

Influenza genetic sequence patents: where intellectual property clashes with public health needs

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A number of advances have recently taken place in influenza virus genomics research, due largely to an extensive genome sequencing project and widespread access to these sequences. If a pandemic virus emerges, whether it is a reassorted A/H5N1 strain or another zoonosis, it is essential that access to information about its genetic sequence is not restricted through intellectual property claims. Products of nature are not patentable inventions, according to US code and the US Supreme Court, and naturally occurring genetic sequences should not be eligible for patenting. Viral genetic sequences represent natural information upon which diagnostics and preventions are necessarily based. Patents covering this fundamental information will limit, or even prevent, crucial and time-sensitive biomedical research.

Recent years have witnessed an unprecedented effort by researchers across the globe to detect, diagnose, prevent and treat influenza infections. Meeting these goals requires a thorough understanding of viral diversity, gene segment reassortment, transmission, and global circulation patterns of both human and nonhuman strains. Advances to this end have been made on epidemiological and molecular levels in a brief period of time. Especially useful in these efforts has been the recent availability of a large number of influenza gene sequences – particularly of the currently circulating A/H3N2 and A/H1N1 human strains, and various avian strains. From these sequences researchers have gained greater insight into influenza circulation among both humans and birds, previously underestimated levels of gene segment reassortment, the emergence and spread of drug-resistant strains, and the rapid evolution and population dynamics of the virus [1–5].

Comparative analyses of the ever-increasing collection of sequences will further the understanding of the significance of particular genomic mutations and gene segment combinations within human, avian and zoonotic strains. This can increase the ability of researchers to identify the dominant strains in present and future seasons and lead to more effective solutions and more informed decisions regarding the strains to include in both routine vaccines and those prepared in preparation for, or in response to, a pandemic.

The unparalleled rate of progress in influenza genomics is largely due to researchers' access to publicly available sequence databases that include thousands of influenza variants with

recorded epidemiological information. This would not be possible without both recent advances in sequencing technology (which have greatly reduced both the cost of, and time required for, genome sequencing) and the commitment, by several groups, to make such information available to all researchers.

One particular viral sequencing effort, the Influenza Genome Sequencing Project (IGSP), initiated by the National Institute for Allergy and Infectious Disease (NIAID) in 2004 [6], has resulted in the generation of approximately 3000 complete genome sequences of influenza viruses. These sequences, along with thousands of other influenza gene sequences submitted by external researchers/institutions, are made available immediately to all researchers through the Influenza Virus Resource [7,8]. This database, developed and run by the National Center for Biotechnology Information (NCBI), has led to a number of related public databases and research tools [7]. Most importantly, it has fostered collaborations among prominent researchers, which has resulted in state-of-the-art viral research.

If this level of commitment from influenza researchers continues, we will likely see improvements in both basic and applied epidemiological and biomedical research. However, if access to viral sequences such as these is slowed or impeded due to influenza sequence patents – and the research restrictions, financial liabilities, lengthy legal battles, uncertainties and broad disincentives which will inevitably follow such misguided patents – these promises for improvements in influenza prevention, diagnosis and treatment may not be realized.

Keywords: A/H5N1, gene patents, influenza, Influenza Virus Resource, intellectual property, virus genomics, WHO

future part of **medicine** **fsg**

Influenza virus sequences & intellectual property

While open-access databases, such as the Influenza Virus Resource, are rapidly increasing our understanding of viral genetics and epidemiology, particularly of currently circulating human and avian strains, the ability to extend this model to a pandemic situation, involving, for example, a reassorted and human-adapted A/H5N1 strain, may prove problematic. Some researchers, governments and public health centers have been reluctant to provide other researchers with access to sequence information, even from currently circulating human and avian strains [9]. If these tensions exist now then they are bound to be exacerbated in the case of an emerging pandemic strain, as sequences from these potentially devastating strains will be highly coveted for their use in the development of diagnostics, vaccines and antivirals. Delay in the availability and accessibility of these sequences, due to financial or other considerations, could be disastrous in a pandemic situation where an immediate response is vital.

Even when sequences are made available, there can be disincentives for researchers to access them for product development. While publication of such sequences (including submission to a public database) prevents others from patenting the given sequences (a practice known as defensive publication [101]), it does not prevent the author from filing for a patent within a year of publication.

A patent is essentially a limited legal monopoly given to an inventor who meets certain constitutional and statutory requirements. Under patent law, the invention must be patentable subject matter [10]; it cannot be a product of nature, a law of nature, or an abstract idea [11]. Furthermore, the invention must be novel [12], nonobvious [13] and useful [10,14]. For 20 years from the date of the filing of the patent application, a patent holder controls the use of the invention [15] and can prevent anyone else from using, making, selling or importing the invention – keeping it away from the public altogether or licensing its use for expensive royalty fees in an exclusive or nonexclusive fashion.

This ability to control all uses of an invention is logical for novel technological inventions, but not for a genetic sequence itself, which is a product of nature. With this ability to control all uses of a gene sequence, the holder of the patent can prevent others from engaging in research involving the sequence. Other scientists deciding to invest in a diagnostic or vaccine development

project, necessarily based on the sequence in question, face the possibility that their efforts will be for naught if the scientist who has submitted the sequence has filed for a patent on the sequence. Since patent applications are not made public until 18 months after filing, the subsequent researcher may spend a significant amount of time and money working with a sequence to develop genetic diagnostics or treatments, only to learn that the sequence, and all of its uses, have been patented.

At this point he or she may have to pay a licensing fee for all subsequent work on the project, share a portion of any future profits with the producer, or abandon the research entirely if the patent holder will not license the use of the sequence. In the realm of viral genetics, these possibilities may translate into widespread reluctance to invest in crucial and time-sensitive viral diagnostics and drugs [16].

Patenting genetic material

The range, scope & consequences of gene sequence patents

A study published in 2005 found that nearly 20% of known human genes were claimed, in US patents, as intellectual property [17]. While there are patents in effect for numerous other naturally occurring genes, sequence stretches and polymorphisms from diverse organisms, it is these human gene patents that have drawn the most attention. In particular, much of the focus has been on human disease-associated gene patents [18].

Because the holder of a gene patent can control any use of the gene for the life of the patent, the holder effectively has a monopoly over diagnostics, prophylactics and treatments based on the sequence. For example, the holder can charge any sum for a test analyzing the patented gene – even if the test is based on technology not invented by the patent holder. This can drive up the cost of diagnostics and treatments for the associated disease to highly prohibitive levels, as revealed by the fact that one in four laboratories has stopped performing certain genetic tests because of patent restrictions or excessive royalty costs [19]. Furthermore, when a single entity controls all testing of a genetic sequence, that entity may lack an incentive to provide the highest quality test or it may decide, for commercial reasons, not to offer testing for all known mutations within the sequence, resulting in an anticommons situation where superior tests are kept off the market and/or research into the effectiveness of current and prospective diagnostics or treatments are not pursued

for fear of patent infringement. By allowing a company or individual to patent a human disease-associated or viral sequence, the patent holder, in essence, ‘owns’ the associated disease.

A few of the problems with genetic sequence patents are exemplified by issues surrounding human *BRCA* gene patents, granted to Myriad Genetics® (UT, USA) by both the US Patent and Trade Office (USPTO) and the European Patent Office (EPO). With the issuing of the patents, Myriad gained market exclusivity for *BRCA1* and *BRCA2* genetic tests, for which they charged over US\$2600 [20]. Furthermore, Myriad’s tests failed to detect significant *BRCA1* deletions and rearrangements, as shown by a team led by geneticist Dominique Stoppa-Lyonnet of the Institut Curie (Paris, France) [21]. In 2006, Mary-Claire King (University of Washington, USA) demonstrated that the Myriad tests also missed other significant cancer-associated mutations in *BRCA1*, which can be detected with alternative tests [22]. In an interview, King maintained that, “a fuller testing process would include more than one technology, and competition would enable that to develop” [23]. Following Myriad’s attempt to enforce its European patent on *BRCA1* (which would have required European scientists to send their samples to Myriad’s headquarters in Utah, USA), the European scientific community successfully challenged the *BRCA1* patent, resulting in a narrowing of the claims [102].

While some of the most highly-publicized discussions about sequence patents, and their downstream effects on healthcare, focus on human disease-associated genes, there are instances where viral sequences, namely those of HCV and SARS coronavirus (SARS-CoV), have been the subject of debate. HCV was first identified as the causative agent of non-A, non-B hepatitis in 1988 by researchers at Chiron (CA, USA). According to the Nuffield Council on Bioethics, Chiron applied for and was granted multiple patents related to the discovery, including gene sequences. When other companies developed diagnostic tests for HCV, Chiron filed suit for infringement. The defendants argued that the patents should be revoked, and some limitations were indeed made, but the claims to a fundamental viral sequence were largely upheld [103].

Discussions of viral sequence patenting surfaced again with the emergence of SARS. In an effort to discover the causative agent there was an unprecedented level of international cooperation among researchers, resulting in the rapid identification of

SARS-CoV and the sequencing of its genome. However, patent applications were then filed for rights to the sequence. Some collaborators declared that they would not file while others, including the CDC, the University of Hong Kong and the British Columbia Cancer Agency, made patent claims which would potentially give them rights to diagnostic tests, drugs and vaccines subsequently developed. Some claimed the filing was done defensively, so as to prevent others, who would be more likely to deny rights to other researchers, from applying for patents. However, pending patent applications or the possibility of them can be a deterrent for scientists to conduct related research on the pathogen [24,104].

Sound medical care and public health – as well as the underlying goals of patent law, namely the encouragement of innovation – necessitate allowing scientists access to sequence information in order to create and provide different, and possibly improved, diagnostics, prophylactics and treatments. These end-stage products are what should be patentable.

Case law

The Supreme Court, over the past 150 years, has consistently held that one cannot patent products of nature, or materials isolated from products of nature, if those materials behave in the same way as they would in nature. Proponents of the patenting of genetic sequences, however, try to dilute this strong precedent [25,26] by referring to the 1980 case, *Diamond versus Chakrabarty* [27]. However, this case provides no basis for asserting that a genetic sequence is patentable. Rather, the case involved a genetically engineered bacterium, which the court carefully described as not naturally occurring. In fact, according to the Court [27]:

“The laws of nature, physical phenomena, and abstract ideas have been held not patentable. Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter ... such discoveries are manifestations of ... nature, free to all men and reserved exclusively to none”.

In June 2006, Supreme Court Justice Breyer elaborated on the issue [28]:

“The justification for the principle does not lie in any claim that ‘laws of nature’ are obvious, or that their discovery is easy, or that they are not useful. To the contrary, research into such matters may be costly and time-consuming; monetary incentives may matter;

and the fruits of those incentives and that research may prove of great benefit to the human race. Rather, the reason for the exclusion is that sometimes too much patent protection can impede rather than 'promote the Progress of Science and useful Arts', the constitutional objective of patent and copyright protection".

Not only have genetic sequence patents been permitted, but unlike Japan and many European countries, the USA does not have a statutory research exception to patent law (other than one that relates to drug research in certain instances). Indeed, the 2002 *Madey versus Duke University* case [29] made it clear that university researchers are not covered by a research exception to patent law. In some instances, holders of patents on genetic sequences have shut down research being undertaken by others. In addition to affecting potential therapies, scientists can be prevented from even trying to replicate, and thus validate, the patent holder's claims, regarding, for example, properties of a gene itself or the prevalence of variants in the population.

It is likely that if genetic sequence patents were challenged in courts, the US Supreme Court would invalidate them as covering unpatentable products of nature. But generally under US law, only someone who is infringing the patent can challenge it (by arguing its invalidity as a defense to the infringement), risking treble damages and the cost of such a lawsuit (on average almost US\$5 million) [30]. In Europe, however, where opposition procedures can be initiated by third parties, patents are revoked in approximately 41% of the cases where they are challenged, and in another 30% of the cases the patent rights are restricted [105].

Patent law is intended to facilitate an exchange where the patent holder obtains the exclusive right to make, use, or sell the invention in return for providing information on how to make the invention. Thus, if one person invents and patents a device, another person can use the description to invent an improved device. However, the system breaks down when it is information, such as a viral sequence, which is patented, as it gives the patent holder the right to prevent others from using that information entirely. Innovation is stifled and a basic theory behind patents (exclusivity in exchange for information) is undermined.

Viral sequence patents

While some downstream effects of patenting genetic sequences have now been brought to the attention of public officials, the ensuing

discussions have focused, primarily, on human disease-associated sequences, not viral sequences. Unfortunately, by adopting this perspective, a number of important distinctions between the two are not considered. In particular, limiting discussions to the genetic material of humans or, for that matter, free-living organisms, will not address the unique properties of viral genomes and some distinct problems which arise when patents for viral sequences are granted.

Owing to their high rates of genomic mutation (often approaching one mutation per genome per round of replication [31]), populations of viruses, particularly those with RNA genomes, harbor extraordinary amounts of genetic variation. Compared with human genes, the genomes of viruses belonging to the same species can differ substantially. Is the sequence of every single isolated virus patentable? Or, given the extant variation and rates of mutation in viral populations, will one patent apply to all genotypes within a given species, or would it extend to the level of viral genera – effectively allowing one entity to control much of the research on an entire group of organisms? If so, what definition is to be used for a viral species or genus? Unlike the case for multicellular organisms, criteria for specific viral taxonomic demarcations are often vague and can differ drastically among families.

In patent law, the Doctrine of Equivalents can be invoked to extend patent rights to inventions which are 'equivalents', for example, where 'unimportant and insubstantial substitutes' have been made and the end result is substantially similar [32]. If the doctrine is applied to genetic material, where is the line drawn within viral populations, the genomes of which can evolve at rates so high that significant differences can be observed in isolates sampled from the same individual, and initiated by a single infection? What is considered a substantial genetic change and when do protein variants represent similar as opposed to different results? Furthermore, would rights to a naturally occurring sequence extend to rights to vaccine sequences derived from (and which, as such, may be nearly identical to) a circulating strain, composed of a viral subunit or an inactivated or attenuated virus, and thus prevent necessary biomedical research and development, either by legal force or through fear of patent infringement?

A/H5N1 & related influenza virus patents

Patent activity related to influenza, and in particular A/H5N1, has grown exponentially in the last few years [101]. It appears that many recognize the

potential market for treatments and preventions if a human-transmissible A/H5N1 strain, with the capacity to cause a human pandemic, does emerge. While such a type-A influenza virus with pandemic potential may be the result of point mutations in the currently circulating A/H5N1, it may, alternatively, result from a gene segment reassortment event between the current A/H5N1 and a co-circulating human strain, such as A/H3N2. In the latter case the virus would not be composed of the same gene segments as the A/H5N1 isolates that have been identified.

To investigate the patent landscape of influenza, focusing on patents related to A/H5N1 sequences, the WHO commissioned a report from the World Intellectual Property Organization (WIPO) [106]. Preliminary studies, completed at the end of 2007, found that 85% of all patent applications in the Patent Cooperation Treaty system (used as an indication of patents which applicants intend to be international in scope) that relate to avian influenza or H5N1 were published since 2000, with approximately 35% of the patents published in 2007 alone [101]. The applicants represent a number of academic institutions, government agencies and private firms. Because the exact segment combinations, sequence and properties of a potential epidemic or pandemic strain are not known *a priori*, some may hedge their bets by applying for patents which cover a range of sequences. Blanket patenting all conceivable variants and derivatives of particular sequences not only goes beyond the bounds of the purpose of patents, but further cripples critical public health efforts.

The possibility of patenting influenza sequences relates to additional policy issues that the WHO is attempting to address, including those raised by Indonesia and Thailand, whose A/H5N1 human influenza cases account for 152 of the 360 reported cases and 120 of the 226 A/H5N1 deaths [107]. Currently, the Global Influenza Surveillance Network asks all countries to share A/H5N1 strains from afflicted citizens with WHO regional centers. Siti Fadilah Supari, Health Minister of Indonesia, a country which has previously refused to share data with the Network, argues that developing countries are expected to release their viruses to the Network, but that they “then lose their right to them and do not know what they are used for”. Supari argues that impoverished countries share their information and are then forced to pay large sums of money for diagnostics and vaccines derived

from this essential information. In response, the WHO is considering proposals and plans aimed at both improving access to viruses and increasing availability, distribution, affordability, and access to derived treatments [108–110].

Pending legislation

In early 2007, following increased awareness of the far-reaching effects of gene patents, US Representatives Xavier Becerra (CA, USA) and David Weldon (FL, USA) introduced the Genomic Research and Accessibility Act. If approved, the bill, H.R. 977, would amend the patent code to include the following: “no patent may be obtained for a nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies”^[33]. Although inspired by patents on human disease-associated genes, it would prevent further patenting of influenza nucleotide sequences, allowing researchers access to these sequences.

Conclusions

The issues surrounding influenza sequence patents must be resolved without delay, for once a pandemic strain emerges, it will be far too late. Furthermore, these discussions must not be limited to influenza or the genomes of human-specific pathogens. The influenza virus is only one of many of the rapidly-evolving viruses which are currently causing, or have the potential to cause, massive amounts of human and animal suffering. It is not the only extant virus with the capacity to cross over from animals to humans and undergo human-to-human transmission. A suitable framework which does not allow for the patenting of naturally occurring viral sequences must be put in place before an outbreak occurs. Only then can we pave the way for the most rapid biomedical response, fair and beneficial competition, the highest quality research, ventures aimed at preventing illness and the loss of human lives, and collaborations promoting access to diagnostics, treatments and preventions.

Future perspective

In the past few years, improvements in sequencing technology have made it possible to sequence entire genomes in a fraction of the time and for a fraction of the cost than before. New genome sequences, from a variety of both previously characterized and uncharacterized microbes, are being generated daily. The pace of sequencing and the discovery of new organisms will only quicken, providing vast amounts of information

which can reveal aspects of microbe populations and will be invaluable for the progress of infectious disease research, prevention and treatment. We are at a critical point in time where we can either choose to tie this information up in patents, for all to see but few to use for the next 20 years, or we can recognize it as what it is – natural information which no one should have a monopoly over and can be utilized to prevent much human illness. Taking the latter path will require an end to the practice of approving intellectual property claims to genetic sequences. As the direct correlation between sequence availability and the quality, affordability and global accessibility of molecular diagnostics and preventions becomes more apparent, ending this practice will not only be recognized as

congruous with the intent of patent law, but also a necessity for biomedical research and global public health.

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Executive summary

Influenza virus sequences & intellectual property

- Many recent advances in influenza research can be attributed to large-scale sequencing efforts and the accessibility of the resulting sequences to researchers.
- Patents on influenza virus genetic sequences could result in disincentives for future research.
- A patent holder controls the use of an invention for 20 years from the date of filing the patent application and can prevent others from using or making the invention.

Patenting genetic material

- The US Supreme Court has held that products of nature, laws of nature and materials isolated from products of nature, which behave in the same way they would in nature, do not constitute patentable subjects. Nevertheless, genetic sequences of naturally occurring organisms have been patented.
- In the case of human disease-associated gene sequences, patents have interfered with research and clinical practice.

A/H5N1 & related influenza virus patents

- Patent law can interfere with essential and time-sensitive research which incorporates viral genome sequences. The quality, affordability and availability of diagnostics, preventions and treatments based on the sequences can be compromised.

Conclusions

- Naturally occurring genetic sequences, including viral genomes and human disease-associated genes, should not be patentable.

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