The impact of patenting on DNA diagnostic practice

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ABSTRACT – Patents on genes often cover the gene sequence and the link between a disease and mutations in a gene, rather than a technology for the identification of mutations *per se*. Normally, patents are important for encouraging the development of new diagnostic tools and kits, but there is evidence that they can have severely deleterious effects on the delivery of genetic services. The difference largely depends on the licensing policy of the patent holder. This article describes different ways in which patents are used in this context and how the effects may be mitigated.

KEY WORDS: BRCA1, BRCA2, cystic fibrosis transmembrane conductance regulator gene, genetic tests, HFE, license models, patents

The molecular basis for many genetic conditions is being defined by increasingly sophisticated research, and the identification of the germline mutation responsible for an inherited condition is a valuable and accurate diagnostic tool. Such tests are now routinely available for a wide range of conditions, and contribute to the management of families at risk of genetic disorders. Genetic tests may be used to:

- confirm a diagnosis of a genetic condition (eg Duchenne muscular dystrophy in a patient with a clinical diagnosis of the disease)
- identify individuals at increased risk of certain conditions (eg familial cancer susceptibility)
- identify individuals predicted to develop a late-onset disorder (eg Huntington's disease)
- diagnose a genetic condition in utero (prenatal test).

The identification of the genes in which mutations cause genetic disease is rarely the work of a single laboratory, and the molecular techniques used are rarely unique.

In this article, how patenting issues may impact upon the availability of such tests within the NHS will be discussed, using three different examples of tests for very different genetic conditions, all with important healthcare implications.

Three models for the impact of gene patenting in the delivery of genetic services

The open model: no one knows, but (nearly) everybody pays

Cystic fibrosis (CF) is a severe autosomal recessive disorder that affects the epithelia of the respiratory tract, exocrine pancreas, intestine, male genital tract, hepatobiliary system and exocrine sweat glands, resulting in complex multisystem disease. Pulmonary disease is the major cause of morbidity and mortality in CF.[1] It is caused by biallelic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The identification of this gene in 1989 was a prime example of 'reverse genetics' or positional cloning.[2] A large international collaboration had led to the localisation of the faulty gene to chromosome 7, but it took several years for laboratories to explore the region of this chromosome to identify and clone the CFTR gene. Once the gene was identified (with the benefit of this prior knowledge) and its sequence was known, it became possible to test patients for mutations in this gene. More than 1,000 different alterations in this gene have now been described. This information has been collated onto a public database initiated by the Cystic Fibrosis Genetic Analysis Consortium and hosted by a group in Toronto.[3] There are common mutations in this gene, however, specifically the deltaF508 (F508del) mutation which accounts for about 70% of those detected in the Caucasian population. A further handful of mutations account for an additional 0.5–5% each, and others are rare, so that in most cases it is sufficient to screen for a limited set of mutations to identify the causal one(s) in a Caucasian patient.

Diagnostic laboratories and companies have taken advantage of this and developed kits for the simplified identification of the most common mutations. The difference between these kits resides in the source technology (which is often the proprietary right of the manufacturers) and not in the sequence interrogated for the mutation. There are guidelines which specify a set of 25 mutations (a mutation panel) that should be included for good practice.[4]

The CFTR gene was patented by the Hospital for Sick Children, Toronto, and the University of

Michigan. The patentees granted free access to gene sequences for diagnostic testing using commonly available technologies for mutation analysis, but they have collected royalties on gene-based commercial test kits and from companies that offer commercial testing. As a result of this broad license, competition between different kit manufacturers has gradually improved the sensitivities of their assays. In the meantime, CFTR testing has become widely available at a reasonable cost. Such a licensing policy is therefore acceptable and practical. By using the commercial kits, the diagnostic laboratories indirectly pay royalties to the patentees yet still retain the possibility of offering testing using 'home brew' methods, on which no royalties have been requested, at least not in the public sector. It seems that the genetic or medical community has no major objections to this model. What is not publicly known is how much the cost of the kits actually represents royalty fees. It would be interesting to get an idea of the 'value' of a gene or mutation in intellectual property terms.

The forbidden model: no one is allowed to use it (but everybody infringes)

Two major genes in which germline mutations cause a strong breast/ovarian cancer susceptibility were identified in the 1990s. The search for these genes was complicated by the fact that there were two important genes (on different chromosomes) accounting for similar proportions of families with autosomal dominant pedigrees of breast cancer. A team at the University of California, Berkeley, located the first gene on chromosome 17q and coined the term BRCA1.[5] The locus for a second susceptibility gene, BRCA2, was then identified on chromosome 13q.[6] The BRCA1 gene was eventually cloned and sequenced by Myriad Genetics, Inc, in 1994,[7,8] but this would not have been possible without the research and results from many other laboratories using samples from families collected collaboratively from many countries. The BRCA2 gene was first identified in 1995 at the Institute of Cancer Research, Sutton, Surrey,[9] and was further characterised by Myriad.[10]

Several patents on BRCA1 and BRCA2 were granted to Myriad and co-inventors by the US Patent and Trademark Office (USPTO) between 1997 and 2000. Similarly, three patents on the BRCA1 gene were granted to Myriad and co-inventors in 2001 by the European Patent Office (EPO).[11,12] The first BRCA2 patent was granted to Myriad in 2003, but a second BRCA2 patent, which was filed earlier by the Cancer Research Campaign (now Cancer Research UK), was granted in 2004.

It is important to note that the Breast Cancer Linkage Consortium (BCLC), an international initiative founded in 1989, pooled data and samples from many international studies, allowing the location of the BRCA1 gene to be narrowed down to a small region on chromosome 17 with odds of 1,020 to 1.[13] From 1993 to 1998 the BCLC was supported by the Fourth Framework Biomed1 and Biomed2 programmes of the European Commission. Eventually the BCLC database held genetic data from over 700 families, from nearly 100 contributing international centres. Thus, patent protection to only one organisation ignores the contribution of all these collaborators. The granted patents related to gene sequences published in 1994 and 1995 respectively. As indicated in the section on CF, once a gene sequence is known it is relatively straightforward to offer mutation testing clinically, using commonly available techniques. Hence, the diagnostic test for BRCA1 and BRCA2 is widely available in European laboratories. Several hundred mutations have so far been identified.[14] There are no mutation 'hot spots', however, apart from certain ancestral mutations such as the 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2, common in individuals of Ashkenazi Jewish descent and accounting for about 90% of mutations in these genes in this population. These three mutations are easy to detect using a kit-based format, but in other populations the entire genes have to be analysed. Myriad has capitalised on the monopoly on the BRCA1 and BRCA2 gene patents, and offers sequencing of both genes with a rapid turnaround. Only recently, however, did the technique detect deletions and duplications in these genes. The latter account for a significant proportion of mutations in some populations.[15–19] Interestingly, these types of mutations were only detected because different genetic laboratories were infringing the patents and continuing to test breast cancer patients for mutations. Furthermore, several manufacturers refrained from developing novel tests for BRCA1 and BRCA2 mutations because of these patents.

Myriad Genetics did offer non-exclusive licenses to some European centres to allow them to develop tests for certain specific BRCA1 and BRCA2 mutations prevalent in the surrounding population, but with the agreement that if this limited test was negative, full screening of the genes would be done in the Myriad laboratories.[20] This can only apply to populations with high frequencies of specific ancestral mutations. Also, costs were unacceptably high for most service laboratories, who often continued to develop their own techniques for genetic testing which infringed the patents. Myriad therefore developed a licensing strategy which exclusively licensed the test to a limited number of commercial genetic laboratories within specific geographical regions. Bioscientia (Germany) and Lab-21 Ltd (UK) are two such laboratories. These laboratories, however, were still only allowed to test for a limited set of BRCA1 and BRCA2 mutations, and the complete sequence analysis is still only performed at the Myriad laboratories in Salt Lake City, USA.

There has been widespread opposition in Europe to the patents granted to Myriad, particularly to the option of the patent holder to strictly exert its monopoly right by requesting that all diagnostic testing be done at its own US-based laboratory. After oral hearings at the EPO in 2004 the first patent was revoked due to errors contained in the initially filed sequence. Subsequently the other two patents were severely limited in their scope. The EPO, however, has not questioned the patentability of the BRCA1 or BRAC2 genes *per se*. The patent owners have filed an appeal against the decisions of the EPO, so the story continues. This has clearly caused widespread consternation and made clear that lasting, affordable solutions to patenting and licensing for genetic testing have to be developed.

The expensive way: no one can afford it

The third approach has been taken by Bio-Rad, the California-based company that acquired the patent on the hereditary haemochromatosis (HFE) gene after the closure of Mercator Genetics. Haemochromatosis is a common autosomal recessive disorder characterised by an excessive deposition of iron in the tissues. The gene was cloned in 1996 and it was found that two mutations were responsible for the majority of cases.[21] According to Merz *et al* the company offered to license laboratories to perform testing, but at a cost that makes Bio-Rad's own commercial test kit more economically attractive due to up-front payments and a per test fee of $20 for two mutations.[22] Thus the owner of the US HFE patent uses a very rigid licensing policy and as a result, many companies have refrained from developing their own kits for the disease. In the meantime, a European patent has also been granted, but few in the diagnostic community appear to have been notified by the patentees.

Discussion

Clearly, patenting can have an important impact on the conduct and expense of genetic tests, which can influence health service costs and test availability. Arguably, it is difficult to justify the patenting of a DNA sequence on many grounds (religious, ethical or moral). As mentioned above, the identification of a gene is always predicated on the accumulated work of other laboratories. The techniques used for gene cloning are rarely novel. The simple identification of a genetic sequence may preclude the fulfilment of the criteria for patenting of the sequence. The link between a (mutation in a) gene and a disease, however, seems to fulfil the criteria of novelty, inventive step and industrial applicability – the three basic criteria for patentability under the European Patent Convention (EPC).

Some critical observers have emphasised that the Myriad case has been an exception. We believe that it is not true: many more genes are covered by patents and, more importantly, an increasing number of gene patents have been exclusively licensed to one or a few diagnostic companies, mainly in the US.[23] One may expect that these claims will soon reach Europe. Recently, several laboratories have received requests for paying license fees for certain genes, for example the familial Mediterranean fever gene. Given the frequency of the disease in Mediterranean countries, this is an important diagnostic gene.

Conclusion

The effect that patents may have on diagnostic genetic testing should not be underestimated. It is hoped that mechanisms will be developed to facilitate – and preferably liberate – access to patented genes and sequences. Suggestions have been made by different international organisations, including the Organisation for Economic Co-operation and Development, to promote licensing models like the 'clearing house'.[24,25] It would be helpful if the genetic and medical community could actively contribute to the development and promotion of these alternatives.

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