

4.2 Serotonergic Receptors

Newer antipsychotics, termed atypical for their lack of EPS production, are multitarget drugs with strong affinities for serotonin (5-hydroxytryptamine; 5-HT) receptors, among others. Although it is not clear which receptor(s) mediates antipsychotic activity, it is thought that the 5-HT_2/D_2 affinity ratio is an important determinant of therapeutic success.[82,83] Antidepressant therapy includes drugs which also target genes coding for proteins of the serotonergic system (SSRIs and SNRIs). It is clear that serotonergic receptors are major therapeutic targets for psychiatric drugs, and therefore alterations in genes coding for these receptors may play a major role in the interindividual differences observed during psychiatric treatment.

The first report of association between a 5-HT_{2A} variant, 102-T/C, and response to the atypical antipsychotic clozapine[84] was contradicted by several studies which failed to observe significant association, although this polymorphism was found to be associated with neuroleptic response.[85] However, a meta-analysis of 6 studies that had published data on clozapine response showed a clear trend of association between this polymorphism and clozapine response.[19] The same meta-analysis included studies investigating the relation between a *5-HT_{2A}* His452Tyr polymorphism[86,87] and clozapine response, and confirmed the correlation between genetic variants of the receptor and clinical outcome. These results constitute the strongest evidence of association between receptor variants and treatment response, suggesting an important role of the 5-HT_{2A} receptors in mediating the therapeutic activity of clozapine. The reported association between a *5-HT_{2C}* structural polymorphism, Cys23Ser, and clozapine response[88] was not confirmed by other investigators.[89,90] However, a later meta-analysis[91] and a finding of association between a *5-HT_{2C}* polymorphic repeat (-330-GT/-244-CT) and clozapine response[92] seem to support involvement of this receptor in mediating therapeutic activity. Although no association was found between 5-HT_{5A} and antipsychotic response,[93] a report of association between a silent *5-HT_6* polymorphism (267-C/T) by Yu and collaborators[94] suggests that other 5-HT receptors may be involved in determining response.

4.3 Neurotransmitter Transporters

Genes coding for transporters regulating neurotransmitter levels have also been investigated. Their regulatory action on neurotransmitter systems makes them strong candidates in the etiology and treatment of psychiatric disorders. A positive finding of association between a polymorphism in the serotonin transporter (5-HTTLPR) and fluvoxamine[95] was followed by studies showing minor contribution of *5-HTT* alleles to antipsychotic response.[92,96] Alleles of the dopamine transporter gene (*DAT1*) were observed to be associated with behavioural response to methylphenidate, a drug used in children for the treatment of attention-deficit hyperactivity disorder (ADHD).[97]

4.4 Other Candidate Genes

Other neurotransmitter receptors including histaminergic, muscarinic and adrenergic receptors have also been investigated. However, several investigators have failed to detect strong associations between these receptors and response.[98-100] Further investigation of genetic variation in these genes is needed to confirm their role in psychiatric disorders. In addition, recent reports of association have related mutations in genes encoding the G-protein β3 subunit (G- β3), methylenetetrahydrofolate reductase (MTHFR), and in the brain-derived-neurotrophic-factor (BDNF) with treatment response (see table III).[101-103]

In summary, these studies show that mutations in genes targeted by psychiatric drugs may influence therapeutic success. However, one of the problems of association studies is the difficulty in replicating results by different groups. Most of the positive association findings reported here have been contradicted by negative reports. The causes for these discrepancies could be several, including chance findings, sample size, sample ethnic origin, and clinical characterization.[104] Nevertheless, replication by independent investigators is vital to confirm the reliability of the findings.

5. Individualization of Treatment: Can Response be Predicted by Looking at Genes?

The overall picture given by association studies is that there is no major gene controlling psychiatric response. Treatment response is controlled by a variety of genes, in agreement with the multitarget profile of most psychiatric drugs. Variants in metabolic genes may influence the development of toxic reactions and adverse effects; reports of association between polymorphisms in CYP enzymes and drug induced adverse effects[58,59] confirm this hypothesis. Contrary to expectations, no strong association has yet been observed between polymorphisms in dopamine receptors and response to dopamine blockers. However, new polymor-

Table III. Significant associations between genetic polymorphisms in neurotransmitter receptors and antipsychotic/antidepressant response

Gene (polymorphism)	Association	Reference
Dopamine receptor genes		
D_2 (-141C Ins/Del)	response to clozapine	43
D_2 (*Taq* I)	response to nemonapride	44
D_3 (Ser9Gly)	response to clozapine	47
D_3 (Ser9Gly)	response to clozapine	48
D_3 (Ser9Gly)	response to antipsychotics	49
D_4 (48bp repeat)	response to antipsychotics	54
D_4 (48bp repeat)	response to antipsychotics	55
Serotonin receptor genes		
5-HT_{2A} (-1438-G/A)	response to clozapine	19
5-HT_{2A} (102-T/C)	response to clozapine	62
5-HT_{2A} (102-T/C)	response to antipsychotics	63
5-HT_{2A} (His452Tyr)	response to clozapine	64
5-HT_{2A} (His452Tyr)	response to clozapine	65
5-HT_{2C} (-330-GT/244-CT)	response to clozapine	70
5-HT_{2C} (Cys23Ser)	response to clozapine	66
5-HT_6 (267-C/T)	response to clozapine	72
Neurotransmitter transporter genes		
5-HTT (5-HTTLPR)	response to fluvoxamine	73
DAT1(VNTR)	response to methylphenidate	75
Other candidate genes		
MTHFR (677-C/T)	response to antipsychotics	79
BDNF (172/176 bp)	response to antipsychotics	80
G-β*3* (825-C/T)	response to antidepressants	81

BDNF = brain-derived neurotrophic factor; **DAT1** = dopamine transporter; **MTHFR** = methylenetetrahydrofolate reductase; **5-HTT** = serotonin transporter.

phisms detected in the promoter regions of D_3 and D_4 receptor genes[105,106] with a potential effect on receptor expression should be investigated. The strongest associations reported in section 4 referred to 5-HT_2 polymorphisms and clozapine response, in agreement with the high affinity of the drug for those receptors. However, minor contributions from other receptor variants are not discounted as the variability observed in response to clozapine treatment could not be explained by *5-HT_2* polymorphisms alone. In the case of multitarget drugs such as clozapine, clinical response is likely to be mediated primarily through one or two systems, with other receptor systems having minor effects.

In spite of the important information provided by individual association studies, these studies are of limited use for the prediction of treatment outcome. A combination of variations in key genes is more likely to determine an individual's therapeutic response. We investigated 33 polymorphisms in 19 genes including metabolic enzymes, neurotransmitter transporters and receptors targeted by clozapine in an effort to identify a combination of polymorphisms that influence both positive and negative response to the drug. We found that a combination of six polymorphisms in genes coding for the 5-HT_{2A}, 5-HT_{2C}, histamine H_2 receptors and the 5-HTT predicted clozapine response with nearly 80% success in a sample of patients with schizophrenia.[92] Although we are hoping to improve the prediction levels with the incorporation of newly detected polymorphisms, this is the first evidence suggesting that response to psychiatric treatment can be predicted by looking at an individual's genes, and opens the possibility for future personalization of antipsychotic therapy. We are currently performing similar studies investigating genetic combinations that would predict response to a variety of psychiatric drugs.

Although still not a diagnostic tool, studies like this will facilitate the early selection of beneficial treatments at the right doses for each individual according to their pharmacogenetic propensities. Pre-treatment genotyping of key polymorphisms will indicate which drugs are more likely to be well metabolized and have a therapeutic effect. This will have a direct impact in clinical therapy by reducing adverse reactions and increasing patient compliance and clinical improvement.

6. Psychiatric Treatment in the 21st Century

Finding drug-response related polymorphisms and analysing their influence is a time consuming process which has been greatly accelerated by high-throughput techniques. Automated sequencing, DNA chips and microarrays are being used for the rapid detection of mutations in the human genome and to investigate their effect.[63,107] As a result, single nucleotide polymorphism (SNP) databanks have already been created for use in medical research.[108] Several pharmaceutical companies have already entered the race and are producing kits for the genetic detection of disease susceptibility and selection of appropriate drugs for their treatment.[63,64] It is hoped that current research will lead to the development of kits for the individualization of psychiatric treatment.

7. Conclusion

Pharmacogenetic objectives in psychiatric research have changed dramatically in the last decade. Genetic association studies have provided information on the contribution of gene mutations to interindividual variability in treatment response. Polymorphisms in metabolic enzymes and in neurotransmitter systems may influence the therapeutic efficacy of psychiatric drugs. Mutations in genes encoding metabolic CYP450 enzymes, neurotransmitter receptors and neurotransmitter transporters have been singled out as responsible for interindividual variation in response to psychopharmacotherapy. With increasing knowledge of the human genome and rapid discovery of mutations, studies of single gene mutations are being replaced by investigations of polymorphism combinations that will ultimately lead to pre-treatment prediction of psychopharmacotherapeutic response. In spite of the difficulties in diagnosis and assessment of psychiatric disorders, pharmacogenetic research has produced the first successful studies correlating genetic profile with antipsychotic response. Similar studies investigating genetic determinants of response to treatment with a variety of psychiatric drugs are currently underway. These studies will ultimately allow for pre-treatment selection of psychiatric drugs most likely to have a positive effect according to the individual patient's pharmacogenetic profile. It is not too optimistic to think that in the next decade psychiatric drugs could be chosen on the basis of individual's genetic background.

References

1. Taylor D. Clozapine: five years on. Pharm J 1995; 254: 260-3
2. Kerwin RW, Osborne S. Antipsychotic drugs. Medicine 2000; 28 (4): 23-5
3. Lee MA, Jayathilake K, Meltzer HY. A comparison of the effect of clozapine with typical neuroleptics on cognitive function in neuroleptic-responsive schizophrenia. Schizophr Res 1999; 37 (1): 1-11
4. Weber WW. Pharmacogenetics. 1st ed. New York: Oxford University Press, 1997
5. Coutts RT, Urichuk LJ. Polymorphic cytochromes P450 and drugs used in psychiatry. Cell Mol Neurobiol 1999; 19 (3): 325-55
6. Fang J, Gorrod JW. Metabolism, parmacogenetics, and metabolic drug-drug interactions of antipsychotic drugs. Cell Mol Neurobiol 1999; 19 (4): 491-510
7. Nebert DW, Dieter MZ. The evolution of drug metabolism. Pharmacology 2000; 61 (3): 124-35
8. Arranz MJ, Kerwin RW. Neurotransmitter-related genes and antipsychotic response: pharmacogenetics meets psychiatric treatment. Ann Med 2000; 32: 128-33
9. Meyer UA. Pharmacogenetics and adverse drug reactions. Lancet 2000; 356: 1667-771
10. Rietschel M, Kennedy JL, Macciardi F, et al. Application of pharmacogenetics to psychotic disorders: the first consensus conference. Schizophr Res 1999; 37: 191-6
11. Glavac D, Dean M. Optimization of the single-strand conformation polymorphism (SSCP) technqiue for the detection of point mutations. Hum Mutat 1993; 2: 404-14
12. O'Donovan MC, Oefner PJ, Roberts SC, et al. Blind analysis of denaturing high-performance liquid chromatography as a tool for mutation detection. Genomics 1998; 52 (1): 44-9
13. Spiegelman JI, Mindrinos MN, Oefner PJ. High-accuracy DNA sequence variation screening by DHPLC. Biotechniques 2000; 29 (5): 1084-91
14. Cotton R. Slowly but surely towards better scanning for mutations. Trends Genet 1997; 13 (2): 43-7
15. Nollau P, Wagener P. Methods for detection of point mutations: performance and quality assessment. Clin Chem 1997; 43 (7): 1114-28
16. Hacia JG, Brody LC, Collins FS. Applications of DNA chips for genomic analysis. Mol Psychiatry 1998; 3 (6): 483-92
17. Day INM, Spanakis E, Chen XH, et al. Microplate array diagonal gel electrophoresis for mutation research in DNA banks. Electrophoresis 1999; 20 (6): 1250-7
18. Mir KU, Southern EM. Sequence variation genes and genomic DNA: Methods for large-scale analysis. Ann Rev Genomics Human Genet 2000; 1: 329-68
19. Arranz MJ, Munro J, Sham P, et al. Meta-analysis of studies on genetic variation in 5-HT2A receptors and clozapine response. Schizophr Res 1998; 32: 93-9
20. Nebert DW. Extreme discordant phenotype methodology: an intuitive approach to clinical pharmacogenetics. Eur J Pharmacol 2000; 410: 107-20
21. Bertilsson L, Dahl ML. Polymorphic drug oxidation: relevance to the treatment of psychiatric disorders. CNS Drugs 1996; 5 (3): 220-3
22. Otani K, Aoshima T. Pharmacogenetics of classical and new antipsychotic drugs. Ther Drug Monit 2000; 22: 118-21
23. Ingelman-Sundberg M, Daly AK, Oscarson M, et al. Human cytochrome P450 (CYP) genes: recommendations for the nomenclature of alleles. Pharmacogenetics 2000; 10: 91-3
24. Marez D, Legrand M, Sabbagh N, et al. Polymorphims of the cytochrome P450 CYP2D6 gene in a European population: characterization of 48 mutations and 53 alleles, their frequencies and evolution. Pharmacogenetics 2000; 7: 193-202
25. Dahl ML, Johansson I, Bertilsson L, et al. Ultrarapid hydroxylation of debrisoquine in a Swedish population: analysis of the molecular genetic basis. J Pharmacol Exp Ther 1995; 274 (1): 516-20
26. Løvlie R, Daly AK, Molven A, et al. Ultrarapid metabolizers of debrisoquine: Characterization and PCR-based detection of alleles with duplication of the CYP2D6 gene. FEBS Lett 1996; 392 (1): 30-4
27. Sachse C, Brockmoller J, Bauer S, et al. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. Am J Hum Genet 1997; 60: 284-95
28. Ferguson RJ, De Morais SMF, Benhamou S, et al. A new genetic defect in human CYP2C19: Mutation of the initiation codon is responsible for poor metabolism of S-mephenytoin. J Pharmacol Exp Ther 1998; 284 (1): 356-61
29. Ibeanu G, Blaisdell J, Ferguson RJ, et al. A novel transversion in the intron 5 donor splice junction of CYP2C19 and a sequence polymorphism in exon 3 contribute to the poor metabolizer phenotype for the anticonvulsant drug S-mephenytoin. J Pharmacol Exp Ther 1999; 290 (2): 635-40

30. Huang JD, Guo WC, Lai MD, et al. Detection of a novel cytochrome P-450 1A2 polymorphism (F21L) in Chinese. Drug Metab Dispos 1999; 27 (1): 98-101
31. Nakajima M, Yokoi T, Mizutani M, et al. Genetic polymorphism in the 5'-flanking region of human CYP1A2 gene: Effect on the CYP1A2 inducibility in humans. J Biochem 1999; 125 (4): 803-8
32. Sachse C, Brockmoller J, Bauer S, et al. Functional signficance of a C/A polymorphism in intron I of the cytochrome P450 CYP1A2 gene tested with caffeine. Br J Clin Pharmacol 1999; 47 (4): 445-9
33. Crespi CL, Miller VP. The R144C cnange in the CYP2C9*2 allele alters interaction of the cytochrome P450 with NADPH: cytochrome P450 oxidoreductase. Pharmacogenetics 1997; 7 (3): 203-10
34. Gill HJ, Tjia JF, Kitteringham NR, et al. The effect of genetic polymorphisms in CYP2C9 on sulphamethoxazole N-hydroxylation. Pharmacogenetics 1999; 9 (1): 43-53
35. Takanashi K, Tainaka H, Kobayashi S, et al. CYP2C9 Ile359 and Leu359 variants: enzyme kinetic study with seven substrates. Pharmacogenetics 2000; 10 (2): 95-104
36. Meyer UA, Zanger UM. Molecular mechanisms of genetic polymorphisms of drug metabolism. Ann Rev Pharmacol Toxicol 1997; 37: 269-96
37. Poolsup A, Po LW, Knight TL. Pharmacogenetics and psychopharmacotherapy. J Clin Pharm Ther 2000; 25: 197-220
38. Watanabe M, Tateishi T, Tanaka M, et al. Role of CYP3A4 in bromperidol metabolism in rati in vitro and in vivo. Xenobiotica 1999; 29 (8): 839-46
39. Prakash C, Kamel A, Cui D, et al. Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions. Br J Clin Pharmacol 2000; 49 Suppl.: 35s-42s
40. Tanaka E, Hisawa S. Clinically significant pharmacokinetic drug interactions with psychoactive drugs: antidepressants and antipsychotics and the cytochrome P450 system. J Clin Pharmacy Ther 1999; 24: 7-16
41. Eiermann B, Engel G, Johansson I, et al. The involvement of CYP1A2 and CYP3A4 in the metabolism of clozapine. Br J Clin Pharmacol 1997; 44: 439-46
42. Shin JG, Soukhova N, Flockhart DA. Effect of antipsychotic drugs on human liver cytochrome P-450 (CYP) isoforms in vitro: preferential inhibition of CYP2D6. Drug Metab Dispos 1999; 27 (9): 1078-84
43. Ring BJ, Catlow J, Lindsay TJ, et al. Identification of the human cytochromes P450 responsible for the in vitro formation of the major oxidative metabolites of the antipsychotic agent olanzapine. J Pharmacol Exp Ther 1996; 276 (2): 658-66
44. Kudo S, Ishizaki T. Pharmacokinetics of haloperidol: an update. Clin Pharmacokinet 1999; 37 (6): 435-56
45. Shiraga T, Kaneko H, Iwasaki K, et al. Identification of cytochrome P450 enzymes involved in the metabolism of zotepine, an antipsychotic drug, in human liver microsomes. Xenobiotica 1999; 29 (3): 217-29
46. Caraco Y. Genetic determinants of drug responsiveness and drug interactions. Ther Drug Monit 1998; 20: 517-24
47. Haritos VS, Ghabrial H, Ahokas JT, et al. Role of the cytochrome P450 2D6 (CYP2D6) in the stereospecific metabolism of E- and Z-doxepine. Pharmacogenetics 2000; 10 (7): 591-603
48. Timmer CJ, Sitsen JMA, Delbressine LP. Clinical pharmacokinetics of mirtazapine. Clin Pharmacokinet 2000; 38 (6): 461-74
49. Rotzinger S, Fang J, Baker GB. Trazodone is metabolized to m-chlorophenylpiperazine by CYP3A4 from human sources. Drug Metab Dispos 1998; 26 (6): 572-5
50. Olesen OV, Linnet K. Metabolism of the tricyclic antidepressant amitriptyline by cDNA-expressed human cytochrome P450 enzymes. Pharmacology 1997; 55 (5): 235-43
51. Lane RM, Baldwin D. Selective serotonin reuptake inhibitor-induced serotonin syndrome: review. J Clin Psychopharmacol 1997; 17 (3): 208-21
52. Lane RM. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. J Psychopharmacol 1998; 32 (5): 554-63
53. Olesen OV, Linnet K. Fluvoxamine-clozapine drug interaction: Inhibition in vitro of five cytochrome P450 isoforms involved in clozapine metabolism. J Clin Psychopharmacol 2000; 20 (1): 35-42
54. Shibata N, Ohnuma T, Baba H, et al. Genetic association between cytochrome P-450 2D6 gene polymorphism and plasma concentration of haloperidol in Japanese schizophrenics. Psychiatric Genet 1999; 9 (3): 145-8
55. Dettling M, Sachse C, Brockmoller J, et al. Long-term therapeutic drug monitoring of clozapine and metabolites in psychiatric in- and outpatients. Psychopharmacology 2000; 152 (1): 80-6
56. Mihara K, Suzuki A, Kondo T, et al. Effect of a genetic polymorphism of CYP1A2 inducibility on the steady state plasma concentrations of haloperidol and reduced haloperidol in Japanese patients with schizophrenia. Ther Drug Monit 2000; 22 (3): 245-9
57. Ellingrod VL, Schultz SK, Arndt S, et al. Association between cytochrome P4502D6 (CYP2D6) genotype, neuroleptic exposure and abnormal involuntary movement scale (AIMS) score. Schizophr Res 1999; 36: 1-3
58. Kapitany T, Meszaros K, Lenzinger E, et al. Genetic polymorphisms for drug metabolism (CYP2D6) and tardive dyskinesia in schizophrenia. Schizophr Res 1998; 32: 101-6
59. Basile VS, Özdemir V, Masellis M, et al. A functional polymorphism of the cytochrome P450 1A2 (CYP1A2) gene: association with tardive dyskinesia in schizophrenia. Mol Psychiatry 2000; 5: 410-7.
60. Hersberger M, Marti-Jaun J, Rentsch K, et al. Rapid detection of the CYP2D6*3, CYP2D6*4 and CYP2D6*6 alleles by tetra-primer PCR and of the CYP3D6*5 allele by multiplex long PCR. Clin Chem 2000; 46 (8): 1072-7
61. Roberts R, Sullivan P, Joyce P, et al. Rapid and comprehensive determination of cytochrome P450CYP2D6 poor metabolizer genotypes by multiplex polymerase chain reaction. Hum Mutat 2000; 16 (1): 77-85
62. Hiratsuka M, Agatsuma Y, Omori F, et al. High throughput detection of drug-metabolizing enzyme polymorphisms by allele-specific fluorogenic 5' nuclease chain reaction assay. Biologic Pharm Bull 2000; 23: 1131-5
63. Marshall A. Getting the right drug into the right patient. Nature Biotechnol 1997; 15: 1249-52
64. Persidis A. Pharmacogenomics and diagnostics. Nature Biotechnol 1998; 16 Suppl.: 20-1
65. Malhotra AK, Buchanan RW, Kim S, et al. Allelic variation in the promoter region of the dopamine D-2 receptor gene and clozapine response. Schizophr Res 1999; 36: 92-3
66. Suzuki A, Mihara K, Kondo T, et al. The relationship between dopamine D-2 receptor polymorphism at the Taq1 A locus and therapeutic response to nemonapride, a selective dopamine antiagonist, in schizophrenic patients. Pharmacogenetics 2000; 10 (4): 335-41
67. Arranz MJ, Li T, Munro J, et al. Lack of association between a polymorphism in the promoter region of the dopamine-2 receptor gene and clozapine response. Pharmacogenetics 1998; 8: 481-4
68. Ohara K, Nagai M, Tani K, et al. Functional polymorphism of -141C Ins/Del in the dopamine D-2 receptor gene promoter and schizophrenia. Psychiatr Res 1998; 81 (1): 117-23
69. Shaikh S, Collier DA, Sham P, et al. Allelic association between a Ser-9-Gly polymorphism in the dopamine D3 receptor gene and schizophrenia. Hum Genet 1996; 97: 714-9
70. Scharfetter J, Chaudhry HR, Hornik K, et al. Dopamine D3 receptor gene polymorphism and response to clozapine in schizophrenic Pakistani patients. Eur Neuropsychopharmacol 1998; 10 (1): 17-20
71. Krebs MO, Sautel F, Bourdel MC, et al. Dopamine D_3 receptor gene variants and substance abuse in schizophrenia. Mol Psychiatry 1998; 3: 337-41
72. Malhotra AK, Goldman D, Buchanan RW, et al. The dopamine D-3 receptor (DRD3) Ser(9)Gly polymorphism and schizophrenia: a haplotype relative risk study and association with clozapine response. Mol Psychiatry 1998; 3 (1): 72-5
73. Steen VM, Lovlie R, MacEwan T, et al. Dopamine D3-receptor gene variant and susceptibility to tardive dyskinesia in schizophrenic patients. Mol Psychiatry 1997; 2 (2): 139-45

74. Basile VS, Masellis M, Badri F, et al. Association of the Msc I polymorphism of the dopamine D3 receptor gene with tardive dyskinesia in schizophrenia. Neuropsychopharmacology 1999; 21: 17-27
75. Segman R, Neeman T, Herseco-Levy U, et al. Genotypic association between the dopamine D3 receptor and tardive dyskinesia in chronic schizophrenia. Mol Psychiatry 1999; 4: 247-53
76. Hwu HG, Hong C-J, Lee YL, et al. Dopamine D4 receptor gene polymorphisms and neuroleptic response in schizophrenia. Biol Psychiatry 1998; 44 (6): 483-7
77. Cohen BM, Ennulat DJ, Centorrino F, et al. Polymorphisms of the dopamine D-4 receptor and response to antipsychotic drugs. Psychopharmacology 1999; 141: 6-10
78. Sanyal S, Van Tol HHM. Review of the role of dopamine D4 receptors in schizophrenia and antipsychotic action. J Psychiatr Res 1997; 31 (2): 219-32
79. Shaikh S, Makoff A, Collier DA, et al. Dopamine D4 receptors: potential therapeutic implications in the treatment of schizophrenia. CNS Drugs 1997; 8: 1-11
80. Liu CM, Lin MW, Hwu HG. No association between twelve-nucleotide repeat polymorphism of D4 dopamine receptor gene and neuroleptic treatment response in Taiwanese schizophrenic patients. Mol Psychiatry 1999; 4 (1): 189
81. Kaiser R, Konneker M, Henneken M, et al. Dopamine D4 receptor 48-bp repeat polymorphisms: no association with response to antipsychotic treatment, but association with catatonic schizophrenia. Mol Psychiatry 2000; 5 (4): 418-24
82. Meltzer HY. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology 1999; 21 (2): s106-15
83. Glazer WM. Extrapyramidal side effects, tardive dyskinesia, and the concept of atypicality. J Clin Psychiatry 2000; 61 (3): 16-21
84. Arranz MJ, Collier DA, Sodhi M, et al. Association between clozapine response and allelic variation in the 5-HT2A receptor gene. Lancet 1995; 346: 281-2
85. Joober R, Benkelfat C, Brisebois K, et al. T102C polymorphism in the 5HT2A gene and schizophrenia: relation to phenotype and drug response variability. J Psychiatry Neurosci 1999; 24: 141-6
86. Arranz MJ, Collier DA, Munro J, et al. Analysis of a structural polymorphism in the 5-HT2A receptor and clinical response to clozapine. Neurosci Lett 1996; 217: 177-8
87. Masellis M, Basile VS, Meltzer HY, et al. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology 1998; 19: 123-32
88. Sodhi M, Arranz MJ, Curtis D, et al. Association between clozapine response and allelic variation in the 5-HT2C receptor gene. Neuroreport 1995; 7: 169-72
89. Malhotra AK, Goldman D, Ozaki N, et al. Clozapine response and the 5HT(2C) Cys(23)Ser polymorphism. Neuroreport 1996; 7 (13): 2100-2
90. Rietschel M, Naber D, Fimmers R, et al. Efficacy and side-effects of clozapine not associated with variation in the 5-HT2C receptor. Neuroreport 1999; 8 (8): 1999-2003
91. Sodhi M, Sham P, Makoff A, et al. Replication and meta-analysis of alleleic association of a 5-HT2C receptor polymorphism with good response to clozapine. Mol Psychiatry 1999; 4 (1): 225-6
92. Arranz MJ, Munro J, Birkett J, et al. Pharmacogenetic prediction of clozapine response. Lancet 2000; 355: 1615-6
93. Birkett J, Arranz MJ, Munro J, et al. Association analysis of the 5-HT5A gene in depression, psychosis and antipsychotic response. Neuroreport 2000; 11 (9): 2017-20
94. Yu YWY, Tsai S-J, Lin C-H, et al. Serotonin-6 receptor variant (C267T) and clinical response to clozapine. Neuroreport 1999; 10: 1231-3
95. Smeraldi E, Zanardi R, Benedetti F, et al. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol Psychiatry 1998; 3: 508-11
96. Arranz MJ, Bolonna AA, Munro J, et al. The serotonin transporter and clozapine response. Mol Psychiatry 2000; 5: 124-30
97. Winsberg BG, Comings DE. Association of the dopamine transporter gene (DAT1) with poor methylphenidate response. J Am Acad Child Adolesc Psychiatry 1999; 38 (12): 1474-7
98. Bolonna AA, Arranz MJ, Munro J, et al. No influence of adrenergic receptor polymorphisms on schizophrenia and antipsychotic response. Neurosci Lett 2000; 280: 65-8
99. Mancama D, Arranz MJ, Munro J, et al. The histamine 1 and histamine 2 receptor genes- candidates for schizophrenia and clozapine response. GeneScreen 2000; 1: 29-34
100. Mancama D, Munro J, Arranz MJ, et al. Association analysis of muscarinic acetylcholine receptor polymorphisms in clozapine treated schizophrenics. Am J Med Genet 2000; 96 (4): 269
101. Joober R, Benkelfat C, Lal S, et al. Association between the methylenetetrahydrofolate reductase 677C/T missense mutation and schizophrenia. Mol Psychiatry 2000; 5: 323-6
102. Krebs MO, Guillin O, Bourdel MC, et al. Brain derived neurotrophic factor (BDNF) gene variants association with age at onset and therapeutic response in schizophrenia. Mol Psychiatry 2000; 5 (5): 558-62
103. Zill P, Baghai TC, Zwanzger P, et al. Evidence for an association between a G-protein beta 3-gene variant with depression and response to antidepressant treatment. Neuroreport 2000; 11 (9): 1893-7
104. Arranz MJ, Munro J, Osborne S, et al. Difficulties in replication of results. Lancet 2000; 356: 1359-60
105. Ishiguro H, Okuyama Y, Toru M, et al. Mutation and association analysis of the 5' region of the dopamine D3 receptor gene in schizophrenia patients: identification of the Ala38Thr polymorphism and suggested association between DRD3 haplotypes and schizophrenia. Mol Psychiatry 2000; 5 (4): 433-8
106. Okuyama Y, Ishiguro H, Nankai M, et al. Identification of a polymorphism in the promoter region of DRD4 associated with the human novelty seeking personality trait. Mol Psychiatry 2000; 5 (1): 64-9
107. Lockhart DJ, Winzeler EA. Genomics, gene expression and DNA arrays. Nature 2000; 405: 827-36
108. Roses A. Pharmacogenetics and the practice of medicine. Nature 2000; 405: 857-65

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