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What is Genomics?

R. Blundell
Department of Physiology and Biochemistry, Faculty of Medicine and Surgery
Biomedical Science Building, University of Malta, Msdia MSD06, Malta

The genome is the complete set of instructions for making an organism. The term "genome" is more than 75 years old and refers to an organism's set of genes and chromosomes[1]. The term genomics was coined later, to describe the scientific discipline of mapping, sequencing and analysing genomes. Currently is understood to encompass all genetic information carried on genes and chromosomal or mitochondrial DNA required for structural organisation and functional living organisms[2].

The term has become universally accepted over the past decade. Genomics is now undergoing, however, a transition or expansion from the mapping and sequencing of genomes (the original stated goals of the human genome project) to an emphasis on genome function. It is felt that the full description of our genome will not be sufficient to understand its functional organisation, neither for individual units nor at a more integrated level[3]. Genome analysis can be divided into two categories:

- Structural genomics represents an initial phase of genome analysis and has a clear end point-the construction of high-resolution genetic, physical and transcript maps of an organism. The ultimate physical map of an organism's genome is its complete DNA sequence.
- Functional genomics represent a new phase of genome analysis. Functional genomics refers to the development and application of global experimental approaches to assess gene function by making use of the information and reagents provided by structural genomics. It provides a fertile ground for creative thinking in developing innovative technologies that make use of the vast resource of information derived from structural genomics. The fundamental strategy in the application of functional genomics expands the scope of biological investigation based on the study of single genes or proteins to the study of all genes or proteins in a single systematic fashion[3].

Computational biology plays a critical and expanding role in this area. While structural genomics is characterised by data management, functional genomics is characterised by high throughput or large-scale experimental methodologies combined with statistical and computational analysis of the results. Functional genomics aims to rapidly narrow the gap between sequence and function of genomes and to yield new insights into the behaviour of biological systems[4].

Why genome mapping?: Although the process of genome mapping is laborious, slow and expensive, its benefits are inestimable. There are various areas by which genome mapping, although still in its early stages has revolutionised our way of thinking, our way of doing and our economy. Some of these major areas are medicine, agriculture, biotechnology, forensics, transgenomics, ecology and evolutionary biology.

Knowledge of the exact locations and sequences of all these genes has the potential for new efficient diagnostic techniques, treatment of disease by gene therapy and the development of animal model diseases produced by transgenic techniques. Transgenic techniques can also be used to produce important proteins, more productive animals in terms of Economic Trait Loci (ETL) and more disease resistant animals/plants.

Genome mapping can be used to marker-assist the selection of socio/economic important plants, animals and micro-organism. Cloning of the whole organisms may be possible and this will help to protect endangered species, safeguard ecological systems and also improve the economy of third world countries. Genome mapping has also helped in the field of forensics especially for paternity/maternity testing, in crime investigation and immigration problems.

Genome mapping strategies: A genome map describes the order of genes or other markers and the spacing between them on each chromosome. There are two main types of genome maps:

- Genetic linkage map depicts the relative chromosomal locations of DNA markers by their patterns of inheritance.
- Physical map describes the chemical characteristics of the DNA molecule itself.

Genetic linkage maps: A genetic linkage map shows the DNA markers along the chromosome. Markers must be polymorphic to be useful in mapping, that is, alternative

forms must exist among individuals so that they are detectable among different members in family studies. Markers can be expressed DNA regions (genes) or DNA segments that have no known coding function but whose inheritance pattern can be followed.

On the genetic map, distances between markers are measured in terms of centimorgans (cM), named after the American geneticist Thomas Hunt Morgan. Two markers are said to be 1 cM apart if they are separated by recombination 1% of the time. A genetic distance of 1cM is roughly equal to a physical distance of 1 million bp (1 Mb) in the human genome.

Physical maps: There are different types of physical maps based on the degree of resolution. The lowest-resolution physical map strategy include the chromosomal (sometimes called cytogenetic) map, which is based on the distinctive banding patterns observed by light microscopy of stained chromosomes and a cDNA map shows the locations of expressed DNA regions (exons) on the chromosomal map. The highest-resolution physical map strategy includes the cosmid contig map and depicts the order of overlapping DNA fragments spanning the genome and a macrorestriction map describes the order and distance between enzyme cutting (cleavage) sites.

Low-resolution physical mapping: There are two types of low-resolution physical mapping:

Chromosomal map: In a chromosomal map, genes or other identifiable DNA fragments are assigned to their respective chromosomes with distances measured in base pairs. These markers can be physically associated with particular banding primarily by *in situ* hybridisation, a technique that involves tagging the DNA marker with an observable label (e.g., one that fluoresces or is radioactive). The location of the labelled probed can be detected after it binds to its complementary DNA strand in an intact chromosome.

A map resolution of 100,000 bp was obtained by utilising FISH and using chromosomes at the interphase stage of cell division[5].

cDNA map: A cDNA map depicts the positions of DNA regions that are transcribed into mRNA (exons) relative to particular chromosomal regions or bands. These short cDNA fragments are known as expressed sequence tags (ESTS). A gene may be represented by multiple ESTS, which may correspond to different portions of a transcript or various alternatively spliced transcripts[6]. Thus for mapping purposes, the fragments having the 3 untranslated regions (3' UTR) of mRNAs were selected and these sequences can be efficiently converted to gene-specific Sequence Tagged Sites (STSs)[7].

cDNA map, usually obtained by FISH, represents the expressed genomic regions, thus these maps have the most biological and medical significance. A cDNA map can provide the chromosomal location for genes whose functions are currently unknown.

High resolution physical mapping: The two current approaches to high-resolution physical mapping are termed 'top-down' (producing a macrorestriction map) and 'bottom-up" (resulting in a contig map).

In the top-down mapping, a single chromosome is digested (with rare restriction enzyme) into large pieces, which are ordered and further digested into smaller fragments. Thus a macro-restriction maps depict the order of and the distance between sites at which rare-cutter enzymes cleave. The resolution of such map is low and may not be useful in finding particular genes; in addition, this strategy generally does not produce long stretches of mapped sites.

In the bottom-up approach the chromosomes digested into smaller pieces, each of which are cloned and ordered in an array library. The ordered fragments form contiguous DNA blocks known as contigs. An advantage of this study is the accessibility of these stable clones to other researchers.

The cloning of large DNA pieces is possible by using artificially constructed chromosome vectors that carry human DNA fragments as large as 1Mb such as in Yeast cells as artificial chromosomes (YACs)[8]. Before YAC were developed, the largest cloning vectors (cosmids) carried insets of only 20 to 40 kb. A more detailed map of a large YAC insert can be produced by subcloning, a process in which fragments of the original insert are cloned into smaller-insert vectors. Due to the fact that some YAC regions are unstable, Bacterial Artificial Chromosomes have been developed, whereby larger inserts (80 to 300 kp) can be accommodated[9].

Radiation Hybrid (RH) panels are being developed and combine features of physical and genetic mapping[10]. These consist of hamster cell lines that contain many large fragments of human DNA produced by radiation breakage[6].

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