Genomic Research

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1. What are the next steps in genomic research?

Discovering the sequence of the human genome was a major goal of the Human Genome Project, completed in 2003. However, sequencing the genome was only the first step in understanding how the instructions coded in DNA lead to a functioning human being. The next stage of genomic research will begin to derive meaningful knowledge from the DNA sequence. Research studies that build on the work of the Human Genome Project are under way worldwide.

The objectives of continued genomic research include the following:

- Determine the function of genes and the elements that regulate genes throughout the genome.
- Find variations in the DNA sequence among people and determine their significance. The most common type of genetic variation is known as a single nucleotide polymorphism or SNP (pronounced "snip"). These small differences may help predict a person's risk of particular diseases and response to certain medications.
- Discover the 3-dimensional structures of proteins and identify their functions.
- Explore how DNA and proteins interact with one another and with the environment to create complex living systems.
- Develop and apply genome-based strategies for the early detection, diagnosis, and treatment of disease.
- Sequence the genomes of other organisms, such as the rat, cow, and chimpanzee, in order to compare similar genes between species.
- Develop new technologies to study genes and DNA on a large scale and store genomic data efficiently.
- Continue to explore the ethical, legal, and social issues raised by genomic research.

2. What are single nucleotide polymorphisms (SNPs)?

Single nucleotide polymorphisms, frequently called SNPs (pronounced "snips"), are the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide. For example, a SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T) in a certain stretch of DNA.

SNPs occur normally throughout a person's DNA. They occur almost once in every 1,000 nucleotides on average, which means there are roughly 4 to 5 million SNPs in a person's genome. These variations may be unique or occur in many individuals; scientists have found more than 100 million SNPs in populations around the world. Most commonly, these variations are found in the DNA between genes. They can act as biological markers, helping scientists locate genes that are associated with disease. When SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene's function.

Most SNPs have no effect on health or development. Some of these genetic differences, however, have proven to be very important in the study of human health. Researchers have found SNPs that may help predict an individual's response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing particular diseases. SNPs can also be used to track the inheritance of disease genes within families. Future studies will work to identify SNPs associated with complex diseases such as heart disease, diabetes, and cancer.

3. What are genome-wide association studies?

Genome-wide association studies are a relatively new way for scientists to identify genes involved in human disease. This method searches the genome for small variations, called single nucleotide polymorphisms or SNPs (pronounced "snips"), that occur more frequently in people with a particular disease than in people without the disease. Each study can look at hundreds or thousands of SNPs at the same time. Researchers use data from this type of study to pinpoint genes that may contribute to a person's risk of developing a certain disease.

Because genome-wide association studies examine SNPs across the genome, they represent a promising way to study complex, common diseases in which many genetic variations contribute to a person's risk. This approach has already identified SNPs related to several complex conditions including diabetes, heart abnormalities, Parkinson disease, and Crohn disease. Researchers hope that future genome-wide association studies will identify more SNPs associated with chronic diseases, as well as variations that affect a person's response to certain drugs and influence interactions between a person's genes and the environment.

4. What is the International HapMap Project?

The International HapMap Project was launched in October 2002 as a scientific effort to identify common genetic variations among people. This project was a collaboration of scientists from public and private organizations in six countries. The HapMap Project released its third and final dataset in 2009. While this project is no longer active,

data that was collected from the project is still freely available to researchers worldwide. Researchers can use the data to learn more about the relationship between genetic differences and human disease.

The project created a HapMap (short for "haplotype map"), which is a catalog of common genetic variants called single nucleotide polymorphisms or SNPs (pronounced "snips"). Each SNP represents a difference in a single DNA building block, called a nucleotide. These variations occur normally throughout a person's DNA. When several SNPs cluster together on a chromosome, they are inherited as a block known as a haplotype. The HapMap describes haplotypes, including their locations in the genome and their frequency in different populations throughout the world.

The human genome contains roughly 4 to 5 million SNPs. It would be difficult, time-consuming, and expensive to look at each of these changes and determine whether it plays a role in human disease. Using haplotypes, researchers can sample a selection of these variants instead of studying each one. The HapMap helped to make carrying out large-scale studies of SNPs and human disease (called genome-wide association studies) cheaper, faster, and less complicated.

The main goal of the International HapMap Project was to describe common patterns of human genetic variation that are involved in human health and disease. Additionally, data from the project can be used to find genetic differences that can help predict an individual's response to particular medicines or environmental factors (such as toxins.)

5. What is the Encyclopedia of DNA Elements (ENCODE) Project?

The ENCODE Project was planned as a follow-up to the Human Genome Project. The Human Genome Project sequenced the DNA that makes up the human genome; the ENCODE Project seeks to interpret this sequence. Coinciding with the completion of the Human Genome Project in 2003, the ENCODE Project began as a worldwide effort involving more than 30 research groups and more than 400 scientists.

The approximately 20,000 genes that provide instructions for making proteins account for only about 1 percent of the human genome. Researchers embarked on the ENCODE Project to figure out the purpose of the remaining 99 percent of the genome. Scientists discovered that more than 80 percent of this non-gene component of the genome, which was once considered "junk DNA," actually has a role in regulating the activity of particular genes (gene expression).

Researchers think that changes in the regulation of gene activity may disrupt protein production and cell processes and result in disease. A goal of the ENCODE Project is to link variations in the expression of certain genes to the development of disease.

The ENCODE Project has given researchers insight into how the human genome functions. As researchers learn more about the regulation of gene activity and how genes are expressed, the scientific community will be able to better understand how the entire genome can affect human health.

6. What is pharmacogenomics?

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

Many drugs that are currently available are "one size fits all," but they don't work the same way for everyone. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects (called adverse drug reactions). Adverse drug reactions are a significant cause of hospitalizations and deaths in the United States. With the knowledge gained from the Human Genome Project, researchers are learning how inherited differences in genes affect the body's response to medications. These genetic differences will be used to predict whether a medication will be effective for a particular person and to help prevent adverse drug reactions. Conditions that affect a person's response to certain drugs include clopidogrel resistance, warfarin sensitivity, warfarin resistance, malignant hyperthermia, Stevens-Johnson syndrome/toxic epidermal necrolysis, and thiopurine S-methyltransferase deficiency.

The field of pharmacogenomics is still in its infancy. Its use is currently quite limited, but new approaches are under study in clinical trials. In the future, pharmacogenomics will allow the development of tailored drugs to treat a wide range of health problems, including cardiovascular disease, Alzheimer disease, cancer, HIV/AIDS, and asthma.

7. What are genome editing and CRISPR-Cas9?

Genome editing (also called gene editing) is a group of technologies that give scientists the ability to change an organism's DNA. These technologies allow genetic material to be added, removed, or altered at particular locations in the genome. Several approaches to genome editing have been developed. A recent one is known as CRISPR-Cas9, which is short for clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9. The CRISPR-Cas9 system has generated a lot of excitement in the scientific community because it is faster, cheaper, more accurate, and more efficient than other existing genome editing methods.

CRISPR-Cas9 was adapted from a naturally occurring genome editing system in bacteria. The bacteria capture snippets of DNA from invading viruses and use them to create DNA segments known as CRISPR arrays. The CRISPR arrays allow the bacteria to "remember" the viruses (or closely related ones). If the viruses attack again, the bacteria produce RNA segments from the CRISPR arrays to target the viruses' DNA. The bacteria then use Cas9 or a similar enzyme to cut the DNA apart, which disables the virus.

The CRISPR-Cas9 system works similarly in the lab. Researchers create a small piece of RNA with a short "guide" sequence that attaches (binds) to a specific target sequence of DNA in a genome. The RNA also binds to the Cas9 enzyme. As in bacteria, the modified RNA is used to recognize the DNA sequence, and the Cas9 enzyme cuts the DNA at the targeted location. Although Cas9 is the enzyme that is used most often, other enzymes (for example Cpf1) can also be used. Once the DNA is cut, researchers use the cell's own DNA repair machinery to add or delete pieces of genetic material, or to make changes to the DNA by replacing an existing segment with a customized DNA sequence.

Genome editing is of great interest in the prevention and treatment of human diseases. Currently, most research on genome editing is done to understand diseases using cells and animal models. Scientists are still working to determine whether this approach is safe and effective for use in people. It is being explored in research on a wide variety of diseases, including single-gene disorders such as cystic fibrosis, hemophilia, and sickle cell disease. It also holds promise for the treatment and prevention of more complex diseases, such as cancer, heart disease, mental illness, and human immunodeficiency virus (HIV) infection.

Ethical concerns arise when genome editing, using technologies such as CRISPR-Cas9, is used to alter human genomes. Most of the changes introduced with genome editing are limited to somatic cells, which are cells other than egg and sperm cells. These changes affect only certain tissues and are not passed from one generation to the next. However, changes made to genes in egg or sperm cells (germline cells) or in the genes of an embryo could be passed to future generations. Germline cell and embryo genome editing bring up a number of ethical challenges, including whether it would be permissible to use this technology to enhance normal human traits (such as height or intelligence). Based on concerns about ethics and safety, germline cell and embryo genome editing are currently illegal in many countries.

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