Question Q 150

Patentability Requirements and Scope of Protection of Expressed Sequence Tags (ESTs), single Nucleotide Polymorphisms (SNPs) and Entire Genomes

1. Introduction

The entire DNA sequence of an individual is known as the genome. A copy of the genome is found in most cells in the body. A large proportion of DNA in the mammalian genome has no known function; it does not appear to encode any known protein. Dispersed within the genome are genes: regions which encode specific proteins. Their codes are read by a mechanism within the cell (transcribed). The transcription process forms a single stranded molecule (RNA) which has a chemical structure similar to DNA, although much shorter. Many RNA molecules have specific functions, but of particular interest are those which encode proteins. These messenger RNAs (mRNAs) are read by a second cellular mechanism (translated) to produce proteins.

The DNA in the genome is divided up into a number of separate molecules, which are neatly packaged into chromosomes. A human being normally has 23 non-identical pairs of chromosomes, one of each pair being provided by each parent. (Each parent provides a copy of half of its genome, reshuffled in a process (recombination), to promote variety among its offspring.) Not every human genome has exactly the same sequence, which is why individuals vary one from another; but most of the sequence is the same between individuals. There are thought to be about 80,000 genes in the human genome.

In recent years a multinational initiative, the Human Genome Project, has sought to obtain sequence data covering the entire human genome (some 3x10^9 base pairs). Much work has been done, but more remains. Initial efforts have focused on producing maps, composed of numerous markers at defined locations, of the 23 chromosomes. The original timetable for sequencing the whole genome has been brought forward two years to 2003 in response to the development of new, faster techniques.

Two types of markers which are of particular interest are 'expressed sequence tags' (ESTs) and 'single nucleotide polymorphisms' (SNPs). ESTs are short, random fragments of DNA. They are sequences isolated from mixed mRNAs and converted back into DNA form (known as cDNA) using a particular enzyme. Because each EST is identified as relating to an mRNA, it represents part of a gene that encodes proteins. ESTs are sequenced using known techniques and their location in the genome can then be determined. ESTs reflect the sequences of portions of those genes which were being transcribed in the tissue from which the RNA was obtained. The full gene sequence, if subsequently discovered, would include DNA corresponding to the EST, or part of it.

SNPs are sites in the genome where there is variation among the population of one particular base in the sequence (for example, an A may be replaced with a G). They occur about once every 1,000 bases. SNPs may be responsible for variations between individuals, including variations which predispose an individual to disease, or cause it. Even if they have no effect on function, SNPs are potentially useful for tracking other variations nearby, as adjacent stretches of DNA tend to be inherited together ('linkage disequilibrium'). Those SNPs which fall within genes (cSNPs) are of particular interest. It is expected that patterns of SNPs can be used to identify people with an increased risk of contracting a particular disease or those who may be susceptible to adverse drug reactions.

2. The Legal Position

AIPPI has considered a number of questions relating to the protection of industrial property in the field of microbiology. These include Question Q 56, resulting in the successful conclusion of the Budapest Treaty; Question Q 82 concerning patent protection for Biological Inventions; and Question Q 93 concerning the relationship between patent protection and biotechnological inventions and plant variety protection, and also patentability of animal breedings. In Question Q 114 AIPPI raised as discussion topics the
The patentability of the human body and body "products", the human genome and DNA sequences. Question Q 142 has examined the scope of patent protection.

There are also policy issues arising from the Rio Convention on Biological Diversity (of 5 June 1992). The Rio Convention provides:

Article 15.1 Recognising the sovereign rights of States over their natural resources, the authority to determine access to genetic resources rests with the national governments and is subject to national legislation.

Article 15.5 Access to genetic resources shall be subject to prior informed consent of the Contracting Party providing such resources, unless otherwise determined by that Party.

Article 16.1 Each Contracting Party, recognising that technology includes biotechnology, and that both access to and transfer of technology among Contracting Parties are essential elements for the attainment of the objectives of this Convention, undertakes subject to the provisions of this Article to provide and/or facilitate access for and transfer to other Contracting Parties of technologies that are relevant to the conservation and sustainable use of biological diversity or make use of genetic resources and do not cause significant damage to the environment.

Article 16.5 The Contracting Parties, recognizing that patent and other intellectual property rights may have an influence on the implementation of this Convention, shall cooperate in this regard subject to national legislation and international law in order to ensure that such rights are supportive of and do not run counter to its objectives.


The United Nations is about to adopt a Universal Declaration on the Human Genome and Human Rights, based on a UNESCO initiative. The text does not explicitly consider intellectual property rights but calls for a balance between safeguarding respect for human rights and fundamental freedoms and the need to ensure freedom of research. It emphasises informed consent to research on an individual's genome and provides that the human genome in its natural state shall not give rise to financial gain.


Recital 12 - Whereas the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)\(^1\) signed by the European Community and the Member States, has entered into force and provides that patent protection must be guaranteed for products and processes in all areas of technology;


Recital 13 - Whereas the Community's legal framework for the protection of biotechnological inventions can be limited to laying down certain principles as they apply to the patentability of biological material as such, such principles being intended in particular to determine the difference between inventions and discoveries with regard to the patentability of certain elements of human origin, to the scope of protection conferred by a patent on a biotechnological invention, to the right to use a deposit mechanism in addition to written descriptions and lastly to the option of obtaining non-exclusive compulsory licences in respect of interdependence between plant varieties and inventions, and conversely;

Recital 14 - Whereas a patent for invention does not authorise the holder to implement that invention, but merely entitles him to prohibit third parties from exploiting it for industrial and commercial purposes; whereas, consequently, substantive patent law cannot serve to replace
or render superfluous national, European or international law which may impose restrictions or prohibitions or which concerns the monitoring of research and of the use or commercialisation of its results, notably from the point of view of the requirements of public health, safety, environmental protection, animal welfare, the preservation of genetic diversity and compliance with certain ethical standards;

Recital 15 - Whereas no prohibition or exclusion exists in national or European patent law (Munich Convention) which precludes a priori the patentability of biological matter;

Recital 21 - Whereas such an element isolated from the human body or otherwise produced is not excluded from patentability since it is, for example, the result of technical processes used to identify, purify and classify it and to reproduce it outside the human body, techniques which human beings alone are capable of putting into practice and which nature is incapable of accomplishing by itself;

Recital 22 - Whereas the discussion on the patentability of sequences or partial sequences of genes is controversial; whereas, according to this Directive, the granting of a patent for inventions which concern such sequences or partial sequences should be subject to the same criteria of patentability as in all other areas of technology: novelty, inventive step and industrial application; whereas the industrial application of a sequence or partial sequence must be disclosed in the patent application as filed;

Recital 23 - Whereas a mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention;

Recital 24 - Whereas, in order to comply with the industrial application criterion it is necessary in cases where a sequence or partial sequence of a gene is used to produce a protein or part of a protein, to specify which protein or part of a protein is produced or what function it performs;

Recital 25 - Whereas, for the purposes of interpreting rights conferred by a patent, when sequences overlap only in parts which are not essential to the invention, each sequence will be considered as an independent sequence in patent law terms;

Recital 26 - Whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law.

Article 5:

5.1. The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.

5.2. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

5.3. The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.

Article 9:

The protection conferred by a patent on a product containing or consisting of genetic information shall extend to all material, save as provided in Article 5(1),
Furthermore, TRIPS provides that:

27(1) Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. Subject to paragraph 4 of Article 65, paragraph 8 of Article 70 and paragraph 3 of this Article, patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced.

27(2) Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their laws.

Accordingly there exists a legal framework within which the patenting of DNA inventions appears possible. In practice however, applicants may still face problems. In the USA much attention was focused on the attempts by the National Institutes of Heath (NIH) to obtain patents for ESTs developed by a team led by Dr Craig Venter. In 1992 the USPTO rejected Venter's claims to ESTs for lack of patentable utility particularly because "Although the oligonucleotides embraced by the claims may be hybridized to a variety of different preparations of other nucleic acids, one of skill in the art has no clue as to the significance of any result of such a hybridization ...". The USPTO also alleged that the invention was obvious. In due course NIH dropped its US application. The USPTO has now changed its position, recently stating that ESTs may be patentable and that 10 sequences can be included in a single application.

3. Issues for patenting ESTs, SNPs and genomic DNA

There are thus a number of significant issues concerning the patenting of DNA. Most of them are based, in some degree, on the fact that DNA is a naturally occurring molecule which codes for the human body. However, it is clear that significant advances are required to elicit the knowledge necessary to work with DNA. Research tools developed through DNA research, be they new processes or DNA products themselves, may have wide-ranging applicability. Issues raised by the possibility of patenting DNA are set out below.

The groups are invited on each of the following questions:

- to state the legal positions in their respective countries;
- to explain the possible difficulties which may arise in applying their national rules; and
- to make proposals for international development in this field.

3.1 Public Policy

Perhaps the most difficult questions are those concerning public policy. The EPO has already seen the wide range of positions adopted by interested parties in relation to modified animals (HARVARD/Oncomouse T19/90), DNA fragments ("Relaxin" (OJ EPO Vol. 6 1995, 388)) and genetically modified plants (PLANT GENETIC SYSTEMS/Glutamine Synthetase Inhibitors T366/93 and 93/95).

There are a number of issues here. First, it can be argued that DNA is common property that should not be patentable at all. Second, the limited number of genes and the need to conserve
should not be patentable at all. Second, the limited number of genes and the need to conserve their sequences to retain functionality means that it may not be possible to engineer around patented genes.

(a) Are ESTs, SNPs and genomes inventions the patenting of which is contrary to "ordre public" or morality (TRIPS, Article 27.2)?

(b) Are patent offices the correct place to determine these questions and do they have sufficient resources to make such decisions?

3.2 Utility

It is a requirement under TRIPS (Article 27(1)) that a patentable invention be capable of industrial application. At the time of their identification ESTs and SNPs may not have any known use. They may provide information about sections of the genome and, in principle, should always be useful as probes.

What level of utility should be required of patents for ESTs, SNPs and genomic DNA?

3.3 Invention

It is arguable that ESTs and SNPs are not patentable inventions because they are not "inventions" but merely pieces of information.

Is an EST or SNP an "invention" at all?

3.4 Novelty

In many systems, an invention is considered to be new if it does not form part of the state of the art. The question may be answered by asking whether sufficient information is available to enable the public to know the DNA, EST or SNP claimed under a description sufficient to work the claimed invention even though the particular sequence of interest may not have previously been identified. It may be argued that genomic DNA free of other animal or human cell products should be patentable simply on account of its purity, or that, on the contrary, it is a mere discovery and not patentable.

A further problem is presented by the prospect of earlier patents for ESTs dominating later patents for longer gene sequences.

(c) Do ESTs, SNPs or genomes form part of the state of the art in relation to full length gene sequences?

(d) If it is possible to patent an EST, SNP, should a later, longer gene sequence including that EST or SNP nevertheless be regarded as novel?

3.5 Obviousness

One of the problems in dealing with inventive step is that for much work in the field of genomic DNA, it is clearly desirable to obtain further information about the human genome
in order to advance medical science. The human genome is finite (although very large). It is thus markedly different from any other field of chemistry in which there is, in theory, no limit to the number of new molecules that might be prepared. It may be argued that it is obvious to try to sequence genomic DNA in order to discover ESTs and SNPs.

A further problem is that many of the techniques for isolating and sequencing genomic DNA are known, if laborious. It is debatable whether work which requires investment of time and money, but arguably not the application of great ingenuity, should be entitled to a patent. The work which follows, for example, elucidating the structure and function of the gene product, may be more inventive, but may be difficult to protect over known sequence data.

(a) **What standard of obviousness should apply to inventions concerning ESTs, SNPs and genomes?**

(b) **What particular difficulties do courts and patent examiners face in assessing inventive step?**

### 3.6 Sufficiency

The requirement of sufficiency raises particular problems with DNA patents. A claim may cover products which the patentee has not made or any way of achieving a result when only one way of doing so is disclosed. This may not satisfy the requirement of sufficiency. Broad claims to groups of ESTs or DNA sequences might be allowed where the patentee cannot demonstrate that they all share some beneficial effect. The discovery of a gene in one species might permit claims covering a closely related gene in others. It is arguable that it is not possible to determine at the time of patenting what is the patentee's technical contribution to the art.

**What should be the sufficiency requirements for patents for ESTs, SNPs and genomic DNA?**

### 3.7 Documenting DNA inventions

This point can be seen as related to one part of the sufficiency issue.

**Are there, and should there be special provisions for the written description or claims (eg considering unity of invention) of ESTs, SNPs and genomes?**

### 3.8 Scope of protection

It may be argued that due to the fact that it may not be possible to engineer around DNA inventions and that such inventions are often used as research tools the scope of patents for such inventions should be limited. This may be achieved in a number of ways. First, it is possible to provide for compulsory licensing. Second, there may be exceptions to infringement for experimental purposes or for private and non-commercial use. On the other hand, patentees may seek to enforce claims which reach through to the products of the use of patented inventions.

(a) **Should patent claims for ESTs, SNPs and genomic DNA afford the same protection as other patent claims?**
(b) If the answer to (a) is "no" could there be restrictions on the scope of protection of such patents, e.g.;

(i) restriction to the known use of the gene (or fragment);

(ii) compulsory licensing by the patentee so as to make research tools available for further inventions.