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REVIEW

Pharmacogenetics and pharmacogenomics: origin, status, and the hope for personalized medicine

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Pharmacogenetics arose with studies of single genes, which had major effects on the action of particular drugs. It turned into pharmacogenomics through realization that the controls of most drug responses are multifactorial. Then, variable gene expression posed new problems, for example what do drugs do to genes, or how useful is any genetic pretesting of a person? A common disease may be caused by different groups of genes in different people, who therefore require different drugs for treatment. Personlized medicine is currently represented by a physician's attention to a patients age, sex, or ethnic backround, that is groups showing smaller genetic variation than is typical for general humanity. Occasionally, there is also the use of single-gene pretesting of a patient before drug administration. Over time, improvements in multigenic testing promise to increase the role of personalized medicine. However, the many pharmacogenomic complexities, and particularly time-dependent changes of gene expression, will never allow personalized medicine to become an error-free entity.
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Pharmacogenetics and pharmacogenomics are two disciplines with overlapping aims, the latter newer and broader than the former. A search of PubMed revealed more than 3000 hits for pharmacogenetics between 1961 and 2005. For the year 2004, 538 publications were counted with 'pharmacogenetics' as search word, and 2503 publications using 'pharmacogenomics' as search word. The number of publications indicates that these are disciplines of broad interest, and that particularly the interest in pharmacogenomics has greatly risen in recent years. The interest is probably still increasing because of the potential beneficial effects of these sciences on medicine and therapeutics, effects which will be analyzed later in this chapter.

Pharmacogenetics

Let me provide a brief history of pharmacogenetics. Its coming was foreseen by Sir Archibald Garrod[1] in his 1931 book 'Inborn Factors in Diseases', and in 1949 by JBS Haldane,[2] who predicted the occurrence of unusual reactions to drugs on the basis of biochemical individuality. Some early, isolated observations presaged the arrival of the area of pharmacogenetics. These were inborn variation of tasting capacity[3] for phenylthiocarbamide (PTC) in 1932, of drug-induced

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porphyria in 1937,[4] and of genetic variation of atropine esterase activity in rabbits[5] in 1943. During the Second World War, it was found that the antimalarial drug primaquine produced hemolytic disease in American soldiers, but only when they were of African descent; a genetic basis was revealed later.[6,7]

Late in the 1950s, pharmacogenetics became a recognized science. The genetic lack of butyryl-cholinesterase ('pseudocholinesterase') in patients who had died following a succinylcholine injection during anesthesia was reported in 1956.[8] The genetic deficiency of *N*-acetyltransferase, an enzyme that destroyed the important antituberculosis drug isoniazid, was described in 1957.[9] All these observations stimulated the 'Council on Drugs of the American Medical Association' to ask Dr Motulsky[10] to summarize and publish all available data (1957). In 1959, Vogel coined and published the word 'pharmacogenetics'.[11] I was already working to summarize all pertinent observations in a book that appeared in 1962.[12]

Key events that created interest in pharmacogenetics in the clinic were the discoveries of genetic variation of the metabolism of debrisoquine[13] (based on Dr Smith's, the author, personal suffering,[14]) and of sparteine;[15] subsequent observations revealed that functional absence of the cytochrome liver enzyme CYP2D6 was responsible for both deficiencies, and that this enzyme was responsible for the metabolism of approximately 60 drugs.[16] As recently described,[17] detailed studies revealed that there were many different genetic changes of the enzyme, which altered its functional characteristics. For instance, the enzyme could be completely inactive, or some variant would selectively not metabolize a particular drug, which was normally metabolized by the enzyme; regulatory variants may lead to a large increase of an enzyme's activity. At present, at least 42 drug-metabolizing enzymes are known to be genetically variable.[18] Other important determinants of a drug response are genetically variable. They include drug receptors (e.g. for dopamine, serotonine, or *N*-methyl-D-aspartate),[19] transporters (e.g. *P*-glycoprotein)[20] and neurotransmitter enzymes (e.g. COMT, MAO).[21]

An important milestone of pharmacogenetics occurred when it became clear that drug effects tended to differ not only between individuals, but also between human populations.[22] A study of the metabolism of a barbiturate in a mixed student population surprisingly revealed an enzymatic deficiency only in students of East Asian descent, and thereby initiated many further investigations.[23] For instance, the metabolism of debrisoquine is on the average slower in Africans and in Chinese than in Europeans, but on the other hand, the enzyme is absent in about 7% of Europeans, but is only 1% or less in the other races.[18] The deficiency of alcohol metabolizing capacity[24] in East Asians reduces the frequency of alcoholism in these populations.[18] As mentioned above, only Africans were poisoned by primaquine. In principle, a difference may consist of a different frequency of a given variant in two populations, or the type of variant may differ, often leading to the structural difference of a protein.

Most of these pharmacogenetic studies were investigations of pharmacological consequences of single gene mutations. However, it seems that most differences of drug responses between people or populations are not caused by the mutation of a single gene, but by the altered function of numerous genes, and by environmental factors, often interacting. That is, most variable drug responses appear to be 'multifactorial'. This realization led to the rise of interest in pharmacogenomics, a rise paralleled by the expansion of genetics into genomics.

Pharmacogenomics

Pharmacogenomic investigations require an increased use of methods designed to study many genes or gene patterns, that is to look simultaneously at the structure and expression of whole sets of genes. Such methods include high throughput sequencing technologies[25] like MALDI mass spectrometry,[26] SAGE,[27] microarrays,[28] linkage and haplotype analysis.[29] This brief review will not further deal with methodologies; there are many specialized reviews (e.g. [30]).

The growth of pharmacogenomics was much stimulated by the realization that gene expression may be changed by mRNA[31] and thus is variable. That is, the amount of a gene may change, changing its transcribed protein in a tissue, thereby changing the gene's functional impact.[32] Gene expression may be altered by innumerable factors. One gene product may increase or decrease the expression of others,[33] there may be epigenetic changes[34] or the expression may be changed by environmental factors. These latter include sleep,[35] emotions,[36] exercise,[37] diet[38] or drugs.[39]

Since gene function is variable, genetic control of any living system is more complex than was initially perceived. Life requires collaboration and interaction of many genes. It has been claimed that the square of a number of protein-producing genes is necessary to properly control their collaborative functions.[40]

In the context of this paper, changes of gene expression by drugs deserve special consideration: Whereas pharmacogenetics dealt with the fact that there are genetic alterations of drug responses, pharmacogenomics also deals with drug-induced alterations of gene function. Such alterations explain a few cases, which have long been known. For example, regular intake of a drug may increase the expression of the gene that controls its drug-metabolizing enzyme;[39] addiction to a drug is the consequence of a drug-induced change of some brain protein.[41]

Unreliability of a drug when used to treat a common disease is not necessarily a result of classical pharmacogenetics, pharmacogenomics or environmental variation.[42] There may be a different kind of genetic problem: Most noninfectious diseases (e.g. cardiovascular, renal, mental diseases, or diabetes and some cancers) are multifactorial and have complex genetic causes.[43] It therefore happens that a clinically similar-looking disease in two people is controlled or caused by different genes. Consequently, if the drug therapy is effective by controlling the underlying

genetic cause of the disease, effective treatment of the disease in these two people may require different drugs; in short, the drug target may depend on genes. As a consequence, some pharmacogenomic studies require a concurrent investigation of disease-causing genes, a task also often performed in general genetics or genomics.

Personalized medicine

A physician may be confronted by a problem when therapeutic drug use shows a lack of reliability of response: A drug may help one person but not another with the same need, or a generally safe and useful drug has toxic side effects in some subjects and occasionally is even fatal. The many potential causes may include age, weight, sex or other concurrent diseases; these factors are routinely considered by a physician when treating a patient. However, pharmacogenetics and pharmacogenomics have taught us that many altered drug responses depend on the genetic constitution of the recipient.[12,44,45] Hence, the question arises whether knowledge of a patient's genes can be used to improve the choice of drug to be administered, thereby avoiding at least some undesirable pharmacological effects. The term 'personalized medicine' has been coined in the hope of creating collaborative uses of drug therapy and genetic knowledge.[46] It represents the seemingly straightforward thought that the choice of drug for treating a given subject may be improved by considering the patient's genetic make-up; however, the frightening complexities on the way to that aim will not allow us to reach it quickly.

Nevertheless, there are some partial settlements. Clinical utilization of the pharmacogenetic sciences has developed in parallel to the development of medicine (and also has helped the development of these sciences). For example, if a drug is known to be metabolized by a genetically variable enzyme, abnormal effects of the drug can be avoided by pretesting this enzyme in a patient,[47] and by giving the drug only when the patient's enzyme activity is normal, or by reducing the drug dose if the activity is low. Such pretesting is usually not performed when the drug is known to be generally safe and not to produce serious side effects. Thus, genetic pretesting of a patient is not a clinical routine.

The situation is different when the drug is potentially quite toxic. For instance, the enzyme thiopurine-methyltransferase (TPMT) metabolizes the immunosupressive drug azathioprine (used e.g. to treat Crohn's disease).[48] If the drug is not so metabolized because the enzyme is lacking, the drug is converted to a toxic thioguanine nucleotide. Hence, TPMT activity is clinically always tested before azathioprine administration. Various other tests are potentially useful and are occasionally but not regularly used. For instance, metropolol tends to cause bradycardia when the cytochrome CYP2D6 is missing,[49] or there is a relationship between warfarin-induced bleeding events and CYP2C9 activity,[50] or isoniacid causes unpleasant effects when *N*-acetyltransferase activity is lacking.[51] Thus, some cases of clinical usefulness of pharmaco-genetics and -genomics are well established.

In short, genetically personalized medicine can be practised only when effects of single-gene mutations are considered. However, as briefly indicated above in the section on Pharmacogenomics, there are many different ways by which genetic factors can influence the response to a drug. We are far from understanding all biochemical and genetic realities, and many of the complex new testing methods are expensive and so far have not much clinical use.

Would it help if genetic profiles were routinely produced for young people, stored electronically, and made available to a physician who had to treat the person in later life? Theoretically this could help. Technical, economic, and ethical problems could probably be solved, and the medical profession could be appropriately trained for utilization of the data. This could mean some improvement of drug safety. However, a predictable shortcoming of any such method lies in the fact that expression of genes is sure to change from time to time.[52] In short, genetic profiling might statistically improve drug safety, but it will never guarantee it.

Since there is less genetic variation within certain groups of people than in all of humanity,[53] one might hope that assignment of a patient to a genetically similar group of people could increase the likelihood that a drug is appropriate for him or her. Let us consider this problem.

People might be classified by age, sex, ethnicity, or race. Aging may change the structure of genes by methylation,[54] but particularly gene expression often changes with age so that there is an age-dependent pattern of genetic activities. Thus, a drug action may differ between children, teens, adults, and old people.[55,56] In the same way, men and women may not be served equally well by a given drug.[57] However, as long as we cannot get full genetic profiles, it can be helpful to use demographics as a predictor of a person's genetic profile; genetic differences between racial groups have been measured extensively, and many of these differences affect drug responses. For instance, deficiency of the multidrug metabolizing enzyme CYP2D6 differs widely between human races. Also, the new drug 'BiDil' used to treat heart failure appears to be effective so far only in people of African descent.[58] These medical effects are clear, but at present, racial or ethnic profiling often raises emotional and ethical antagonism. In the long run, medical benefits should be the determinants.

In summary, one may state that there is currently some clinical use of genetic information to improve drug therapy. A substantial improvement may be expected over the next few decades through development of techniques, their medical availability, and through reduction of the cost of methods, which will allow effective screening of a patient for genes that control his or her response to a given drug. The statistical likelihood of drug safety or efficiency for a given patient may lead to earlier improvement as we learn more of the importance of grouping patients by age, sex, or ethnicity. However, the complexities and variable gene expressions will never allow a 100% assurance that a drug will act exactly as expected.

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