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The human genome project : Impact of patenting of human genes on further development of knowledge of human genome*

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Summary — The Human Genome Programme (HGP) an ambitious 15 y project is currently being implemented in several laboratories spread across the globe. It aims to ultimately construct a high resolution genetic map of human genes — the centi Morgan genetic map, produce a variety of physical maps of all human chromosomes and determine the complete sequence of human DNA, etc. In the very beginning of this international collaborative effort some researchers have filed patent applications on several such gene fragments which have no assignable use or utility. The implications of this filing on the HGP as such and on scientific community and mankind at large are discussed.

Gene mapping as a scientific programme is relatively of recent origin. The first description of a human karyotype was proposed in 1956 and the first correct assignment of autosomal gene was reported in 1968. It was only after 1968 that this area witnessed an increased activity presumably due to development of techniques such as somatic cell hybridization which made available rodents as model for genetic studies. Similarly the development of recombinant DNA techniques increased the number of genetic markers available for linkage studies and made physical mapping and sequencing of genes possible. The development of this technique has helped to produce meiotic maps for several human chromosomes. The first meiotic map of the whole human genome is already a reality and it is expected that complete restriction map of human DNA shall soon be proposed.

Human Genome — Its Characteristics

The human geneome contains an estimated 100,000 genes which encode information in DNA, first for creating a human individual and then for sustaining the every day life of individual. These genes are distributed among 23 pairs of chromosomes (22 pairs of autosomes and a pair of sex chromosomes X and Y), each chromosome containing a long DNA molecule combined with various protein molecules, which determine the overall structure of the chromosomes. This DNA molecule is composed of four units, known as nucleotide bases linked together in varying combinations. A total of three billion such base pairs exist in a human genome and the order of these bases, the "sequence" is the important feature that distinguishes individuals and species from each other. More than 60 per cent of the genetic messages seem to be redundant, they do not appear to be contributing to the genes that code for the proteins that constitute life. However to build a complete map even this redundant part is necessary.

So far only about two per cent of human genes have been assigned to specific chromosomal locations and only a few of the genetic diseases out of about 4000 such diseases have been understood at molecular level. This ambitious project of genome mapping thus aims to locate the position of all these genes, and the genetic information encoded in them, including the aberrant information in disease genes.

Human Genome Mapping — The Need and the Goals

The idea to unravel the genetic complexity of *Homo sapiens* was conceived in 1985 when it was realized that human genome map holds the key to understand the function of cells and tissues and all the inherited information needed to make a human being.

Thus, set with a goal to determine the nucleotide sequence of the human genome, the genomes of some model organisms, and genes with aberrant function, an international research effort, the Human Genome Project (HGP) has participation of France, Germany, Italy, UK, erstwhile USSR, the European Community,

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Japan, and USA. The project would ultimately construct a high resolution genetic map of the human gene — the centi Morgan genetic map; produce a variety of physical maps of all human chromosomes and the chromosomes of selected model organisms, determine the complete sequence of human DNA and of the DNA of selected model organisms, develop capabilities for collecting, storing, distributing, and analyzing the data produced and create appropriate technologies necessary to achieve these objectives.

The project spread over a period of 15 y has been divided into a three stages, each stage lasting 5 y. The first stage of the project (1991-95) would develop improved technologies for mapping and sequencing and developing a data bank. During this phase itself attempt to complete low-resolution genetic and physical maps of the whole genome would be completed.

The second phase lasting from the year 1995-2000 would attempt to produce refined physical and genetic maps of the human genome and would undertake large scale sequencing projects. The complete sequencing of the genome is expected during the last phase covering the period 2001-2005.

HGP — The Work Plan

The total project is planned around creating first the genetic map, then the physical map, and finally the complete DNA sequence.

Under the HGP it is aimed to produce a map showing general location of genes which show characteristics associated with disease, physical traits and genetic markers. It shows which genes are located close to which other genes. For example, the genes for characteristics that are always inherited together must be located close to each other on the same chromosomes and the genes for those characteristics which are inherited together frequently but not always are perhaps located on the same chromosome, relatively close together. Analysis, such as this produces a map that shows general location of the genes for these characteristics as they occur on chromosomes.

The physical map is a description in which the distance between certain specific points is worked out in terms of actual length of DNA and not inferred indirectly from inheritance pattern. This map will help to locate precisely the position of any piece of DNA within the genome.

The final phase of the work plan is to get a read-out or the "sequence" of the order of the nucleotide bases in the genome. It visualises that every element of the genome — genes, control regions, other regions — will be identifiable and the instructions they contain interpretable. This phase of work is the most challenging one of the entire HGP.

Patenting of Gene — A Damper in the HGP

No body could have imagined just a year ago that a project so ambitious in its goals and hitherto a fine example in international collaboration would become so controversial soon after its start in 1989 when the US project team based at National Institute of Neurological Disorders and Stroke and responsible for sequencing partially every gene active in human brain decided to file patent applications on these sequences. The first application carrying information on 347 segments of DNA was filed in mid-1991 and the second having 2375 additional gene fragments was filed in eary 1992. These two applications from USA have been followed by an application from Medical Research Council of Britain which has filed a patent application in USA, covering more than 1000 complementary DNA fragments. These DNA fragments have a recognisable sequence of bases at one end but no known biological function. They are used in mapping sequences of longer stretches of DNA. Further, there are reports that a US company Incyte Pharmaceuticals, Inc., has filed for patent rights on thousands of cDNA sequences that will lead to genes that are involved in inflammatory diseases and other ailments.

The US laws permit patenting of genes once they have been isolated and characterized. But in the present case US team simply selected random clones from a collection of complementary DNAs which correspond to active genes. Then using automated sequencing machines and robots they sequenced a short stretch of each one to create a tag or identifier, which can later be used to pull out the full gene. Of the two US patent applications, the first one has very sweeping claims; they cover the "tags", full length genes and their proteins, whereas the second one has narrowed down claims, only the tag and the gene.

Patent Applications — What it Bodes for HGP

The filling of these patent applications has created a furore in the world community of molecular biologists. The critics of the patent applications charge that:

(i) These patent applications for right on genes of unknown function, on the basis of incomplete sequences run counter to the spirit of international collaboration and could clutter the commercial scene with patents that are all but useless.

(ii) The filing of these applications may inhibit collaboration and the free exchange of data, both nationally and international. Already, because of Britain's application, scientists in Germany, Italy, and France are reluctant to place DNA sequences, worked out by them, in a database located in Britain at MRC's unit at Northwick Park, London.

Patenting of Genes — What it Bodes for Mankind

The applications filed by USA and UK on gene sequences having no specific use has given a set back to the collaborative efforts on genome mapping and bodes ill for the world's health care programmes as well.

Some recent developments on this account, however, show some hope. First is the rejection, in an initial ruling by the US Patent and Trademark Office, of the patent application of the US National Institute of Health. The major grounds for rejection of patent application are: (i) The gene fragments sequenced by NIH scientists lack legal novelty "as the claimed invention was known or used by others in this country (USA). The claims are broad enough and vague and indefinite enough" and "embrace the cDNA libraries that were used to determine the nucleotide sequences. The NIH scientists have themselves acknowledged that the cDNA libraries used to obtain the sequence data were purchased from Stratagene of USA", (ii) The fragments lack patentable utility because their value as probes is unclear and also nearly 80% of the ESTs as claimed in the application have a poor probability of coding for any protein at all, (iii) The fragments sequenced are obvious because 15-base stretches (15- mer) of The fragments have already been reported in the literature, and (iv) The application fails to provide an adequate written description of the invention thus one having ordinary skill in the art cannot know what the invention is. The NIH scientists had six months time up to February 20, 1993 to appeal against the decision.

The second is the recent publication of some reports on human DNA sequences which will eventually stymie the attempts to file patents on human genome. One such publication is on successful cloning and mapping of Y or male chromosome and the other is mapping of chromosome 21, containing the genes involved in Down's syndrome, Alzheimer's and other neurological diseases. Each of these reports contain map of an actual physical representation of the chromosome consisting of chunks of cloned DNA pieced together in correct order. These reports shall not only make the task of filing patent applications by other groups extremely difficult but will also speed up the physical mapping of all human chromosome as they have used an almost identical mapping approach in which maps are assembled from giant clones, known as YACs (Yeast Artificial Chromosomes) with the aid of a new type of marker that can be detected by polymerase chain reaction (PCR).

The third development is the circulation among member countries a draft directive by Commission of the European Communities (EC) which, *inter alia*, stipulates that no patent could be granted on "a human gene neither the function of which nor the protein for which it codes is known". According to some experts, "this restriction, if adopted by EC would prohibit patents on complementary DNA fragments of unknown function".

However, not withstanding these developments, if the National Institute of Health, Bethesda, USA, appeals against the decision of US Patent and Trademark Office's ruling which, in all probability, it will do and wins the case, the scenario which will emerge is indeed a cause of concern. It is likely that :

(i) Treating some human chronic diseases will be impossible as for the use of any drug based on, say brain proteins shall have to first settle the royalty question with the patentees of the DNA sequences of the brain genes. One such case has already been reported wherein a doctor of St. Mary's Hospital in Manchester, UK, who was screening people for the defective gene that causes cystic fibrosis has received a notice for payment of US$ 6000 as royalty from two US scientists who discovered and sequenced the cystic fibrosis gene in 1989,

(ii) It might open a flood-gate for filing of patent applications, the information contained in them becoming patent subject matter. If such information lies locked up in patents then the whole purpose of HGP would be defeated,

(iii) Aberrant genes responsible for monogenic diseases, such as thalassaemia, huntington's disease, and duchenne muscular dystrophy will take years to be identified and any cure will hence be far off as patenting shall block international efforts to find cure for these diseases, and

(iv) It will hinder the creation of linked international data banks/information systems envisaged to be set up for handling vast amounts of data that should have generated over the course of the project.

Conclusion

Until a clear policy on patenting of genes is not agreed to by the collaborators , this international effort will result in a patent stampede that will destroy international collaboration and hinder product development. The patent should be filed on the "use" of sequences rather than on the sequences themselves.

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