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Untapped resources for pharmacogenomic discovery in psychiatry

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Variation in individual clinical response to psychotropic drug treatment remains a critical problem in psychiatry. In general, only a minority of patients experience complete symptom remission while a larger proportion of patients continue to experience significant psychiatric symptoms. In addition, significant subsets of patients often develop drug-induced adverse events that range from troublesome to life threatening. Moreover, psychotropic drugs generally require weeks of treatment before therapeutic responses are expected, so critical time is often lost before a clinician can determine whether a specific treatment is effective or not and consider alternative pharmacotherapy. During this period, treated patients may experience the substantial morbidity associated with these conditions continue.

Therefore, psychiatry is one specialty where pharmacogenomic results are highly likely to be applied for improved patient outcome. However, the current published findings are inadequate and insufficient for utilization as routine clinical predictors of treatment efficacy, safety or dosing [1, 2]. Therefore, it is timely to reconsider and revise current approaches to pharmacogenomic discovery in psychiatry before expensive and ethically problematic prospective studies are undertaken. In this commentary, we consider two largely untapped resources that could help to identify, in an unbiased manner, high-quality candidate biomarkers for prospective pharmacogenomic studies of psychotropic drugs.

Behavioral neuroscientists have developed dozens of well-validated and carefully controlled methods for measuring the therapeutic and adverse effects of nearly all classes of psychotropic agents in laboratory mice [3]. For example, therapeutic responses to antidepressants, antipsychotics, and anxiolytics can be monitored using the tail suspension test, pre-pulse inhibition of the acoustic startle response and the elevated plus-maze, respectively. Over the past 30+ years, these methods have yielded important insights into psychotropic pharmacology and now, with recent advancements in mouse genomics, these behavioral assays are poised to increase our understanding of individual variation in drug response.

The mouse has recently become a powerful tool for pharmacogenomic studies, due to the genetic diversity found among inbred strains and the development of powerful new gene mapping technologies, such as haplotype association mapping (HAM)[4]. HAM is a genetic mapping methodology that uses the phenotypic and genotypic variation occurring in common laboratory inbred mouse strains to calculate measures of genetic association (i.e., *in*

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silico mapping). HAM has many advantages over traditional murine QTL mapping strategies, including no need to breed or genotype animals, increased levels of phenotypic diversity, a high recombination frequency, and availability of a dense genotype map. These characteristics result in more precisely defined QTL regions, facilitating identification of genes underlying QTL, which has traditionally been the rate-limiting step [5]. We believe there is great promise in using HAM to identify genes that explain variation in the therapeutic and adverse responses to psychotropic drugs. In particular, studies of this sort minimize several factors that often confound human pharmacogenomic studies, including treatment adherence, diet and other environmental influences, and ancestral background. Nevertheless, mice are not humans, and therefore might not always be appropriate models of a given disease or appropriate surrogates for humans in pharmacogenomic studies.

A second avenue that we feel has been underutilized in psychiatric pharmacogenomic discovery is the study of peripheral blood and lymphoblastoid cell lines (LCL) from human patients with variable responses to psychotropics. Peripheral blood represents an attractive tissue source in clinical pharmacogenomic studies, given the feasibility of its collection from patients and its potential as a sentinel tissue to monitor perturbations of physiology in many disease states [6]. This is particularly true for psychiatric disorders, for which the tissue presumably involved (brain) is inaccessible. Indeed, a growing number of studies are rapidly identifying transcriptional biomarkers in peripheral blood cells and Epstein-Barr virus (EBV) transformed LCL that function as biomarkers of disease [7–10], evidence of pharmacodynamic effect [11], predictors of clinical outcomes [12–14], and risk of toxicity [15].

Among the advantages of *ex-vivo* LCL based studies are: 1) the cells can be grown under identical conditions eliminating *in vivo* confounders; 2) they represent an unlimited resource; 3) genome-wide SNP data are often available; and 4) they offer ease of experimental manipulation and established methodologies to study gene expression and pharmacodynamic effects. Among the disadvantages of LCL studies are: 1) they represent one tissue type which may not be the most appropriate for the phenotype; 2) information on confounding factors that may alter the phenotype of interest, such as smoking or other drug use, may not be available; 3) EBV transformation can introduce phenotypic and gene expression changes; and 4) drug studies must take into account the lack of significant metabolic activities. Furthermore, a number of methodological issues and hurdles need to be overcome, with issues of standardizing blood sample collection and processing of paramount importance. The specificity of gene expression signatures for individual disease states also needs to be established. Despite these limitations, we feel that peripheral blood holds great promise for biomarker discovery and as with gene discovery, it may be best to perform these studies in mice before embarking on a prospective study in humans.

Psychiatry has a particularly high need for routine clinical predictors of treatment efficacy and adverse events, but these are severely lacking at the present time. While the ideal study may perhaps be a genome-wide association study of several thousand patients all taking the same medication in a highly-controlled, long-term clinical study, the unfortunate fact is that even if a large discovery study is constructed, there remains a challenge to secure appropriate patient cohorts for validation. We believe that these problems can be circumvented by utilizing animal and peripheral blood models to identify high-priority candidate biomarkers prior to human trials. This would effectively reduce the search space necessary for prospective pharmacogenomic studies of psychotropic drugs in human patients.

Suggested Reading

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