

Gene mutations and pharmacogenetics

Editorial

Over the past decades, there has been an excessive interest in some genetic diseases that have a heritable abnormality in their DNA. The genomes of humans and other organisms were decoded in a significant detail. This has opened the gate to novel approaches to research and therapy. It is well-known that some patients respond to certain drugs with greater than usual sensitivity to standard doses. These individual differences are determined by genetic factors, and non-genetic variables as age, sex, liver function and many others. However, predicting the fate of a drug in a particular patient and subsequent response is still a vision and far away from application in routine clinical practice. Recognizing the sources and understanding the factors that contribute to the unusual pharmacokinetic and pharmacodynamic variables among individuals remains a challenge of particular importance for drugs with narrow therapeutic index.¹

Gene mutations related to differences in drug response among individuals or populations is named pharmacogenetics. This area that constitutes an integration of pharmacology and genetic factors to study individual differences in metabolic rate depend on the nature of the drug itself. Whereas understanding Pharmacogenomics can be interchangeable with pharmacogenetics. Thus, a Pharmacogenomics study is about adverse drug reaction deal with genome while a pharmacogenetics study deals with individual gene in a genome. A study of adverse drug reactions into individuals related to genetic defects, especially for CYP₄₅₀ gene family, can be directed onto Marker Aid Selection (MAS), when molecular markers are ready to be used for identifying specific gene.² DNA sequence of human genome was completely finished in 2002 and already known gene sequence for specific trait, hence, it can be used as a marker to detect gene mutation of individuals when they are suspected to severe genetic diseases based or metabolic defects based on phenotype performance. Molecular biology methods are common techniques which share between plants and humans as well as for DNA identification, DNA separation, RNA isolation and DNA detection for genetic polymorphism.

Now sequencing of the human genome is finished, with completion much information on the underlying genetic causes of many inherited and acquired diseases and has been made available. Several genetic diseases were found to be as a result of a change of a single base pair. These alterations, termed single nucleotide polymorphisms (SNP), may cause changes in the amino acid sequence of important proteins. Some SNPs, on the other hand, may not cause a change in protein expression but may be close on the chromosome to other unknown deleterious mutations, and can, thus, serve as genetic markers for these. One example of a disease-causing SNP is the G-A transition at position 20210 in the 3'-untranslated region of the Prothrombin or Factor II gene. Prothrombin is the precursor of the serine protease thrombin, which catalyses the last reaction in the blood clotting cascade which converting fibrinogen to fibrin. Prothrombin is a key in the balance between pro-coagulation and anti-coagulation. The presence of the mutation causes an up regulation of 3'-end processing leading to increased mRNA. This, in turn, leads to an increase in protein synthesis and Prothrombin plasma concentration.^{3,4} The mutation occurs in only 2.3% of the Caucasian population but in 6% of the patients with deep vein thrombosis (DVT) and 18% of those

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patients with a family history of DVT. The presence of the mutation was also found to increase the risk of myocardial infarction in young women four-fold: this risk was elevated in the presence of other risk factors such as smoking, hypertension, diabetes or obesity.^{5,6} In addition, mutation of CYP₄₅₀ gene family can alter biochemical pathway of drugs metabolism, since a lot of gene products of CYP₄₅₀ related to drugs metabolism as CYP_{2D6} and CYP_{2C9} which involved pharmacokinetic and pharmacodynamic genes function and can lead to adverse drug reactions in human. Several studies suggest that smokers may be predisposed to nicotine addiction through the effects of gene responsible for metabolizing nicotine. Thus, smoker's carrying a defective variant of CYP2A6 metabolize nicotine more slowly and exhibit reduced nicotine dependence. Conversely, smokers with a normal CYP2A6 pattern may respond particularly well to nicotine replacement therapy. Researchers have found that non-smokers are twice as likely to carry a mutation in gene that helps to rid the body of nicotine. In addition, smokers who carry mutations in the gene, "known as CYP2A6" are likely to smoke less because nicotine is not rapidly removed from the brain and blood stream. By contrast, smokers with the efficient version of the gene will tend to smoke more heavily to compensate for nicotine being removed more rapidly. A similar phenomenon was founded on gene mutation that involved drug receptor interaction which influenced drug transport into cell target. It can be rapid or slow. Therefore, consideration about genetic factors that influence drug metabolism should be a part of medication for the patient.⁷ Thus, methods sensitive to single base pair mutations for the rapid screening of patients' samples to detect these and other disease-causing mutations will be important in prevention and treatment. Hybridisation analysis where a short probe oligonucleotide (15-20 base pairs) bearing some kind of label is used to identify a DNA or RNA sequence by hybridising to complementary base pairs, is one of the most powerful tools for the detection of genetic sequences.

In addition, with the development of new technologies for more accurate understanding of the genome and potential gene therapies, the detection of mutations has an increasingly central role in various areas of genetic diagnosis including pre implantation genetic diagnosis (PGD), prenatal diagnosis (PND), pre symptomatic testing, conformational diagnosis and forensic/identity testing. Two sets of tests, molecular and cytogenetic, are used in genetic syndromes. In general, single base pair mutations are identified by direct sequencing,

DNA hybridization and/or restriction enzyme digestion methods. However, there are two approaches for genetic diagnosis; indirect approach depends on the results from a genetic linkage analysis using DNA markers such as STR (short tandem repeat) or VNTR (variable number tandem repeat) markers flanking or within the gene. The direct approach for diagnosis essentially depends on the detection of the genetic variations responsible for the disease.^{8,9}

Conclusion

In conclusion, the prospects for mutation detection in research and treatment in the future seem fairly promising in these exciting times.

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Conflict of interest

Author declares that there is no conflict of interest.

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