THE HUMAN GENOME PROJECT

Dr. Ronald Worton
Geneticist-in-Chief
Hospital for Sick Children
Toronto, Ontario
Chair, Management Committee
Canadian Genome Analysis and Technology Program

Society today is on the verge of a genetic revolution that promises to change the way we think about disease. At the centre of the revolution is the Human Genome Project, an international effort to identify all the genes in the human genome. It is assumed that with a complete catalogue of human genes it will be possible to determine how each contributes to life processes. This new knowledge will impact dramatically on our understanding of disease and on our ability to prevent, treat or cure many diseases that are today intractable.

This exciting future also has another dimension. It is already challenging our definitions of disease and will confront us for the first time with the opportunity to predict, in advance, certain of our future illnesses. Being able to predict our likelihood of developing cancer, heart disease, emphysema, psychiatric illness and other genetically determined conditions will force society to reflect carefully about the implications of such knowledge. An educated public will be the key to such careful reflection.

The Four Letter Code

The genetic material (the genome) is contained in a Long thread-like molecule of deoxyribonucleic acid or DNA, composed of a string of chemical structures called bases. There are only four distinct bases, referred to by the first letters of their chemical names, A, T, C and G. The order or "sequence" of the bases (e.g., ATTACGGCTACTGG...) provides the genetic code for the assembly of other molecules - the proteins. A gene is simply a portion of a DNA molecule that provides the code to make one protein. The human genome is estimated to contain about 100,000 genes encoding 100,000 different proteins. Each person's genome is slightly different from every other person's genome - the basis for our individuality, including our individual susceptibility to a variety of diseases.

Genetic disease is the result of a change (mutation) in the base sequence of a gene, causing it to produce either no protein or an abnormal protein. Inherited genetic disease is the result of a faulty gene or genes being passed from one or both parents to an individual who is destined from birth to develop the genetic condition. Acquired genetic disease, on the other hand, is the result of mutation that takes place in the cells of the body after birth causing, for example, loss of genetic control over cell growth and the development of cancer.

The Human Genome Project

The international human genome project is massive, expecting to take 15 years and to cost $3-5 billion - a price tag that puts it into the same league as putting a man on the moon. The reason for this enormity is simple. The size of the human genome is about 3 billion bases. Since one "sequencing reaction" can determine the order of the code letters in a DNA fragment of only 300-500 code letters, the genome project requires, at a minimum, 10 million DNA fragments to be sequenced, probably double this to account for necessary overlaps and double again to check for accuracy. A dedicated research team purifying segments of human DNA and running 10-20 reactions per day for 10 years would cover only 0.1% of the genome. And after this they still wouldn't know the order in the genome of the individual DNA fragments whose sequence had been determined. Determining the order of the DNA fragments is the other aspect of the genome project - the part referred to as genome mapping.

The Impact on Medicine

In the field of medicine the establishment of a detailed genome map will allow any disease gene or any predisposing to disease to be identified quickly and easily. Instead of taking 25 person-years of effort as it did to identify the genes responsible for muscular dystrophy and cystic fibrosis, it will taken only months for a group of researchers to identify genes for common disorders. Within the 15 years of genome project a majority of the approximately 4000 genes responsible for genetic disorders will be identified. For these diseases the new knowledge will be applicable immediately to diagnostic tests, and for some it will lead to the development of new therapies. Such therapies might include, for example, gene therapy to replace a defective gene, use of the sequence information to create "anti-sense" genes to counter the deleterious effect of a mutant gene, or use of the knowledge of protein function to design new drugs.

And it will not be just the rare inherited diseases that the Genome Project will affect. Many common diseases are caused, at least in part, by a defect in the genes. Many forms of cancer, for example, are caused by mutations in genes controlling cell growth. Heart disease can result from mutations in genes controlling cholesterol metabolism. Schizophrenia, manic depressive illness and Alzheimer's disease occur when genetically controlled pathways in the brain are disrupted. And the list goes on - diabetes, asthma, epilepsy, hypertension and many more all have clear genetic components that render these diseases more frequent in certain people than others. The genome project will uncover all these genes. The impact will be dramatic. It will change the face of medicine and will give us a level of understanding of human development and disease that would have been unthink-able only a decade ago.

The Impact on Society

All this will raise challenging questions for society. This is partly because the identification of disease genes will not, in most cases, lead to an immediate cure. If cure or treatment does come it will likely be several years after the identification of the gene. But in the meantime diagnostic test will reveal who has a particular disease, and will even reveal who is susceptible to late-onset disease long before the disease is expressed.

At the same time it will become possible to screen entire populations to reveal those who carry a recessive disease gene - one which by itself is harmless, but when inherited by a child who also receives a similar gene from the other parent, causes disease. Indeed, it is already possible to identify most carriers of the gene for cystic fibrosis. In the case of couples who both carry a defective gene it is possible to provide prenatal diagnosis and selective termination of pregnancy, thereby preventing the birth of most children with CF.

But do we really want to do this? And who decides? The issues are far from simple. In the case of cystic fibrosis the discussion is complicated by the fact that palliative care has improved dramatically so that many who would have died in infancy only 30-40 years ago, now live to be young adults. Furthermore, as a result of the gene discovery in this hospital (the Hospital for Sick Children, Toronto) only five years ago, new treatments are being tested and the probability of an effective treatment coming along during the lifetime of a CF child born today is quite high. Gene therapy for this disease is one possibility that is high on the research priority list in this hospital.

The problem becomes magnified further when one considers other genetic traits. It is common in North America to offer prenatal diagnosis from Down syndrome in the case of women at high risk due to late maternal age. Many couples seek this procedure and terminate the pregnancy when the syndrome is confirmed. What about less handicapping conditions such as blindness, deafness, or hemophilia? What about behavioural disorders such as schizophrenia? What about physical appearance, intelligence and personality? Would some individuals consider it reasonable to terminate a pregnancy simply because a genetic analysis of the fetus did not turn up genes associated with high intelligence? And finally, what about sex? Already we know that in certain cultures it is common to seek abortion simply on the basis of the sex of the fetus. Should this be outlawed in societies that claim to support equality of the sexes? In Canada the Royal Commission on Reproductive Technologies suggested such a ban and most geneticists have supported this view.

In addition to the problem of defining a genetic disease there are other ethical, legal, and social issues raised by the Human Genome Project. There may well be pressure from the insurance industry to have access to sensitive genetic information in determining insurability. Genetic formation, like any medical information, must remain private yet this will be difficult to achieve in the face of large scale screening programs. We must not allow the presence of a potentially harmful gene to result in discrimination based on predictions of future illness, no matter how good the predictive value to the tests may be.

It is clear that we are entering interesting times - times in which the gifts of the Human Genome Project will lead us to a dramatically improved understanding of human disease and human suffering. Those same gifts will test the wisdom of our species in dealing with the information in a way that preserves human dignity.