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Spotlights on Pharmacogenetics of Schizophrenia and Depressed Mood

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Short Commentary

Pharmacogenetics is the study of the genetic basis for variation in drug response, which examines the single gene interactions with drugs.

This important branch of pharmacology has two main aspects:

Identifying specific genes and gene products associated with various

Identifying genes and allelic variants of genes that leads to variability in drug response

There is an important issue in pharmacogentics which is "polymorphism": it is a variation in the DNA sequence that is present at an allele frequency of 1% or greater in a population. It is most commonly in the form of Single base pair substitutions named Single Nucleotide Polymorphisms (SNPs), the location or the number of repeats, deletions, or critical splice sites. The interfaces between genetics and drug metabolism have recently been the subjects of intense research activity. Pharmacogenomics uses molecular biological techniques to study genes in relation to drug therapy for specific diseases in order to identify new treatments. Pharmacogenetics investigates the genetic basis for differences in individual responses to drugs with regard to their metabolism and transport in the body. It involves the role of many drugs, acting on different body systems, in the development of genetic polymorphism especially that responsible for metabolising enzyme as cytochrome p450 isozymes that affect their abilities in either induction or inhibition of drug metabolism and elimination. Genes of these drug- metabolizing enzymes possess Single Nucleotide Polymorphisms (SNP) with an allelic site that may also have more than one SNP. Genotype is the detailed gene structure of an individual whereas the more commonly measured phenotype is the outcome of metabolism of a drug in an individual. Since phenotype is the result of interactions between genetic make-up and the environment it is not always concordant with genotype [1-4].

When polymorphism occur in genes that encoding drug transporters or drug metabolism which are determinants to drug pharmacokinetic it is called pharmacokinetic genetic polymorphism which is more common and much more clinically important. The clinical importance of polymorphism may occur in genes that encoding drug receptors or cell signaling pathways which are determinants to drug pharmacodynamics and so called pharmacodynamic genetic polymorphism. On the other hand, both pharmacokinetic/pharmacodynamics (PK/PD) genetic polymorphism can lead to variability in drug response. PK/PD models have to take into consideration the characteristics of drug dosage forms, its biopharmaceutical activities, its pharmacokinetic and pharmacodynamic properties, and its possible drug or food interactions on genetic basis. All those aspects are actually the main determinants of successful gene therapy by the transfer of genetic material (DNA or RNA) to somatic cells in order to obtain a therapeutic effect. Mathematical models of pharmacokinetics will help to characterize and quantitatively describe the intracellular processes of therapeutic gene expression systems can be developed to identify the main events controlling the desired transgene expression. While, The disposition of the DNA inside the nucleus will allow its integration into host's genome (main characteristic of retroviruses) or maintain an extra chromosomal location and to induce a mechanism of action that leads to a beneficial therapeutic effect of such gene therapy with the initiation of PD process including nuclear stability, transcriptional efficiency, protein synthesis etc. [5,6].

Important Notes on Relationship between Pharmacogenetics and psychopharmacology

The success of psychopharmacology is mainly related to many factors such as gene variants that regulate both pharmacokinetic properties of the drug, such as uptake, metabolism and elimination of the substances, and pharmacodynamic properties, i.e. the interaction with the target proteins. Researchers do a lot of work in the field of pharmacogenetic research in psychiatry. They already discovered that at least some polymorphisms in genes of the serotonin receptors, the serotonin transporter and the dopamine receptors possess an important role in the therapeutic as well as adverse effects of psychotropic drugs. Recent studies concentrate on structures beyond the initial target proteins of drugs, such as signal transduction genes, neuronal development, regulation and plasticity. Pharmacogenomics, which is a broader study of the entire genome to assess multigenic determinants of drug response, have already revealed the profiles of gene expression in psychiatric diseases in addition to the inclusion of environmental factors especially polution and irradiation that have essential impact on the mechanism (s) of action and adverse effects of drugs used in psychopharmacology at the molecular level of pharmacogenetic researches [7,8].

Schizophrenia and Pharmacogenetics

The pharmacogenetics of schizophrenia is apparently to be related to the phenomenon of "polymorphism" of genes responsible for the development of this disease, which will help a lot in the development of the proper antipsychotic drugs now and in the future. There is a great improvement in the identification of the response of the phenotype "that is the observable properties of psychiatric patient by the exposure to a drug". This phenotype needs to be carefully assessed and to be selected from homogeneous subject groups. Genetic predictors of outcome of schizophrenic patient to drug therapy will

inform psychiatrists to the best choice of pharmacotherapy and such patients in the near future [9,10].

Newer atypical antipsychotic agents are investigated in various genetic studies. It was found that genetic variation in the dopamine D2 receptor and the serotonin (5-hydroxytryptamine) 2A receptor are very helpful in the prediction of clinical efficacy and the good response of schizophrenic patients to these drugs. The incidence of tardive dyskinesia and weight gain, as antipsychotic drug-induced side-effects, are also related to variation in dopamine and serotonin receptor genes. These results direct the researchers that pharmacogenetic studies are very informative for the clinical response and prognosis of the patients [11,12].

Depressed Mood, Anxiety and Pharmacogenetics

Statistical analysis in multicenter clinical studies showed that effective treatment for mood and anxiety disorders have been reported since more than 40 years, however, 30-50% of depressed patients and 25% of patients with anxiety disorder do not respond in an effective manner to many antidepressants [13,14]. Researchers thought that this ineffective response is related to genetic factors that result in both variation of treatment response and more incidence of adverse effects to antidepressants. Pharmacokinetic and pharmacodynamics-induced changes by specific genes on the mechanism (s) of action of antidepressants have been documented from many pharmacogenetic studies. A famous example is that two functional polymorphisms of the serotonin transporter gene, 5-HTTLPR and STin2 have been demonstrated in a large number of pharmacogenetic studies of depression; additionally specific genes, include serotonin receptor genes, brain-derived neurotrophic factor, P-glycoprotein, G-proteins, TPH1 and TPH2, MAOA, the noradrenaline transporter gene, FKBP5, or cytochrome P450 (CYP450) genes, are playing important role in the loss of response to many antidepressants in both depressed mood with or without anxiety. Moreover, CYP450 genes play a major role in the metabolism of a substantial part of psychotropics, including antidepressants. These genes are affected by large numbers of single-nucleotide polymorphisms resulting in variation in the response to antidepressant treatment in anxiety disorders [15,16].

Summary

Pharmacogenetic researches may provide psychiatrists by many data that are very necessary to begin to identify the phenotype of response to antipsychotic and antidepressant drugs. Future studies should be focused on more comprehensive genomic analyses as well as the identification of mutations in genes related to many psychaitric diseases as schizophrenia, depression and anxiety topredict successful psychotherapy and the incidence of adverse effects to reach the so-called ”tailored“ treatment.

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