Introduction to DNA Microarrays

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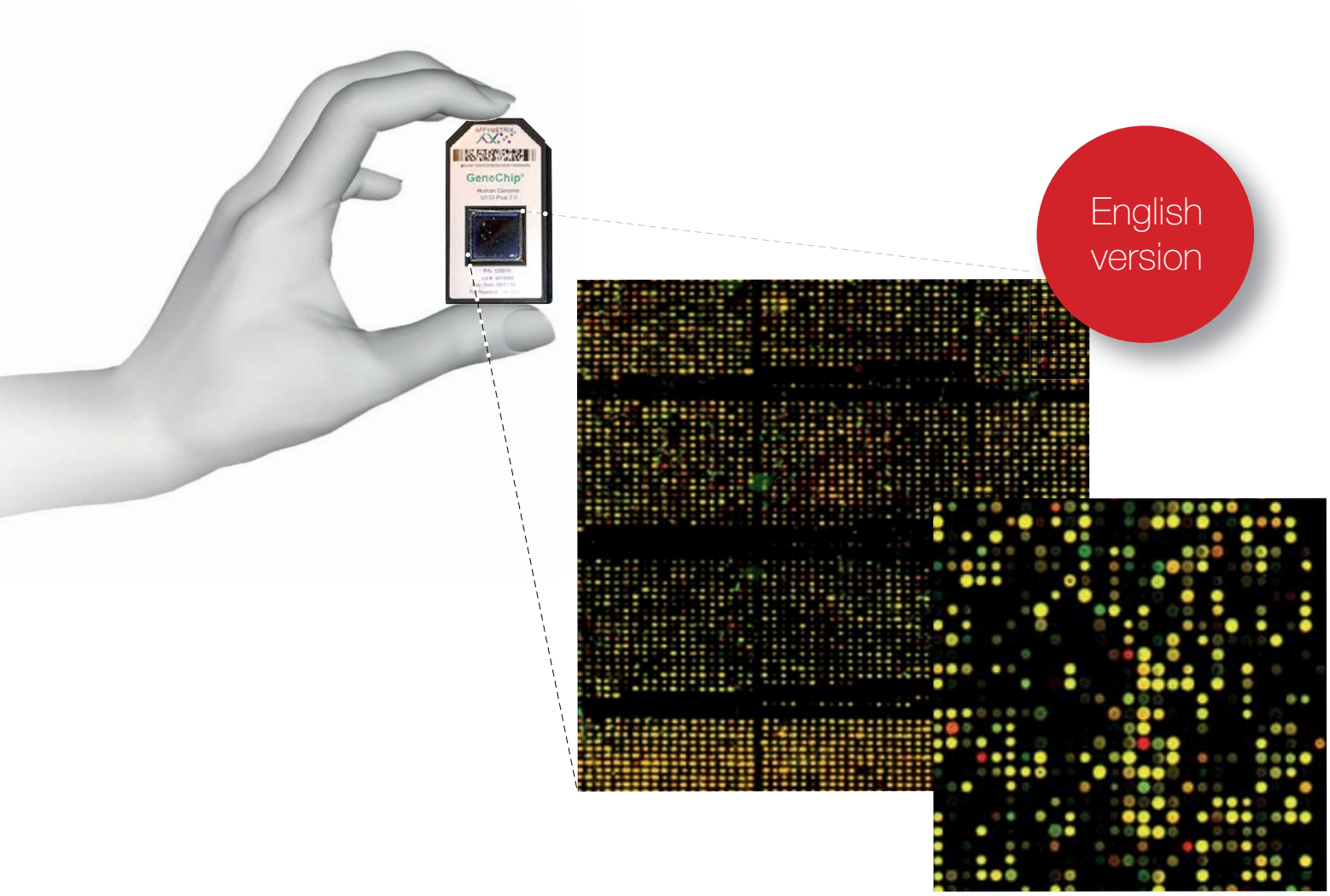
Version 2.3



English version

ELLS – European Learning Laboratory for the Life Sciences

EMBL

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1.1 Introduction

We are living in what historians in the future will refer to as the “Genomic age”, a time when scientists around the world are working on one of the most ambitious projects ever thought up by man “The human genome project” (HGP). Its primary aim was to map out the 3 billion nucleotide bases (the A’s, C’s, G’s and T’s) found on the 23 pairs of chromosomes that make up the human genome.

The publication of the “draft” sequences in 2001 was set to revolutionize molecular biology by largely eliminating the need to clone and sequence genes involved in human health and disease. Biologists could go to the web to look up gene sequences in public online databases. But the draft sequences contained hundred of thousands of gaps and had misassembled regions where portions of the genome were flipped or misplaced.

Since publication of the drafts, work has continued to fill in the gaps: by October 2004 there were just 341 remaining! What is the next step? Well this is perhaps the biggest, that is to find out what the genes actually do and how they work in concert to perform all the tasks required to keep us alive. And perhaps more importantly how the expression of certain genes can lead to diseases such as cancer, with the possibility of designing tailor-fit medical treatments to suit an individual’s particular genetic make up.

It is not only the HGP which is producing vast amounts of data. By using techniques such as the “whole-genome shotgun’ (WGS), in which the entire genome is shattered into bite-size pieces, sequenced, and then assembled by software in one conceptually simple step, biologists are sequencing the genomes of model organisms which have been used in biological research for years. Knowing which gene is involved in the animal version of a disease can help pinpoint the gene in humans. Moreover, comparing human DNA to animal DNA can also provide clues about basic biology and evolution. So as the list of completely sequenced organisms, which includes microorganisms, invertebrates, plants and a menagerie of animals—rat, mouse, chimpanzee, grows, new tools are being developed to interpret the vast amount of information flowing out of genomic mapping to understand gene expression.

1.2 Gene expression in the cell

With only a few exceptions, every cell of the body contains a full set of chromosomes and identical genes. Only a fraction of these genes are turned on however, and it is the subset that is “expressed” that confers unique properties to each cell type. “Gene expression” is the term used to describe the transcription of the information contained within the DNA, the repository of genetic information, into messenger RNA (mRNA) molecules that are then translated into the proteins that perform most of the critical functions of cells. Scientists study the kinds and amounts of mRNA produced by a cell to learn which genes are expressed, which in turn provides insights into how the cell responds to its changing needs. Gene expression is a highly complex and tightly regulated process

that allows a cell to respond dynamically both to environmental stimuli and to its own changing needs. This mechanism acts as an “on/off” switch to control which genes are expressed in a cell as well as a “volume control” that increases or decreases the level of expression of particular genes as necessary.

1.3 Gene expression analysis

Examining gene expression involves looking at the amounts of mRNA or protein produced by a cell at a given time. Up to the 1990s, scientists could only examine a handful of genes at a time. Now they have developed a new tool called the DNA microarray, also known as a DNA chip, which promises to carry the science of understanding genomes to a whole new level by analysing the expression of thousands of genes in a single experiment quickly and efficiently.

The principle behind gene expression analysis basically involves a comparison of samples, for example tissues – young and old – to examine, development and aging, simple and complex organisms to study evolution, and diseased and healthy tissues to study gene expression in specific diseases.

1.4 Microarrays - How chips work

The basic principle exploited in DNA chips is that an mRNA molecule will bind selectively, by base pairing, with DNA that has a complementary sequence. And the idea is to print thousands (20,000) of spots of single- stranded DNA sequences in a microscopic grid, a few centimetres across, which act as an array of minute “sticky pads” that attract complementary mRNA flooded over the surface. DNA microarrays are very compact and can easily be produced in the lab at low cost using glass slides rather like the ones used for microscopy. As you can imagine, printing 20,000 minute spots of DNA (each spot corresponding to a specific gene) on such a small surface is a difficult task. Not only do the spots have to be exactly the same shape, they also have to be equidistant from one another. These problems have been solved by robotics.

1.5 Chips at EMBL

Several research groups at EMBL use microarrays. The group of Wilhelm Asorge has been at the forefront of microarray manufacturing and analysis, building a microarray for human genes.

The laboratory of Matthias Hentze has used microarrays to investigate a disease in human called “hemochromatosis”, a metabolic disorder that causes increased absorption of iron, which is deposited in the body tissues and organs. The iron accumulates in the body where it may become toxic and causes damage.

In the context of development, Eileen Furlong has used microarrays to find out which genes are expressed at different stages of development of the fruit fly (*Drosophila melanogaster*). Finally, the laboratory of Fotis Kafatos is using microarrays to identify genes of the immune system of the mosquito (*Anopheles gambiae*), which might help to destroy the malaria parasite within the insect before it infects humans.

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