# PSYCHIATRIC GENETICS '99
# The Challenges of Psychopharmacogenetics

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Residing at the intersection of two relatively young fields—psychopharmacology and pharmacogenetics—psychopharmacogenetics is only now becoming recognized as a biomedical discipline in its own right. The introduction of chlorpromazine, in 1952, for the treatment of psychotic disorders, may be considered to mark the birth of psychopharmacology. Since that time, a wide array of psychotropic drugs have been applied to the treatment of various psychiatric conditions, including anxiety disorders and such mood disorders as depression and mania.

Clinical experience quickly accumulated, indicating that these drugs are of variable usefulness. Stark interindividual differences in outcome and side effects are distressingly common for this group of therapeutic drugs. Early on, and continuing to this day, psychiatrists have relied on clinical experience and, not infrequently, guesswork to predict the outcome of prescribing a standard dosage of a psychotropic drug. Increasingly, however, evidence—which is often anecdotal but which is sometimes based on the results of family and twin studies—has suggested that genetic factors underlie (1) the observed interindividual and interethnic or racial differences in psychopharmacological response (Smith and Mendoza 1996; Frackiewicz et al. 1997; Varner et al. 1998) and (2) the concordant responses, among relatives, to antidepressant therapy (Franchini et al. 1998). Thus, perhaps to their own surprise, psychiatrists have found themselves concerned about familial patterns of drug kinetics and about polymorphisms in genes for receptors or enzymes, although both of these issues have traditionally been the province of pharmacogeneticists.

As originally defined by Vogel (1959), pharmacogenetics is the study of the heritable differences in the metabolism and activity of exogenous agents such as drugs or environmental toxins. In recent years, researchers in pharmacogenetics have focused on evaluating structural and regulatory polymorphisms both in genes coding for drug-metabolizing enzymes and in genes coding for other enzymes or receptors. Here, I wish to argue that psychiatry should not overuse psychopharmacogenetics as a tool to solve its own uncertainties, nor should psychopharmacogenetics be viewed as a special facet of pharmacogenetics. Instead, psychopharmacogenetics should be seen as a separate field of inquiry with a specific set of challenges. Mental disorders are intrinsically heterogeneous and can seldom be defined or diagnosed by the same rigorous methods applied to other conditions of interest to medical geneticists. In addition, the interactions between genetic and environmental factors that make psychiatric phenotypes difficult to study may render equally difficult the pursuit of optimal individual treatments for these diseases. Nevertheless, there is reason for optimism, since, in this era of molecular biology, psychopharmacogenetics now has appropriate tools at its disposal for addressing these challenges.

Before the advent of molecular tools, researchers in psychopharmacogenetics were restricted to examination of questions about the kinetics and dynamics of psychoactive drugs. Animal models, which were a staple of such work, have proved to be poor predictors of the range of drug responses in humans. The ability to work at the DNA level now allows researchers to identify and score polymorphisms with ease. It also allows them to tap into the insights of molecular neuroscientists, who are concerned with the physiological and developmental roles of genes that have come to our attention because of their possible pathological roles.

Pharmacogenetics has often been used to solve the problem of the biological heterogeneity of psychiatric diseases. However, both the use of markers, such as human leukocyte antigens, that have a questionable relevance to the disease process and the lack of reliable diagnoses have led to inconclusive and contradictory findings about the nosology of schizophrenia and affective (mood) disorders. Differences in response to treatment do indeed provide potentially important clues to these problems, primarily because they suggest different etiopathogenetic hypotheses, but they absolutely cannot

Received April 16, 1999; accepted for publication July 12, 1999; electronically published August 9, 1999.

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This article represents the opinion of the author and has not been peer reviewed.


0002-9297/1999/6503-0005$02.00

take the place of the reliable diagnostic criteria that we are still obliged to seek. In its molecular form, however, psychopharmacogenetics could help refine diagnoses and provide a tool for independent genetic testing of a given drug-responsive phenotype.

## Drug-Metabolizing Enzymes and Receptor Pharmacology

The earliest applications of molecular data in psychiatric treatment did little to address the familiar methodological difficulties that arise from working with poorly defined clinical entities. Unfortunately, psychiatric nosology has not seemed to have kept up with progress in neurobiology and molecular biology (van Praag 1997; Smoller and Tsuang 1998), and the etiologic factors of major psychiatric disorders are still unknown, despite considerable efforts and methodological advances (Peroutka 1997). This may reflect, in part, an overly simplistic focus on individual receptor molecules, despite the fact that most psychotropic drugs target multiple signaling pathways.

Although much of the variability in psychotropic drug action is linked to genetic factors, the results of studies of drug-metabolizing enzymes (DMEs) and receptor variants have proved, on the whole, to be confusing and inconsistent. Thus, polymorphisms within the *CYP2D6* gene, which encodes a cytochrome P450 DME, have been extensively screened in psychiatric patients, although there have been no conclusive results (Andreassen et al. 1997; Armstrong et al. 1997; Kawanishi et al. 1997; Mihara et al. 1997*a,* 1997*b;* de Leon et al. 1998; Kapitany et al. 1998). No clear-cut explanation for interindividual differences in drug plasma levels has emerged from this research. Drug efficacy and side-effect patterns cannot be predicted by genotyping at this locus, although there are some consistent data regarding the variable risk of extrapyramidal side effects, including such movement disorders as tardive dyskinesia (Armstrong et al. 1997; Kapitany et al. 1998).

The dopamine D4 receptor (*DRD4*) gene, which exhibits considerable genetic variability both within and between populations, was initially studied as a candidate risk factor for major psychiatric disorders; however, no convincing associations have emerged. The pharmacology of this receptor suggests that it might still be related to variability in clinical response. DRD4 binds to the antipsychotic drug clozapine, and several study groups (Rietschel et al. 1996; Hwu et al. 1998) have obtained conflicting results on how sequence variants effect responsiveness to this drug. An in vitro study on an expressed variant of DRD4 failed to show significant variation either in the receptor's affinity for clozapine or for other drugs or neurotransmitters or in its functional properties (Zenner et al. 1998). However, clozapine also interacts with the serotonin receptors 5HT2C and 5HT2A (Meltzer 1994; Kuoppamaki et al. 1995), which raises the question of whether variation at the corresponding loci affects the efficacy of this drug. Indeed, although some of the study groups (Sodhi et al. 1995; Malhotra et al. 1996; Chen et al. 1997; Rietschel et al. 1997; Arranz et al. 1998*a;* Masellis et al. 1998) that have examined this question have reported equivocal results, Arranz et al. (1998*b*) have shown, by meta-analysis, that 5HT2A variants do appear to influence the response to clozapine.

Psychopharmacogenetics clearly has not succeeded in its pursuit of the DME polymorphisms that are at the heart of much of pharmacogenetics, nor has it succeeded in borrowing candidate genes from psychiatric genetic studies. It remains possible that these approaches will prove useful in the tailoring of individualized therapies. However, if the goal is to identify effective drug therapies for individuals with specific genetic backgrounds, then it seems that research should be guided, as far as possible, by a molecular description of the relevant disease processes and by the presence of functional polymorphisms in candidate genes. I would like to suggest that our experience with two psychiatric conditions—delusional depression and panic disorder—points the way toward a more sophisticated use of genetic data in psychiatric therapy.

## Depression and the *5-HTT* Promoter

Depression with psychotic features is a particularly severe form of mood disorder, associated with high recurrence rates, great long-term morbidity, and a low response rate to either placebos or tricyclic antidepressants. Therefore, delusional depression seems to represent a syndrome that is biologically more homogeneous than other mood disorders. Evidence from studies in biochemistry, neuroendocrinology, and pharmacology suggests that dysfunctions in serotonergic pathways could play a pivotal, albeit nonexclusive, role in mood disorders. Patients with delusional depression are commonly treated with the selective serotonin-reuptake inhibitor (SSRI) fluvoxamine, but SSRI nonresponders are not uncommon. The addition of pindolol (a mixed $\beta$-adrenergic receptor [$\beta$AR] and 5-$HT_{1A}$ antagonist) has been proposed as augmentation therapy for SSRI nonresponders or partial responders, but reliable predictive criteria are needed. The serotonin transporter 5-HTT plays a critical role in the termination of 5-HT neurotransmission and represents the prime target for SSRIs, a finding that suggests the *5-HTT* gene as a candidate for pharmacogenetic studies.

Heils et al. (1996) first identified an allele of *5-HTT* with a 44-bp insertion in the promoter region. Studies of transfected cells in culture show that the long and short variants exhibit different transcriptional properties (Lesch et al. 1996). The basal transcriptional activity of the long variant is more than twice that of the short variant, and choriocarcinoma cells containing the short variant produce concentrations of 5-HTT mRNA that are 30%–40% lower than those produced by the long variant. Significantly, these differences in 5-HTT mRNA synthesis result in different 5-HTT expression and 5-HT cellular uptake (Lesch et al. 1996), which raises the possibility that individual differences in antidepressant response, in the face of comparable SSRI bioavailability, could result from differential expression of 5-HTT.

The presence of a functional polymorphism within the promoter region of *5-HTT* made the gene a good candidate and prompted my team and me to test whether this sequence variability affects response to the use of fluvoxamine, either alone or supplemented with pindolol, in cases of delusional depression. In a recent study (Smeraldi et al. 1998), we reported that, in patients with delusional depression, the promoter polymorphism correlates with the clinical response to fluvoxamine. To avoid extreme differences in the bioavailability of the drug, we excluded from the study those patients whose steady-state fluvoxamine plasma levels were >1.96 SD outside the mean value of the sample. Individuals who were homozygous for the long variant of the *5-HTT* promoter showed a better response to treatment with fluvoxamine alone than did those who were either heterozygous or homozygous for the short variant. Hence, the antidepressant efficacy of fluvoxamine seems to be related to allelic variation within this regulatory sequence. Moreover, this correlation appears to apply more broadly to other depressive conditions for which SSRIs are used. We obtained similar results when we used the SSRI paroxetine in a sample of individuals with nondelusional depression (Zanardi et al., in press).

Genotyping of the *5-HTT* promoter appears to represent a promising approach to individualization of the treatment of depression, since it identifies a subset of patients—those who are homozygous for the short variant in the promoter—who may require pindolol augmentation therapy. Given the well-known and frustrating latency of antidepressant response, the ability to identify such patients in advance could represent a significant advance in the care of depression. Because pindolol causes substantial side effects, primarily as a result of its antagonism to $\beta$AR, genotyping of the *5-HTT*–linked polymorphic region could spare a large number of patients the risk of harm from unnecessary drug treatment. However, our results should be regarded cautiously, since data on independent replication in other samples and in other ethnic groups are still lacking.

## Panic Disorder and the *MAOA* Promoter

The monoamine oxidase A (*MAOA*; see Shih and Thompson 1999 [in this issue]) gene provides another example of the use of genetics to tailor psychotropic-drug administration to individual cases. Because MAOA inhibitors are effective in the treatment of panic disorder, the X-linked *MAOA* gene might be expected to underlie the disease or to affect the efficacy of these drugs in its treatment. Therefore, we investigated a novel repeat polymorphism in the *MAOA* promoter, to determine its association with panic disorder. This polymorphism consists of a 30-bp motif that repeats two to five times. One variant, termed "3a," carries three full repeats and one partial repeat of this sequence. We found that these polymorphisms affect *MAOA*-promoter function. Alleles with longer repeats—3a, 4, and 5—are consistently more active in transfected cells than is the shorter, three-repeat allele. We have not tested allele 2, which is very rare in the populations that we have studied. Furthermore, the more actively expressed alleles are found at a significantly greater frequency among affected females than among control females. Curiously, no significant differences were observed between male patients and male controls (Deckert et al. 1999), although, given the linkage of *MAOA* to the X chromosome, males would be expected to be more, not less, sensitive to differences in genotype at this locus, as has been seen in studies of aggression (Shih and Thompson 1999 [in this issue]). These findings may indicate that, in panic disorder, the etiopathogenetic pathways that are important are different in males versus females; this possibility is supported by other psychopharmacogenetic data. A nearly concomitant clinical study, which used artificial neural networks to model the efficacy of treatments for this condition, appears to confirm the sex difference that we observe and to suggest that, to control the symptoms of panic disorder, different therapies be applied in males versus females. Politi et al. (in press) have shown that moclobemide, a reversible MAOA inhibitor, works better in women with prominent anxiety symptoms than in men with similar symptoms. This difference seems to be specific to this class of drugs; no significant difference in responsiveness to SSRI treatment, which is commonly used in patients with panic and anxiety disorder, can be found between sexes. These results, along with our association data, may suggest that MAOA inhibitors are a good choice in the treatment of females with panic disorder.

## The Future of Psychopharmacogenetics

Recent trends justify some measured optimism about the prospects for psychopharmacogenetics. It now seems clear that psychiatrists and pharmacologists should not

regard each other's fields merely as tools to solve their own problems but, rather, should note that an interesting set of questions is developing as a result of interactions between these disciplines. Both the development of more sophisticated molecular approaches and the growing interest in regulatory-sequence polymorphisms may finally make the pharmacogenetic approach useful in the psychiatric clinic.

Genetic analysis of responses to psychoactive drugs clearly has much to offer, but large and small challenges remain. The goal of applying well-tailored individual therapies to relieve or even prevent the onset of symptoms will require us to make precise psychiatric diagnoses and to develop selective drugs. At present, establishing a diagnosis still seems to present intractable problems, and patterns of drug responsiveness are of limited help in this regard. Response to the same drug does not always mean that there are identical pathogenetic pathways: SSRIs are advantageous in the treatment of both depression and obsessive-compulsive disorder, but the effects of the *5-HTT*–promoter polymorphism on SSRI response seem to be restricted to the former condition (Billet et al. 1997). Conversely, lack of responsiveness to a given drug does not always mean a misdiagnosis, since refractory patients are an unfortunate reality. Molecular geneticists will likely concentrate their efforts either on genes with relatively large effects on pathogenesis or on those genes whose products represent direct targets of specific drugs. It is worth recalling, however, that psychiatric disorders are multifactorial and multigenic and that genes that are associated with a minor risk of disease could play a significant role in determining the response to treatment.

## Acknowledgments

I gratefully thank John Ashkenas for valuable discussion and friendly advice, Klaus-Peter Lesch and Jürgen Deckert for friendship and confidence, and my team for faithful support.

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