

PERSPECTIVES

SCIENCE AND SOCIETY

Whole-genome patenting

Maureen A. O'Malley, Adam Bostanci and Jane Calvert

Abstract | Gene patenting is now a familiar commercial practice, but there is little awareness that several patents claim ownership of the complete genome sequence of a prokaryote or virus. When these patents are analysed and compared to those for other biological entities, it becomes clear that genome patents seek to exploit the genome as an information base and are part of a broader shift towards intangible intellectual property in genomics.

News of genome patenting is often met with surprise, disbelief or dismissal. Nevertheless, several whole-genome patents have been issued by the **US Patent and Trademark Office** (USPTO) and further applications are pending. Although gene patenting has been challenged on ethical grounds and in regard to data access and criteria for patentability^{1,2,3}, whole-genome patenting has so far gone almost unnoticed. Even the recent controversy surrounding patent applications for the genome sequence of the SARS-associated **CORONAVIRUS**^{4,5} (see also Online links box) is primarily concerned with whether patenting is an appropriate and effective way to control access to data and stimulate research. The SARS discussion does not address the implications of patenting a whole genome instead of the more common patenting of DNA fragments.

Perhaps genome patents have escaped scrutiny because, at least superficially, they seem to be no more than simple extensions of the DNA patenting that has flourished with the increased ease of entire genome sequencing. At first glance, patent offices certainly do seem

to be treating genome patents as if they were nothing other than standard DNA patents. However, further analysis reveals that patent specifications describing whole-genome inventions use arguments that imply that genomes are qualitatively different from individual genes. Whole-genome patents also use different arguments from microorganism patents, which might be thought of as a similar category of 'whole' biological patent. These distinctions are further complicated by the way in which the **European Patent Office** (EPO) has dealt with genome patent applications — a treatment that leads our exploration of genome patenting to the key issue of how arguments for the utility of DNA fragments apply in genome patents.

Genome patenting has emerged as an expression of the recent informational shift in genomics and patenting. This shift is of potential interest to several groups of interested parties and observers. For patent professionals, genome patenting gives an indication of how developments in genomics and bioinformatics might be changing the nature of patenting. For scientists, genome patents blur the supposed line between research and its applications, with implications for how research is financed and data shared. For social scientists, the interactions between genomics and the patent system are of great interest for understanding how society might benefit from the genomics revolution and how commercial interests might shape the future development of this science. Finally, for philosophers of biology, genome patenting raises issues about the consequences of conceptualizing genomes as sequence information or biochemical

material, and indeed, what the study of genomes means for our understanding of biological entities.

Patenting criteria

Although a key tenet of patent law is that naturally occurring substances cannot be patented, substances that have been isolated and purified — such as DNA — can be patented as long as they fulfil the criteria for patentability⁶. In the United States, the basic criteria are novelty, non-obviousness and utility; in Europe, the equivalent criteria are novelty, inventive step and industrial applicability.

An invention is novel if it has not previously been made public. Even if some gene sequences in a genome have already been published, genome sequences could be argued to be novel because not all features of the invention have previously been disclosed in a single publication⁷. Non-obviousness or inventive step means that the invention would require more than a routine procedure by an individual who is "skilled in the art".

DNA patents have been subjected to heavy criticism from lawyers, scientists and the public for inadequately fulfilling the utility requirement. Some of the strongest objections have been against attempts to patent ESTs for their use as probes in gene discovery. Following public consultation, the USPTO has recently tightened its assessment criteria. Rather than just being generally useful, applications must now show "specific, substantial, and credible" utility⁸. Once the function of a gene is disclosed (producing a specific protein, for example), it is considered to have such a use. The EPO has adopted similar standards⁹.

Furthermore, EPO patent applications must satisfy a "unity of invention" requirement, the implementation of which is currently being considered at the USPTO. This standard allows several sub-inventions to be linked together by a common "general inventive concept", but prevents unrelated inventions from succeeding as a single

Table 1 | **Claim-specific whole-genome patents granted by the USPTO, ordered according to the date of filing**

Organism	Genome argument	Utility	Assignee	Inventors	Sequence publication date (reference)	Filing date	Issue date	US patent number
Adult T-cell leukaemia virus	Clarifying genome structure	Diagnosis; prevention; therapy	Juridicial Foundation, Japanese Foundation for Cancer Research (Japan)	Yoshida & Sugano	June, 1983 (33)	5 October, 1987	18 October, 1988	4,778,756
Non-A non-B hepatitis virus	Distinguishing subtypes; better diagnosis and vaccines	Detection; prevention; treatment	Immuno (Japan)	Okamoto & Nakamura	December, 1990 (34)	7 August, 1992 (cont.* 1992)	27 June, 1995	5,428,145
Bacteriophage RM378	Genome modification	Thermostable enzymes and proteins	Prokaria (Iceland)	Hjorleifsdottir <i>et al.</i>	Published only in patent application	1 June, 2000 (cont.* 1999)	10 December, 2002	6,492,161
Haemorrhagic enteritis virus	Isolating and identifying genes; genome manipulation	Diagnostic; vaccine (turkeys); gene therapy (general)	ABIC Ltd (Israel)	Pitcovski <i>et al.</i>	30 September, 1998 (35)	20 November, 2000 (cont.* 1999)	16 December, 2003	6,663,872
<i>Buchnera sp.</i> APS	Genetic information	Pesticidal; metabolic mechanisms	Riken (Japan)	Shigenobu <i>et al.</i>	7 September, 2001 (36)	23 February, 2001	14 October, 2003	6,632,935

*This is a continuation of an earlier filing from the date shown. USPTO, US Patent and Trademark Office.

application. If, for example, a group of DNA fragments or sequences can be linked together by an overarching concept, they can then be covered by one patent. It seems reasonable to think of the genome as a concept with the potential for serving that unifying function, and patent documents provide a good basis for examining the extent to which this suggestion is supported in patent practice.

Genome patents and applications

A few publications mention the existence or prospect of whole-genome patenting^{10,11,12}, but do not discuss the actual patents. To pursue the cross-disciplinary implications of such a practice, we searched the online databases of the USPTO and the esp@cenet worldwide database of the EPO with terms such as 'whole genome' or 'complete nucleotide sequence'. We discarded all search results that only asserted specific DNA fragments without significant reference to the entire genome and those in which the genomes had been modified before sequencing. We ended up with 10 whole-genome patents that were issued (making no claims to exhaustiveness), 6 of which were for viral genomes and the remainder for prokaryotic genomes.

The patents fell into two categories. In the first, the genome is the primary object of the patent's claims section (TABLE 1). This section is legally the most significant in defining the protection that the patent provides. Patents in the second category, which we call 'contextual whole-genome patents', list

genomic fragments but embed these claims in a broader argument that the whole genome constitutes a useful invention (TABLE 2). It is not the legal status of any of these patents that concerns us (in fact, they are still untested in court), but the ways in which they make their arguments and show how genomes have been used in recent patenting.

Claim-specific whole-genome patents. The first category of genome patents, claim-specific whole-genome patents, places the whole sequence of a specified genome in the claims section as the primary invention. For example, the patent for bacteriophage RM378 claims the isolated and sequenced genome of the phage, as well as any recombinantly produced DNA. Although the *Buchnera sp.* strain APS patent has only one claim — the isolated genome as represented by its sequence description — the other claim-specific genome patents extend their claims to cDNA, proteins, vectors and host cells (as would most patents for DNA fragments).

Utilities for genome patents in this category range from disease diagnosis and therapy to the development of thermostable enzymes and pesticides (TABLE 1). Although these utilities are often elaborated in relation to particular DNA fragments or encoded polypeptides (for example, non-A non-B hepatitis virus (NANB) in TABLE 1), the descriptions of the inventions avoid excluding other genomic fragments from the overall invention by regularly invoking the rest of the genome. Arguments are also made for the

general advantages of having a whole genome as the invention: the "clarification of the structure" of the genome (for example, adult T-cell leukaemia virus in TABLE 1), identification of constituent genes (for example, haemorrhagic enteritis virus (HEV) in TABLE 1) and the capacity to distinguish similar genomes (for example, NANB).

Contextual whole-genome patents. Genome patents in the second category direct their claims to specified open reading frames (ORFs) or polynucleotides, but do so in the context of a broader specification of the invention that argues for the whole sequenced genome as an integral part of the invention. The patents for *Haemophilus influenzae* and *Mycoplasma genitalium* were first filed as claim-specific genome patent applications, but during examination, their potentially far-reaching claims were restricted to specific ORFs. This restriction was probably the result of objections by USPTO examiners. The specifications of these patents, which do not normally change after filing, still persistently refer to the whole-genome sequence (and any sequence that is 99.9% similar) as comprising or providing the basis of the invention. Likewise, in the *Methanococcus jannaschii* patent, the summary of the invention begins with the whole-genome sequence, after which the invention is further directed to the ORFs in the claims. The claims of the two virus genome patents in this category

Table 2 | **Contextual whole-genome patents granted by USPTO, ordered according to the date of filing**

Organism	Genome argument	Utility	Assignee	Inventors	Sequence publication date (reference)	Filing date	Issue date	US patent number
Maize chlorotic dwarf virus	Distinguishing strains; understanding genome structure and organization	Diagnostic; resistance engineering	Novartis Financial Corporation	Law <i>et al.</i>	May, 1997 (37)	4 April, 1995	2 February, 1999	5,866,780
Tospovirus (Tomato spotted wilt virus)	No explicit argument	Diagnostic; resistance engineering	Novartis Financial Corporation	Goldbach <i>et al.</i>	December, 1990 (38) September, 1991 (39) November, 1992 (40)	26 November, 1996 (cont.* 1989)	21 November, 2000	6,150,585
<i>Mycoplasma genitalium</i>	Understanding chromosomal organization; comparative genomics; minimal genome knowledge	Diagnostic; therapeutic; pharmaceuticals; industrial fermentation	The Institute of Genome Research (TIGR); Johns Hopkins University; University of North Carolina	Fraser <i>et al.</i>	20 October, 1995 (41)	19 October, 1995 (cont.* 1995)	25 March, 2003	6,537,773
<i>Haemophilus influenzae</i>	Comparative genomics; chromosome structure and function	Pharmaceutical; industrial fermentation	Human Genome Sciences; Johns Hopkins	Fleischmann <i>et al.</i>	28 July, 1995 (42)	23 August, 2000 (cont.* 1995)	4 March, 2003	6,528,289
<i>Methanococcus jannaschii</i>	Comparative genomics; identifying open reading frames	Probes; primers; general function of any fragment	TIGR; Johns Hopkins	Bult <i>et al.</i>	23 August, 1996 (43)	20 October, 2000 (cont.* 1996)	28 September, 2004	6,797,466

*This is a continuation of an earlier filing from the date shown. USPTO, US Patent and Trademark Office.

similarly focus on particular sequence fragments but base their inventions on the whole genome. The inventions of all of these patents are described very broadly, covering an extensive range of related biological material and its demonstrated and postulated uses.

The three TIGR/HGS (The Institute of Genomic Research and Human Genome Sciences) patents also originally claimed the computer-readable sequence as the invention. These claims now exist only in the specifications, which describe the “computer-related embodiments” of the genome as “a contiguous string of primary sequence information” suitable for storage and analysis by computer. Having the genome in this *in silico* form, argue these patents, allows scientists to move beyond a gene-by-gene approach towards larger discoveries of genomic structure, function and evolutionary history, as well as the identification of “commercially important fragments”. Although the virus patents do not specify the *in silico* or machine-readable nature of the invention, they too rely on the knowledge provided by the whole-genome sequence for purposes such as engineering plant resistance to the virus or for establishing boundaries between strains (for example, maize chlorotic dwarf virus (MCDV-Tn) in TABLE 2).

Microorganism versus genome patents

Genomes are often thought of in a holistic way, which makes it logical to compare them to whole organisms. Patenting microbes is a long-established practice, not only for modified microorganisms¹³, but also for naturally occurring strains that have been isolated and cultured¹⁴. All the genome patents listed in TABLES 1,2 are for microorganismal genomes (we include viral genomes in this category). The tradition of allowing microorganism patents might partly explain the absence of any patented eukaryote genomes and also why whole-genome patenting has not given rise to particular public concern.

But what is the difference between whole-genome patents and patents that have been issued on whole microorganisms? Not surprisingly, the utility arguments made for microorganism patents^{15–21} are generally similar to those for genome patents (TABLES 1,2). Microorganism patents for Archaea, for example, argue for utilities that are related to enzyme production in harsh environmental conditions, and bacteria patents claim applications that range from human health to BIOREMEDIATION. However, novelty is established in subtly different ways. Organism patents are based on previously unknown organisms that might have been isolated in unusual circumstances, whereas genome

patents are usually based on the genomes of well-known but previously unsequenced organisms.

The main difference between whole-genome and organism patents is the extent to which the patent attempts to cover further biological material. Both categories of genome patent describe their inventions in terms that stretch to any and every nucleotide and polypeptide implicated by the sequence, as well as to vectors and host cells. The only organism patents that follow this strategy are the few that refer to the DNA of the specified organism, either to extend the coverage to further biological material^{18,19} or to encompass all organisms in the same genus with a certain percentage of sequence similarity¹⁵. In these cases, it seems that the DNA and its potential uses are called on to reinforce the organism patent and expand the protection it provides. Genome patents take this strategy one step further by claiming the complete sequence. The obvious question is whether a genome patent achieves more protection for the inventor than does a patent on a collection of DNA fragments.

USPTO versus EPO perspectives

Archived EPO examiners’ reports (on the [EPO Online Public File Inspection](#) page) of past and present applications for whole-genome

patents take one step towards answering this question. Most of these reports agree that a genome sequence is novel even when parts of the genome have already been sequenced, although some dispute the novelty of newly sequenced genomes from closely related strains. One examiner, for example, objects that a submitted genome sequence (*Chlamydia pneumoniae*) is merely a definition of a particular strain from the many isolates available, thereby questioning the patentability of genomic variation. In another case (Influenza A), the report notes that the identified genes are well known from other related strains and that their presence should therefore be expected. Both these reports also argue that the sequencing of a genome is routine and does not in itself entail an inventive step.

Most tellingly, some of the reports argue that genomes can only be considered as a single invention if they share a uniting feature that is novel, inventive and technically relevant. According to the examiners' comments, the application examples of Influenza A and *C. pneumoniae* do not constitute a unified invention that would meet EPO standards. Our initial hypothesis that the idea of a genome is sufficient to unite several genes and their functions into one invention is not, therefore, supported by these examples. A genome, at least in these cases, does not have the taken-for-granted unifying capacity of an organism: it is seen as merely a collection of fragments of DNA.

Gene versus genome utility

If there are any qualitative differences between patents for whole genomes and those for DNA fragments, it seems likely that they will be found in the utility arguments — the most contested feature of recent gene patenting. Are any special uses attributed to genomes that are not attributed to isolated fragments of DNA?

Both claim-specific and contextual genome patents rely on the utility of the information provided by the whole sequence. Such information is considered to be valuable because it allows better understanding of the organism, of specific genes, of chromosome structure and function, and of relationships with other genomes. These genomic utilities seem to be primarily research-orientated, in contrast to commercial applications that might arise directly out of the more specific biochemical functions attributed to genes and gene products. By exploiting the whole genome as the informational basis of the invention, these patents distinguish themselves from standard DNA fragment patents that articulate their inventions as compositions of matter, analogous to chemical patents²².

Conclusion

Once the surprise that whole-genome patents exist has dissipated, it might be tempting to conclude that such patents are either so few or so weak that their existence does not matter. However, the characteristics of whole-genome patenting indicate an important movement in DNA patenting from biochemical tools and products to information resources^{12,23,24}. Had the computer embodiments remained in the TIGR/HGS claims, these patents would have attempted to control information in a way not yet realized in patent practice. As bioinformatics and *in silico* modelling gain deeper and more extensive purchase on every aspect of genomic science²⁵, a full shift to allow claims on intangible informational property seems inevitable.

“Is the genome just ... used to unite several nucleotide sequences into a single invention, or ... a causally efficacious phenomenon that does something more than an aggregation of genes can do?”

So far, there seem to have been no obvious commercial benefits from whole-genome patents, but industry has a long way to go before it catches up with all the DNA patenting of the past two decades. Harbingers of how this trend might develop can be seen in new patents for computer programs and business methods. In discussions of how commercial protection is increasingly being sought for the information that is produced by bioinformatics^{24,26}, unannotated genome sequences (that is, primary information) are considered less patentable than secondary information about how gene products might interact in a cell.

As yet, there have been no high-profile cases in which genome patents have been publicly or legally challenged, although the EPO examiners' reports give an indication that future genome patents might be treated sceptically in Europe with respect to unity of invention and novelty. Because the validity of genome patents has yet to be tested in court, the extent to which they will restrict research on the patented genomes is still only a matter for informed speculation. Patent

applications for the SARS genome provoked worries that a privately held patent would function as a gatekeeper to all SARS-related research and inhibit drug development. It is likely that similar fears would arise with any increase in the numbers and awareness of issued genome patents. Although empirical work on the impact of conventional DNA patents shows that they do not always have negative effects on research access^{27,28}, informational patents could be much more restrictive²³.

Anticipations of genome patenting could extend to questions about whether prokaryotic genome patents set precedents for eukaryotic genome patents (our non-exhaustive search found none of these, nor did we find any in a search of pending whole-genome patent applications). We see two general factors that inhibit this potential trend: tradition and genomic organization. As we noted earlier, prokaryotic microorganism patenting is well established, but unmodified multicellular organisms are far less commonly the objects of patents. We believe that resistance to the patenting of ‘higher life forms’ — including genetically modified ones such as the ONCOMOUSE — is likely to similarly discourage patenting the genomes of these organisms. At the human level, ethical arguments have been made stating that patenting a whole human genome violates the integrity of an individual in a way that patenting parts of the genome does not²⁹. Differences between the USPTO and other patent offices on the patentability of life forms³⁰ will no doubt continue to be reflected in the international treatment of future whole-genome applications.

Moreover, the genomes of most eukaryotes have proportionately less protein-coding DNA, meaning that it is more difficult to assign function to large amounts of sequence.

Glossary

BIOREMEDIATION

The use of microorganisms to degrade hazardous contaminants in soil and water to environmentally safe levels.

CORONAVIRUS

A genus of virus named after the projections that create a crown-effect around the outside of each virus particle. They infect various mammals and birds, causing respiratory and enteric illness. The SARS-associated coronavirus is a previously unrecognized member of the genus with no close genetic relationship to known coronavirus sequences.

ONCOMOUSE

(Also known as the Harvard mouse.) A type of laboratory mouse that is genetically modified to carry genes that increase susceptibility to cancer (oncogenes).

Therefore, genomic organization militates against the success of eukaryote genome patenting. If the complete genomes of complex multicellular organisms are ever to be commonly patented, it will probably be as informational components that are incorporated into system models that have diagnostic and other purposes.

Overall, the aspect of whole-genome patenting that lends itself most readily to investigation is conceptual. All the patents we have identified raise important questions about how genomes are conceptualized, especially in regard to how the utility of a genome can be specified. Is the genome just a concept that is used to unite several nucleotide sequences into a single invention, or is it a causally efficacious phenomenon that does something more than an aggregation of genes can do? What is the relationship between the utility of a part (a gene) and any utility associated with the whole (the genome)? The answers to these questions will be different depending on whether the genomes are thought of in terms of biochemistry or bioinformatics.

When the relationship between organism and genome patents is examined, further conceptual questions arise, especially in terms of classification. Is the genome sequence the representative of the organism? The genomic mosaicism of many viruses and microbes makes the construction of taxonomic relationships very complex, and reducing this complexity to single measures of overall relatedness is likely to obscure biologically meaningful connections^{31,32}. Existing whole-genome patents not only settle for simple measures of genomic relatedness, but do so inconsistently. Some use sequence differences between strains as the basis of their genome-patent claim (for example, MCDV-Tn), whereas others discount such variations between strains by arguing that the patent covers other sequences within a certain range of similarity (for example, *M. genitalium*, *H. influenzae* and HEV). The informational patenting of genomic variation could have the benefit of bringing about better patent recognition of the complexity of genomic relationships.

Our overview of current practices of whole-genome patenting shows how these patents raise fundamental questions about genome utility, classification and the ownership of intangible biological information. All these issues mean that the future of genome patenting should be carefully watched by scientists, as much as by legal theorists, social scientists and philosophers of biology — not to mention the patent owners themselves.

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Competing interests statement

The authors declare no competing financial interests.

Online links

FURTHER INFORMATION

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European Patent Office: <http://www.european-patent-office.org>
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World Health Organization — Patent Applications for SARS Virus and Genes: www.who.int/ethics/topics/sars_patents/en
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World Health Organization — Patent Applications for SARS Virus and Genes:
www.who.int/ethics/topics/sars_patents/en