In this issue of Clinical Chemistry, two groups, Badano et al. (1) from Baylor College of Medicine and Latour et al. (2) from France, report on PCR of short tandem repeats (STRs) for the diagnosis of Charcot-Marie-Tooth type 1A (CMT1A). CMT1A is caused by the duplication of a 1.4-Mb region on chromosome 17p12 that includes the peripheral myelin protein 22 (PMP22) gene. The increased gene dosage of PMP22 caused by the duplication event is thought to be responsible for the pathogenesis of CMT1A, producing a peripheral neuropathy. When the duplication was reported in 1991, the method developed for diagnosis was densitometric analysis of a Southern hybridized with a region-specific probe, allowing assessment of the presence of one to four copies of the 17p12 region. For diagnostic laboratories that began testing for CMT1A, the method was laborious and time-consuming. Other methods for diagnosis of CMT1A subsequently were developed, including pulsed-field gel electrophoresis for detection of recombination-specific junction fragments, fluorescent in situ hybridization using a PMP22 probe, and several PCR methods. Initial use of STR PCR of a single locus looking for the presence of three different alleles for diagnosis of CMT1A was able to diagnose only approximately one-third of cases. Use of additional STR loci increased the detection rate to ~85%. Although the STR PCR method was easier for the laboratory, it could not be done without the back up of a second more sensitive method [see Refs. (1, 2) for methods].

Both reports in this issue describe improved STR PCR methods with the ability to diagnose 100% of CMT1A cases tested. The Baylor group (1) identified a larger set of 42 STR loci in the duplicated region and defined a subset of 15 STRs that can be amplified in two multiplex PCRs. The panel was tested on 39 unrelated individuals with a diagnosis of CMT1A by another test method, with 100% having three different alleles at 1 or more of the 15 tested loci. The test was developed with 10 loci in one multiplex reaction using fluorescent-labeled primers, with analysis by a single lane of an ABI 377 automated sequencer. The 10-locus reaction detected 37 of 39 patients, and could therefore be used as the first-line test, with the additional 5-locus reaction being done only if the first 10-locus set was uninformative. The French group (2) selected 10 STR loci from the duplicated region and defined 3 of these loci for diagnostic testing. The three-STR panel was tested on 130 unrelated individuals with CMT1A diagnosed by Southern analysis, with 100% having three different alleles for at least one of the three STR loci. The three STR loci were run as individual PCRs and then analyzed either by silver-stained polyacrylamide gel electrophoresis or by separation of the combined PCR products on an ABI 310 capillary electrophoresis instrument. Either method is easily adapted by molecular diagnostic laboratories and represents a vast simplification over previously available methods for CMT1A diagnosis.

The question is: Will laboratories develop CMT1A testing based on these STR PCR methods? To understand why this question is even being asked, it is useful to review one laboratory’s experience with CMT1A testing. This testing was the laboratory’s first encounter with the daunting issue of disease gene patents. After the publication of the causative CMT1A mutation in 1991, the Molecular Diagnostic Laboratory at the University of Pennsylvania (UPenn) developed CMT1A testing using Southern analysis followed by densitometric analysis of the bands to determine gene dosage. The laboratory had no idea that the published information was also submitted as a patent application because United States patent applications are not available to the public until the patent is issued. In this case, there was no precedent for even being concerned about a patent on information used for molecular diagnostic testing. The laboratory became aware of the issue several years later when it received a letter from Athena Diagnostics (Worcester, MA) stating that they had an exclusive license to the CMT1A patent from Baylor College of Medicine, and the laboratory would have to stop performing CMT1A testing. The UPenn laboratory stopped performing CMT1A testing.

A problem then came to the attention of the UPenn laboratory. Athena Diagnostics was not performing prenatal diagnosis for CMT1A. Genetic counselors called the UPenn laboratory to discuss the problem that they did not have access to prenatal CMT1A testing. UPenn and Athena Diagnostics then arranged that the UPenn laboratory could perform an unlimited number of prenatal CMT1A tests, and up to 30 adult tests per year. This arrangement continued until the Baylor Cytogenetics Laboratory developed a better method for prenatal CMT1A diagnosis based on fluorescent in situ hybridization analysis. The UPenn laboratory then felt that it was no longer cost-effective or ethically necessary to continue performing this low-volume service, and thus stopped performing CMT1A testing in 1997.

CMT1A testing is only the first in a list of tests for which the UPenn laboratory has received patent notices containing a variety of terms. Patent holders can do whatever they choose with patented information, from allowing no one to use the information, to providing a single exclusive license to one user, to broad licensing either with or without royalty fees, to holding the information for the public good so that anyone can use it. The UPenn laboratory has experienced most of these options over the past 10 years.

Disease gene patents and the licensing of these patents raise many concerns, although the process of patenting and licensing gene sequences is completely legal according to patent law (3, 4). Establishment of a single provider of a laboratory test service, either by the patent holder directly or through exclusive licensing, raises the greatest concern. A single provider of a test service can determine
who has access to testing and for what reasons. For example, certain types of insurance may not be accepted for payment, or the provider may not perform prenatal testing. This is in contrast to testing that is provided by many laboratories where access to testing may be broader with all forms of payment accepted somewhere among all of the laboratories and where appropriate reasons for testing are established by professional consensus. Proficiency testing is difficult for a single provider of a test service, although this is a standard requirement for CLIA laboratory certification. Second opinions or repeat testing at a second site are not possible when there is a single provider of a test. There is also no competition for the price of testing or the quality of service.

From a personal and professional perspective, it is frustrating to spend time and money developing tests in my laboratory and teaching medical professionals about the proper use of the testing, and then to have to stop performing the test once a patent is issued. Laboratory directors have no way of knowing what genetic information has been filed for a patent (although the assumption should be that all genetic information is going to be patented) or how the patent will be enforced once it is issued. It is like watching your medical practice grow smaller and smaller, one patent at a time. How much will be left by the time the entire human genome and its variations are unraveled and patented en toto?

So, given that disease gene patents are legal, are there possible solutions? A group of concerned professionals has been meeting for ~18 months to develop solutions. The first step for the group was the development of a position statement that was taken to professional organizations for approval. The statement raises the concern that exclusive licensing of disease gene patents is not in the best interest of the public and recommends requiring mandatory broad licensing at reasonable royalty rates. The position statement, or a similar version of the statement, was adopted by the Association for Molecular Pathology, the Academy of Clinical Laboratory Physicians and Scientists, the College of American Pathologists, and most recently by the American Medical Association, and can be found on their respective Web sites.

Although the implication of the position statement is that new laws for disease gene patent licensing are needed, the working group acknowledges that introduction of new laws is a long and arduous process. Therefore, the group is also working on a model license agreement that Technology Transfer Offices may use as a template when licensing disease gene patents. To date, most of the exclusive licenses have been granted by academic medical centers, which hold most of the existing disease gene patents, thus the targeting of the Technology Transfer Offices. This pattern will almost certainly change in the future, however, as the genomics industry takes the lead as the major developer of genomics intellectual property. Academic medical centers may remain major players because of their access to the patient populations needed for correlation of genetic variations with disease risk. The hope is to raise awareness of the problems that exclusive licensing of a diagnostic test creates and to encourage voluntary broad licensing at a reasonable royalty rate. Some family disease organizations are now aware of these same issues and are requiring at least partial control of how patents are used that result from the research in which they participate.

Although patent protection is needed for pharmaceutical drug development based on disease gene discoveries, the same protection is not required for the translation of genetic information into diagnostic tests performed by laboratories. Those of us who practice molecular diagnostics ask to be allowed to continue our medical practice. So, will my laboratory develop CMT1A testing based on STR PCR? Has the patent application for the method been filed?

References

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