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COMMENTARY

# Psychiatric Pharmacogenetics: A Developing Science

The report in this issue by Malhotra et al. (2001) on the emerging field of pharmacogenetics in psychiatry is timely and useful. This report is timely because this meeting was the first of many in the field of psychiatric pharmacogenetics. This report is useful because it outlines many of the critical issues in this developing field that is of interest to many readers of Neuropsychopharmacology.

The emergence of this field is stimulated by two genomic developments, the first being the sequencing of the human and mouse genomes, and the second, the emerging single nucleotide polymorphism (SNP) maps of these genomes. With these advances as background, the paper usefully outlines what types of industry-academic collaborations might optimally exploit opportunities to define gene variants which increase (or decrease) "risk" for a therapeutic effect (or an adverse effect). Malhotra et al. delineate the notable success for tardive dyskinesia TD), a serious and potentially irreversible adverse effect of antipsychotic medications. Several groups of investigators have established that a coding SNP in the D3 dopamine receptor gene increases risk for TD, as does a SNP in the cytochrome P450 gene, CYP1A2, which encodes an enzyme responsible in part for metabolism of antipsychotics.

There are at least two key observations regarding the types of studies which may succeed in the endeavor to detect genetic influences on drug response. First, substantial sample sizes will be required to detect the small effect sizes mediated by individual genes in therapeutic response and adverse effects of a given drug. The large sample sizes required (thousands of cases) for adequate power suggest that multicenter industry-academic collaborations are likely to succeed in achieving these sample sizes within reasonable time frames.

Another key observation by Malhotra et al. (2001) regards the nature of case-control association studies. Case-control studies have greater power than family-based associations studies, and will be the study design of choice. The disadvantage of such studies lies in their susceptibility to population stratification. In a case-control study, investigators compare genotypes (or allele frequencies) in cases and controls, but there is the risk for false positives because of subtle genetic differences between the case and control populations, differences which are independent of disease risk. Sometimes this is termed "population stratification." This danger can be illustrated by the following example. Suppose we are interested in testing the hypothesis that glucose-6-phosphate dehydrogenase (G6PD) is a disease gene in diabetes mellitus, using the case-control method. Let us also suppose that we are unaware that G6PD deficiency protects against malaria, and is found at increased frequency among individuals of Mediterranean coastal origins. We select cases from an American population enriched for individuals of Mediterranean coastal origins, where G6PD deficiency is fairly common, because malaria was prevalent in these regions until about 70 years ago. Our controls also come from an American population of European ancestry, but mostly northern Europe, where G6PD deficiency is relatively uncommon. We test our cases and controls, and find that the diabetics have increased frequencies of alleles which result in marked G6PD enzyme deficiency. We conclude falsely that these G6PD alleles are risk factors for diabetes mellitus. It is likely that subtle ethnic differences in allele frequencies exist for most genes, making population stratification a common difficulty.

Malhotra et al. correctly observe that new statistical methods can correct for population stratification risk, making case-control association studies less subject to these errors. These new statistical methods rely on testing for case-control allele frequency differences at multiple sites across the genome (for details, see Reich and Goldstein 2001; Pritchard and Rosenberg 1999).

Although the future is bright for this field, there are problems which remain. For example, it is widely recorded that placebo response rates in 6–8 week antidepressant medication trials are about 30–40%. The active treatment response rate is often about 70%. This outcome implies that about half the active drug "responders" are

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really "placebo" responders, who would have recovered without an active drug treatment. In pharmacogenetic studies, these individuals potentially represent a large group of false positive observations. How are the false positives to be differentiated from the true positives? We cannot recommend stopping the active treatment to determine who relapses, without encountering serious ethical difficulties.

In summary, the field of psychiatric pharmacogenetics is one which will develop rapidly over the coming decade. We will observe there a wonderfully complex interaction between heterogeneous disease risk alleles for behavioral disorders, heterogeneous "adverse event" risk alleles, and the environment. Unless we improve our network of communication for psychiatric pharmacogenetics (through regular meetings of the type recommended by Malhotra et al. 2001), we may resemble the blind men describing different aspects of the same elephant.

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## REFERENCES

Pritchard JK, Rosenberg NA (1999): Use of unlinked genetic markers to detect population stratification in association studies. Am J Hum Genet 65:220–28

Reich D, Goldstein DB (2001): Detecting association in a case-control study while correcting for population stratification. Genetic Epidemiology 20:4–16

Malhotra AK, Kennedy JL, Collier DA, Rietshel M (2001): Meeting report: Pharmacogenetics in psychiatry. Satellite meeting at the American College of Neuropsychopharmacology, 2002. Neuropsychopharmacology 26: 123–127