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A Few Words about Pharmacogenetics

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Abstract

Pharmacogenetics deals with genetically determined variations in response to drugs. Pharmacogenetics studies interindividual differences in DNA sequence that lead to a variable response to drug therapy. The ultimate goal of pharmacogenetics is to establish treatment on the principles of the personalized medicine in which each person, i: e patient, is approached as an individual. The way to achieve this is to use molecular diagnostic methods to determine the pharmacogenetic status of the patient and to provide the possibility of adjusting the treatment to his needs.

Keywords: *Pharmacy, Genetics, Pharmacogenetics, Drugs, Medicine.*

Introduction

The history of genetic variations in drug responses is traced to the 1950s with the observations that relaxant suxamethonium chloride and medicines metabolized by Nacetyl transferase exhibit differences in response in patients [1]. One in 3500 caucasians was found to possess the less efficient variant of the enzyme, butyryl chlolinesterase that metabolizes suxamethonium chloride; an anesthetic. As a consequence, the drug's effect is prolonged with slower recovery from surgical paralysis.

The term pharmacogenetics evolved from the mix of two areas of study namely pharmacology and genetics. Pharmacology is that the study of how drugs work in the body and genetics is that the study of how characteristics that result from the action of genes acting together are inherited and the way they function within the cells of the body. Therefore, pharmacogenetics refers to genetic differences in metabolic pathways which might affect individual responses to drugs both in terms of therapy and adverse effects. Pharmacogenetics helps our understanding of why some individuals respond to drugs and others don't and why some require higher or lower doses to realize optimal therapeutic responses.

In addition, pharmacogenetic information helps the physician to identify those patients who will respond favorably to therapy or develop side effects.

The study of genetic factors determining drug response is called pharmacogenetics, and also the use of gene sequencing or expression profile data to tailor therapies specific to an individual patient is named personalized or precision medicine [2]. For instance, somatic mutations affecting the tyrosine kinase domain of the epidermal protein receptor in lung cancers can confer enhanced sensitivity to kinase inhibitors like gefitinib. This effect enhances the antineoplastic effect of the drug, and since the somatic mutation is particular to the tumor and not present within the host, the therapeutic index of those drugs are often significantly enhanced in patients whose tumors harbor such mutations. Genetic analysis can even predict drug resistance during treatment or identify new targets for therapy supported rapid mutation of the tumor within the patient.

A common misconception within the medical profession is that genetic disorders accommodate a group of extremely rare conditions that are seldom relevant to day-to-day clinical practice [3]. In fact, essentially every medical condition affecting humankind has a minimum of some genetic component to its etiology. The study of how mutations in single genes cause rare disease (genetics) is gradually being eclipsed by research on how mutations in multiple genes interact with one another and also the environment to lead to health and disease (genomics). Knowledge derived from genomic discoveries is reshaping the underpinnings of much of practice, and can still do so for many years to come. At a practical level, recent advances have taught us an incredible amount about the premise of common conditions like diabetes, heart condition, and cancer. This new knowledge is being rapidly translated into approaches for disease risk assessment, prevention, and treatment. Likewise, the study of how genes affect drug metabolism (pharmacogenetics) is being increasingly used to inform drug prescribing. Importantly, primary care physicians shouldn't lose sight of the actual fact that so-called rare single-gene disorders collectively represent a significant proportion of pediatric and adult illnesses.

Primary care physicians are during a unique position to diagnose genetic disorders because they're often the primary contact for patients and also provide take care of multiple family members. Recognition of, and subsequent attention to, the presence of genetic risk factors for disease in an individual may be lifesaving for people and their relatives. Further, as pharmacogenetics becomes increasingly important to drug therapy, primary care providers will have to be aware of and comfortable with ordering and interpreting this sort of testing prior to prescribing a spread of medications.

Principles

The basic principles of pharmacogenetics and pharmacogenomics are reviewed in depth [4]. Additionally, a more recently published primer provided a fast review of the central dogma of molecular biology, followed by descriptions on genetics, genomics and proteomics. Other topics included structure, evolution, genetic variation like SNP alleles, haplotype and linkage disequilibrium, enabling technologies (genomics, proteomics and bioinformatics), implications for gene discovery and mechanisms of human disease, therapeutic and predictive medicine, and dermatology and dermatopathology. Identifying gene clusters answerable for biological processes, the primer suggested that the individual genomic signatures would enable the practice of predictive medicine.

According to the central dogma, the genetic code is passed, through transcription, from DNA to mRNA, and subsequently, through translation, from mRNA to protein synthesis. These proteins could also be drugmetabolising enzymes, transporters, receptors, target modulators and other biomolecules involved in signalling pathways. Thus, DNA genetic variations would change the enzyme activity, transporters and receptor sensitivity. the discovery of RNA interference and therefore the emerging evidence for epigenetics have impacted on this easy relationship.

Genetics

Genetics is the study concerned with hereditary and variation [1]. One in all the foremost fundamental properties of all living organisms is that the ability to reproduce. All organisms therefore inherit the genetic information specifying their structure and performance from their parents. Within the same manner, all cells arise from pre – existing cells, therefore the genetic material must be replicated and passed from a parent to progeny cell at each cell division. The hereditary molecules that are transmitted from one generation to the next i.e. inherited are called genes. These molecules (genes) reside within the desoxyribonucleic acid (DNA) that exist within all cells. The DNA in conjunction with a protein matrix forms nucleoprotein and become organized into structures called chromosomes located within the nucleus or nuclear region of cells. The genes contain coded information for the synthesis of proteins and a few ribonucleic acids (RNA). Occasionally, a change may occur spontaneously in some a part of the DNA. This variation is named mutation and should lead to an alteration of the code designated for a specific function leading to production of a defective protein.

A mutation may result in a change within the physical appearance of an individual or change in another measurable attributes of the organism called a character or trait. Through the method of mutation, a gene could also be turned into two or more alternative forms called alleles. Each gene occupies a specific position on the chromosomes called the gene locus. All allelic forms of a gene therefore are found at corresponding positions on genetically similar (homologous) chromosomes.

Psychopharmacogenetics

Pharmacogenetics is the science of pharmacological response and its modification by hereditary influences [5]. Psychopharmacogenetics is the application of pharmacogenetics to the sphere of clinical psychiatry. These are important terms to understand due to this and future influence upon the practice of prescribing medications.

The traditional method of prescribing is to follow evidence-based guidelines based upon the client's symptoms. However, this approach doesn't address the individual response of every client. These individual responses are partially determined by genetics and also the manner within which the body metabolizes drugs. The environment, diet, age, lifestyle, and overall state of health all can influence a person's response to medications, but understanding an individual's genetic makeup is believed to be the key to making personalized drugs with greater efficacy and safety.

A large percentage of people with mental illness are nonresponders, partial responders, or toxic responders to treatment. this trial and error prescribing contributes to much personal suffering as well as cost.

Currently, the FDA reports that over 100 prescription medications (approximately 30% are psychotropics) have pharmacogenomics information on product labels. Although additional research is required for a more complete understanding of genetic influences upon drug metabolism, perhaps psychopharmacogenetics is providing an extra tool to help clinicians in selecting the right drug, for the right client, within the right dose. This approach to prescribing is usually referred to as “individualized medicine” and holds the hope of decreasing adverse effects, increasing efficacy, and decreasing cost. Perhaps in the future, most medications are going to be prescribed according to genotyping.

Variation

Variation in drug metabolism and drug response among individuals of the identical weight and on the identical drug dose is because of temporary causes like transient enzyme inhibition, induction or permanent causes like genetic mutation, gene deletion or amplification [1].

Genetic variability is known to affect drug absorption, drug metabolism and drug interactions with receptors. These therefore form the idea for slow or rapid drug absorption, poor, efficient or ultrarapid drug metabolism and poor or efficient receptor interactions.

Consequences

The underpinning factors for the growing importance of pharmacogenetics are the need to stop adverse drug reaction, obtain maximum benefits from drug therapy and reduce therapeutic failure [1].

Pharmacogenetics will therefore permit gene profiling to answer questions on drug responses and promote the design of better and safer drugs. additionally, individualized dosing has the potential of better therapeutic outcome. Therefore, pharmacogenetics is expected to revolutionize drug dosing and therapy. However, there are still many challenges to overcome. These include cost implications, standardization, quality control of testing, and relevance of biomarkers and tests. Nevertheless, the appearance of pharmacogenetics and establishment of guidelines by regulatory bodies like Food and drugs Administration (FDA) European Medicines Agency (EMEA) and American Association of Clinical Chemists (AACC) are expected to impact individualized dosing of the many drugs.

CVD

Pharmacogenetics is the study of variations in DNA sequence as associated with drug response (European Medicines Agency [EMA]) [6]. Several gene-drug interactions are discovered within the field of cardiovascular diseases (CVDs). These gene-drug interactions can help to identify nonresponse to drugs, estimate dose requirements or identify an increased risk of developing adverse drug reactions. An individualized approach supported pharmacogenetic testing will provide physicians and pharmacists with tools for deciding about pharmacotherapy. While pharmacogenetic testing is already a part of everyday practice in oncology, it's not widely implemented within the field of CVDs. However, within the near future, pharmacogenetics will probably also play a valuable role in this field as well.

Prophylaxis and treatment of CVD is complex. Patients often have quite one cardiovascular risk factor (e.g., hypertension and hypercholesterolemia) and/or CVD, or other comorbidities like diabetes. Frequently, quite one drug is used by the patient and this might potentially cause serious drug interactions with adverse health outcomes. Therefore, not only the comorbidities but also the interaction between co-medications should be taken under consideration if a pharmacogenetics-based dosing strategy is developed.

Cardiovascular drugs are widely used for prevention or treatment of CVD. Gene-drug interactions were demonstrated within the treatment with platelet inhibitors, anticoagulants, antihypertensive drugs and statins. The findings of the numerous studies that are conducted on pharmacogenetics of antihypertensive drugs, aren't suitable for clinical implementation, actually because the results couldn't be replicated or the clinical relevance was low. the foremost commonly pharmaceuticals within the management of CVD with important gene-drug interactions are statins, clopidogrel and coumarin derivatives.

Alcoholism

Alcohol could be a psychoactive (mind-altering) chemical that, like heroin and tranquilizers, depresses the CNS (central nervous system) [7]. It's an efficient tranquilizer with the flexibility to reduce short-term anxiety. However, alcohol first affects the a part of the brain that controls inhibitions: Drinkers talk more, exude self-confidence, and will get foolish or maybe rowdy; there's a general loss of self-restraint.

Alcohol could be a complex substance that affects variety of neurotransmitter and receptor systems within the brain: endorphin, dopamine, serotonin, and glutamine. When alcoholics imbibe, their brains release elevated levels of endorphins, triggering rewarding sensations that entice the person to drink more. However, at low doses, alcohol acts as a stimulant, and initially, the user of alcohol often experiences it as an energizer with euphoric effects. like most other psychoactive substances, this is often the results of alcohol stimulating the dopaminergic reward pathway within the brain.

Regular use of moderate daily amounts of alcohol can produce psychological dependence, the lack of alcohol leading to anxiety and mild panic attacks. Prolonged or chronic drinking produces both psychological and physical dependence. The stronger depressant effect lasts about two hours, while a weaker stimulation of the CNS lasts about six times as long. because the time since the last drink increases, the longer-lasting stimulating effect becomes dominant, and also the drinker becomes agitated—the "morning-after hangover." this is often the beginning of the drinker's withdrawal syndrome. due to alcohol's primary depressant effect, calm is temporarily restored by more drinking. For the alcoholic the morning drink encompasses a calming effect that's a part of a positive feedback of continued alcohol use.

At age 65, the body's ability to reply to alcohol is quite different from that at age 45. Thus, older adults can get into trouble after drinking an amount of alcohol that will not be considered immoderate at a younger age. As people age, they lose muscle, bone, and lean body mass and acquire a greater percentage of body fat. As a result, there's a decrease in body water, during which alcohol is soluble, replaced by fat, within which alcohol isn't soluble. Aging also leads to a decline in a very stomach enzyme that breaks down alcohol before it reaches the bloodstream. As a result, there's greater burden on the liver, where most alcohol metabolism takes place. Advancing age also causes a decline within the blood flow through the liver, so alcohol is eliminated more slowly from the blood. Thus, blood alcohol levels in older people are 30–40 percent above those in younger people.

Alcoholism could be a complex relapsing disorder of heterogeneous etiology, affecting people internationally [8]. Alcohol dependence could be a cumulative response of inability to prevent drinking, craving and developing the symptoms of physical dependence and tolerance. In past few decades, mounting evidence has suggested that alcoholism or inebriation may be a host of major psychological, social, financial and health problems. in step with World Health Organization, alcoholism is liable for 4% of world disease burden and is that the third major preventable risk factor for premature death and disability in developed nations. Although, the exclusive biological mechanisms underlying the development of alcoholism are still uncertain, the foremost risk factors contributing towards the development of alcoholism are age (adolescents are at higher risk of developing alcoholism), gender (men are more prone to develop alcoholism as compared to women due to depression), personality (experience seeking), and psychiatric or behavioral disorders. The prevalence, age of onset, clinical symptoms and outcome of alcoholism differs from individual to individual and varies consistent with ethnicity. additionally, to the present, lower social status and low education have also been found to be related to alcoholism in cross sectional and longitudinal studies.

Genetic factors are found to play a critical role within the etiology of alcoholism. Researchers have suggested that 50-60% of alcohol dependence is set by genetics. supported results of adoption, twin, and family studies it's now clear that the vulnerability to alcoholism is set by genetic factors also as by environmental factors. However, it's difficult to work out the individual determinant of alcoholism. The candidate gene approach has revealed variety of biomarkers, which are accountable for alcoholism. Certain variants of alcohol dehydrogenase and aldehyde dehydrogenase genes (genes encoding for alcohol metabolizing enzymes) are found to change the metabolism of alcohol during a dramatic way. additionally, to the current, polymorphisms in neurotransmitter genes (target receptor genes) like gamma amino saturated fatty acid and opioid receptor genes have also been reported to be related to marked risk of alcohol dependence. Current treatment approaches to alcoholism are moderately effective with perhaps as many as half the patient's receiving treatment because of abstinent or significantly reducing episodes of binge drinking.

Drug Effects

Drugs are the cornerstone of recent therapeutics [9]. Nevertheless, it's well recognized among physicians and among the lay community that the end result of drug therapy varies widely among individuals. While this variability has been perceived as random, and thus inevitable, accompaniment of drug therapy, this can be not the case.

Drugs interact with specific target molecules to provide their beneficial and adverse effects. The chain of events between administration of a drug and production of those effects within the body will be divided into two important components, both of which contribute to variability in drug actions. The first component comprises the processes that determine drug delivery to, and removal from, molecular targets. The resultant description of the connection between drug concentration and time is termed pharmacokinetics. The second component of variability in drug action comprises the processes that determine variability in drug actions despite equivalent drug delivery to effector drug sites. This description of the connection between drug concentration and effect is termed pharmacodynamics.

Unusual drug responses, segregating in families, are recognized for many years and initially defined the field of pharmacogenetics. Now, with an increasing appreciation of common polymorphisms across the human genome, comes the chance to reinterpret descriptive mechanisms of variability in drug action as a consequence of specific DNA polymorphisms, or sets of DNA polymorphisms, among individuals. This approach defines the nascent field of pharmacogenomics, which can hold the chance of allowing practitioners to integrate a molecular understanding of the idea of disease with an individual's genomic makeup to prescribe personalized, highly effective, and safe therapies.

Pharmacogenetic research can aid within the development of optimal drugs, i.e., drugs with higher efficacy and lesser side effect potential [10]. Furthermore, the applying of pharmacogenetics has been found to expedite the method of drug discovery and development. The spectrum of pharmacogenetic application in drug discovery and development stretches from drug target identification, through selecting favorable subpopulation for clinical trials, choosing appropriate doses and their modifications, assessing the trial results based on the pharmacogenetic data, and, finally, to imparting necessary drug label changes after regulatory approval. Utilization of the large genomic knowledge, available currently, had broadened the scope of developing drugs exclusively for a selected subset of population with distinct genetic profiles. as well known, the branch of oncology has its strong foothold within the application of genomic medicine. Currently, however, there are other therapeutic areas including hematology, endocrinology, and cardiovascular systems which are garnering rapid pace in pharmacogenetic application. Nowadays, world over, the gamut of pharmacogenetics is very well integrated within the drug regulatory review process and deciding in patient selection and clinical trial design. a significant ethical issue because of the application of pharmacogenetics in drug research can be the event of "orphan genotypes," i.e., drugs being developed just for populations with certain genotypes whereas the opposite nonresponding genotypes are abandoned without access to potential pharmacotherapeutics, thus violating one amongst the essential principles of medical ethics, namely, the principle of equality.

Conclusion

Pharmacogenetic differences (e.g., acetylation, hydrolysis, oxidation, or other enzymatic activities) have clinical implications. For example, people who break down certain drugs quickly need higher and more frequent doses to achieve therapeutic levels, and people who break them down more slowly need lower and less frequent doses to avoid toxicity, especially when it comes to drugs of low therapeutic range. Most genetic differences, however, are unpredictable. In addition, many environmental and developmental factors can interact with each other and with genetic factors and thus change the therapeutic response. Each person responds individually to the drug given to them and the only way to determine what that reaction will be is to analyze genes that are crucial for drug metabolism, its transport in the body, binding to receptors or some other mechanism. In addition, this diagnostic procedure is crucial for the huge savings in the health care system associated with prescribing medications as well as the consequent treatment of complications caused by drug side effects.

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