Biology and Society

Unit Four: Genetics and Medicine

Topic Three: The Human Genome Project

"In short, the international Human Genome Project, which involves hundreds of scientists worldwide, is an investigation of ourselves."

What is the Human Genome Project?

The Human Genome Project (HGP) is an ambitious international research program to understand the hereditary instructions that make each of us unique. The goal of this effort is to determine the complete nucleotide sequence of human DNA, all 3 billion bits of information, and to localize the estimated 20,000-25,000 genes within the human genome.

Even before it is complete, the Human Genome Project promises to transform both biology and medicine. Our genes orchestrate the development of a single-celled egg into a fully formed adult. Genes influence not only what we look like but what diseases we may eventually get. Understanding the complete set of genes, known as the human genome, will shed light on the mysteries of how a baby develops. It also promises to usher in an era of molecular medicine, with precise new approaches to the diagnosis, treatment, and prevention of disease. In short, the international Human Genome Project, which involves hundreds of scientists worldwide, is an investigation of ourselves.

From the inception of the HGP, it was clearly recognized that acquisition and use of such genetic knowledge would have momentous implications for both individuals and society and would pose a number of policy choices for public and professional deliberation. Analysis of the ethical, legal, and social implications of genetic knowledge, and the development of policy options for public consideration are therefore yet another major component of the human genome research effort.

Launched in 1990, the project is supported in the United States by the National Institutes of Health and the Department of Energy.

Web Reference

http://www.ornl.gov/hgmis/project/hgp.html

James D. Watson and The Human Genome Project

The genesis and history of the Human Genome Project has been intertwined to a remarkable degree with the career of one man, Dr. James D. Watson (1928-). Watson is known internationally for his discovery with Dr. Francis Crick (1916-2004) of the structure of DNA in 1953, for which he shared the 1962 Nobel Prize in Physiology and Medicine. He later helped start the human genome project which, less than 50 years later, is coming to fruition. "I would only once have the opportunity to let my scientific career encompass a path from the double helix to the three billion steps of the human genome." Dr. Watson wrote in explaining his decision to become the first director of the human genome project at the National Institutes of Health in 1988. Dr. Watson was director until the early 1990s. The project, headed now by Dr. Francis Collins, is ahead of schedule, and accelerating toward completion.

What has the Human Genome Project cost?

The Human Genome Project is sometimes reported to have a cost of three billion dollars. However, this figure refers to the total projected funding over a 15 year period (1990-2005) for a wide range of scientific activities related to genomics. These include studies of human diseases, experimental organisms (such as bacteria, yeast, worms, flies, and mice); development of new technologies for biological and medical research; computational methods to analyze genomes; and ethical, legal, and social issues related to genetics. Human genome sequencing represents only a small fraction of the overall 15 year budget.

Web Reference
http://www.ornl.gov/hgmis/project/budget.html

What have we learned about ourselves from molecular genetics?

There are three types of genetic studies done on humans.

Mitochondrial DNA Studies

These were the first gene sequence studies of human genetics and were only possible because of the small number of genes on the loop of DNA found in each mitochondria. Because mitochondria are only passed from the mother in the egg cell, mtDNA is only passed through the female lineage.

Nuclear DNA Studies

It is more difficult to study the genetic material found in the nucleus of cells because of the greater number of genes. However, the Human Genome Project now holds the promise doing detailed studies of the genetic variation in our nuclear DNA.

Y- Chromosome Studies

Genetic studies of the Y- chromosome are a form of nuclear DNA studies where, uniquely, genes are past only from fathers to sons.

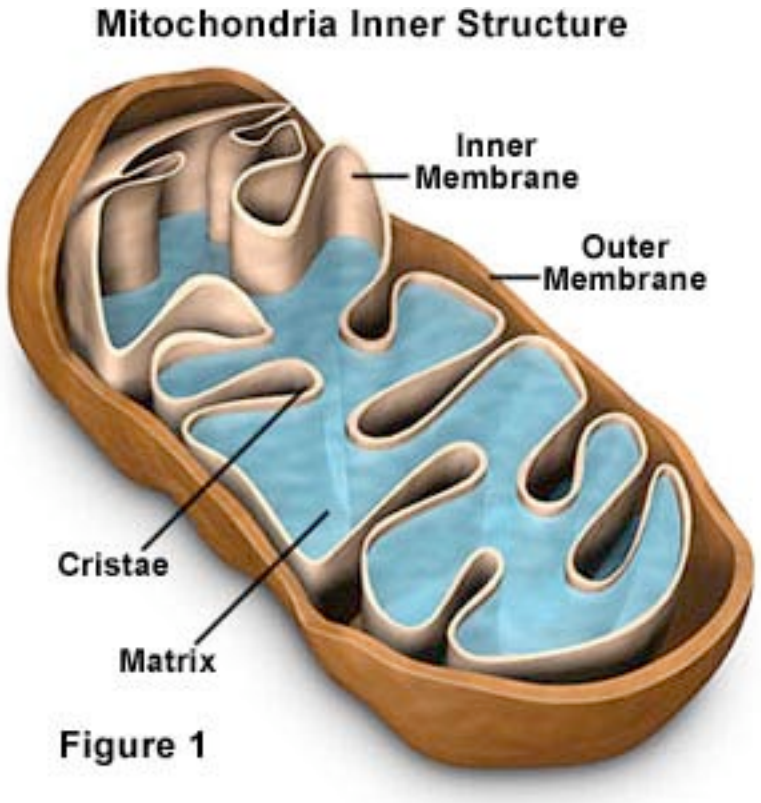
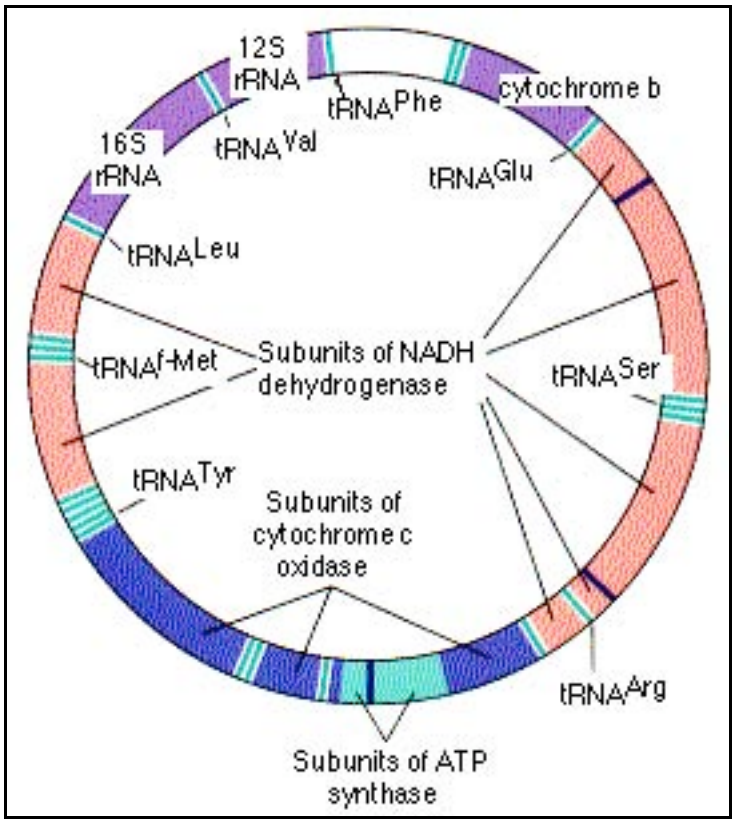


Figure 1

A eukaryotic cell may contain thousands of individual mitochondria organelles. A mother's egg cell contains as many as a 100,000 mitochondria.



The entire DNA sequence of the human mitochondrial (mt) genome, some 16,569 nucleotides, was determined in 1981, well in advance of the Human Genome Project. The mt genome contains 37 genes, all of which are involved in the production of energy and its storage in ATP.

• “Recent research based on the full sequence of mtDNA reduced the estimate for the origin of modern humans to slightly less than 150,000 years ago.” (Cavalli-Sforza 1998)

• “Population genetic studies are in approximate agreement with archaeological observations indicating that anatomically modern humans (i.e. similar, as far as bone morphology goes, to living humans) are found in the past 100,000 years exclusively in Africa, or very close to it (the Middle East) and spread from it to the other continents.” (Cavalli-Sforza 1998)

• “The number of our ancestors just before the expansion (“origin”) of modern humans was small. Many genetic systems provide reassuringly congruent estimates: all indicate that the approximate population size was on the order of 10,000 breeding individuals [this is 20,000 individuals total].” “Although the size of this population must have fluctuated over time, it was often reduced to the level of several thousands of adults.” (Harpending 1998)

• “A current estimate [for the genetic separation of Africans and non-Africans] gives a value closer to 60,000 y.a. with a standard error of close to 20% [72,000 y.a. to 48,000 y.a.].” (Cavalli-Sforza 1998)

Out of Africa

In a report on the "African Origin of Modern Humans in East Asia." A team of geneticists took samples from 12,127 men from 163 Asian and Oceanic populations, tracking three genetic markers on the Y chromosome. They discovered that every one of their subjects carried a mutation at one of those three sites that can be traced back to a single African population some 35,000 to 89,000 years ago. Their paper marks a major victory for the "Out of Africa" hypothesis that all modern people can trace their heritage to Africa. It is also a significant blow to the "Multiregional" hypothesis that modern human populations have multiple origins dating back many hundreds of thousands of years.

One of the chief defenders of Multiregionalism, anthropologist Vincent M. Sarich of the University of California at Berkeley, is well known for his vigorous and energetic defense of his beliefs and theories. Yet when this self-proclaimed "dedicated Multiregionalist" saw the new data, he confessed in the journal *Science*: "I have undergone a conversion—a sort of epiphany. There are no old Y chromosome lineages [in living humans]. There are no old mtDNA lineages. Period. It was a total replacement."

The Case of Humanity's Missing Mutations

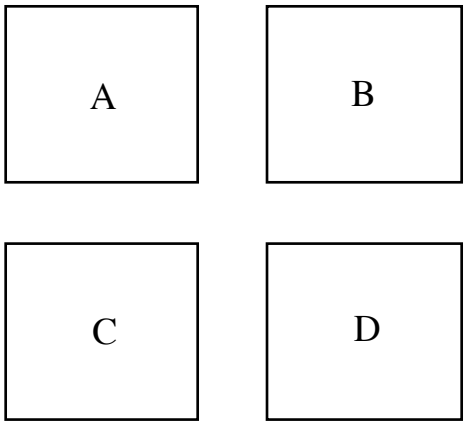
Humanity today numbers over 6.4 billion, but how closely are these 6.4 billion individuals genetically related to each other? The answer is "too closely"—we are missing the number of mutations, and therefore the genetic variation, expected in organisms similar to us, such as chimpanzees and gorillas. Population geneticists think that the explosive population growth that occurred in the past 10,000 years may be the cause. According to computer simulations of population growth, the widespread reproduction that accompanies rapid growth mixes genes up throughout a population to a greater degree than in a small population that isn't reproducing as frequently. The result is an overall genetic sameness."

This is reinforced by studies of genetic variation between human populations. It has been known for some time that human genetic variation is largely between individuals within populations, rather than between populations or even continents. Recent genetic studies have confirmed this, giving very nearly the same apportionment of genetic variation as classical markers—88 to 90% among individuals within populations and 10 to 12% among populations.

For more on the origin of modern humans go to:
http://fire.biol.wwu.edu/trent/alles/Cenozoic.pdf

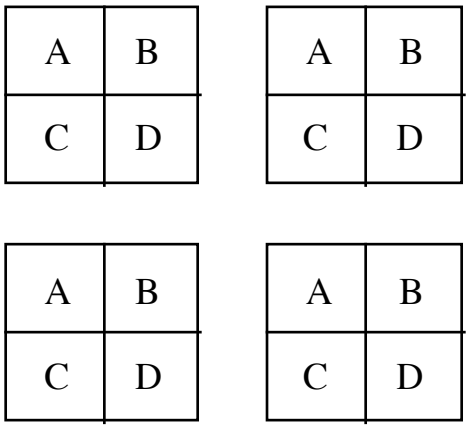
Genetic Variation Between Populations versus Variation Within a Population

Scenario One



Allelic variation is 0% within and a 100% between populations.

Scenario Two



Allelic variation is a 100% within and 0% between populations.

Excerpt from **What We all Spoke When the World Was Young**

by Nicholas Wade (2000)

"In the beginning, there was one people, perhaps no more than 2,000 strong, who had acquired an amazing gift, the faculty for complex language. Favored by the blessings of speech, their numbers grew, and from their cradle in the northeast of Africa, they spread far and wide throughout the continent.

One small band, expert in the making of boats, sailed to Asia, where some of their descendants turned westward, ousting the Neanderthal people of Europe and others east toward Siberia and the Americas.

These epic explorations began some 60,000 years ago and by the time the whole world was occupied, the one people had become many. Differing in creed, culture and even appearance, because their hair and skin had adapted to the world's many climates in which they now lived, they no longer recognized one another as the children of one family. Speaking 5,000 languages, they had long forgotten the ancient mother tongue that had both united and yet dispersed this little band of cousins to the four corners of the earth.

So might read one possible account of human origins as implied by the new evidence from population genetics and archaeology."

Excerpt from **Teaching Human Evolution**

by David L. Alles and Joan C. Stevenson (2003)

"At some point between 200,000 and 100,000 years ago a population of early humans in Africa crossed the morphological threshold to fully modern humans. The timing of this watershed event is supported by a variety of genetic studies. These same studies estimate the number of individuals in this population to be from 20,000 to as few as 2,000 individuals.

A population of two thousand individuals is about the size of a large high school in America today. It challenges the imagination, then, to understand that a population of just two thousand individuals may have been the common ancestors of all six billion plus living human beings. What a stunning moment in time to think of those two thousand poised on the brink of a brave new world. But in looking back to that moment, we can only wonder what our small band of ancestors might think of our world today."

For more on human evolution go to:
http://fire.biol.wwu.edu/trent/alles/Human_Evolution.pdf

References

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Cavalli-Sforza, L. L. (1998). The DNA revolution in population genetics. *Trends in Genetics*, 14(Feb.), 60-65.

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