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Facing Your Genetic Destiny, Part II

Finding treatments that match individual gene profiles is the next frontier in drug research and the objective of a new science called pharmacogenomics. Virtually every major pharmaceutical company is now investing millions in its pursuit

By Sergio Pistoi

My Aunt Wilma refuses to take the drug her doctor prescribed for hay fever. It makes her dizzy, she says, and doesn't help her symptoms. Aunt Wilma complains a lot. But soon researchers could develop a test that might reveal she is genetically incompatible with the drug. The doctor might then prescribe a product that is more effective and better tolerated for her genetic profile.

Finding treatments that match individual gene profiles is the next frontier in drug research and the objective of pharmacogenomics, a new science that combines pharmacological research with the latest advances of genomic studies.

To read part I of this story, click here.

Pharmacogenomics promises to have a formidable impact on health care. A study published in the *Journal of the American Medical Association* estimated that adverse reactions to drugs caused at least 100,000 deaths and two million hospitalizations in 1994 in the U.S. alone. Many such tragedies, experts say, could be avoided if doctors knew an individual's genetic makeup.

Saving lives aside, pharmaceutical companies also count on pharmacogenomics to limit the economic burden associated with adverse drug reactions, which often oblige them to withdraw their products from the market. They further hope that pharmacogenomics will make clinical trials cheaper and faster because researchers will be able to test only those patients whose genetic backgrounds makes them good "responders" to the drug. Once approved, the treatment could then be given only to people with the same characteristics.

Genetic variety is the key to understanding why a drug works in some people and not in others or, worse yet, makes them sick. It's no wonder then that virtually every major pharmaceutical company is now investing millions to comb through human DNA in search of the individual variations that might affect drug response.

Sniping the Genome

One year ago, in February 2001, scientists announced that they had finally mapped out the human genome. That map, however, is far from being a faithful representation of our species and its diversity. Instead the published sequence of the human genome serves only as a standard reference because it was created using the DNA from only a few anonymous donors. A few years ago, though, a handful of laboratories started to address the next challenge in genomic research: making a systematic catalogue of the most relevant individual variations in the human genome.

On average, the DNA of two individuals will differ by about one nucleotide in every thousand (nucleotides are the "letters" that make up the genome). Because human DNA contains about three billion nucleotides, researchers estimate that our genome contains at least three million "variable spots." Scientists call these spots single nucleotide polymorphisms (SNPs), or, as the streetwise pronounce the abbreviation, snipes. The study of SNPs is now serious business for dozens of companies, ranging from start-ups to giant pharmaceutical corporations.

A SNP consortium, established in 1999, has already published a map of 1.4 million SNPs along the genome. The consortium includes at least 11 major pharmaceutical companies, public laboratories, the Wellcome Trust, and IT giants IBM and Motorola. Another project at the National Institutes of Health (NIH) is mapping SNPs at the speed of about 90 every month. Companies such as Genset, Curagen and Celera are also compiling private SNP databases.

Making SNP lists, however, is only the beginning. The next step is to find

COMPUTER GUESSES

An Internet-based program that calculates your genetic risk profile and suggests the best measures to secure your health is under development at Interactive Predictive Medicine (IPM), a spin-off company founded by researchers from the University of Clermont-Ferrand in France. The program analyzes personal information such as age, diet, previous medical treatments, and the results of aimed genetic tests and provides a personalized risk

which of these variations account for clinically significant differences. Researchers now analyze thousands of SNPs in minutes "to find which are more frequent in people with a particular disease or that respond differently to a drug," says Dale R. Pfost, CEO at Orchid BioSciences, a Princeton-based company that specializes in SNP analysis. To analyze DNA samples, Orchid technicians use a huge automatic system that spots all the known SNPs at the vertiginous rate of a million a day.

Such systems currently fill an entire room, but the advent of microarrays, or DNA chips, has led to miniaturization. DNA chips are made using photolithography, the same technology used for creating tiny computer processors. But instead of producing an array of semiconductors, DNA chipmakers use the process to fix thousands of different stretches of DNA onto a tiny silicon support. Using these chips and a computerized laser reader, it takes mere minutes to analyze thousands of SNPs in a given sample. Companies such as Affymetrix already produce thumbnail-size DNA chips that contain more than a million different DNA sequences in the space of a few millimeters.

Read DNA Notice Before Use

Scientists have already listed hundreds of genetic variations that affect individual responses to drugs. Some of these variants work by changing the rate at which the drugs are eliminated from the body. A liver enzyme called CYP2C6, for example, is responsible for clearing the system of at least 30 different classes of drugs, including beta-blockers, tricyclic antidepressants, morphine derivates and antiarrhythmics, as well as many other chemicals and neurotransmitters. Variations in the gene coding for this enzyme can therefore strongly influence a person's reaction to many commonly used compounds: people with a "fast" form of the enzyme need higher doses because they tend to rid themselves of the drugs more quickly.

profile for many pathologies, including cardiovascular disorders, cancers, and autoimmune diseases.

The system can also suggest further tests or preventive measures, when available. Other companies, too, are experimenting with predictive systems for one or several diseases. Predictive Medicine in Belmont, Mass., for example, is using neural networks to choose the best drug treatment for depression. The program works by comparing a patient’s profile with those of people who have already received successful treatment.

Another enzyme, called TPMT (Thiopurine Methyltransferase) heavily influences the outcome of chemotherapy for acute lymphoblastic leukemia, the most frequent cancer in children. The TPMT enzyme breaks down a class of chemotherapic compounds called thiopurines. Before a specific genetic test was available, children with a "lazy" form of the enzyme were at risk of dying: the thiopurines reached toxic levels because the kids eliminated the drug too slowly. Today doctors adjust the dose according to an individual's TPMT speed, which has dramatically improved the survival rate of affected children.

Hundreds of other genes affect drug response in different ways--among them, by producing enzymes that make the drug more effective or by facilitating its transport into the cells. Each variant of these genes may have tremendous relevance in pharmacogenomics, and that’s exactly what the snipe hunters are hoping to discover.

FURTHER READING:

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