NATIONAL HUMAN GENOME RESEARCH INSTITUTE

F A C T S H E E T

GENETIC MAPPING

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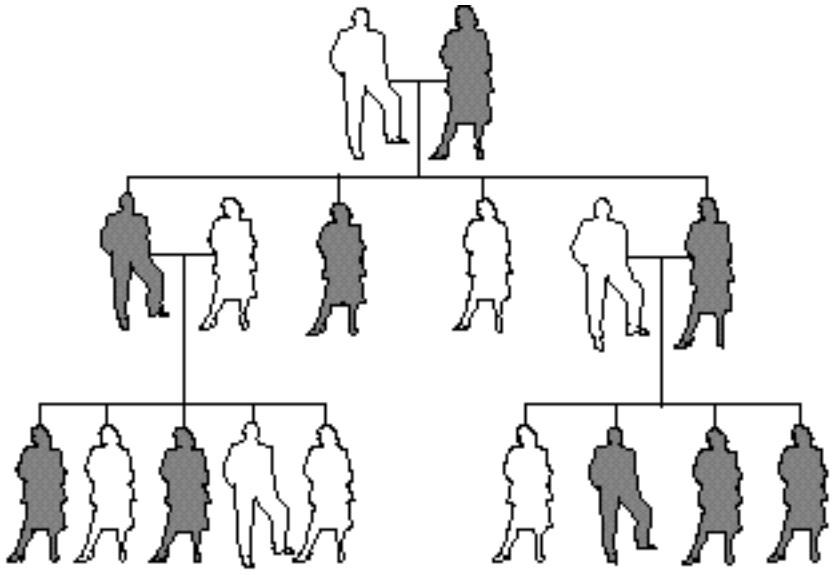
FINDING A SINGLE GENE IN THE huge morass of DNA that makes up the human genome--some 3 billion base pairs of it--requires a set of powerful tools. The Human Genome Project is developing three basic types of tools to make gene hunts and DNA analysis faster, cheaper, and practical for almost any scientist to do. These tools include genetic maps (also called linkage maps), physical maps, and DNA sequence--a detailed description of the order of the nucleotide bases in DNA. Developing new technologies to provide better and better tools is an ongoing goal of the Human Genome Project.

Genetic mapping is the first step in isolating a gene. It offers firm evidence that a disease or trait is linked to the transmission of one or more genes from parent to child. At the same time, genetic mapping provides clues about which chromosome contains the gene and precisely where on that chromosome the gene lies. Genetic maps have been used successfully for several years to seek out single genes responsible for inherited disorders. With steady improvements on the maps, they have become more useful in guiding scientists to the many genes that interact to bring about more complex, every-day disorders, such as asthma, heart disease, diabetes, cancer, and psychiatric illness.

Genetic mapping begins with collecting blood or tissue samples from members of families in which a disease or trait is prevalent. DNAis isolated from these samples and examined for characteristic molecular patterns, or markers, that are inherited by family members along with an inherited disease.

Even before researchers have identified the gene actually responsible for a trait, markers tell them roughly how close by the gene is. That's because of a genetic process called "recombination." During the development of eggs and sperm, each pair of chromosomes in those cells mix and exchange (recombine) genetic material. If a particular gene is close to a marker, the gene and marker will likely stay together during recombination and be passed on together to a child. If they are far apart, the odds are low that the gene and marker will be passed on together. So, if each family member who has a particular trait or a disease also inherits a particular marker, chances are high that the gene responsible for the disease lies close to that marker. Consequently, knowing where the marker is also tells a scientist roughly

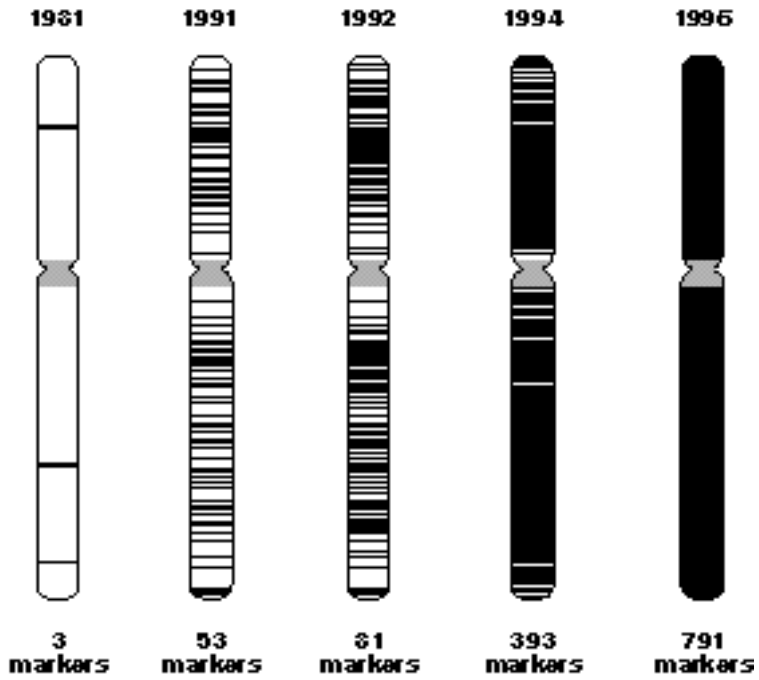


In this family tree, or "pedigree," a tendency to develop breast cancer is inherited. Children of a parent who carries a mutated BRCA1 gene (shown in gray) have a 50:50 chance of also inheriting the mutated gene. Pedigree information, plus the development of reliable DNA markers, helped researchers track the gene and determine that it is located on chromosome 17.

where the gene is. The more markers there are on the map, the more likely one will be closely linked to a disease gene, and the easier it will be to zero in on that gene.

An early major goal of the Human Genome Project was to develop dense maps of markers spaced evenly throughout the genome. With increasing quality of the markers and higher density on a chromosome, genetic mapping can now help a researcher localize almost any gene. In 1994, the human genetic map became the first of the major goals of the Human Genome Project to be reached. At that time, a large, international group of investigators published a comprehensive genetic map of the human genome containing nearly 6,000 markers. With markers spaced less than 1 million bases apart on average, this map is more detailed than the goal originally called for. What's more, this goal was reached a full year ahead of schedule. Subsequently, scientists have continued to put finishing touches on the genetic map, but that phase of the Human Genome Project is now essentially complete.

Markers consist of slight differences in the arrangement of letters in the genetic alphabet--A, T, C, and G-- on individual chromosomes. Because these differences, called polymorphisms, usually occur in DNA that does not contain a gene, they don't usually affect a person's health. But they can tell a researcher which person the DNA came from, which makes them extremely valuable in tracking inheritance of traits through several generations of a family. They are also useful for forensic applications.



Genome project scientists have made genetic maps much more detailed by adding hundreds of new markers to each chromosome. The markers on this genetic map of chromosome 4 help scientists pinpoint the location of a gene.

Although there are several different types of genetic markers, the type most used on genetic maps today is known as a microsatellite. These markers are of high quality and easy to use with automated laboratory equipment, so mapping a trait in a large number of family members can be done rapidly.

The development of high-resolution, easy-to-use genetic maps promises to revolutionize genetics research. Using current genetic maps, an investigator can rapidly localize a suspect gene to a chromosomal region "just" a few million base pairs in length. The improved quality of genetic linkage maps has reduced the time required for such gene mapping from a period of years to, in many cases, a matter of months or weeks.

Genetic mapping data generated by Human Genome Project laboratories is stored in databases scientists can freely access. In the United States, the Genome Database (GDB, http://gdbwww.gdb.org/gdb/docs/gdbhome.html) serves as a public repository for mapping information.

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