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The American Society of Human Genetics (ASHG) has a deep-rooted responsibility—the understanding of and care for patients with genetic disease. We have embraced and developed new technologies to answer the questions our patients raise. Our membership has interest in and empathy for the patient and family with genetic disease. We recognize the importance of our patients' contributions to new knowledge, and we are sensitive to patient care needs. It will continue to be our study of the *special patient* with sensitive new genetic technologies that provides the ASHG incredible potential for gaining new knowledge of disease and human biology. I wish to illustrate here a few of the outstanding contributions of physicians, geneticists, and molecular biologists.

Denis Burkitt recognized that his young African patients with lymphoma were such special patients. In an effort to resolve the unusual, initial success was found in cytogenetic studies. The 8;14 chromosomal translocation associated with this endemic lymphoma suggested that a somatic genetic event caused the neoplasia (Zech et al. 1976). Molecular biologists such as Phil Leder and others recognized that the chromosomal breakpoints were coincident with the map location of the *myc* and immunoglobulin genes. These groups proved that the translocation event had placed *myc* under regulation of the immunoglobulin genes and that this led to a transition to neoplasia (Taub et al. 1982; Adams et al. 1983; Dalla-Favera et al. 1983; Erikson et al. 1983; Hamlyn and Rabbits 1983). Thus, unusual patients and molecular genetic research led to understanding of a new mechanism for cancer. Following the characterization of the Burkitt lymphoma translocation, the description of other neoplasias resulting from similar mechanisms include chronic myelocytic leukemia [t(9;22)] (Heisterkamp et al. 1983), follicular lymphoma [t(14;18)] (Tsujimoto et al. 1984), acute myeloblastic leukemia [t(8;21)] (Rao et al. 1988), and acute promyelocytic leukemia [t(15;27)] (Borrow et al. 1990; de Thé et al. 1990; Alcalay et al. 1991).

Other patients have a more obvious genetic basis for their disease. Nancy Wexler's dedication to the study of Huntington disease brought the genetic world's attention to a group of patients in Maracaibo, Venezuela (Wexler et al. 1984). This unusual lake-resident community with the highest known incidence of Huntington disease offered Jim Gusella and the Huntington disease research group the opportunity to attempt DNA-based genetic linkage. Their interest and attention turned the tragedy of this disorder into a hopeful experience for all—physicians, social workers, molecular biologists, and, most important, patients. Neglected patients received medical care, investigators became involved, and fortunately Gusella succeeded. He had taken advantage of special patients, new DNA polymorphic markers, and family linkage analysis to determine that the Huntington disease gene was located on chromosome 4 (Gusella et al. 1983).

This localization of the Huntington disease locus provided an approach to gene isolation via positional mapping, an exciting new concept. Such mapping has succeeded in determining the location of the genes responsible for Charcot-Marie-Tooth disease type 1a (Vance et al. 1989), Werdnig-Hoffmann disease (Gilliam et al. 1990), and others. This is painstaking work. I was recently excited to hear of the positional mapping of facioscapulohumeral muscular dystrophy (FSHD). In this case, Gusella's approach had failed, as reflected by the exclusion of the FSHD gene from over 90% of the genome (Sarfarazi et al. 1989; Wijmenga et al. 1990*b*). However, Cisca Wijmenga from

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Leiden traveled to Jim Weber's laboratory and in only 6 wk mapped FSHD to chromosome 4 by using highly informative PCR-based short tandem repeat polymorphisms (Wijmenga et al. 1990*a*). What appeared to be a depressing research effort had been suddenly reversed. The patients had done their part, but investigators had to be very creative to solve the problem of this disease.

We have been rewarded in a few of these positional mapping efforts by actual discovery of the gene. The success of Lap-Chee Tsui and Francis Collins in the isolation of the cystic fibrosis gene has boosted our enthusiasm for the approach (Rommens et al. 1989). Again, the families had provided material, the chromosome 7 position was rapidly identified, and the gene finally was isolated with the careful use of special techniques. The reward has been great for many, in terms of diagnosis (over 100 cystic fibrosis mutations have now been described), understanding of the disease, and prospects for therapy. We continue to strive for technology which will allow the rapid identification of disease genes mapped to a genetic position.

Each of these discoveries required the cooperation of hopeful families, interactive scientists, and effective molecular studies—things the ASHG does well. In some circumstances, a single unusual patient provides the critical insight into a disease. These informative patients are brought to public attention by well-trained physicians and geneticists. Let me illustrate a few. Hans Ochs diagnosed a young man with Duchenne muscular dystrophy who had, in addition, chronic granulomatous disease, retinitis pigmentosa, and McLeod syndrome. The patient was shown by high-resolution cytogenetics to have a deletion in Xp21 and was presumed to have a contiguous deletion syndrome (Francke et al. 1985). Pat Jacobs should be acknowledged for bringing a rare group of females with Duchenne muscular dystrophy to our attention. Each of the reported females had an X-autosome translocation involving the site Xp21 (Jacobs et al. 1981). Her speculation that this was the location of the Duchenne muscular dystrophy gene was to be proved correct. These rare patients led two investigative groups, one headed by Lou Kunkel and one headed by Ron Worton, independently to seek the Duchenne muscular dystrophy gene. Kunkel used a technique of subtractive enhancement, referred to as "PERT" (Koenig et al. 1987), while Worton used translocation-junction cloning and characterization (Burghes et al. 1987). Both succeeded.

Knowledge of the human Duchenne muscular dystrophy gene led Jeff Chamberlain to the development of a simple PCR-based method for detection of deletions within this 2-million-bp gene prone to new mutations, the majority of which are deletions (Chamberlain et al. 1988). Simultaneous amplification of nine exons in a single reaction enables the identification of 81% of all deletions (Chamberlain et al., submitted), thus greatly simplifying diagnosis of Duchenne muscular dystrophy. An additional nine-component reaction brings the accuracy of deletion detection to 98% (Beggs et al. 1990). The worldwide application of this technology is illustrated in figure 1.

It is not always so obvious when a family or patient is rare and offers a special opportunity for investigation. Such identification comes to the informed mind. This can be illustrated by observation of the pedigree in figure 2, in which a mother and both her children were affected with neurofibromatosis. Cytogenetic study was indicated on the basis of multiple miscarriages in the sibship of the mother, and consequently Virginia Michels discovered in this family a translocation involving chromosome 17, where the neurofibromatosis gene had been mapped (Schmidt et al. 1987). It was this case and one other which provided Ray White and Francis Collins with knowledge of where to search for the neurofibromatosis gene, and, as you know, this search has been rewarded (Cawthorn et al. 1990; Viskochil et al. 1990; Wallace et al. 1990). Two rare patients with independent translocations provided the critical biological materials allowing identification of the gene involved in this common disorder.

Some diseases offer major technology challenges after the gene discovery. An example is Lesch-Nyhan syndrome, which is a new mutation disorder in which the lesions are usually small within a 40-kb gene. We determined by automated DNA sequencing the complete sequence of this disease gene (Edwards et al. 1990), and, armed with this information, Richard Gibbs developed PCR multiplex amplification of all the exons, followed by automated DNA sequencing of the products (Gibbs et al. 1990). Even without material from a deceased affected male, direct DNA sequencing can identify carrier females. The use of sequencing techniques for routine mutation detection is a relatively new concept but one which is gaining rapid use.

It has been the application of molecular methods to disease study which is now bringing the rare and informative patient to our attention. Such an example is a young lady with both cystic fibrosis and short

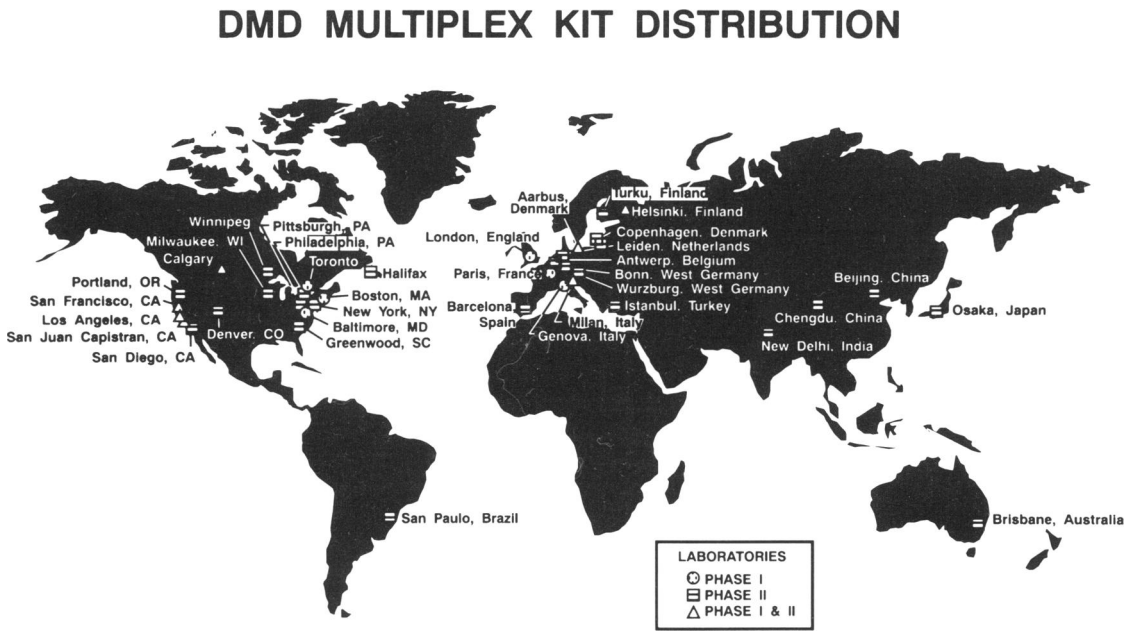

Figure 1 Worldwide distribution of Duchenne muscular dystrophy multiplex PCR deletion detection kit. (Fig. supplied by Jeff S. Chamberlain.)

stature. Art Beaudet carried out linkage analysis on her family and found the surprising result that the patient lacks her father's chromosome 7 polymorphic marker (Spence et al. 1988). Some may have dismissed the situation as one of disputed paternity, but this is not the case. This young patient has cystic fibrosis and short stature on the basis of an unusual inheritance mechanism—uniparental disomy—such that she carries two copies of her mother's chromosome 7. This mechanism has now been observed in a second case of cystic fibrosis (Voss et al. 1989), in a phenotypically abnormal familial balanced 13/14 Robertsonian translocation carrier (Wang et al. 1991), and in cases of Prader-Willi (Nicholls et al. 1989) and Angelman (Knoll et al. 1990) syndromes. These are examples of new discoveries made possible by molecular methods—more will follow.

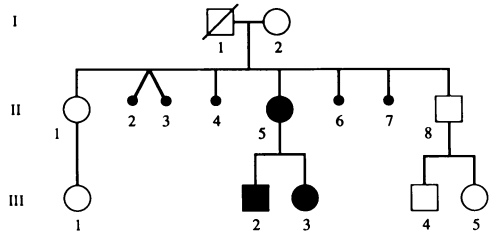

Figure 2 Pedigree of neurofibromatosis family. Cytogenetic studies on the mother, II-5, revealed a 46,XX,t(1;17)(p34.3;q11.2) chromosomal constitution. The same translocation was subsequently found in her two children, III-2 and III-3. (Redrawn from Schmidt et al. 1987, with permission.)

I would like to wrap up my illustrations of special patient/technology interfaces by discussing a societal benefit that our genetic technology has in a nonmedical arena. Members of your society have made significant contributions to the area. Let me be specific. Two young ladies were brutally raped and murdered near Leicester in the UK. The murders went unsolved until Alec Jeffreys offered his assistance with a totally new forensic tool which he referred to as "DNA fingerprinting" (Jeffreys et al. 1985*a*, 1985*b*). In the very first application of the method (Gill et al. 1985) he proved the innocence of an individual who had confessed to the crimes, and he subsequently identified the true murderer.

Let me illustrate the power of this technology by using cases studied in our laboratory. On the basis of eye-witness accounts by two young women who had been assaulted, male suspects were identified with 98% certainty. DNA evidence clearly did not support the eye-witness account (fig. 3), and the wrongly accused suspect was released. One has to see only a few such cases to realize that genetic technology has improved the justness of the court. However, the second type of case in which the DNA evidence supports the eye-witness account has been the subject of strong at-

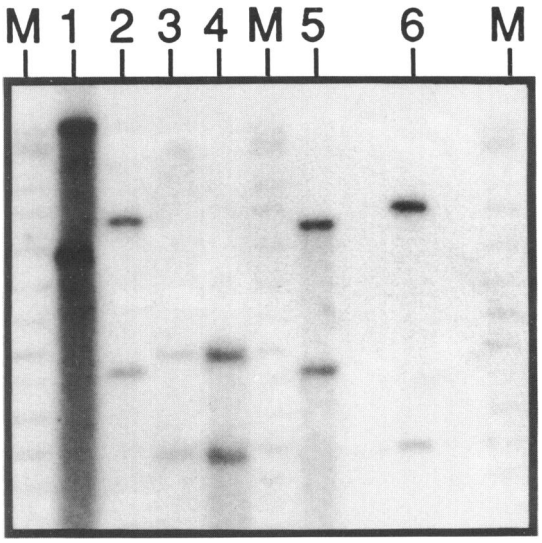

Figure 3 Exclusion of suspect by DNA analysis. DNA samples from a rape victim (lanes 2 and 5) and from semen stains left by the assailant (lanes 3 and 4) were tested to determine the alleles of a polymorphic VNTR. Similar analysis was performed on DNA from a control (lane 1) and from a suspect identified by eye witnesses. (lane 6). The evidence here clearly indicates that the suspect is not the assailant. Lanes M, Molecular-weight markers. (Fig. supplied by Holly A. Hammond.)

tack by defense councils. There are molecular biologists and population geneticists in the ASHG who have given considerable time to explaining the technology and documenting its validity for the courts and juries. I would recognize Ken Kidd, Steve Daiger, Mike Conneally, David Housman, and many others as leaders in this area. Your society published a "Points to Consider" paper under Phil Reilly's leadership this past year (Ad Hoc Committee on Individual Identification by DNA Analysis, The American Society of Human Genetics 1990). You are involved, and I am pleased to report a conclusion of a recent congressional OTA report: "The Office of Technology Assessment (OTA) finds that forensic uses of DNA tests are both reliable and valid when properly performed and analyzed by skilled personnel" (United States Congress, Office of Technology Assessment, 1990, p. 7).

I wish to close with a few summary thoughts. Our patients provide daily reminders that we need new knowledge. It is the power of DNA-based and genetic technologies which offer the ASHG the opportunity to provide an interface of medical need and methods for solving disease, in a very special way. We have our roots in both the solution of human diseases and, in that experience, an appreciation for the patients' needs. I can think of no other society of which I would prefer to be president. I can think of no other scientific field which would be so encouraging for young investigators. The ASHG is making a positive impact on health and society.

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