The Beneficial Effects of DNA Crunching

The Human Genome Project

BY TERRY NG

An examination of the complexities of the Human Genome Project.

All humans have genomes – the complete library of genetic material comprised of deoxyribonucleic acid (DNA) molecules. These storages of hereditary information consist of one pair of one sex chromosome and 22 pairs of autosomes – non-sex chromosomes – within each normal human cell. The DNA molecules that carry these genetic instructions are made up of four simple nitrogenous bases – adenine (A), cytosine (C), guanine (G) and thymine (T) – where G pairs up with C, and A with T, using hydrogen bonds, to form the double-helical molecule of DNA. About 99.9 percent of the human genome sequence is homologous in all human individuals (Patrinos and Drell, 1997). Scientists think that there is approximately one base-pair difference of one thousand cases among each individual. See Figure 1 (U.S Department of Energy, 2002).

New technologies for understanding and working with DNA were developed in the 1980s. The realization soon dawned upon scientists that, by decoding human DNA, the blueprint of our heredity, they would be able to fully understand the underlying processes and causes of the various "effects" in the human body. Hence, the idea to sequence the entire human genome arose, and with this idea came the birth of the Human Genome Project (HGP).

The Human Genome Project – an overview

In simple terms, the HGP is an attempt to map the complete set of coded instructions – DNA – that is responsible for creating and conserving the life of all human beings. See figure 2 (Human Genome Sequencing, 2002).

The Human Genome Project was formally initiated and sponsored by the U.S. Department of Energy (DOE) in 1990, and is now managed in joint effort with the National Institute of Health (NIH). It is also a 13-year effort that was originally planned to last 15 years, but rapid technological advances have accelerated the expected completion date to 2003 (Casey, 1999). A historic initial draft of the human genome was completed, and published in the journals *Science* and *Nature* in February of 2001.

Despite multiple revisions of the project goals – such as a 5-year plan for 1990-1995, a revision for 1993-1998, and a revision for 1998-2003 – the ultimate goals of the project have remained more or less the same. They are:

- To *identify* all of the approximate 30,000-35,000 genes (Patrinos and Drell, 1997) in humans
- To *determine* the sequences of the 3 billion chemical base pairs that make up human DNA
- To *improve* current tools and *develop* new technology for data analysis to increase effectiveness and reduce cost
- To *identify* useful model organisms for comparison with the human genome
- To *improve* content and utility of genomic information in databases to make the data more accessible to the public
- To *address* the ethical, legal, and social issues (ELSI) that may arise from the project
- To *nurture* the training of genomic scientists [Human Genome Management Information System (HGMIS), 2001].

The complete DNA sequence of a typical human cell will serve as a comprehensive public reference source that others will be able to build upon without having to repeat the same research. It will also provide information and resources to understand some of the critical differences that make us individuals, as well as factors that often contribute to diseases.

The future of the HGP in medicine...possibilities and limitations

All diseases have a genetic component, whether inherited or resulting from the body's response to environmental stresses, such as viruses or toxins (HGMIS, 2001). By understanding the biological function(s) of each gene and the molecular events that arise from them,

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May I Have Your Attention Please...

BY: REBECCA MCEVILLY

Attention. To focus, divert, and maintain it are all tasks that involve the brain, which researchers are examining in order to better understand Attention Deficit Hyperactivity Disorder (ADHD). Externally, the symptoms of ADHD appear rather simplistic, involving such criteria as lack of attention and inability to sustain it, as well as fidgeting, interrupting and other such hyperactive, impulsive behaviours (Long, 2000). In order to examine the causes of these symptoms and develop a more specific treatment, ADHD is now classified into three subsets. Based on various evaluations of the behaviours, the patient is diagnosed as a predominately *hyperactive type*, predominately *inattentive type*, or a *combined* type (Long, 2000). Even with this breakdown, however, the mechanisms for brain action remain complex behind such a multifaceted diagnosis.

A major factor that affects attention in ADHD is a developmental failure in the brain circuitry, which underlies inhibition and self-control. Researchers have found that children with ADHD are less capable of preparing motor responses in anticipation of events, and are less sensitive to feedback about errors (Barkley, 1998). Many brain regions also appear to be involved in the integration of these tasks. Researchers at the National Institute of Mental Health found areas of the right prefrontal cortex, the two basal ganglia (caudate nucleus and globus pallidus) as well as the vermis region of the cerebellum to be significantly smaller in children with ADHD. The prefrontal cortex may be involved in "editing" behaviour, while the basal ganglia is more involved in switching off responses to allow for deliberation. The vermis region may have a role in motivation (Barkley 1998). None of these regions act in isolation, and it appears that, when looking for an anatomical

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scientists will be able to investigate the profound causes of human diseases (Patrinos and Drell, 1997). This will lead to a future in which potential interventions that can be more effective and targeted; prevention will potentially be the norm in medicine (Hood, 1992).

Scientists have been developing several tools that will utilize the fully sequenced human genome database to find new ways to treat, cure, or even prevent the thousands of diseases that trace back to the human genome. Such applications include gene testing, gene therapy, and pharmacogenomics.

Gene testing, also called DNA-based testing, one of the newest and most sophisticated techniques used to test for genetic disorders, involves direct examination of a DNA molecule, and is used to diagnose a condition or to estimate the likelihood for developing one. The required DNA sample can be obtained from any tissue, including blood. To do a gene test, scientists scan the tissue sample to look for a specific mutation in a particular DNA region that has been linked to a certain disorder. One method of scanning is by designing short pieces of DNA, called probes, whose sequences are complementary to the mutated sequences (HGMIS, 2001) and are usually tagged with radioactive substances. If the mutated sequence is present in the patient's genome, the probe will bind to it and label the mutation. Another type of DNA testing involves comparing the sequence of DNA bases in a patient's gene to a normal version of the gene.

Gene testing will allow researchers and medical professionals to pinpoint the defective gene that is causing the particular disorder. The potential benefit of gene testing is enormous. The tool, however, is new, and some researchers are still unsure how to interpret the test results (Casey, 1999). In addition, there are very few medical options available to treat or prevent the disorders for which gene tests are used, simply due to the amount of time it takes to link a gene mutation to a disease and to then find an effective therapy. Despite the limitations, the study of genes will better enable an understanding of the normal biological processes, and how these processes deviate during the body's diseased state. These insights will enable improvement for better predictive measures earlier on in disease development, and will eventually bring about a field of prevention-based medicine (Casey, 1999). As John McKenzie from ABC News put it, "Within 30 years, your regular checkup may include predictions of diseases before you even get them." (McKenzie, 1999).

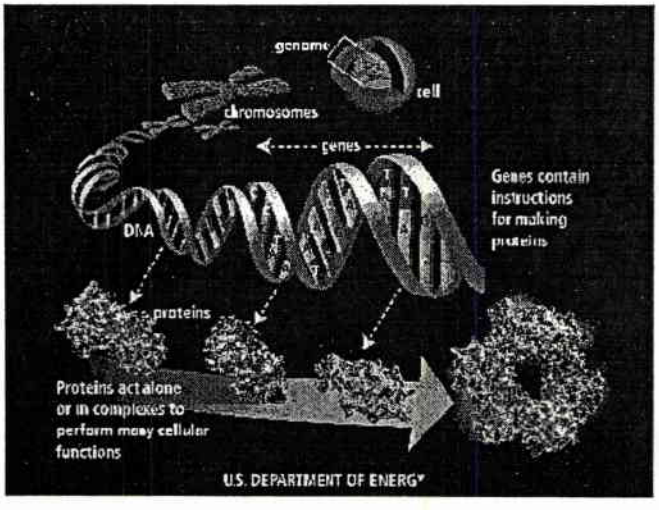


Figure 1:
Genome → chromosome → DNA base sequence → genes → proteins

The use of genes themselves to treat disease, known as gene therapy, is a rapidly developing field that holds great potential for treating, curing and ultimately preventing genetic and acquired diseases (Wilson, 1999). Gene therapy uses normal genes to replace a defective gene or to change its expression to increase the body's immunity to the disease (e.g. by adding a gene that suppresses tumor growth). There are basically two types of gene therapies: somatic gene therapy and germline gene therapy.

Somatic gene therapy targets somatic (body) cells where the recipient's genome is changed; change is not passed along to the next generation. It is the type of therapy that is being researched by most laboratories around the world. On the other hand, germline gene therapy changes the genome of egg and sperm cells, with the result of passing on the changes to the next generation. Research on germline gene therapy is strictly limited to animal model systems because of significant technical and ethical challenges. Thus, human clinical trials will not be performed anytime in the near future (Wivel, 2001).

Gene therapy would essentially be futile without knowing the function(s) of each gene

One of the most basic and important tasks of gene therapy is to deliver the gene to the appropriate cell in a specific, efficient, and safe manner. Genes are inserted into the body via vectors (gene carriers), which deliver therapeutic genes to the patients' cells. Currently, the most common vectors are viruses that have evolved a way of encapsulating and delivering their genes to human cells in a pathogenic manner. Scientists have tried to take advantage of the virus's biology by removing the disease-causing components of the virus and inserting recombinant genes that will be therapeutic to the patient. The modified virus cannot replicate within the patient, but it still retains the ability to efficiently deliver genetic material (Wilson, 1999).

Viruses, while effective as carriers for gene therapy, introduce other problems to the body such as toxicity, immune and inflammatory responses, as well as gene control and targeting issues. An alternative strategy is based on non-viral vectors in which complexes of DNA, proteins, or lipids are constructed as particles capable of efficiently transferring genes. As part of their effort in looking for better ways to transfer modified viral genes to cells, scientists are also experimenting with a 47th, artificial human chromosome existing in the human body. The 47th chromosome would exist along side the typical 46 chromosomes without affecting their function(s) and without causing any mutations. Because of chromosome 47's construction and anatomy, the body's immune systems would not produce the negative responses that are posed by viruses (HGMIS, 2002).

Perhaps even more important than the problem of transferring a therapeutic gene safely into a patient's cell, is that gene therapy would essentially be futile without knowing the function(s) of each gene. Most genetic disorders involve more than one gene. Only in a handful of genetic diseases, such as Huntington's disease, is a single gene the only determining factor for the development of the disorder.

Explorations into the function of each gene will shed light on how faulty genes play a role in disease causation. In the newly-established field of pharmacogenomics – the study of how genes affect the way people respond to medicine – drug design will be revolutionized as researchers use information about gene sequence and protein structure function to create new classes of drugs targeted to specific sites in the

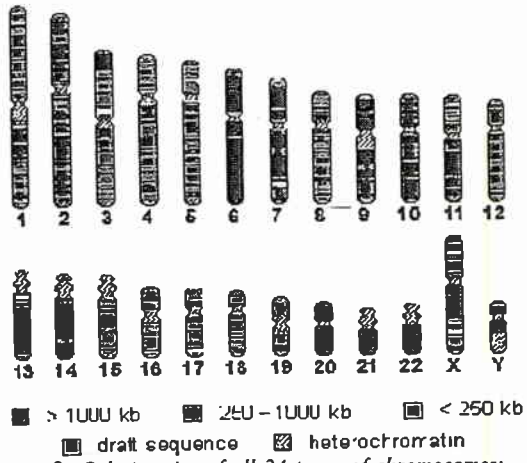


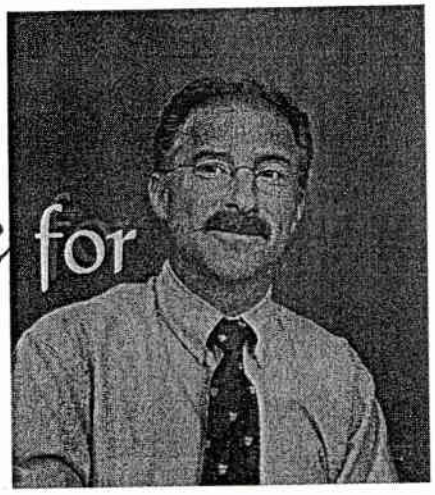
Figure 2: *Relative size of all 24 types of chromosomes; Number of bases along chromosome measured in kilobases (kb)–1000 nucleotide bases*

body. Doctors can eventually tailor doses of drugs to a person's unique genetic make-up. These novel drugs hold the promise to have fewer side effects and to be more effective than much of today's medicine (Casey, 1999).

Current drug therapy often attempts the treatment of large patient populations, disregarding the potential for individual, genetic-based differences in drug responses. In contrast, pharmacogenomics may help focus effective therapy on smaller patient subpopulations that, although demonstrate the same disease phenotype – the observable physical and biochemical characteristics of an organism (The American Heritage Dictionary of the English Language, 2002) – are characterized by distinct genetic profiles. The result of this individual-specified, genetic-based approach to medicine to provide an improved, economically feasible therapy, remains to be seen. All of the obstacles involved in developing any new medical therapy apply to pharmacogenomics as well. To exploit these opportunities in genetic medicine, novel technologies will be needed, health care professionals must be educated, and the public must be informed about the implications of genetic testing in drug therapy and disease management (Mancinelli et al., 2000).

The Human Genome Project is of great scientific importance and has already shown great promise. The discovery of two genes involved in the origins of breast cancer in 1994 is one such example of a vital breakthrough (Miki, 1994; Wooster et al., 1994). In lieu of such advances, the Department of Energy (DOE) and the National Institute of Health (NIH) expect to complete 100% of the high-quality sequenced – only a single error in every 10,000 bases – human genome by the year 2003 (HGMIS, 2001). Although gene tests and gene therapy have yet to demonstrate their full potential in preventive-based medicine, the next step to be taken in genome research – functional genomics: study of gene function – will enable scientists to predict the formation of any disease and to offer a therapeutic gene that replaces or corrects the defected gene(s) (HGMIS, 2001). In addition, pharmaceutical companies will be racing to develop customized drugs that will be tailored to specific gene sites. As amazing as the prospects of the HGP's effects on society may be, according to Daniel Drell (DOE) and Anne Adamson (HGMIS), "We need to be alert to challenges and misuses of the knowledge about ourselves. Society as a whole, not just genome scientists, must address these considerations. It has to be all of us." (Drell and Adamson, 2001).

A Vaccine for HIV



BY JEFFREY LI AND JONATHAN NG

McMaster University professor of pathology and molecular medicine, Dr. Ken Rosenthal, is leading breakthrough research into the development of a vaccine against HIV (Human Immunodeficiency Virus), the world-wide killer virus responsible for AIDS (Acquired Immunodeficiency Syndrome). He has successfully developed a mucosal vaccine for an HIV equivalent in mice that may be applicable to humans in the coming years. As the disease responsible for the death of 3 million last year and about 21.8 million since the beginning of the epidemic (AVERT, 2002), AIDS has established itself as a formidable opponent. Through these findings, Rosenthal and his colleagues are providing a glimmer of hope for ending the epidemic. Join us as we delve into the immunology behind the potential AIDS vaccine of the future.

HIV Basics

One of the most common modes of HIV transmission occurs through sexual contact. Infected semen or vaginal fluid containing the virus may enter the system of an uninfected person through the mucous membrane, the protective tissue layer lining the mouth, vagina, and rectum (The Body: New Mexico AIDS InfoNet Fact Sheet, 2002). After gaining access to the bloodstream and lymphatic system, HIV binds to cells that are recognized by its outer glycoprotein complex, gp120. The deadliness of the virus is a result of gp120's high affinity for the cell-surface protein, CD4, found on immune system cells (leukocytes) that help defend the body against pathogens and other foreign agents. Of the several targets, CD4 T cells are one of prime importance. These cells are responsible for helping B cells of the immune system to produce antibodies and activating macrophages that defend the body against intracellular bacteria and other pathogens (Janeway, 1999).

How the Vaccine Works

Under normal circumstances, the immune system responds to HIV infection by increasing production of HIV antibodies and cytotoxic T lymphocytes that target and destroy infected cells. Despite this response, however, the defense is usually unable to eliminate HIV. The aim of Dr. Rosenthal's vaccine is to boost the immune system so that it is capable of a powerful initial response to infection that will control the virus at manageable levels. Following the same principles of vaccines of the past, the vaccine introduces an antigen into the body that mimics natural disease exposure, in this particular case it is a whole killed envelope-deprived virus. Following antigen exposure, the body responds by producing antibodies that fight against the infection and stores this defensive ability in immunological memory. This allows the immune system to respond rapidly and effectively to the real disease when it strikes (Janeway, 1999).

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