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GENES, CAN IT AFFECT BODY RESPONSE TO MEDICINES? AN UNDERSTANDING OF THE CONCEPT OF PHARMACOGENETICS

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Abstract
It has become increasingly evident that diagnostics, pharmacogenetics, and pharmacogenomics are likely to converge in the near future. Although medical science is evolving rapidly, the identification of DNA alterations appears poised to remain a central component of future medical practice. The gradual transition from studying single genes or variants to analyzing multiple genes-or even entire genomes-has finally begun to demonstrate clear benefits.
The development of broad, high-throughput gene-screening technologies, along with the economic potential associated with pharmacogenetics and pharmacogenomics, has attracted significant interest from pharmaceutical companies. With the rapid expansion of genetic data, the individualization of treatment can be confidently anticipated, although it may not occur in the immediate future. Considerable work is still required, including advancements in analytical technologies, global acceptance of these approaches, and solutions to production and implementation challenges. Progress in genomic research will continue to support the rapid development of diagnostic and therapeutic products that rely on genetic information. Pharmacogenetics aims to improve patient health and quality of life by identifying individual genetic variations. Its initial goal is to detect disease-associated genes and classify patients into responders and non-responders for specific drugs. This classification provides a valuable foundation for linking genetic variation to phenotype-specific drug responses. Ultimately, pharmacogenetics and genetic testing for drug response offer promising opportunities for the future of personalized medicine, with the potential to significantly improve patient outcomes and overall quality of life.

Keywords: Pharmacogenetics; Pharmacogenomics; Personalized Medicine; Genomic Diagnostics; High-Throughput Screening; Genetic Variability.

Introduction
Cells are microscopic structures, as typically eukaryotic cell is about 10 to 100 micrometers (μm) in diameter, though some exceptions also exist. It was not seen until the 17th century when the microscope as first invented. Cells were first noticed under microscope in 1665 by the English natural philosopher Robert Hooke; although he calls it cork cellulae which is a Greek word means small rooms [1]. Cells were also called "animalcules," or little animals by the Dutch Anton van Leeuwenhoek, a microscopis who considered of the first people who managed to see the cell as we know it today under microscope [2]. It was not until 1839, when the cells acknowledged as thethe anatomical and functional units of living organisms by the German physiologist Theodor Schwann who depicted that all animals bodies consist of tissues which compose cells as their main components [3, 4]. Cells could either exist alone or in a groupin what is known as multicellular organisms. In general, there are two type of: eukaryotic, which can be either be single-

celled or multicellular and prokaryotic a single-celled organisms, as the first contain a nucleus, while the second type does not [1,3].

The word eukaryotic means true nucleus as these cells are characterized by the presence of a membrane-bound nucleus and another compartment bound to a membrane called organelles means little organs, as each of it has specialized functions in the cells [3,4].

Cell content

The components of a typical human body cell consist of main parts and supported parts which are related to its function. Main parts include each of the followings:

The plasma membrane

It is a bilayer phospholipid membrane.Separates internal cellular metabolic events from the external environment, it also and act as the controller of the materials moving in and out of the cell, such as proteins distribution throughout the phospholipid membrane, which might also attachedto the surface of the membrane, or they may extend into the membrane.

Proteins in the plasma membrane play vital roles such as being an ion channels for ions to cross the membrane. These ion channels also known as gated channels in nerves and muscles, it allow the passage of specific ions (such as Na+ and K+) when being opened and closedas a response to specific chemical or electrical stimuli.

The selectivity of the phospholipid membrane allows onlyhydrophobic molecules (nonpolar molecules like O2, CO2, and lipid-soluble molecules such as hydrocarbons) and small, uncharged, polar molecules (such as H2O) to pass across the membrane.

The stability of plasma membranes can be achieved mainly through cholesterol molecules that distributed throughout the phospholipid bilayer membrane. It helps in controlling the firmness and flexibility of the membrane at higher and low temperatures respectively [5].

The Cytoplasm

Cytoplasm consists of organelles suspended in the gel-like cytosol, the cytoskeleton, and various chemicals. Water forms about 70 to 80% of cytoplasm, while the rest of the percentage comes from the protein which gives the semi-solid consistency in it. In addition to protein, many other organic molecules also found in the cytoplasm, such as glucose and other simple sugars, amino acids, nucleic acids, polysaccharides, fatty acids. There are also ions of potassium, sodium, calcium, and many other are also dissolved in the cytoplasm. All cellular content between the plasma membrane and the nuclear envelope, are located within the cytoplasm. Many metabolic reactions also occur in the cytoplasm [6].

The Nucleus

The nucleus is the most projecting organelle in a cell. It contains the cell's DNA in the form of chromatin through which the synthesis of ribosomes and proteins can be directed. The double-membrane structure surrounded the nucleus and constitutes the outermost portion of itknown as the nuclear envelope which is a phospholipid bilayers.The nuclear envelope contain pores through which the passage of ions, molecules, and RNA between the nucleoplasm and the cytoplasm can be controlled. Within the nucleus a structures called chromosomes are exist which are made up of DNA (the hereditary material) and proteins. This combination of DNA and proteins is called chromatin. The number of chromosomes in the nucleus is different between species. In human's cells, thereare 46 chromosomes that can only be visible and distinguishable from one another during cell division, as the DNA condenses or compacts in preparation for cell division [7].

Other Part

Cells also contain some important other contents including ribosome, endoplasmic reticulum, Golgi apparatus, lysosomes, mitochondria,vesicles and vacuoles and flagella and cilia, which each have it main function in the cell that the cell cannot overcome it [4,5].

DNA structure

DNA, abbreviation of deoxyribonucleic acid, organic chemical of complex molecular structure that is found in all prokaryotic and eukaryotic cells and in many viruses. DNA codes genetic information for the transmission of inherited [6].

Each DNA strand is cosist of a long chain of monomernucleotides, which itself consist of a deoxyribose sugar molecule with a phosphate group attached to and one of the four types of nitrogenous bases: two purines (adenine and guanine) and two pyrimidines (cytosine and thymine). Acovalent bondsjoined the nucleotides formed between the phosphate of one nucleotide and the sugar of the next, forming a phosphate-sugar backbone from which the nitrogenous bases protrude. The two strands are holding together by hydrogen bonds between the bases; the sequencing of this bonding is specific-i.e., adenine bonds only with thymine, and cytosine only with guanine [6]. DNA is vital for all living beings. The role it plays in inheritance, genetic instruction guide for life and coding for proteins. It holds the instructions for each cell's development, reproduction and ultimately death [7].

Genomes

Like the genomes of all other living animals, the human genome is a group of long polymers of DNA bound together. The ability of thegenome to replicate, repair, package, and otherwise maintain itself are all conserved through the very specific sequence, organization and structure of these polymers, and also the chemical modifications they contain which provide the machinery needed to express the information held within the genome. The genome is essential for the survival of the human organism; without it no cell or tissue could live beyond a short period of time, such as red blood cells (erythrocytes), which live for only about 120 days, and skin cells, which on average live for only about 17 days,

must be renewed to maintain the viability of the human body [8].

- A chromosome consists of smaller segments called genes:Chromosomes are very long structures consisting of two DNA polymers, joined together by hydrogen bonds connecting complementary base pairs. A chromosome is divided into segments of double-stranded DNA called genes [9].
- Each gene is further divided into three nucleotide sub-segments called codons. A codon is a segment (or piece) of double stranded DNA that is three nucleotides long. A gene can be thought of as many three-nucleotide codons strung together [10].

Genes

Genes are made up of DNA. It is considered as the basic physical and functional unit of heredity. Some genes act as a guide for proteins building. Yet, many genes do not code for proteins. In humans, genes size is vary from a few hundred DNA bases to more than 2 million bases. It was estimated that humans have between 20,000 and 25,000 genes [11].

Every person has two copies of each gene, one inherited from each parent. Genes are mostly the same in all people;however, a slight difference between people could be identified in a small number of genes (less than 1 percent of the total). These small differences are suggested to be due to theunique physical featuresof each person [11].

Scientists give genes unique names in order to be able to track it, and because gene names can be very long, so, a assigned symbols could be used when refer to genes, which are short combinations of letters (and sometimes numbers) as an abbreviated version of the gene name. For example, a gene on chromosome 7 that has been associated with cystic fibrosis is called the cystic fibrosis transmembrane conductance regulator; its symbol is *CFTR* [11]. New genetic materilas can be acquired in animals via hybridization and subsequent introgression [12].

Gene duplication is considered as important foundations of novel gene functions. But, more often, a duplicate gene maybecome a pseudogene through losing its function. However, it was recently suggested that about 50% of all gene duplications will lead to functional divergence [13].

Gene Transcription

Is the process of genes copying into different types of RNAs, such as messenger RNA (mRNA) which is the early stage of protein synthesis through translation, or noncoding RNA such astransfer RNA (tRNA), micro RNA (mRNA), and ribosomal RNA (rRNA). To start the transcription, a transcription bubble must be formed at the site of the DNA which contains the gene of interest. It is a region of opened-up DNA , which is formed as a result of DNA unwinding near the gene that is getting transcribed.

Transcription is the first step of gene expression. During this process, the DNA sequence of a gene is copied into RNA 14).

During Transcription one of the two exposed DNA strands is used as a template; and called the **template strand**. The RNA strand is complementary to the template strand and is almost identical to the other DNA strand, that called the **nontemplate** (or **coding**) **strand**. Yet, there is in the newly made RNA strand, the T nucleotides are all replaced with U nucleotides. If the transcribed gene is encoding a protein, so the RNA strand will be then translocated to the ribosome in the cytoplasm for translation process to take place which will be ended by producing the protein that the gene encoding for [14,15].

Genetic variations, where it is come from?

Genetic variationis the variation in alleles and genes, both within and among populations. It is generated by the mutational process,which can create entirely new alleles in a population, random mating, random **fertilization**, and recombination between homologous chromosomes during meiosis (which reshuffles alleles within an organism's offspring).

Nevertheless its persistence in the genome is determined by different historical and genomic factors. Some of these factors leave an imprint on sequence variation across the whole genome; others only influence local patterns of variation.

Genetic variation within a species can result from a few different sources. Mutations, the changes in the sequences of genes in DNA, are one source of genetic variation. Another source is gene flow, or the movement of genes between different groups of organisms. Finally, genetic variation can be a result of sexual reproduction, which leads to the creation of new combinations of genes [16,17].

Genetic Disorders

Genetic disorders are of different types [11].

A. Chromosomal disorders. These are identified bykaryotyping, e.g. 21 trisomy.
B. Single gene defect, sometimes identified bybiochemical methods, e.g. phenylketonuria.
C. Mitochondrial abnormalities.
D. Multifactorial disorders [11].

Mutations

i. A mutation is a change in DNA nucleotidesequence. The change either includeslarge areas of chromosome or a few nucleotides only.
ii. Mutation may be also known as an unexpected origin of new characterspontaneously.
iii. Statistically, one mutation takes place in every 106 cell divisions [11].

Causes of Mutations

Errors in DNA Replication

Rarly, DNA polymerase will integrate a non-complementary base into the daughter strand. This would lead to a mutation during the next round of replication. This, however, is very rare, as the exonuclease enzyme that work by cleaving nucleotides one at a time from the end of a polynucleotide chain, act as a proofreading mechanism recognizing mismatched base pairs and excising them [18].

Errors in DNA Recombination

DNA often rearranges itself by a process called recombination.DNA recombination is the exchange of DNA strands in order to produce new nucleotide sequence arrangements. Recombination occurs typically, between regions of similar sequence, or could be of different sequences also, by breaking and rejoining DNA segments. This process is vital for generating genetic multiplicity and for maintaining genome integrity. DNA recombination isccur throughdifferent mechanisms. Infrequently DNA lost during replication would lead to a mutation [19].

Chemical Damage to DNA

Many chemical mutagens, such as exogenous, man-made, or environmental mutagens ,chemotherapeutic drugs and intercalating agent drugshave the ability to damage the DNA.

Radiation

Different types of radiation such as Gamma rays,UV light, X-rays, can cause chemical damage to DNA via interacting with cell compounds and generating free radicals [18, 19].

Drug Response

Variability in the human drug response

There is a wide variety in patient response to drug administration. This situation is well noticed in case of drugs of low therapeutic ratio, means that the toxic and the therapeutic doe is very close, as the dose that could not even therapeutically affect one patient, could be toxic to other one.Such differences can be indicated clinically by quantitative measurements.

In these, variability is expressed either as differing responses to the administration of a pecificdrug dose or, more accurately, differing doses necessary to produce a defined pharmacological effect [20].

Theoretically, differencesin a body tissue response to specific drug administration could be due to two main reasons:

- ✓ **First:** differences indrug concentrations reach the tissue.
- ✓ **Second**: differences in tissue response to the particular drug concentration.

Generally, variability risesfrom differences in rates of drug absorption, distribution, metabolism and excretion between individuals.Changes of any of these factors could lead to changes in the rest of the factor ultimately [20,21]. The way an individual may respond to a drug is affected by many factors, including

- Genetic factors
- Patient age
- Weight: large person generally needs more of a drug than a smaller person for the same effect.
- Use of other drugs and dietary supplements (such as medicinal herbs)
- Food consumption
- Health status (such as kidney or liver disease)
- Status of drug storage (the drug was stored too long or in the wrong environment)
- Development of drug resistance or drug tolerance(20).

How does genetics affect our body response to a drug?

As mentioned above, genetic construction of our bodies could affect our body respond to a specific drug in a specific concentration. In addition to the variability in drug response between individuals due to differences in the levels or functions of absorption, distribution, metabolism or excretion (pharmacokinetics) [21]. There are also the differences in drugs effect on target protein (receptor) or downstream protein signalling (pharmacodynamics) between individuals.

The study of dissimilarity of drug responses under genetic control is known as pharmacogenetics. Pharmacogenetics focuses on the impact of **single genes differences** on drug response. While another close term Pharmacogenomics takes a widermeans and include the influence of the **whole genome of an individual** on body response to drug therapy [22].

As previously mentioned, DNA nucleotide sequence could be changed during mutations. Single nucleotide polymorphisms (SNPS) (variation occur in DNA sequence when a **single nucleotide** adenine (A), thymine (T), cytosine (C), or guanine (G]) in the genome (or other shared sequence) differs between members of a species or paired chromosomes in an individual) are very common(23). SNPS could lead to a change in the function or in the level of expression of the protein that corresponding to this specific nucleotide sequence. However, SNP not always accompanied by protein changes as the fact that there is more than one codonfor each amino acid, so a change in one nucleotide does not always change the amino acid coded by the codon, leaving the structure of the coded protein unaltered [24].

Polymorphisms could on the other hand be beneficial, during heterozygotes involvement in some selective advantage which is called balanced polymorphism.It is anticipated that by outlining an individual's DNA sequence from a blood sample, physicians will be able to select a drug that will have the therapeutic effects without the adverse effects [21].

Pharmacogenetics in cancer therapy and the concept of targeted medicine

It was previously suggested that about half of all adversative drug reactions occur as a result of polymorphic genes expression. Of the therapeutic lines that always facing such issues is the anticancer drugs which have a very low therapeutic index. Toxicities of life threatening type is widely seen in cancer patients treated with the maximal tolerated doses of anticancer agents, this is mostly occur due to specific polymorphisms in genes encoding target proteins or drug metabolizing enzymes that been acquired genetically (24). Such polymorphisim in cancer patient could include but not specific to:

a) TPMT gene (thiopurine S-methyltransferase)leading to thiopurine toxicity [25].
b) Dihydropyrimidine dehydrogenase gene resulting in adverse reactions to 5-flourouracil treatment [27].
c) Thymidylate synthase gene giving rise to 5-flourouracil treatment failure [26].
d) Genetic variation in ABC transporter genes (ATP-binding cassette) such as MDR1 and BCRP can affect cancer risk and clinical outcome to anticancer agents [27].

So, a comprehensive characterization of all genetic polymorphisms in the human genome ogether with a consideration of thepart that each of these polymorphism played clinically should enhancethe selection of the type and the dosage of cancer chemotherapeutic drugs for each patientspecific treatment regimens, which is also known as target medicine.

Obstacles facing targeted medicine

There are a number of potential obstacles to be addressed in our pursuit of targeted medicine.

The next generation sequencing platforms will be needed to accelerate the identification of rare SNPs and from that being able to grow the SNP database, and by that will be possible to accurately classify alleles linked to specific side effect of any given drug. However, the high cost of genome scanning using this technology about $1000 per genome would affect the possibility of applying such technique [28]. Since increasing the number of patients in pharmacogenetic studies is always important to increase the strength of the statistics in terms of the number and types of polymorphisms recorded for each drug responses in the clinical setting. This would also associated with the high cost issue of the as sequencing for genotyping and would render the possibility of using such life changing technique in the near future [28].

Another factor of a major importance is the cancer health inequalities, which can be explained by the fact that for example African Americans have a higher incidence and/or mortality for breast, lung, prostate and colon cancers compared to white American. For at least some of these cancers, these differences were not able to be understood even when taking in considerations the cultural, socioeconomic and health care differences [29]. It is believed that biologically thesedifferencescould be due to the type of polymorphisms exist in in genes seems to be different between the different genetically associated group of people than others, as in case of white and African American [29].

Conclusion

The effect of deviation in genes which act as a code for drug targets protein and for the enzymes involved in drug metabolism has emphasized the importance of looking at the genetic component of drug response. Studying of the drug response can be accompanied by the genetic variation, or what is known as pharmacogenetics, is similar to the study of complex genetic disease in the examination approach in terms of the questions need to be answered and the analysis of the possible causes. For example, as DNA variants are associated with specific disease susceptibilities, so will they be associated with individual response to certain drugs?, is one of the questions that need to be answered by pharmacogenetics. The testing for drug response are now following the same direction as the inherited disordersgenetic testing, and now at the stage of replacing the analysis of single genes with genome-wide analysis.

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Conflict of Interest

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