



HUMAN GENOME

An introduction to aging science brought to you by the
American Federation for Aging Research



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WHAT IS THE GENOME AND WHY IS IT IMPORTANT?

Genome is a term referring to all of the biological information necessary to create and maintain a particular organism—such as a human being. That information is encoded into the organism's DNA (deoxyribonucleic acid), which is self-replicating material present in all of the organism's cells. The DNA in humans comes in strands, and small portions of those strands are called genes.

Genes are considered the basic units of heredity. The human genome is estimated to contain about 20,000 genes, representing two percent of its DNA. The other 98 percent contains what are called non-coding regions. What the non-coding regions are used for is not yet entirely known, but they do have some functional roles.

HOW CAN GENOMICS HELP US UNDERSTAND AND TREAT AGE-ASSOCIATED DISEASES?

Scientists are using the knowledge gained from the Human Genome Project, a comprehensive study of the human genome completed in 2003, to determine which genes are involved in specific metabolic or disease processes. Although using genomics to study something as complex as aging itself remains a challenge, scientists are making progress in identifying genes related to specific age-related diseases.

HOW DO SCIENTISTS STUDY THE HUMAN GENOME?

Since the completion of the Human Genome Project, researchers have combined the information it yielded with the availability of numerous advanced technologies to greatly increase

our understanding of human genetics. Important resources for scientists include:

- **Experimental genomics techniques**
The technology through which genes are studied is a new and exciting field called experimental genomics. Now that researchers have deciphered the human genome sequence, they can apply a wide variety of molecular biology tools to learn more about our genes. Experimental genomics includes a number of techniques, including gene expression array analysis, which looks at what DNA is actively transcribed into RNA, the first step in the making of proteins. Other newly developed and emerging laboratory techniques include DNA chip technology, genetic mapping,

and spectral karyotyping. For more information on various experimental genomics technologies, see the National Human Genome Research Institute's [Fact Sheets About Science](#).

- **Comparative genomics**
Scientists have gained great insights into the workings of cells, as well as the molecules that make up cells, by looking at more primitive organisms such as bacteria and yeast. More recently, scientists have sequenced important laboratory animals, such as the mouse and the rat, as well as other mammals such as the chimpanzee, dog, and opossum. Researchers in aging are particularly interested in sequencing the genomes of long-lived animals, such as the naked mole rat, which has the longest lifespan among rodents, and the capuchin monkey, which can live for over 50 years.

Sequencing the genomes of other organisms may yield insights into the human genome. Scientists can often identify aging-related genes in simpler organisms. Subsequent comparison to the human genome can often help researchers identify similar genes in humans, helping them target their inquiries more effectively.

HOW MIGHT GENOMICS RESEARCH HELP US UNDERSTAND THE AGING PROCESS?

Controversy has long existed in scientific circles as to the precise roles genetics or environment play in the aging process and the determination of potential lifespan. When reduced to the level of the cell, lifespan does seem to be genetically determined. Healthy, non-cancerous somatic (or body) cells placed in tissue culture in the laboratory will undergo a defined number of divisions or replications, and then they stop reproducing, entering what is called a *senescent* phase. Of course, there are also non-genetic influences on cellular aging. For example, free radicals, byproducts of the body's natural metabolism of oxygen, are involved in a process called oxidation. Exposure to radiation is another example.

Research on lower life forms and aging

Work done on some of the lower life forms whose genomes have also been sequenced has contributed much to scientists' understanding of normal aging. *Caenorhabditis elegans*, the roundworm, is one of the organisms whose genome has been fully sequenced. Scientists found that manipulating *daf-2* or *daf-16*, genes involved in the roundworm's insulin signaling pathway, can increase its lifespan in the laboratory three- to five-fold. A gene mutation called *Methuselah* in the fruit fly *Drosophila melanogaster*, another organism whose genome has been sequenced, can increase its lifespan by 35 percent. While humans share many genes with these other life forms, we also have a far more complex genetic structure, so the genes that most

significantly affect our lifespans are different from those that affect other animals.

Genes and human longevity

To what extent our longevity is determined by our genes is undergoing intensive study. Scientists have known for several years that people who live longest often have very long-lived children. Adoptees' lifespans are more closely correlated to those of their birth parents than to those of their adoptive parents.

We can inherit one of several different forms of a given gene, depending on which forms our parents carry and then pass on to us. Some of these gene variants are associated with a shorter lifespan because they are linked to certain diseases, such as the BRCA1 and BRCA2 genes associated with breast cancer and apoB, which is associated with high blood levels of cholesterol. Variants of other genes have been associated with longer lifespans, and inheriting these increases our likelihood of achieving greater longevity. Among these, perhaps the most important is the FOXO3A gene, which has been validated by nine independent research groups.

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CHALLENGES AHEAD

Longevity research in genomics is exciting, but it is still in its infancy. Most scientists believe that human longevity is likely a polygenic trait, that is, multiple genes contribute to a longer life. And of course, environmental factors (and the interaction between genetic and environmental factors) are also

likely to play important roles. This contrasts with the data from yeast, flies, worms, and mice, where mutation in a single gene can cause an extension of lifespan. Determining the genetic component of longevity (or some other complex human trait) typically requires novel types of quantitative and statistical studies, usually involving families or sibling pairs.

Scientists compare these families' genetic makeup to that of other families with similar traits, as well as the general population. This can help scientists identify certain chromosomal sections (and eventually genes) that are powerfully correlated to the trait in question. From there, researchers can estimate how much of a particular trait is caused by a particular

gene. For example, scientists may implicate a gene that accounts for 40 percent of the genetic effect on aging. On the other hand, these types of studies may identify 20 or more genes that contribute much smaller effects. Only additional research will tell.

THE FUTURE OF GENOMICS RESEARCH

An important piece of work that is ongoing and will continue is the correlating of clinical information and the mapping of the genome. A genotype refers to the genes one inherits; a phenotype describes how those genes present themselves as traits, such as curly hair, blue eyes, or a predisposition to cancer. By identifying phenotypes that represent patterns of disease and noting the occurrence of those phenotypes in large populations or even large families, scientists can then go back and correlate those phenotypes with the genotypes the people with the disease possess. Although the issue of “genetic privacy” arises (i.e., who has the right to know that a person has inherited genes that could possibly correlate with future illness), Dr. Todd E. Golde, MD, PhD, professor, department of neuroscience, College of Medicine, University of Florida, and former Beeson

Award recipient, points out that ethical researchers can collect this extremely valuable data without jeopardizing their subjects’ rights.

The mapping of the human genome and the development of new technologies will help us hone in more rapidly on which genes are linked with which diseases. Rather than focus on slowly teasing out one or a very few specific genes that can cause a disease, scientists can now identify regions of 50 to 100 genes that correlate with a given disease.

Perhaps just as exciting are technological advances that now allow us to sequence the entire genome of single individuals much more affordably and accurately. In an effort that involves AFAR through the the Archon Genomics X PRIZE, presented by Express Scripts, a competition for whole genome sequencing, the whole genome of 100 centenarians and super-centenarians will be soon sequenced and contribute, we hope, to our understanding of the mechanisms of exceptional longevity.

Another area that genomics researchers will continue to focus on is proteomics, the determination of which proteins are produced by which genes. This has important clinical

ramifications. Many diseases are known to be associated with specific abnormal proteins; the mapping of the genome will allow scientists to learn which genes code for those abnormal proteins.

One of the most exciting areas for future genomics research is called *epigenetics*. As important as the study of genes themselves may be, they don’t explain everything about the way an organism develops. For example, even identical twins with the same sets of genes will gradually begin to show slight differences in appearance from each other. This is because genes don’t work in a vacuum. They interact with the environment around them in unpredictable ways and give each twin a set of unique physical characteristics. Epigenetics, then is the study of the dance of nature and nurture, as it occurs at the genetic level.

Although the Human Genome Project was completed in 2003, the work of understanding the human genome is still in its infancy. The potential for a greater understanding of human disease and health is enormous.

American Federation for Aging Research (AFAR)
55 West 39th Street, 16th Floor
New York, NY 10018

Phone: (212) 703-9977
Toll-free: (888) 582-2327
Fax: (212) 997-0330
Email: info@afar.org

Websites:
www.afar.org
www.afar.org/infoaging

Facebook and Twitter:
AFARorg