The future of psychiatric pharmacogenomics

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Clinical need for biomarkers that predict treatment outcome

Psychiatric disorders are common and have high levels of morbidity and mortality. They strike early in life and are usually lifelong and chronic disorders. Currently, mental illness is ranked as the second in leading source of disease burden in established market economies by the WHO. It is estimated that 10–15% of the general population will experience clinical depression during their lifetime and 5% of men and 9% of women will experience a depressive disorder in a given year (as established by the WHO) [1]. Although there are a variety of pharmacological treatments available, response and tolerability to drugs are highly individual and vary from patient to patient, with some patients responding to one treatment but not another. In general, response and remission rates to pharmacological treatment are limited [2,3]. There are several potential explanations for these poor drug response rates, including clinical heterogeneity and diagnostic uncertainty, comorbidity, environmental, social and genetic factors. Identification of genetic biomarkers, that can help to predict treatment response of psychotropic medications and aid in the effective treatment of mental illness, would greatly enrich current clinical practice and is of high importance to the field.

Current state of psychiatric pharmacogenomics

Despite the clear need for better and more effective treatments for psychiatric illnesses, little progress has been made in drug development over the last several decades. Most available drug treatments were initially discovered serendipitously and developed in the 1950s to 1960s. While some refinement has occurred over the last several decades (better tolerability, the overall efficacy and effectiveness of psychotropes has improved dramatically. More troublesome however is that the mechanism of action of psychotropic drugs and the pathophysiology of most psychiatric disorders remains elusive.

By developing ‘personalized’ treatment strategies, psychiatric pharmacogenetics holds the promise to change this dire picture. Numerous studies have been carried out over the last several years attempting to identify genetic markers that predict drug efficacy and safety. Similar to the field of psychiatric genetics, results have been ambiguous and disappointing and so far there is no clear genetic biomarker that can be used in routine clinical care. To date, there is only one US FDA-approved commercial pharmacogenetic test available (Roche Diagnostic, Amplichip CYP450) which can be ordered through a few selected commercial and academic laboratories. This test was introduced in 2005 and provides genotypes for the two cytochrome P450 genes, CYP2D6 and CYP2C19. Theoretically, by genotyping patients for variation in these genes, the clinician should be able to predict the metabolizer status of a patient, which might influence medication choice and dosing. There are currently no general guidelines regarding who should be tested; however, several suggestions have been published [4,5].

Nevertheless, new enthusiasm for pharmacogenetics and personalized medicine has been generated over the last several years. Several new findings on gene variants with strong effects prove that pharmacogenetics can be clinically useful. Carbamazepine (CBZ), a drug used to treat seizure disorders, bipolar disorder and chronic pain, has been associated with several severe adverse events, including aplastic anemia, fatal arhythmias and life-threatening cutaneous disorders. The major histocompatibility complex HLA-B*1502 allele is a strong predictor for CBZ-induced Stevens–Johnson syndrome in Han Chinese individuals [4]. The odds ratio for developing CBZ-induced Stevens–Johnson syndrome if positive for HLA-B*1502 was 2504 with a positive predictive value of 93.6%. As a result of these data, the FDA issued a black box warning in 2007 for CBZ, and in addition, recommended that patients of Asian descent be genotyped for this allele before initiating CBZ therapy. Similar strong associations for genetic biomarkers and severe drug-induced adverse events have been reported in other areas of medicine, such as the association of a specific HLA allele and increased risk for liver injury under flavoxacin therapy [8]. With the rapid advance in technology in the field of genetics, it is now reasonable to sequence entire individual patient genomes at relatively low costs. Technological advances in how we study the genome, transcriptome, proteome will likely identify novel personal markers that predict drug response and adverse events.

Challenges & future directions

In order to develop clinically meaningful biomarkers for the clinician, there are several methodological challenges that must be overcome. One of the most fundamental issues in psychiatric pharmacogenetics is...
that almost all studies so far have used DNA samples from clinical trials that were actually not designed for pharmacogenetic purposes. While it is reasonable to develop hypotheses with post hoc analyses, ultimately prospective pharmacogenetic trials are needed. This poses in particular a challenge for psychiatric drugs, as multiple major pharmaceutical companies have abandoned psychiatric drug development. The field of pharmacogenetics is challenged by weaknesses in both disciplines. Psychiatric drug development has been plagued by negative trials, partly owing to ineffective compounds, but also as a result of clinical heterogeneity, high placebo response rates, weakness in clinical assessments and rating scales and poor study designs. On the genetics side, most studies are underpowered and the selection of genetic markers and gene coverage is insufficient. In order to advance, the field of psychiatric pharmacogenetics needs to develop clear phenotypic definitions, robust outcome measures and comprehensive molecular analysis of biomarkers.

New computational approaches will be necessary to deal with the massive amount of data that will be available and in order to address complex gene–gene interactions and environmental influences. As demonstrated for some HLA associations with severe adverse events, it is possible to detect meaningful effects in moderate samples sizes. With advances in DNA technology over the past 5 years (e.g., with SNP chips and high-throughput DNA sequencing), the design of well-powered prospective pharmacogenetic trials is feasible. In addition, valid biomarkers will guide and inform research on the biology and mechanism of the underlying disorder and phenotype.

Besides the strong need for methodological changes, the field must be aware and address ethical concerns of personalized medicine. As many medical centers have moved to electronic medical records, there is increased concern regarding privacy and protection of human subjects. In particular, given that platforms such as Wikileaks are able to obtain highly classified material, it should raise our concern for the privacy of the genetic information of our patients. In addition, no clear regulatory requirements for marketing, intellectual property claims and conduct of pharmacogenetic tests exist today. Society and the scientific community need to address the ethical implications of routine biomarker testing, in particular for the more vulnerable population of psychiatric patients.

Although pharmacogenetics in clinical practice is currently limited to ‘side effects’ and ‘metabolism’, comprehensive pharmacogenetic profiling will likely soon become a reality. While the technological advancements will offer new possibilities, there are also risks associated with the development of biomarkers (e.g., privacy, limitations of insurance coverage and genetic discrimination). The development of comprehensive pharmacogenetic policies and regulations is critical in order to avoid the misuse of genetic information [9]. While psychiatry has entered a new area of pharmacogenetics, treatment of psychiatric patients will always remain personal. Genetic biomarkers are only one part in the complex constellation of external and internal factors that influence psychopathology and mental health.

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