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Pharmacogenomics- Personalized Treatment of Cancer, Diabetes and Cardiovascular Diseases

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Abstract

Pharmacogenomics is the study of genetic variations between individuals to predict the risk of toxic side effects and the probability that a patient will respond to single or multiple drug treatment. The ways people respond to drugs are complex traits that are influenced by many different genes. Pharmacogenomics intends to develop rational means of optimizing drug therapy, with respect to the patients' genotype, to maximize efficacy with minimal adverse drug reactions. Pharmacogenomics has the potential to revolutionize the practice of medicine, and promises to guide in an area of personalized medicine, in which drugs and drug combinations are optimized for each individual's unique genetic makeup. This review gives information regarding principles of pharmacogenomics and how pharmacogenomics can advance the development of personalized treatments by revealing genetic variations that predict individual responses to therapeutic interventions.

Keywords: Pharmacokinetics; Single nucleotide polymorphism; Estrogen receptor; Breast cancer susceptibility genes (BRCA1, BRCA2); Cardiovascular diseases; Cytochrome P450 enzymes

Introduction

It has been recognized for more than 50 years that genetic differences between people contribute to interindividual differences in the response to many commonly used drugs. Pharmacogenetics is the term used to denote the science about how heritability affects the response to drugs. Pharmacogenomics is an apparently new science about how the systematic identification of all the human genes, their products, interindividual variation, intraindividual variation in expression and function over time may be used both to predict the right treatment in individual patients and to design new drugs. The term pharmacogenomics was coined in connection with the human genome project, but there is no internationally accepted consensus depicting any semantic differences between pharmacogenetics and pharmacogenomics, and in practice the two terms are used interchangeably.

Findings from the Human Genome Project [1,2] made it clear that 99.9% of the information in the estimated 23,000 human genes is identical from one person to the next. The small differences in the remaining 0.1% of genes present in the human cells are key to each individual.

Usually these differences do not cause any problem with how their body grows, develops or works although they may influence an individual's susceptibility to certain health problems or determine how an individual's body reacts to different treatments – in particular, how different medicines are metabolized. The study of the interaction between genetics and therapeutic drugs is variously called pharmacogenetics or pharmacogenomics. The differences between the two are the initial approach of the science:

- Pharmacogenetics starts with an unexpected drug response result and looks for a genetic cause

- Pharmacogenomics on the other hand begins with looking for genetic differences within a population that explain certain observed responses to a drug or susceptibility to a health problem

Traditionally, pharmacogenetics has focused on the role of genetic variation in pharmacokinetics [3] (e.g., the absorption, distribution, metabolism, and excretion of drugs) and pharmacodynamics (e.g., drug-response proteins, such as receptors, channels, and transporters).

The term pharmacogenetics comes from the combination of two words: pharmacology and genetics. Pharmacology is the study of how drugs work in the body and genetics is the study of how characteristics that result from the action of a single gene or of several genes acting together are inherited and how they work in the cells of the body. Factors that influence how an individual responds to medication include their external and internal environments and overall health, as well as their genetic make-up.

Principles of pharmacogenomics

Pharmacogenomics focuses on variation within the human genome. The human genome is composed of 3.1 billion nucleotide bases, and the number of genes is about 26.000. Every person inherits two copies of most genes, one from each parent. Although any two individuals' DNA is over 99 percent identical, the number of nucleotides is so large—approximately 3 billion—that millions of variant sequences still occur across the human population. Variants that are found in

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more than 1 percent of the population are called polymorphisms. The most abundant type of variant is the single nucleotide polymorphism (SNP) [4]; other common types are deletions, insertions, and tandem repeats. Each gene's nucleotide sequence encodes a molecular product, usually a protein. Sequence variation may result in alterations in the gene's product, which in turn may have an effect on phenotypes that the product influences. Genetic researchers use several types of studies to establish and explore gene-phenotype relationships. Heritability studies can indicate the relative contributions of genetic and nongenetic (e.g., environmental) influences to a particular phenotype. Linkage studies analyze pedigrees of related individuals and genetic markers to hone in on regions in the genome that may harbor genes associated with phenotypes of interest. Candidate gene association studies can be used to investigate gene-phenotype relationships suggested by linkage studies, as well as to focus on genes selected for their physiological or pharmacologic relevance to a phenotype.

Single nucleotide polymorphisms

Genetic variations in drug-metabolizing enzymes, transporters, receptors and other drug targets have significant effects on the efficacy and toxicity of many drugs. Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins and single nucleotide polymorphisms (SNPs) [5,6]. It is believed that drugs might one day be tailor-made and adapted to each individual's genetic makeup. Although factors such as environment, diet, age, lifestyle and state of health can influence an individual's response to medicines, their genetic make-up is the key to creating personalized drugs with greater efficacy and safety.

SNPs are the most frequently found DNA sequence variations in the human genome [7], compared with infrequent variants (mutations), the primary cause of genetic disorders. It is believed that SNPs may contribute significantly to genetic risk for common diseases [8]. It is estimated that the average nucleotide diversity is 1 difference/1200 base pairs. Approximately 1 million SNPs are likely to occur in human genes, with approximately 500,000 being non-coding SNPs, 200,000 being silent coding SNPs and 200,000 being replacement coding SNPs [9]. SNPs found in the coding and regulatory regions of genes are likely to be the most relevant variants. Efforts to identify all SNPs and their relevance to disease (cancer) susceptibility and treatment outcome are continuous, and may take several more years. However, the approach taken by many scientists at present is the candidate gene approach in which one examines the SNPs of the chosen gene that are likely to have an effect.

Benefits of pharmacogenetics

Improving patient safety: Pharmacogenetic testing may help identify patients who are likely to experience dangerous reactions to drugs, enabling doctors to monitor them closely and possibly adjust the dosing of the drug or choose another treatment, thereby improving patient safety and potentially saving lives [10].

Improving health care costs and efficiency: The time and resources that doctors and patients spend finding appropriate medications and doses through "trial and error" is likely to decrease as pharmacogenetic tests are developed.

More accurate methods of determining dosages: Instead of dosages being based on body weight and age, it would be based on an individual's genetics. This would decrease the likelihood of an overdose

Better vaccines: Vaccines made of genetic material could activate the immune system to have all the benefits of existing vaccines but with reduced risks of infections (e.g. Cancer vaccine) [11].

Breast Cancer

Breast cancer is the most common form of cancer affecting women in many countries. One in every eight women will develop breast cancer at some point in their lives [12]. Several factors both inside and outside of the body may contribute to the development of many cancer types [13,14]. Identification of markers that can predict the outcome in an individual or the response of a tumor to a specific therapy has become an important aspect of cancer research. Estrogen receptor (ER) [15,16] and HER2/neu [17] are the only two markers that are used in routine screening of breast cancers for effective therapy.

Most breast cancers are carcinomas, i.e. malignant tumors of epithelia. Less than 1% of breast cancers are sarcomas that arise from connective tissue, bone, muscle or fat. Among carcinoma, approximately 75% of breast cancers are ductal carcinomas, arising in the tissues that line the milk ducts and approximately 7% are lobular carcinomas, arising from the lobules where the milk is produced. Carcinomas that do not spread outside of the duct or lobule are called ductal carcinoma in situ (DCIS) [18] or lobular carcinoma in situ (LCIS). If ductal or lobular carcinoma spreads into nearby tissue, it is called invasive or infiltrating ductal carcinoma (IDC) or lobular carcinoma (ILC). It is estimated that approximately 95% of all breast carcinomas are invasive.

Breast cancer development is a multistep process with transformation of normal cells via hyperplasia, premalignant change and in situ carcinoma [19]. As in other tumors, breast cancer development also involves the accumulation of various genetic alterations, including amplification of oncogenes and mutation or loss of tumor suppressor genes [20-22]. Both local and systemic treatments are employed for women with primary invasive breast cancer [23]. Local treatments, which include surgery and radiation therapy [24,25], are used to reduce the risk of recurrent cancer in the breast, chest wall and regional lymph nodes. Surgery remains the most common modality for most breast cancers. However, the radical mastectomy has been replaced by wide excision of the tumor with preservation of the breast (lumpectomy), followed by whole breast radiation therapy. In addition, surgical dissection of ipsilateral axillary lymph nodes is carried out to determine the lymph node status with respect to cancer spread. The probability of recurrence is higher for women with histologically positive axillary lymph node.

Predicting the risk of developing breast cancer

The lifetime risk of a woman developing breast cancer is approximately 10%. The protein products of the breast cancer susceptibility genes BRCA1, BRCA2 and p53, CHEK-2 and HER2/neu are all components of the molecular pathways accelerated in response to impaired DNA damage repair [26]. Germline mutation in breast cancer susceptibility genes BRCA1, BRCA2 are most commonly responsible for developing approximately 80-90% of hereditary breast cancer, whereas they are not very frequent in sporadic breast cancers [27] In women, both BRCA1 and BRCA2 are thought to account for most hereditary breast cancers [28].

Studies of BRCA1 and BRCA2 signaling pathways are discovering newer genes that also appear to play important roles in breast cancer susceptibility. Mutations in the cell cycle-checkpoint kinase gene (CHEK2) confer a small but appreciably enhanced risk of breast

cancer [29]. CHEK2 encodes a cell-cycle checkpoint kinase and is implicated in DNA repair processes involving BRCA1 and p53 [30,31]. The penetrance of BRCA1/BRCA2 mutations is modified by other genetic and/or environmental factors. Identification of such modifiers would help in facilitating more accurate risk assessment in carriers who face difficult clinical choices regarding prophylactic mastectomy and oophorectomy. Candidate modifiers include genes with products that are known to interact with BRCA1 and BRCA2 [32]. RAD51 is a homolog of bacterial RecA, which is required for meiotic and mitotic recombination and for recombinational repair of double-strand DNA breaks. Both BRCA1 and BRCA2 interact with RAD51 [33,34]. The presence of an SNP in the 5'-untranslated region of RAD51 (135 G-C) increased breast cancer risk by 4-fold among BRCA2 but not BRCA1 mutation carriers [35,36]. It is possible that this SNP could affect the mRNA stability and/or translation efficiency, leading to altered RAD51 protein levels. The differential effect of RAD51 polymorphism on BRCA1 versus BRCA2 mutation carriers may relate to the different pathways by which BRCA proteins function. The finding of a novel tumor suppressor gene (ANXA7) in a chromosomal region with frequent mutations/ deletions in human cancers raised important questions as to its use as a prognostic factor for the triple-negative breast cancer. Biochemically, it is found that ANXA7 codes for a membrane-associated, Ca_2^+-activated GTPase and is involved in exocytotic secretion [37,38].

Pharmacogenetic testing in practice

Research on genetic testing holds special promise to improve the health of children and adults [39]. Despite the current barriers to widespread use, pharmacogenomic testing is now used to help guide treatment for people with certain types of cancer:

Colorectal cancer: The epidermal growth factor receptor (EGFR) has become an important therapeutic target in gastrointestinal cancers, especially in colorectal cancer. Stimulation of the EGFR [40] activates at least five intracellular signal cascades such as RAS/RAF/MEK (mitogen-activated ERK activating kinase)/ERK (extracellular signal-regulated kinase) [41], PI3K (phosphatidylinositol 3-kinase)/PTEN (phosphatase and tensin homolog)/AKT (v-akt murine thymoma viral oncogene homolog) [42], STAT (signal transducer and activator of transcription), pospholipase C, and SRC/FAK (focal adhesion kinase) [43].

The proto-oncogene BRAF is important player in colon cancer genetics. BRAF functions in the MAP kinase/ERK pathway, regulating cell differentiation and division [44]. The Val600-to-Glu (V600E) mutation in BRAF, due to 1799T-A transversion in the gene, is commonly found in malignant melanoma, gastric and colorectal carcinoma, and other cancers [45,46]. Irinotecan (Camptosar) is a type of chemotherapy commonly used for the treatment of colorectal cancer [47,48]. In some people, genetic variations cause a shortage of the UGT1A1 enzyme, which is responsible for the body's metabolism (breakdown) of irinotecan. Higher levels of irinotecan remain in the body in people with lower levels of this enzyme, which may lead to severe and potentially life-threatening side effects, especially when the drug is given at higher dose levels. Doctors may use a pharmacogenomic test called the UGT1A1 test to see which patients have this genetic variation, allowing them to prescribe a lower dose of irinotecan for those patients. Often the lower dose is just as effective but less toxic in those individuals whose bodies are programmed to make the less efficient form of UGT1A1.

Acute lymphoblastic leukemia: Genetic variations in an enzyme called thiopurine methyltransferase (TPMT) are found in about 10% of children. TPMT is responsible for the metabolism of chemotherapy that is used to treat ALL. To avoid severe side effects, children with lower levels of TPMT are treated with lower doses of these drugs.

Other cancer types: Fluorouracil (5-FU, Adrucil) is a type of chemotherapy that is used to treat several types of cancer [49,50], including colorectal, breast, stomach, and pancreatic cancers. A genetic variation in some people causes them to have lower levels of the enzyme called dihydropyrimidine dehydrogenase (DPD), which helps the body metabolize fluorouracil. Doctors may use a pharmacogenomic test to detect this variation in patients, allowing them to lower the dose of the drug to avoid serious side effects in these patients.

Diabetes

Diabetes mellitus, one of the most prevalent diseases in developing world, is a metabolic disorder characterized by hyperglycemia and other metabolic alterations due to relative or absolute insulin deficiency [51-53]. It could affect more than 400 million people by 2030 [54,55].

The hepatocyte nuclear factor 4-α (HNF4α) gene codes for a transcription factor which is responsible for regulating gene transcription in pancreatic beta cells [56], in addition to its primary role in regulation of hepatic genes, HNF4α has also been implicated in the regulation of glucose transport and metabolism [57]. Disruptions in this gene can lead to maturity-onset diabetes of the young (MODY), an uncommon, autosomal dominant, non-insulin dependent form of diabetes [58,59].

Type 1 diabetes is an autoimmune disease [60]. An autoimmune disease results when the body's system for fighting infection turns against a part of the body [61]. Type 2 diabetes is one of the most important public health problems and it is characterized by insulin resistance which may be combined with relatively reduced insulin secretion. The increasing prevalence of Type 2 diabetes is mainly due to reduced physical activity and consumption of unhealthy food and larger portion sizes in genetic susceptible individuals [62]. Individuals with type 2 diabetes are at higher risk of cardiovascular diseases (CVD) [63]. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. Several classes of antidiabetics such as sulfonylureas, meglitinides, biguanides, a-glucosidase inhibitors, thiazolidinediones [64] or insulins belong to the approved drugs for patients with type 2 diabetes. The action of oral antidiabetic drugs [65] and their adverse drug reactions such as hypoglycemia are subject to wide inter-individual variability. Most oral antidiabetic drugs are metabolized with participation of cytochrome P450 enzymes of the class 2C, which is genetically polymorphic. Whereas sulfonylureas are mostly CYP2C9 substrates, CYP2C8 is the main enzyme responsible for the biotransformation of thiazolidinediones and repaglinide.

Both nateglinide and repaglinide are meglitinides, which, like sulfonylureas, act by stimulating insulin release from beta cells of the pancreas via ATP-sensitive K^+ channels and on voltage-sensitive Ca_2^+ channels [66]. For nateglinide, predominantly metabolized via CYP2C9, it could be shown that CYP2C9*3 polymorphism, but not CYP2C9*2, has a moderate impact on pharmacokinetics and pharmacodynamic effects of the drug in healthy volunteers. Furthermore, following administration of repaglinide, which is metabolized via CYP2C8, reduced plasma concentrations have been determined in carriers of CYP2C8*3 variant allele.

Biguanide metformin [67,68] belongs to oral antidiabetics widely used in overweight patients with type 2 diabetes. The mode of action of metformin may be linked to an increase of insulin sensitivity [69].

It could be shown that organic cation transporter 1 (OCT1) is mainly responsible for metformin entry into enterocytes and hepatocytes. To date, several genetic polymorphisms in OCT1, some of them leading to reduced transporter activity, have been identified. In one clinical study, carriers of at least one OCT1 variant allele, determining reduced function of the transporter, showed higher glucose levels following administration of metformin. However, before OCT1 genotyping could be established as a reliable method for prediction of clinical response to metformin, prospective clinical studies in large numbers of patients must be performed.

Cardio Vascular Diseases

CVDs are a group of disorders [70] of the heart and blood vessels and include- coronary heart disease [71], cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart and pulmonary embolism [72]. One of the major causes of CVDs is essential hypertension [73]. It appears that pharmacogenetics throws some new light on the question of treatment amendment with respect to cardiovascular diseases.

For several beta-blockers, which belong to the most often prescribed drugs in patients with cardiovascular diseases [74], possible effects of genetic polymorphisms in drug metabolizing enzymes like CYP2D6 were assessed. CYP2D6 is the key enzyme in metabolism of metoprolol and pronounced differences between CYP2D6 extensive and rapid metabolizers with respect to the pharmacokinetics of the drug have been observed. Moreover, CYP2D6 polymorphism has been shown to contribute to pharmacodynamic response following the administration of metoprolol.

Another class of drugs, AT 1 (angiotensin II type 1) [75,76] receptor antagonists (sartans), used to treat hypertension or heart failure [77], could be potential candidate for consideration of pharmacogenetic data in therapy optimization. Most sartans are metabolized with participation of genetically polymorphic CYP2C9. The genes encoding CYP2C19, CYP2C9, and CYP2D6, CYP3A4/5 [78] isoenzymes are highly polymorphic, with great allelic variation in different ethnic groups [79].

Recently, importance of pharmacogenetic implications has also been discussed for statins (HMG-CoA reductase inhibitors) [80,81], administered to lower cholesterol level in numerous patients with or at risk for cardiovascular problems. Statins are the most prescribed and most effective drugs in lipid lowering therapy but large variability in response is observed and in nearly one of three patients treatment goals could not be met. It has been reported that in patients treated with pravastatin, cholesterol lowering effects are poorer in carriers of two common and tightly linked single nucleotide polymorphisms localized in the gene coding for HMG-CoA reductase, which is the target enzyme for statin therapy.

Two polymorphic genes, *CYP2C9* and vitamin K epoxide reductase complex subunit 1 (VKORC1) [82,83], can contribute significantly to the known inter-individual variability in the effectiveness of oral anticoagulants. The role of the enzyme CYP2C9 in metabolism of the warfarin and its analogues acenocoumarol and phenprocoumon is well documented. The variant alleles with decreased enzymatic activity *CYP2C9 *2 and CYP2C9 *3* have been demonstrated to impact considerably the pharmacokinetics of S-warfarin (which is 3 to 5 times more potent than the R-isomer) and so to influence the antithrombotic activity of the drug. Patients carrying at least one variant allele, show a longer induction period to achieve a stable warfarin dosing and tend to have increased values of international normalized ratio (INR). They are also at increased risk of life threatening bleedings. Similarly, there is a good evidence for the role of *CYP2C9* polymorphism in the anticoagulation effects of acenocoumarol and phenprocoumon in the literature data. For that reason, *CYP2C9* genotyping was suggested as a useful approach to select a population of patients who are potentially at risk of complications associated with oral anticoagulants and who may require a reduced dose of the drugs.

VKORC1 is the target molecule of vitamin K antagonists and polymorphisms in *VKORC1* gene, in addition to *CYP2C9* and demographic factors seem to explain a significant part of the inter-individual variability in pharmacokinetics and dynamics of the drugs and consequently could be essential for determination of the individual dose.

Conclusion

The main aim of pharmacogenetics is to understand the role that an individual's genetic make-up plays in how well a medicine works, as well as what side effects are likely to occur in the individual's body. Understanding this can help tailor drugs in the future best suited for a particular individual (personalized medicine) or group. The small differences in the genes between different population groups, or some families within a population group that have built up over the generations can mean that they react differently to medicines.

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