Gene Mapping Essay, Research Paper

Gene Mapping began when the U.S. Government held a conference to explore if DNA damage occurred in people exposed to low levels of radiation in Japan after the 1945 Atomic Bombs. There, scientists quickly realized that observing the human genome could be useful in discovering environmental mutates. Shortly afterwards, Renato Dulbecco revealed the entire sequence of human DNA and had a great impact on cancer research (Purves, et al. 1998).

In 1990, scientists from around the world began the Human Genome Project and would set out to map the human genome to provide a key to the collective history of human disease that will allow an unprecedented acceleration of the study of pathogenesis. The first stage of the project was the construction of a genetic linkage map followed by a variety of physical maps (see illustration one).

The Human Genome Project (HGP) is a federally funded research project that was expected to take 15 years from the start and cost several billion dollars. The project was controversial from the start over its scientific worth relative to other projects and had considered the private sector for financing the HGP (Annas and Elias, 1992).

With the overall intent of furthering the basic scientific understanding of human genetics and the role of genes in health and disease, the project’s initial goals were:

+ Construction of a high-resolution genetic map of the human genome.

+ Production of a variety of physical maps of all human chromosomes and of the DNA of selected model organisms with emphasis on maps that make the DNA accessible to investigators for further analysis. The series of maps would be of increasing fine resolution.

+ Determination of the complete sequence of human DNA and DNA of selected model organisms (Annas and Elias, 1992).

In fact, with the development of new technology, faster, more accurate and less expensive methods of mapping have developed. Speculating that it may be finished before its target date of 2005 (Murray, et al. 1996).

The Human Genome project was to gain a basic understanding of the entire genetic blueprint of a human being. This genetic information is found in each cell of the body, encoded in the chemical deoxyribonucleic acid (DNA). The project is intended to identify all the genes in the nucleus of a human cell, to establish, by a process known as mapping where those genes are located on the chromosomes in the nucleus (see illustration two). Then, determine by a progress known as sequencing the genetic information encoded by the order of the DNA’s chemical sub units (Murray, et al. 1996).

DNA typically comes from small samples of blood or tissue obtained from many different people. Although the genes in each person’s genome are made up of unique DNA sequences, the average variation in the genomes of two different people is less than one percent. DNA fingerprints are derived from traces of human biological material such as blood, semen, hair, or other tissue. This DNA technology is applied to samples to identify patterns of genetic sequences that are unique of each human being. Matched DNA fingerprints can establish the identity of a given person with near certainty. Therefore, DNA technology has given the practical use of identifying criminals, family members, and bodily remains (Gibbons, 1998).

Currently, the HPG is ahead of schedule and under budget. More than 4800 genes have been mapped at least to a specific chromosome, 2900 genes of known functions have been cloned, 1000 genetic diseases have been associated with a defect in a mapped gene, and more than 35 million base pairs of unique human DNA had been sequenced. Maps of the entire human genome have been published, with an average of 110,000 base pairs apart. The ultimate goal is to sequence all 3 billion base pairs by the year 2005 (Murray, et al. 1996).

There are two main categories of gene mapping, linkage and physical. The linkage mapping method identifies only the relative order of genes along a chromosome. Physical mapping can place genes at specific distances from one another on a chromosome. Both types of mapping use genetic markers, detecting physical or molecular characteristics that differ among individuals and that are passed from one generation to the next (Shook, et al. 1991). The linkage of genetic maps describes the positions of genes on chromosomes relative to one another by determining how frequently two marks are inherited together (see illustration three). Based on the principle that any two markers or genes that are positioned closely together are more likely to be inherited together when reshuffling of chromosomal DNA occurs during Meiosis, genetic maps describe the distance between markers in centimorgans. Two markers are said to be one centimorgan apart if they are separated during recombination 1% of the time. This unit of measure, while highly variable, is approximately 1,000,000 base pairs. Markers must be polymorphic, existing in more than one form (Schook, et al. 1991).

Now virtually all polymorphic markers useful for mapping are variations in DNA sequences; those found on exons, which are portions of a DNA molecule that codes part of a polypeptide, are potentially associated with visible differences among individuals such as eye color. While those found on introns, which are portions of a DNA molecule that is not involved in coding parts of polypeptide molecules, usually have little effect on the organism but are detectable at the DNA level and can be utilized as markers. In 1994 the first comprehensive report was published including nearly 6,000 markers spaced an average of less than 1 million base pairs apart (Schook, et al. 1991). The most important part of physical mapping of the chromosome is the single continuous molecule of DNA. This double stranded molecule, shaped like a twisted ladder, is composed of linked chemical compounds known as nucleotides. Each nucleotide consists of three parts: A sugar known as deoxyribose, a phosphate group, and any one of four which join in pairs to form the rungs of a ladder – specifically Adenine always pairs with thiamine and Guanine always pairs with cytosine (Schook, et al. 1991).

In contrast, Physical mapping also determines the physical distance between landmarks on the chromosomes. With its measurement of relative distances between markers, the physical map measures the actual physical distance between chromosomal sites and describes the chemical characteristics of the DNA molecule itself. The earliest of these, the cytogenetic map, relied on microscopic analysis of the banding patterns of stained chromosomes to determine the location of genes relative to visible markers. The most accurate mapping is now done with robotics, lasers, and computers to measure the distance between genetic markers. The DNA fragments can be duplicated numerous times in the laboratory so that the resulting identical copies called clones can be tested for the presence or absence of specific genetic landmarks. This has brought about higher resolution analysis. The high-resolution physical maps now assembled use a variety of approaches for purifying pieces of DNA. One method relies on restriction enzymes isolated from bacteria whose natural function is to attack viral and other foreign DNA to recognize short sequences of DNA and cut the molecules at those sites. In one approach, “Top-down” mapping, the small fragments then can be amplified by cloning or by polymerase chain reaction techniques. Polymerase chain reaction (PCR) is technique for rapid production of millions of copies of a particular stretch of DNA. Next, the pieces are reassembled in various ways and their order and distances are established. “Bottom-Up” mapping also involves cutting the chromosome into fragments, then cloning and ordering the fragments into overlapping sequences of DNA known as contigs (see illustration four)(Gibbons, 1998). Contigs are linked into a library of chromosomal segments and reassembled by sophisticated automated sequencing machines. Contig mapping of the Human genome favored the following strategy: to map the genome one chromosome at a time, dividing and subdividing each chromosome into smaller and smaller segments before beginning restriction enzyme mapping and ordering of clones. After subdivision, restriction maps of these smaller segments would be determined and the information linked together to form continuous maps of whole chromosomes. In principle, this strategy could be broken down into five consecutive steps (Gibbons, 1998):

1. isolation of each human chromosome,

2. division of each chromosome into a collection of overlapping DNA fragments 0.5 to 5 million base pairs in length,

3. subdivision and isolation of each of these chromosomal fragments into overlapping DNA fragments about 40,000 base pairs in length,

4. determination of the order of the 40,000-base-pair DNA fragments as they appear in the chromosomes and determination of the positions of cutting sites for a restriction enzyme within each of these fragments, and

5. use of the mapping information gained in step 4 to link together each of the overlapping 0.5-to 5-million-base-pair fragments isolated in step 2.

The goal of the progressively more sophisticated mapping is the ability to definitely connect a gene and a disease.

In addition to physical maps, genetic maps were useful to the project in two ways. First, the linkage studies tracking disease – causing genes by positional cloning. Secondly, by providing new markers for physical mapping (Gibbons, 1998).

Duplicating DNA accurately and quickly is important to both mapping and sequencing. Scientists first replicated fragments of human DNA by cloning them in single – celled organisms that divide rapidly, such as bacteria or yeast. Now the common use of cloning DNA is known as the polymerase chain reaction, which is easily automated and can copy a single molecule of DNA many millions of times in a few hours. However, the entire DNA has not been sequenced from libraries of different tissues at different stages of life. In fact, only short unique regions, called expressed – sequence tags, have been developed to act as chromosome markers (Gibbons, 1998).

Some benefits, in general, are the genetic information we have and when the Genome Project is completed, it will have generated a catalog describing 50,000 to 100,000 human genes at some level of detail; high-resolution maps of the chromosomes, including hundred of thousand of landmarks (see illustration five). Three billion base pairs of DNA sequence information. The project has laboratory information management systems, robotics, database management systems, and graphical user interfaces that are for the computing tools required for helping researchers make sense of this flood of data (Purves, et al. 1998).

A new field of research, known as bioinfomatics, has developed to address the computing challenges raised by the project. Moreover, the researchers in bioinfomatics have developed public databases connected to the Internet to make Genome Project data available to scientists worldwide. Regardless of who completes the sequencing, by what method, and when, the mapping of the 8 billion base pairs that together make up human structure, functioning and propensity to disease is only the beginning. The real challenge will lie in interpreting the information and relating it to human health and disease (Schook, et al. 1991).

In conclusion, the HGP has enormous possible benefits for the identification of the genes that are altered in diseases and may even lead to cures. It can tell us about ourselves and is a strong advocate of reproduction and procreative freedom. This research covers the significance of genetic information of reproductive choices. Consequently, this information could be used in making decisions about having children or even seeking an abortion. The side effects deal with the more profound ethical questions of possible applications of genetic data for altering the basis of human disease, human talents, and social behavior.

Questions about personal freedom, privacy, and society versus individual rights of access to genetic information (Gibbons, 1998).