Review

Biological Psychiatry

The Promise of Psychiatric Pharmacogenomics

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ABSTRACT

Clinicians already face "personalized" medicine every day while experiencing the great variation in toxicities and drug efficacy among individual patients. Pharmacogenetics studies are the platform for discovering the DNA determinants of variability in drug response and tolerability. Research now focuses on the genome after its beginning with analyses of single genes. Therapeutic outcomes from several psychotropic drugs have been weakly linked to specific genetic variants without independent replication. Drug side effects show stronger associations to genetic variants, including human leukocyte antigen loci with carbamazepine-induced dermatologic outcome and *MC4R* with atypical antipsychotic weight gain. Clinical implementation has proven challenging, with barriers including a lack of replicable prospective evidence for clinical utility required for altering medical care. More recent studies show promising approaches for reducing these barriers to routine incorporation of pharmacogenetics data into clinical care.

Keywords: CYP2C19, CYP2D6, Depression, GWAS, Pharmacogenetics, Schizophrenia

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Patients and clinicians quickly learn that "standard doses" and "one-size-fits-all" pharmacotherapy, particularly in psychiatry, are exceptions rather than the rule. Variability among individuals in the clinical response to drug treatment occurs despite identical disease severity or etiology. Although intraindividual heterogeneity of response can be explained by various factors (e.g., age, gender, disease pathophysiology, coadministered drugs, diet), interindividual differences may be better explained by genetic variation among patients. Of equal concern are adverse drug reactions (ADRs), which are common and largely preventable in outpatients (1). The known action of a medication can result in ADRs, or ADRs may be unexpected (2). Also, ADRs are correlated with numerous patient factors, including sex, age, drug-drug interactions, and primary biology of the disease process. Genetic determinants influence rare and idiosyncratic ADRs as well as predictable common side effects (3). The long-known recognition of the role of genetic factors in drug response and ADRs, embedded in the field of pharmacogenetics, provides a way to look at how genes and environment interact at the patient level in psychiatric drug treatment. This article discusses the current state of pharmacogenetics research, including research incorporating genome-wide studies of DNA variation. The promise of precision medicine in psychiatry is also discussed.

CURRENT CHALLENGES OF PHARMACOGENETICS

Insightful pioneering work in the 1950s that relied on astute clinical observations to identify the genetic determinants of ADRs with drugs such as primaquine, isoniazid, and succinylcholine set the stage for the development of pharmacogenetics. This section discusses how early observations in pharmacogenetics provided useful clinical information and led ultimately to current approaches for discovering correlation between genes and drug-response phenotypes on a genome-wide scale. The central focus of these early studies related to understanding uncommon and potentially damaging drug effects first at biochemical and genetic levels. These classic observations show the logic behind discovering specific genetic variants influencing drug response. However, these findings and many other more recent examples (4) highlight simpler models connecting drugs and drug-metabolizing enzymes. Psychotropic drug tolerance and efficacy represent highly complex traits that are influenced by numerous genetic variants in multiple combinations of genes acting with even less definable environmental factors. Defining response and side-effect phenotypes on clinical observation and not on measurable physiologic processes guarantees that phenotypes are several steps removed from simple biological pathways. An additional challenge is introduced with the prominent heterogeneity in drug tolerance and response across populations. Various human groupings have accumulated genetic variation altering the activity of drug-metabolizing enzymes such as CYP2C19, TPMT, and CYP2D6 (5–7). Finally, a considerable obstacle to large-scale study of pharmacogenetics phenotypes involves the practical challenge not only of identifying and characterizing individuals with the disorder of interest but also of carrying out controlled clinical trials with careful longitudinal assessment of outcome.

PHARMACOGENOMICS

Starting in the late 1990s, a series of mostly technical innovations gave pharmacogenetics researchers tools facilitating current investigations. Theoretical work in human genetic epidemiology justified population-based, case-control studies that would come naturally to pharmacogenetics study designs (8). For example, a sample of patients

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all treated with the same medication for the same illness could be assessed for quantitative measures of response or side effects, and associations with collections of DNA variants from those patients could be measured for statistical association. Similarly, dichotomous drug-response phenotypes could be described, with "cases" corresponding to subjects showing efficacy to a medication and "controls" being defined as subjects who do not show efficacy. Concurrently, the Human Genome Project enabled the accumulation and understanding of immense amounts of data regarding human genetic variation, with a focus on single nucleotide polymorphisms (SNPs) (9–12). The incorporation of SNPs from these catalogues of variation promoted efficient genotyping of large samples with hundreds of thousands to millions of SNPs. The era of the genome-wide association study (GWAS) developed rapidly, with 1738 GWAS publications covering 914 phenotypes being catalogued by late 2013 in the National Human Genome Research Institute GWAS database (13). Most GWAS phenotypes represent dichotomous disease phenotypes and some quantitative biochemical or anthropometric traits, although a growing subset relates to drug-related phenotypes. Many of these pharmacogenomics studies, especially studies with strong findings, are derived from cancer, cardiovascular, and drug toxicity phenotypes.

Psychiatric Pharmacogenomics

DNA variation shows great promise for individualizing psychopharmacologic treatment given the great variability in response and tolerance among individuals (14). Pharmacogenomics research in psychiatric disorders is accumulating to address this promise, although current results are not strong and do not have clinical applicability. Because we know so little about the mechanism explaining the therapeutic effect of current medications or even the etiology of the underlying disorder, great hope was expressed that pharmacogenomics investigation would point toward more targeted treatment. The studies summarized in this review focus primarily on predicting both treatment response and important drug side effects. Studies were identified from published pharmacogenetics literature.

General Considerations. Of the 121 pharmacogenomics markers for drugs currently described by the U.S. Food and Drug Administration, 26 are for psychiatric drugs, but specific guidelines for how to use these genetic markers are lacking. Specific recommendations for a small set of cytochrome P-450 genotypes for medication prescribing have been published but are not widely implemented (15,16). More recent recommendations from the Clinical Pharmacogenetics Implementation Consortium of the National Institutes of Health Pharmacogenomics Research Network suggest that current data indicate that genotypes for *CYP2D6* and *CYP2C19* can lead to specific recommendations (17).

Antidepressants. Response to antidepressants differs greatly among individuals being treated for depression. Remission rates are approximately 35%–45% in clinical trials, with few good clinical predictors of response (18). Early conjecture about the influence of genetic variation on treatment outcomes in depression led to analysis of pedigrees where family members often showed concordance of medication response (19), an observation that was replicated more recently (20). Prior studies evaluated the influence of drug metabolism, resulting in suggestions for tricyclic antidepressants that pharmacogenetics data be taken into account during treatment. For example, individuals with the "poor metabolizer" phenotype of *CYP2D6* or *CYP2C19* would require significant dose reductions (17). Higher rates of dysfunctional *CYP2C9*, *CYP2C19*, and *CYP2D6* alleles were noted in analyses of patients with psychiatric disorders (21) and were predictive of longer hospital stays for patients with depression (22), and earlier work suggested an association between deficient *CYP2D6* alleles and drug side effects (23–25).

Intriguing data also raise the possibility that treating clinicians adjust dosages empirically for medications based on the patient's genotype, yet without that knowledge. For example, a retrospective study of *CYP2D6* genotypes in patients with psychiatric disorders taking risperidone indicated that clinicians prescribed lower doses in *CYP2D6* poor metabolizers and higher doses in ultra-metabolizers (26). This connection was specific to *CYP2D6* and did not apply to *CYP3A5* or the transporter gene *ABCB1*. Similarly, clinicians blind to genotype status were observed to prescribe fewer *CYP2D6* substrates for shorter periods of time in subjects ultimately documented as *CYP2D6* poor metabolizers (27). These naturalistic findings suggest that a pretreatment genetic test might provide patients and clinicians an alternative to time-consuming trial-and-error treatment trials. This idea is promising because there appears to be substantial interest among psychiatrists in using pharmacogenetics information (28). When several academic psychiatry departments providing a small set of pharmacogenetics tests for physicians were surveyed, it was seen that the clinicians used these tests, and when they did, the clinical question focused on assessment of medication intolerance and treatment-resistant depression (29). Similar work in a psychosomatic medicine department showed that poor tolerability and treatment resistance were the reasons outpatients were referred for genotyping (30).

Antidepressant pharmacogenetics joined the pharmacogenomics era when multiple GWAS were published for numerous drug-response phenotypes (31–35). None of the individual studies showed compelling associations between common DNA variants and antidepressant drug response (36). When three of these studies—the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the Genome-Based Therapeutic Drugs for Depression (GENDEP) project, and the Munich Antidepressant Response Signature (MARS) project comprising 2256 individuals of Northern European ancestry—were combined for meta-analysis, no findings reaching genome-wide levels of statistical significance were observed for dichotomous or quantitative response phenotypes (37). This result points toward many plausible situations explaining the influence of genetics on antidepressant drug response. The simplest explanations involve assessment of the "exposure" being assessed, in this case, drug response or tolerability. For example, placebo response or medication noncompliance may influence treatment outcome and may be unmeasured as a potential confounder in many pharmacogenetics studies.