# Psychopharmacology

In psychiatry, the identification of genes associated with schizophrenia, autism, bipolar affective disorder, Tourette’s syndrome has been a major focus for several decades. After years of research investigation, genetic linkages and susceptibility genes have now been identified, yet a number of problems have yet to be addressed. One issue involves the pattern of inheritance of each psychiatric disorder, wherein non-Mendellian modes of transmission may be the major condition that a certain psychiatric disorder is transferred to siblings.

Another obstacle that has to be resolved is the scarcity of phenotypic descriptors for each psychiatric condition. Most importantly, there is currently a limited number of standards to follow for psychiatric ascertainment or valid diagnoses for each mental disorder. Recent advances in genetic technologies and the completion of the Human Genome Project has generated a plethora of information that is essential to the understanding of specific aspects of human biology and medicine.

Alongside the goal of sequencing the entire human genome and identifying genes associated to every disease, there has been a tremendous drive to design and maximize technologies that would have a profound impact on drug discovery, development and therapy within the pharmaceutical industry. Automated instrumentation such as the DNA microarray system has enabled economic high-throughput DNA sequencing and gene mapping for genomic research. Such revolutionary genomic techniques have also determined that there are specific variations in genetic markers within the genome.

These polymorphisms are distributed throughout the human genome, and there is an estimated 10 million single nucleotide polymorphisms (SNPs) existing in the human genome. Such minute differences may confer inconsistencies in individual drug responses to particular drugs. In this light, there have been strong proposals for individualized genetic testing to improve drug therapy, efficacy and safety. The field of pharmacogenomics or toxicogenomics is a recent revolutionary area in biomedicine which merges the genomic information generated from DNA analysis and the pathophysiology of preventive medicine.

Once an individual’s genetic profile in terms of disease risk and drug response is determined, a personalized approach to treatment and therapy may be designed. It is a novel field where the norm “ one drug fits all” is circumvented. The concept is based on “ therapy with the right drug at the right dose in the right patient” (Mancinelli et al. 2000). The approach involves classification of patients according to their phenotypic disease profile into discrete subcategories, which are, in turn, defined by genetic variations associated with the disease, or drug response, or both.

One advantage to this type of approach is that drug therapy in genetically defined populations can be more effective and more importantly—less toxic than broad-range target populations. Approximately ten years ago, the application of genetically-defined drug therapy to psychiatry was weak. It was then observed that interindividual differences in the genetic makeup dramatically alter the ability of inherent enzymes to deactivate pharmacological agents, which then lead to prolonged anesthetic effects (Kalow, 1997).

Other notable observations include differences in clearance time for certain drugs or modification of certain antidepressants to active metabolites leading to a drug overdose, or a reduced capacity of a patient to reach plasma level of therapeutic range. Hence, in psychiatry alone, the one-to-one relation of genotype to phenotype ratio may not be followed. The employment of pharmacogenetics in psychiatry involves two aspects. One involves the use of drug-responsiveness as a tool for a better understanding of complex genetic traits, and the other aspect concerns the role of genetic variation to individualized pharmacological therapy.

In the case of schizophrenia, which affects 1% of the human population, a broad list of drugs is used for its treatment. The conventional way of treating schizophrenia involves a trial and error approach, with the intention to determine the optimal drug and the correct dose to illicit a drug response yet limit or avoid drug toxicity. It is a normal scenario when 10 to 20% of patients do not respond to treatment using antipsychotic drugs. The other 20 to 30% of patients usually respond to the drug treatment but eventually relapse or experience serious side effects that may prevent the patient from continuing the intake of the drug.

Further studies of the disorder resulted in a generation of newer drugs yet each novel drugs came together with novel side-effects. The observation of that schizophrenia can be classified according to either positive or negative symptoms generated the notion that treatment of patients with schizophrenia should then be performed cautiously. Clozapine, an anti-psychotic drug, was then employed for treatment, wherein 30 to 60% of

patients unresponsive to regular antipsychotic drugs, regardless of type of symptoms manifested by the patient.

The field of pharmacogenomics now enters the field of psychiatry by determining the genetic variations that exist in the targets of clozapine—serotonin and dopaminergic receptors of the central nervous system. Several investigations are needed to confirm and validate any variations in the target genes before such observation can be called robust and reliable. This type of research involves screening a large population of patients for single-nucleotide polymorphisms in both target genes and at the same time, taking note of the patient's response to the drug treatment.

Currently, it has been determined that there are 19 candidate polymorphisms that are associated with schizophrenia, in turn generating six genetic variants for schizophrenia (Arranz et al. 2000). This screen has resulted in 76. 7% success in predicting clozapine response to treatment. A good example of the application of psychopharmacology is major depressive disorder, which is a serious disabling illness that affects approximately 10% of children and 16% of adults. This mental health disorder is strongly associated with short- and long-term morbidity and death (Kessler et al. 2003). Major depressive disorder is strongly correlated with dysfunctional capabilities in daily routines including school activities and work responsibilities (Myers, 2007). The symptoms of this mental disorder are the same among affected children and adults, with the exception that pediatric patients do not present a despondent mood but instead show a significant frequency of irritability. Depression among individuals may be observed in

individuals who show a sudden decrease in the quality of work productivity or an abrupt decrease in school grades.

Patients also show some kind of modifications in terms of interrelationships with friends, by simply decreasing and at times, refusing to interact and spend time with his usual peers and relatives. Depression also involves significant changes in patterns of sleeping and eating, which can be observed at extremes of either not sleeping well or sleeping during most of the day that the individual does not get to finish what he is expected to do or complete for that day.

Depressed individuals also chronically feel tired and carry a sense of worthlessness, hopelessness. In a considerable portion of depressed individuals, thoughts of committing suicide are also reported. Among depressed adolescents as well as adults, an increased activity of substance abuse is also detected. Pharmacological treatment of major depressive disorder involves the administration of anti-depressants, which are classified as either first-generation or second-generation anti-depressants.

The first-generation antidepressants include tricyclic antidepressants and monoamine oxidase inhibitors, while second-generation anti-depressants include the serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (Hazell et al. , 2002). Specific examples of SSRIs include fluoxetine, citalopram, escitalopram, paroxetine and sertraline, while SNRIs include mirtazapine, nefazodone and venlafaxine. The effectivity of these two generation types of anti-depressants has been reported to be the same (Song et al. , 1993).

Yet, it has also been observed that first-generation anti-depressants generally cause several side effects that provide discomfort and intolerability among patients that receive such specific treatment regimen (Anderson, 2001). In some cases, an overdose of first-generation anti-depressants is associated with a great risk for harming oneself. Such observations resulted in the created of second-generation anti-depressants. Patients diagnosed with major depressive disorder generally recover from their mental illness after 1 to 2 years, with or without pharmacological treatment.

However, approximately 40% to 70% of these individuals succumb to a second episode of depression. For depression, polymorphisms in the liver cytochrome P450 isoenzyme result in differences in drug response to antidepressants. The gene related to the isoenzyme is CYP2D6, which produces the protein product debrisoquine hydroxylase. Several antidepressants such as the tricyclics and selective serotonin reuptake inhibitors (SSRIs), venlafaxine metabolized primarily by debrisoquine hydroxylase. The CYP2D6 gene is highly variable, and so far, approximately 70 genetic variants have been identified and characterized genetically.

In addition, allelic variation in the gene complicates its genetic profiling, wherein a homozygous null condition generates poor metabolism of debrisoquine hydroxylase, and a heterozygous null condition creates an intermediate metabolic capacity for debrisoquine hydroxylase. There are also cases wherein the CYP2D6 gene is duplicated in certain patients, which results in extremely high levels of drug metabolism. More large-scale prospective studies are needed to determine the effect of specific genotype

constitutions on the metabolism of these drugs, as well as the efficiency of these genotypes to reach plasma levels for drug effectivity.

Another polymorphic gene that has been studied in psychopharmacogenomics is the serotonin transporter gene, SLC6A4. A deletion/insertion polymorphism in the promoter region of this gene has been discovered in depression patients treated with fluvoxamine. This gene is also known to affect the expression of 5-HT transporter protein (Heils et al. , 1996). It has been theorized that SSRIs act through inhibition of the 5-HT transporter, so a genetic variant that affects the expression of this protein could affect treatment response even though the protein structure is unchanged.

There has been active research on the efficacy and safety of anti-depressants in the past decade. This is mostly due to the controversy that originated from cases that involved violence and suicidal tendencies among adolescent patients, especially those treated with the second-generation anti-depressants. Currently, it is difficult to determine whether the suicidal thoughts of a patient are due to the drug itself, or is caused by a significant worsening of the depressive disorder itself. Research programs often include a control placebo group that would facilitate any comparative analysis of the efficacy of these pharmaceutical drugs.

To date, there are no specific predictive factors that may facilitate a clinician to determine whether the pharmacological treatment of a patient diagnosed with depression will be helpful or harmful. It is therefore imperative that the clinician be cautious regarding the presentation of any abrupt changes in the

individual during his treatment. Hence, a good interaction between the clinician and the patient's immediate family should be established so that any unexpected and untoward actions that the patient may attempt to do, such as suicide or pain instigation, may be avoided and prevented.

In addition, the clinician should assess every patient with complete objectivity, in terms of whether the individual fits the criteria for the diagnosis of major depressive disorder. And once depression is diagnosed, the patient and the members of his immediate family should be educated about the mental health disorder. The clinician should also discuss options that are available for the treatment of such disorder, as well as disclose the side-effects of each treatment.

It is also important that the clinician determine whether the family of the patient shows any history of suicidal behavior, as well as any new ideas and thoughts even during the treatment period. Pharmacological treatment for depression generally starts at the low dose, and the dosage is increased at regular intervals until the maximum effective dose is achieved. It is also essential that weekly or biweekly monitoring of the clinician be performed in order to adjust the treatment dose of the patient.

There is only a small number of pharmacogenetic studies performed on mood stabilizers because the identification of candidate genes has been difficult due to the elusive mechanisms of action of these drugs. The usual drug used as mood stabilizer is lithium, which inhibits the activity of enzymes associated with phosphatidylinositol cycle and phospholipase C signal transduction. An initial screening of patients resulted in the identification of

the inositol polyphosphate 1-phosphatase C973A variant in only half of the patients, thereby slowing down progress in this gene (Phiel and Klein, 2001).

Other investigations aiming to identify associations between polymorphisms in tryphtophase hydroxylase A/A genotype and lithium treatment response resulted in a weak association. Currently, personalized medicine in the field of psychiatry has been limited to screening small patient populations for only a single nucleotide polymorphism or a small number of SNPs. There is much research left to be conducted, knowing that there are approximately 106 genes playing essential role in the normal functioning of the central nervous system. Case-control studies are important to pharmacogenomic studies, as well as investigations on unresponsive patients.

Researchers should, however, be very cautious during the implementation of pharmacogenomic studies, because there is a large chance of generating false positive results alongside screening categories. Family-based approaches to pharmacogenomic studies are not that informative because it will only complicate analysis due to the addition of patterns of horizontal inheritance. As research in pharmacogenetics strengthens, more tests for robustness and reliability of data should be performed, in order to apply the findings in a clinical setting.

The amount of variance in each gene associated with a psychiatric condition will be well-characterized and explained in terms of genetic mechanisms and control. Pre-treatment testing of patients for more specific molecular targets will be possible after disorder- and gene-specific genotyping, resulting in a quicker, more effective, and less costly treatment of psychiatric conditions.

Therefore, pharmacogenetic approaches provide a new opportunity to identify biomedical predictors to psychotropic drug responses at an individualized level, and more importantly—provide a method to identify the molecular targets of specific psychiatric drugs.