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Report:

Pharmacogenetics, pharmacogenomics and ecogenetics*

MOTULSKY Arno G.[1,2], QI Ming[2,3,4]

([1]*Department of Medicine (Medical Genetics) and Genome Sciences, University of Washington, Seattle, WA 98195, USA*)

([2]*School of Medicine, Zhejiang University, Hangzhou 310003, China*)

([3]*Beijing Genome Institute, CAS, Beijing 101300, China*)

([4]*University of Rochester, NY 14642, USA*)

E-mail: agmot@u.washington.edu; qiming_14618@yahoo.com

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Abstract: Pharmacogenetics and pharmacogenomics deal with the role of genetic factors in drug effectiveness and adverse drug reactions. The promise of a personalized medicine is beginning to be explored but requires much more clinical and translational research. Specific DNA abnormalities in some cancers already have led to effective targeted treatments. Racially determined frequency differences in pharmacogenetic traits may affect choice of treatment requiring specific testing rather than basing treatments according to racial designation.

The role of genes in variable responses to foreign chemicals (xenobiotics) has been termed ecogenetics or toxicogenetics raising problems in public health and occupational medicine. Nutrigenetics refers to genetic variation in response to nutrients and may affect nutritional requirements and predisposition to chronic disease.

Key words: Pharmacogenetics, Pharmacogenomics, Ecogenetics, Nutrigenetics, Adverse drug reactions
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Pharmacogenetics refers to the role of genetic variation affecting drug response or adverse reactions to drugs (Weinshilboum, 2003). The field had its origin in the 1950s with the emergence of human biochemical genetics. Certain single-gene controlled enzyme abnormalities (polymorphisms) were found to predispose to unexpected adverse drug reactions such as hemolytic anemia due to G6pd deficiency and prolonged apnea from suxamethonium−a muscle relaxant routinely used during anesthesia.

The likely role of genetics in potentially causing adverse drug reactions was set out in my 1957 paper with the programmatic title "Drug Reactions, Enzymes and Biochemical Genetics" (Motulsky, 1957). The term pharmacogenetics was coined by Friedrich Vogel of Heidelberg, Germany in 1959 (Vogel, 1959). In the late 1960s, Vesell showed remarkable similarity of disposal for several drugs in identical twins who share 100% of their genes as contrasted to fraternal twins who only share 50% (Vesell and Page, 1968). These data together with bell-shaped distribution of drug disposal after standard dosage in unrelated members of a population supported the inference of polygenic control of drug metabolism for many drugs.

The development of pharmacogenetics over the years remained slow since relatively few drug responses or adverse drug reactions were under control of a single gene. Family studies were difficult and a direct DNA study of drug response was not yet possible. There was little or no impact on clinical pharmacology, drug development and clinical medicine. The increasing availability of DNA technology and in vitro molecular tests advanced the field. The term pharmacogenomics was introduced in the 1990s with emergence of the Human Genome Project and the development of the genome sciences. New technology such as microarrays allowed search for multiple genes and their expression affecting drug responses. Search for characteristic cellular DNA abnormalities in disease is now beginning to guide construction of therapeutic drugs acting on disease specific DNA

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mutations (Couzin, 2004). A somatic mutation in chronic myelocytic leukemia responds to the drug Gleevec in almost 100% of cases. While multiple therapeutic measures for the long QT syndrome are targeting defects in potassium channels, specific sodium channel inhibitors would be more effective for improving malfunction of sodium channel mutations.

Methodology from population genetics is often required to detect relevant pharmacogenetic mutations such as the HapMap approach, which uses genomic marker DNA (SNPs) as sign posts for linked genes of pharmacogenetic interest (linkage disequilibrium) (Andrawiss, 2005). Finding common traits of more than 3%~5% frequency by this method is promising while techniques detecting rarer traits of pharmacogenetic interest need to be explored, such as by resequencing of critical portions of DNA (Need *et al*., 2005).

The frequency of pharmacogenetically relevant genes often differs−sometimes significantly−between populations of different geographic origin, such as between those of European, African and Asiatic origin, and may be practically significant for drug therapy (Tate and Goldstein, 2004). Ideally, the specific genes that determine a pharmacogenetic response should be tested without regard to genetic ancestry since the relevant traits usually exist in all populations except at different frequencies. In the absence of a specific test, choice of optimal drug treatment based on "racial" assignment therefore may be justified.

There is a tendency to over promise the future impact of pharmacogenetics or personalized medicine (Nebert *et al*., 2003). Considerably more research by basic academic and clinical scientists, clinicians and researchers from the pharmaceutical and biotechnology industries is required before wide clinical applications of pharmacogenetics and pharmacogenomics will be realized.

Brewer in 1971 coined the term ecogenetics to extend the concept of the role of genetic variation in response to "foreign" chemicals (xenobiotics) and to environmental agents other than drugs. Drugs are only a small fraction of environmental chemicals to which humans are exposed. Pharmacogenetics therefore should be considered a subfield of ecogenetics. The terms "toxicogenetics" and "toxicogenomics" have also been applied to genetic and genomic variation in response to any kind of toxic exposure. Ecogenetics and toxicogenetics are therefore new approaches to epidemiology to explain why only some members of a population exposed to equal doses of a damaging agent will get sick. Just like pharmacogenetics, ecogenetics remained somewhat neglected until recent years. In 1997, the Environmental Genome Project was initiated by the Institute of Environmental Health Sciences of the National Institute of Health (USA). Its aim is to explore the role of genetic variation by various polymorphisms on susceptibility to adverse effects of environmental agents (Motulsky, 2002).

A developing field of ecogenetics is nutritional ecogenetics (nutrigenetics). Genetic variability of human biochemical make-up affects most metabolic and cellular processes involved in nutrition and may affect nutritional requirements (Motulsky, 1987). Genetic polymorphisms affecting blood lipids and dietary lipids may interact to produce hyperlipidemia, ultimately causing atherosclerosis and vascular disease. The role of the enzyme MTHFR (methylenetetrahydrofolate reductase) involved in folic acid metabolism has a frequent polymorphism of nutritional and medical interest.

References

Andrawiss, M., 2005. First phase of HapMap project already helping drug discovery. *Nature Reviews. Drug Discovery*, **4**(12):947. [doi:10.1038/nrd1918]

Couzin, J., 2004. Pharmacogenomics: cancer sharpshooters rely on DNA tests for a better aim. *Science*, **305**(5688):1222a-1223a. [doi:10.1126/science.305.5688.1222a]

Motulsky, A.G., 1957. Drug reactions, enzymes and biochemical genetics. *Journal of the American Medical Association*, **165**:835-837.

Motulsky, A.G., 1987. human genetic variation and nutrition. *American Journal of Clinical Nutrition*, **45**:1108-1113.

Motulsky, A.G., 2002. from pharmacogenetics and ecogenetics to pharmacogenomics. *Medicina nei Secoli Arte e Scienza* (*Journal of history of Medicine*), **14**:683-705.

Nebert, D.W., Jorge-Nebert, L., Vesell, E.S., 2003. pharmacogenomics and "individualized drug therapy": high expectations and disappointing achievements. *American Journal of Pharmacogenomics*, **3**:361-370. [doi:10.2165/00129785-200303060-00002]

Need, A.C., Motulsky, A.G., Goldstein, D.B., 2005. priorities and standards in pharmacogenetic research. *Nature Genetics*, **37**(7):671-681. [doi:10.1038/ng1593]

Tate, S.K., Goldstein, D.B., 2004. Will tomorrow's medicines work for everyone? *Nature Genetics*, **36**(11s):S34-S42. [doi:10.1038/ng1437]

Vesell, E.S., Page, J.G., 1968. Genetic control of drug levels in man: phenylbutazone. *Science*, **159**:1479-1480.

Vogel, F., 1959. Moderne problem der humangenetik. *Ergeb. Inn. Med. U. Kinderheilk*, **12**:52-125.

Weinshilboum, R., 2003. Inheritance and drug response. *New England Journal of Medicine*, **348**(6):529-537. [doi:10.1056/NEJMra020021]