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Pharmacogenomics

Factsheet

FROM THE LABORATORIES OF DNALYSIS

DNALYSIS BIOTECHNOLOGY

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Key points

It is estimated that approximately 5% of hospital admissions are caused by adverse drug reactions[1], and in low- and middle-income countries this statistic is likely to be as high as 8%[2].

- In 2014, the prescription drug market was roughly $374 BILLION in the U.S.A., a 13% increase from 2013
- 100,000 deaths in the U.S.A. occur annually due to adverse drug reactions (ADRs)
- The Centre for Disease Control and Prevention has estimated that the healthcare system in the U.S.A. spends $3.4 billion on extra medical costs due to ADRs[3]

Inter-individual variation in drug metabolism is a factor affecting successful drug therapy.

Pharmacogenomics, sometimes referred to as pharmacogenetics, is the study of how genes affect an individuals' response to particular drugs. This field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications at doses that will be tailored to variations in a person's genes.

The goal of pharmacogenomics is to identify genetic biomarkers affecting drug response, and use them to better guide drug therapy decisions for each individual (personalised medicine).

Benefits of pharmacogenomics

- For the patient: it may decrease the length of treatment time, eliminate a trial and error approach in finding an effective medication, minimise the effects of disease on the body through early detection and ultimately save money.
- For the physician: it streamlines clinical decision making by distinguishing in advance those patients most likely to benefit from a given treatment from those who will incur unnecessary costs and suffer side effects. It will also provide more accurate methods of determining dosage.
- Clinical Drug Trials: pharmacogenomics may decrease the number of failed drug trials and the time it takes for a drug to be approved; excluding those individuals from the trials whose genotype would make the drug being tested harmful or ineffective for them, will increase the likelihood that the particular drug will show its usefulness and safety to another population group with a different genotype.
- Medical insurance: medical funders should save money through the reduction of hospital costs associated with ADRs, or by no longer paying for ineffective medications.

Potential limitations of pharmacogenomics

- Physicians, for the most part, are not aware of the commercial availability of pharmacogenomic testing. It is a common belief that this testing is still limited to large research laboratories.
- Most physicians do not receive training in the field of genetics and exposure to accessible, reputable pharmacogenomics education resources is limited.
- The influence of drug-drug interactions as well as environmental factors will still need to be determined before any conclusions can be made about the genetic influence on drug metabolism.
- Personalised drug therapy based on pharmacogenomic testing is an attractive offering, yet may be costly, which could impact equity and accessibility, possibly posing an ethical concern.
- The pharmacogenomics test results require precise interpretation based on a high level of scientific evidence to insure sound prescription-making.

Pharmacogenomics in practice

Genes are made up of DNA (deoxyribonucleic acid) and are the template to make proteins.

Findings of the human genome project revealed:

- The DNA of any two individuals is 99.9% identical
- The majority of the 0.1% variation has no functional significance
- Small genetic variations within the 0.1% of an individuals' DNA can influence the ability of genes to perform their required functions, in turn, affecting the biological pathway in which the gene is active, possible impacting response to a drug.

How is pharmacogenomics affecting medical treatment?

Currently, doctors base the majority of their drug prescriptions on clinical factors, such as a patient's age, weight, sex, and liver and kidney function. For a small subset of drugs, researchers have identified genetic variations that influence how people respond. The Food and Drug Administration, which monitors the safety of all drugs in the United States, has included pharmacogenomic information on the labels of more than 150 medications.

This information, which can cover dosage guidance and possible side effects or differences in effectiveness for people with certain genomic variations, can help doctors tailor their prescriptions for individual patients.

Examples of clinical utility:

Dosage guidance for Warfarin

Warfarin is the anticoagulant of choice for cardiovascular disease, thromboembolic disease, and prophylactic post-surgery application. It ranks in the 40 most prescribed drugs and is one of the most common to cause admission to hospital due to adverse reactions. Due to its very narrow therapeutic index, individualised dosing is mandatory and the effective daily dose ranges from 0.5 to 80mg. Typically, dosing is determined by patient history and physical exam, in conjunction with INR.

Warfarin targets the VKOR1C1 gene product, K-epoxide reductase. This enzyme mediates the production of active vitamin K, an essential blood clotting factor. Warfarin and other related anticoagulants inhibit K-epoxide reductase activity in order to prevent or treat thromboembolic events.[4]

A commonly occurring VKORC1 variant (1639G>A) potentiates the effects of warfarin and as a result, a lower starting dose is recommended for these patients. Patients receiving warfarin have 31% fewer hospitalisations over a six-month period if they underwent pharmacogenomic testing.[5]

Drug metabolism and preventing ADRs

Codeine is classified as a prodrug, which is broken down to morphine via the phase 1 enzyme Cytochrome P450 2D6, encoded by the CYP2D6 gene. Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.[6]

When a breastfeeding mother has a rapid metabolizer genotype, she can unintentionally pass on a deadly dose to her infant when given a drug like codeine. Understanding a mother's pharmacogenomic profile enables a physician to protect both mother and child.[7]

Drug responsiveness and effective treatment

Dopamine, a key neurotransmitter, exerts its action by binding to five different receptors, including the dopamine D2 receptor, encoded by the DRD2 gene. Therapeutic and adverse events of several antipsychotics both result from their high affinity to antagonize DRD2.[8]

Bupropion, a medication primarily used as an antidepressant and smoking cessation aid, is a weak inhibitor of dopamine and norepinephrine reuptake and may serve as a non-competitive inhibitor of nicotinic acetylcholine receptors.

The DRD2 A1 allele is associated with nicotine dependence and the efficacy of bupropion and nicotine replacement therapy. Smokers with the DRD2 A2/A2 genotype using bupropion for smoking cessation, are three times more likely to be abstinent at the end of treatment than non-carriers of this genotype. Smokers carrying the DRD2 A1 variant seem to derive greater benefits from nicotine replacement therapies compared to treatment with bupropion.[9]

Personalised medicine

Personalised medicine is an emerging practice of medicine that uses an individual's genetic profile to guide the prevention, diagnosis and treatment of disease.

Technological advances have made it possible to test even the smallest variations in a person's genetic make-up. This enables medical practitioners, to identify genetic variants in order to pre-emptively manage a particular patient's adverse side effects to prescribed medication and improve the efficacy of drug therapy.

Useful resources:

https://www.pharmgkb.org/
https://cpicpgx.org/

[1] Bouvy et al. Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies. Drug Saf. 2015; 38(5): 437–453. [2] Mouton et al. Adverse Drug Reactions Causing Admission to Medical Wards. A Cross-Sectional Survey at 4 Hospitals in South Africa. Medicine. 2016; 95(19): 1-10. [3] Institute of Medicine. Committee on Identifying and Preventing Medication Errors. Preventing Medication Errors, Washington, DC: The National Academies Press 2006. [4] Rost, S. et al. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. Nature 427, 537-541 [5] Epstein, R. S. et al. Warfarin genotyping reduces hospitalization rates results from the MM-WES (Medco-Mayo Warfarin Effectiveness study). Journal of the American College of Cardiology 55, 2804-2812 [6] http://pediatrics.aappublications.org/content/early/2012/04/04/peds.2011-2538
[7] Koren G et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet DOI: http://dx.doi.org/10.1016/S0140-6736(06)69255-6 [8] Zai et al. Meta-analysis of two dopamine D2 receptor gene polymorphisms with tardive dyskinesia in schizophrenia patients. Mol Psychiatry. 2007 Sep;12(9):794-5. [9] David et al. Pharmacogenetic clinical trial of sustained-release bupropion for smoking cessation. Nicotine Tob Res. 2007 Aug; 9(8): 821–833.

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A pharmacogenomics test gives insight into how a patient metabolizes, transports, and binds specific prescription drugs, which in turn allows physicians to prescribe those compounds that are most likely to prove efficacious. Such a personalised approach to medicine has the power to produce better results, particularly for individuals whose genetic profile puts them at risk of experiencing either treatment failure or an adverse reaction from a given drug.

The DNAlysis Biotechnology mygeneRx test analyses 62 genetic variations within 20 genes and is able to give accurate and actionable recommendations on approximately 150 different prescription drugs within 35 different drug classes (please see full medications list for details).

The genetic variants tested in the mygeneRx test include:

ABCG2 421C>A;	CYP3A5 *3, *3C, *6, *7;
ADRA2A C-1291G;	CYP4F2 1347G>A;
ANKK1/DRD2:Taq1A;	Factor II 20210G>A;
BDNF 434C>T;	Factor V Leiden 1691G>A;
COMT Val158Met;	MC4R g.60215554C>A;
CYP1A2 *1F, *1K;	MTHFR 1298A>C, 677C>T;
CYP2B6 *6, *9, *11, *18;	OPRM1 A118G;
CYP2C19 *2, *3, *4, *4B, *6, *7, *8, *9, *10, *17;	SLCO1B1 521T>C;
CYP2C9 *2, *3, *4, *5, *6, *8, *11, *27;	UGT2B15 *2;
CYP2D6 *2, *3, *4, *4M, *6, *7, *8, *10, *12, *14A, *14B, *17, *29, *35, *41;	VKORC1 -1639G>A
CYP3A4 *3, *12, *17, *22;	

Drug metabolism can be affected by a single nucleotide polymorphism (SNP) or by multiple SNPs. For example, Simvastatin is affected by 1 SNP, Codeine by multiple haplotypes and copies of a gene, and Warfarin is affected by a combination of a diplotype of one gene and a SNP from another. Pharmacogenomics interpretation is therefore complex and vital. The DNAlysis Biotechnology mygeneRx reports provide accurate, easily actionable information with changes to the standard prescription guidelines outlined where appropriate

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