

OPINION

Is there a future for 'speculative' gene patents in Europe?

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In the face of increasing public opposition to patents claiming property in gene sequences, is it right to deny the validity of patent applications that seem to have firm, if somewhat hypothetical, scientific basis? In this article we review the recent state of the law in Europe as it applies to gene patents in order to determine whether there is any hope for the modern heirs of Galilean innovation.

As every high-school student learns, a scientific approach relies on the use of practical experimentation to confirm or refute a hypothesis. Without any corroborating data, how can a theory be anything other than mere speculation? Yet some of the greatest advancements in science have been based on theories without any accompanying experimental evidence. Indeed, Galileo Galilei's law of uniformly accelerated motion might have resulted from the great man's own inspiration rather than from days of hard grind at the laboratory bench¹.

In fast-moving fields of technology, many researchers have come to rely on hypothetical data in order to provide a basis for filing commercially important patent applications to protect their innovations. This practice has become increasingly common in the field of genomics, with a plethora of so-called speculative gene patents underpinning the hopes of research institutions to cash in on the genomic revolution.

The public view

The debate about whether patents should be allowed to cover gene sequences has continued for a number of years around the world. In

Europe, this debate has been brought to a head most recently with the grant of patents covering the DNA sequences of the *BRCA1* and *BRCA2* genes, granted to Myriad Genetics². Both of these genes have significant applications in diagnosing predisposition to a number of cancers. To the person in the street, the grant of a patent covering all potential uses of these genes raises the visceral fear of corporate interests claiming ownership over our very bodies!

Although the debate has been ignited by the grant of these patents to Myriad Genetics, the ethics associated with the grant of gene patents have been the subject of intense scrutiny from a number of worthy institutions in Europe and around the world. In one such study, the independent Nuffield Council on Bioethics concluded that in the future the granting of patents that assert broad rights over DNA sequences should become the exception rather than the rule³.

Genes as products

It is a tenet of European patent law enshrined in the European Community Biotechnology Directive that an element isolated from the human body or otherwise produced by means of a technical process, which is susceptible of industrial application, including the sequence or partial sequence of a gene, can constitute a patentable invention⁴. The Directive has been incorporated into the European Patent Convention and allows patenting of a human DNA sequence as long as it is isolated from a human body. The isolated gene sequence is then treated in the same way as if it were a chemical compound (BOX 1).

However, there is a feeling among some sections of the public that DNA sequences are distinguished from other chemical compounds because they provide the fundamental means for recording genetic information. It is certainly true that whereas, say, a new compound might exert one or more pharmaceutical effects, a novel gene sequence can be put to many different uses, such as in diagnostics and gene therapy, as well as encoding a protein with its own set of uses.

There is a strong groundswell of opinion that the human genome is a particularly special case and should be common property to all of humanity. In this utopian view the human genome should be free from the claws of corporate interests (although it is interesting to note that some of the most prolific patent filers are publicly owned institutes and universities).

In an attempt to clarify the issues that have accumulated around the gene patent debate, the World Intellectual Property Organization (WIPO) has sought to dispel a number of patent myths that have emerged⁵. WIPO suggests that it is socio-economic factors rather than patents that bar access to health care and drugs in the developing and developed worlds.

Speculation as an abuse

Will presently pending gene patent applications be affected in any way by the shift in European public attitudes towards restricting the scope of these patents?

Most pending patent applications in Europe that are potentially at risk were filed at the end of the last century when genomics was coming to the fore as an exciting new technology (FIG. 1). Rapid developments in the fields of bioinformatics and genomics enabled researchers to mine data out of the huge genome databases that had recently become available. Scientists combined powerful computational techniques with their own detailed knowledge of molecular biology in order to identify potential genes from the masses of raw sequence data produced by organizations such as the Human Genome Project consortium.

Box 1 | Patentability

Before a patent can be granted, the patent examiner must determine whether the claimed invention satisfies the basic criteria of patentability. The invention must be novel, that is, never before known in the state of the art. It must not be obvious to a person skilled in the field; in other words, an inventive step must have been taken in its conception. The invention must also be susceptible of industrial application, in that it can be used in any kind of industry, including agriculture. In addition to these fundamental criteria, the subject matter of a European patent must not be in an excluded field, for example, it must not be a mere discovery, a method of medical treatment or contrary to morality. The present patent laws provide that a claim to a product (composition of matter) includes all potential uses and applications to which that product can be applied. It is important to note, however, that a patent does not provide a permit to work the invention, but is rather a time-limited contract with the state that allows the patent owner to prevent others working the invention. In essence, a patent is a right of exclusivity that can be exercised by the patentee or licensed against others.

One can almost hear the cry of “there’s gold in them thar genomes!” (FIG. 2), followed by the stampede of prospectors seeking to stake their claims on the human genome. Then, as now, patent law was in a form that on the face of it allowed for novel gene sequences and proteins to be treated as new chemical compounds. Understandably, there was a desire among many research institutions to file patent applications first and ask questions later. The desire was further heightened by massive capital investment associated with the economic boom of the ‘technology bubble’.

Patents are intended to be a reward for innovation — the identification of a non-obvious solution to a problem in a technical field. This is perhaps contrary to the view held by some in industry, that patents are simply the logical reward for investment in research. There is no question that there has been considerable research effort directed at the cloning and isolation of putative novel proteins and nucleic acid sequences. But, if at the end of all this research, the claimed sequence is obvious, then no patent will be granted. Very often, potential genes were identified in raw

sequence data within computer databases by *in silico* processes (BOX 2). The unqualified success of these data-mining expeditions in identifying putative genes resulted in an explosion in the number of patent applications filed claiming these novel sequences. With the lure of identifying the next *BRCA1*, the considerable investment in research and development continues to seem justifiable. Of course, this approach assumes that the primary means for protecting innovation — that is, the patent system — will provide the much-needed protection for that investment. Many biotech companies have pursued a course of characterizing and isolating novel gene sequences and will have filed many hundreds, if not thousands, of patent applications.

Where research institutions have massive screening programmes, it can take a number of months or years after the patent application is filed before a definitive function is assigned to the novel gene sequence. It is common practice for a patent applicant to rely on their own scientific skill and knowledge, together with reasonable expectations and informed guesses, to provide hypothetical examples of the subject matter of the patent. This has become particularly evident where the patent applicant is seeking to ascribe a function to an as yet uncharacterized gene sequence⁶.

The question for many is whether these non-experimentally obtained data are sufficient to allow a patent to be granted that will have a broad scope. The answer in Europe might be closer to ‘no’ than to ‘yes’, as, in the mind of the European Patent Office (EPO) examiner, patents founded on these data constitute speculation in place of genuine human inventive effort and are an abuse of the patent system.

The state of the law

Following our analogy to the discoveries of Galileo, it is undeniable that good thought experiments do play a genuine role in scientific progress. Defining the boundary between a good thought experiment and rank speculation is not so easy. Guidance as to where this boundary lies needs to be taken from the few legal sources that have considered this issue.

Probably the clearest signal of how the EPO views patents covering gene sequences is provided in the Trilateral Project B3b Report⁷. The Trilateral Project was a combined effort by the patent offices of Europe, the United States and Japan. It demonstrated how each of these patent offices would approach the matter of gene sequence claims. The EPO stated that according to their practice a claim to a nucleic acid molecule is considered to be a product claim to a biological

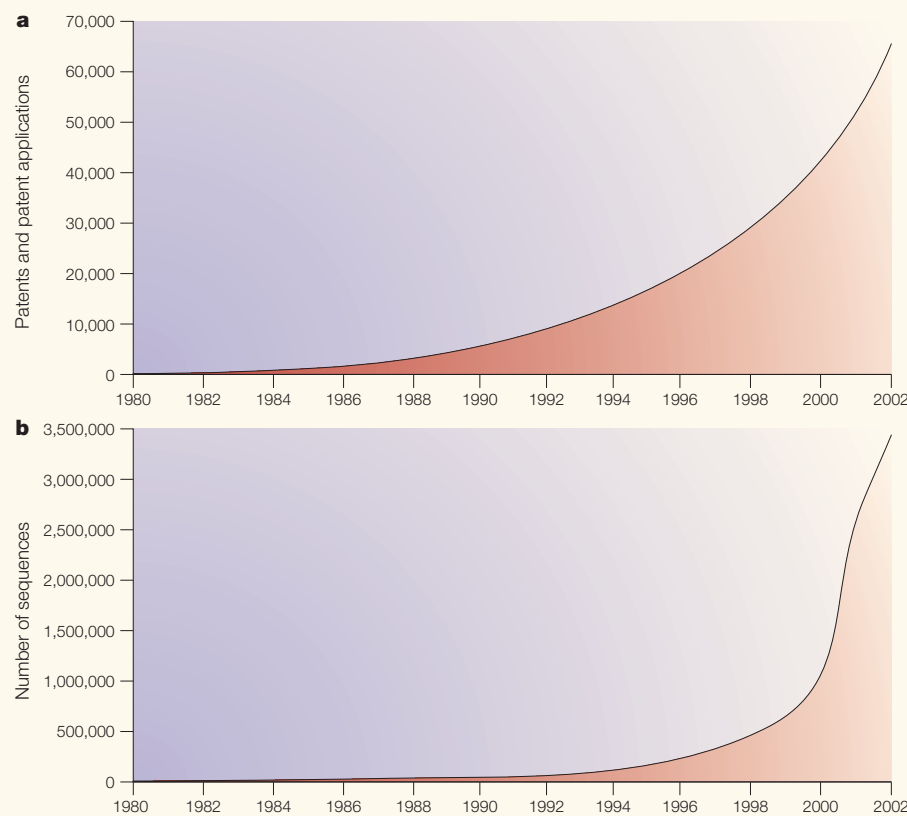


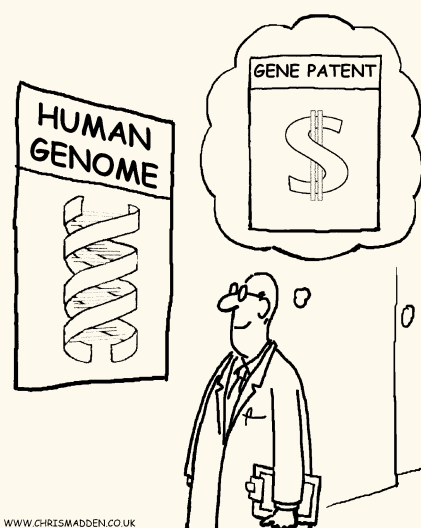
Figure 1 | **The explosion in the number of gene patents and patent applications.** **a** | The number of patent applications and patents containing nucleic acid or protein sequences by year. **b** | The number of these sequences published in patents and patent applications by year. Reproduced with permission from Derwent Geneseq.

material (that is, a compound). The EPO also required that the function performed by a claimed nucleic acid sequence and the protein it encodes should be certain to the degree that a specific use for the sequence becomes apparent beyond the realm of mere speculation. The EPO went on to state that if the alleged function of a claimed nucleic acid molecule were not credible then they would request that experimental evidence be supplied demonstrating the claimed function.

The clear message is that to support a product claim to a novel DNA sequence the patent applicant needs to provide a genuine function for the putative protein encoded by the claimed sequence at the date of filing the patent application. This ascribed function can be illustrated further by submission of more detailed experimental results later in the application process.

But what happens if a credible function cannot be ascribed on the basis of homology or sequence similarity to other known proteins? This can occur where similarity is low or the novel sequence is predicted to have a number of different domains corresponding to different proteins with different functions. Some applicants have been tempted to prepare a wish list of predicted functions, thereby nudging their application close to the line dividing speculation from hypothesis. In the authors' own discussions with EPO examiners it is apparent that the EPO will act firmly if any hint of this practice is evident in an application. If an examiner suspects that the applicant does not know the specific or credible function of the claimed gene sequence, then the isolated sequence will be held to represent nothing more than an arbitrary selection of a gene sequence from the mass of genomic information available. In this case, the application will fail.

In proceedings before the UK Patent Office (UKPO), speculation based on knowledge accrued from the experiments of others was considered in the case of Prendergast's applications⁸. Although these applications related to new uses for pharmaceutical compounds, the conclusions are relevant to gene sequence patents. The UKPO believed that although the letter of the law does not require that an applicant provide evidence that the invention has actually been performed, an applicant must support an assertion that the invention works, otherwise it could be rooted in mere speculation. This decision was based on established English jurisprudence and perhaps provides guidance as to how the Courts would regard a gene sequence patent containing only hypothetical examples.



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Figure 2 | The gene rush.

The issue of whether accurate speculation is a sound basis for a patent was further considered in a pivotal decision of the EPO Opposition Division⁹. In the case of ICOS' application, a novel sequence predictive for a seven transmembrane spanning receptor was identified. The evidence of function supplied by the applicant was that it was a predicted receptor. The prediction was based on sequence similarity to other known members of this class of proteins, and was correct. The Opposition Division revoked the patent, holding that to provide, at the time of filing, a list of speculative functions of a protein is not in itself a reliable basis for acknowledging an industrial application of the protein, even if one function turns out to be correct. The Opposition Division went on to state that a DNA sequence encoding a protein without a credible function is not a patentable invention.

In the ICOS decision, the Opposition Division returned to the original wording of the European Biotechnology Directive and in particular the portion that states that "a mere DNA sequence without indication of a function does not contain any technical information [and] is therefore not a patentable invention"⁴. The Opposition Division interpreted the requirement of an indication of function to be a requirement for indications that are more than speculative. In reaching this decision the EPO has adopted a similar approach to that used by the **US Patent and Trademark Office**, by implementing a requirement that applications covering sequences with indications of function should be substantial, specific and credible — otherwise they lack a technical character.

In our experience, the justification for the refusal of a gene-based patent application, in

Europe at least, tends to fall under the guise of a lack of inventive step. This provides a point of distinction between Europe and the United States, as the US requirement for non-obviousness appears in practice more easily satisfied than the inventive step approach adopted in Europe. No wonder many US-based patent applicants seem to find difficulty in understanding why their US gene-based patent applications proceed swiftly to grant, whereas their corresponding European applications get bogged down in inventive step rejections.

In theory, a novel gene sequence can be patented along the same lines as a novel pharmaceutical compound. However, new genetic sequences can be easily identified by routine laboratory techniques. Hence, unlike many novel drugs, the means for isolating novel genes are likely to be commonplace in the technical field. An inventive step could lie in a credible and specific function for the new sequence. Of course, if the function is based on very high sequence similarity to another known protein, then this function itself might be considered obvious. In such a case the patent applicant will have to show some unexpected advantage or other non-obvious feature that would provide an inventive step for the novel gene sequence.

Satisfying the EPO

The EPO is reluctant to grant patents to gene sequences on the basis of vague descriptions of predicted function. They wish to be presented with concrete evidence disclosing the actual function and biological activity of the claimed protein. It might be apparent, therefore, that the applicant for a gene sequence patent is almost drawn into a no-win situation, because on the one hand there is the need to file early (without data to support function) in order to avoid being scooped by a competitor, and on the other hand there is the need to state a specific and credible function for the claimed gene on filing of the application to obtain valid rights (with the delay this imposes).

What kind of gene sequence application is likely to be allowed? Given the present state of case law, an application of broad scope might be allowed if it covered a new class of protein whose specific function is clearly characterized. Where an application is already pending without functional data, it is advisable to invest some time and effort into producing some solid experimental data that supports the specific function predicted at the time of filing. Alternatively, the claim scope can be limited to a credible use disclosed in the application, such as use of the gene sequence as a diagnostic tumour marker. Evidence of function, included at the time of filing, will prevent a later allegation that the patent is based,

Box 2 | **In silico gene cloning**

Using established bioinformatic techniques, information from expressed sequence tag (EST) databases can be correlated with raw genomic data in order to identify putative open reading frames as potential gene sequences in the genome. It is now routine in genetics research to initially propose a function for a novel gene by studying its similarity to other known sequences, through sequence analysis and tertiary structure prediction, and from the range of expression of the sequence either in terms of tissue location or temporal expression. Often a combination of all of these approaches leads the scientist to propose, on the balance of probabilities, a putative function for the new gene sequence. Such a procedure for mining data from genome sequence information can be highly mechanized, thereby allowing many thousands of putative genes to be identified. A very large number of European patent applications presently pending have been filed on the basis of these types of data alone.

unacceptably, on speculation. Lists of possible functions should be avoided. In the absence of data, limited assertions of function might be acceptable if these are specific and credible — it helps if the inventors have experience in the particular field of the invention, as their prediction of function is more plausible; it does not help if it is apparent that function is being predicted by a computer, as computers do not make inventions.

Innovation, investment and patents

In view of the considerable public concern surrounding the Myriad Genetics case, it is conceivable that legislation in Europe might change at some point in the future to restrict the scope of patents claiming gene sequences. Legislation could be enacted to acknowledge the perceived 'special status' of DNA. The UKPO have even said that in the case where an applicant has prepared a known protein by recombinant means it would be rare these days to allow claims to related sequences¹⁰.

Mechanization and the rise of bioinformatics seem to have spelled the downfall of broad gene sequence patents. Many at the EPO believe that at least some human inventive input should be required in order to justify the grant of a patent. It also follows that the more information published about the genomes of humans and other animals and the functions of the many genes that are contained within these genomes, the more difficult it will be to satisfy the requirements for patentability in a supposedly novel gene sequence.

The future for gene patents

At present, legislators the world over seem to be hostile to the grant of broad patents for gene sequences. In France, legislation has been tabled to outlaw gene sequence patents altogether. The European Commission is considering similar proposals.

The current public disquiet regarding Myriad Genetics' chosen means of exploiting their patent (by insisting that all genetic testing on the *BRCA1* and *BRCA2* genes is performed

by Myriad's own laboratories in the United States) is perhaps a matter better served by debate on the nature of patent exploitation. So far, the three Myriad patents covering *BRCA1* and *BRCA2* are currently the subjects of Opposition Proceedings before the EPO². The Oppositions to Myriad Genetics' patents have been broadly supported by many mainstream European governments, including the European Parliament.

Even in staunchly pro-patent North America, concerns have been raised about the grant of so-called overly broad gene patents¹¹. In March 2002, US Congresswoman Lynn Rivers proposed a bill which seeks to ease the laws relating to intellectual property rights covering diagnostic testing for genetic diseases in respect of academic research and healthcare providers — an action prompted in part by the controversy surrounding diagnostic testing for susceptibility to haemochromatosis¹². In Canada, the Government of Ontario has published a draft report proposing amendments to the Federal Patents Act¹³.

The worry for many in the biotechnology industry is that through the actions of a minority of dominant patent proprietors with particularly restrictive licensing practices, the fundamentals of patent law the world over will be reformulated. However, it should be remembered that for the legislators a vital dynamic exists on the one hand between the economic pressures in favour of fostering and developing the biotechnology industry, and on the other the public concerns about the scope of gene patents in general.

As technology progresses, the number of patent applications in particular subject areas increases. Naturally, the expertise of the patent examiners also increases as a consequence. The number of human genes is finite, and so every published patent application and journal article adds a further brick to the wall of prior art against future gene sequence patents. Perhaps patent applicants should not measure their future success in terms of the exceptionally broad gene patents granted in

the late 1990s, but should focus more on the type of patents being granted today. Well-supported patent applications directed towards specific diagnostic uses of a novel gene sequence, or therapeutic applications of novel peptides, stand a greater chance of proceeding to grant. Evidently, today's patent applicants should revise their expectations if they are hoping to obtain broadly based gene sequence patents now and in the future.

Lastly, the few decisions on which the EPO examining policy is based have not been challenged at the appeal level. We urgently need an applicant, who has been refused a patent for the sorts of reasons set out in the ICOS case, to take the matter higher and force a substantive assessment of patentability in these cases. There is plenty of evidence that justifiable speculation leads to patents in other technical areas. Why should gene patents be any different?

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 **Online links****DATABASES**

The following terms in this article are linked online to: **LocusLink:** <http://www.ncbi.nlm.nih.gov/LocusLink/BRCA1|BRCA2>

FURTHER INFORMATION

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