

Many human subjects in medical research studies participate primarily for philanthropic reasons. This is particularly true for research into recessive genetic diseases, where research subjects may be carriers not themselves afflicted with the disease. When the research produces commercial applications, there are ethical issues concerning whether the philanthropic motives of the subjects should affect: (a) who shares in the profits from the research; and (b) how widely the benefits of the research should be made available. Because it involves research subjects who were unusually well organized and were also instrumental in promoting the research, the ongoing litigation over a patent covering the gene that is defective in children suffering from Canavan disease (“CD”) brings these bioethical issues into sharp focus.

BACKGROUND

Canavan Disease. In CD, a deficiency in aspartoacylase (ASPA) leads to the brain progressively becoming spongy and degenerating due to leukodystrophy and demyelination.¹ Symptoms of mental retardation appear about three months after birth.² Death usually ensues in less than ten years.³ CD is most prevalent among Ashkenazi Jews, but has also been found in non-Jewish patients.⁴

ASPA is an enzyme that catalyzes the hydrolysis of N-acetyl aspartic acid to aspartate and acetate.¹ CD is an autosomal recessive disorder resulting from mutations in the human *ASPA* gene.^{4,5} The most prevalent mutation causing the disease among Ashkenazi Jews is a 854A_C missense mutation, which is present on approximately 85% of the chromosomes of Jewish CD victims.^{4,5} The mutation results in glutamine_alanine change at codon 285 and a form of ASPA with approximately 2.5% of the activity of the wild-type enzyme. That mutation, together with a nonsense

mutation (693C_A) and a splice-site mutation that results in exon-skipping and a frameshift, account for approximately 98% of the mutations in Ashkenazi Jews.⁴

Research. In 1987, the cause of CD was unknown, Dan Greenberg had fathered two children with CD, and Dr. Reuben Matalon was running a laboratory performing clinical testing and research of familial disorders at the University of Illinois in Chicago.³ Mr. Greenberg was looking for someone to develop carrier and prenatal tests for CD and persuaded Dr. Matalon to pursue it. To assist Dr. Matalon, Mr. Greenberg provided blood and urine samples from his children and located other affected families and arranged for them to provide urine, skin and even post-mortem tissue samples.^{3,6} In addition, the National Tay-Sachs and Allied Diseases Association (NTSAD) and other not-for-profit organizations provided some funding, established a Canavan registry, and provided additional samples.

Dr. Matalon was able to identify the ASPA deficiency as the cause of the disease and developed carrier and prenatal tests assaying for enzyme activity.^{1,5} However, particularly in prenatal tests, because the level of ASPA activity found in direct or cultured chorionic villi cells and in amniocytes is about 2 orders of magnitude lower than that found in normal cultured skin fibroblasts, the enzyme activity assay proved unreliable.^{5,7} A genetic test would be preferable. After moving to the Miami Children's Hospital Research Institute, Inc. (MCH), Dr. Matalon's lab was eventually able to clone the human *ASPA* gene, to identify the mutations commonly associated with CD, and to develop assays for the presence of the mutations.^{4,5,7}

Patent. As part of his arrangement with MCH, Dr. Matalon had agreed to disclose and assign all of his inventions to MCH and to cooperate with MCH to obtain patents on

those inventions.² He did so with respect to his work on ASPA and CD. On October 21, 1997, the U.S. Patent and Trademark Office issued Patent No. 5,679,635 (the “Patent”).⁷ The Patent covers the sequence of the *ASPA* gene (in both its wild-type and mutant forms), the ASPA protein encoded by the gene, DNA sequences that hybridize to critical gene sequences under stringent conditions, and various methods of using the gene sequences to assay for mutations.⁷ The methods suggested included hybridization assays, restriction fragment length polymorphism assays, PCR assays (using gel mobility to determine PCR fragment length), and immunoassays. The Patent also notes that the patented amino acid sequences might be useful as drug leads, and that the patented gene sequences might, with an appropriate delivery vehicle, be useful in gene therapy.⁷

Dispute. Shortly after issuance of the Patent, MCH began informing clinical labs, which had begun to do genetic testing for *ASPA* mutations based on Dr. Matalon’s findings, that they would require licenses from MCH. The labs would be required to pay royalties of \$12.50 per test and would be permitted to perform only a limited number of tests.^{2,3} MCH’s demands resulted in a decrease in the number of labs offering Canavan screening and caused Canavan Foundation to discontinue its free carrier screening program.^{2,3} Mr. Greenberg and the organizations that had been involved in assisting Dr. Matalon objected to the actions of MCH. In October 2000, they filed suit against MCH and Dr. Matalon in Illinois to obtain a share of the royalties earned by MCH under the Patent and to prohibit MCH from continuing to restrict access to Canavan screening tests.^{2,6,8} The suit was transferred to a Miami court in July, 2002 and is still pending.⁶

ISSUES

Who Should Share in Profits of the CD Research? The plaintiffs in the lawsuit

argue that their primary purpose in assisting Dr. Matalon was philanthropic: to aid those at risk of CD. They sought no financial gain, and they assumed no one else would.⁸ They argue that Dr. Matalon and MCH have taken genetic information that belonged to the CD victims and their families (as well as cash donations) under false pretenses and used it to obtain a Patent and make money.^{2,6,8} Under those circumstances, the Patent holder should be required to compensate those who made the Patent possible.

Dr. Matalon notes that he is not receiving any royalties under the Patent. Rather, he is complying with his agreement with MCH, which contributed far more money to his lab than the plaintiff group.² MCH believes it is entitled to exploit the Patent to attempt to recoup some of the expenses it incurred in funding Dr. Matalon.

In this particular case, each side may have missed opportunities to protect its interests and avoid a dispute. For Dr. Matalon's part, one commentator has suggested that he failed to obtain appropriate informed consents from early donors.³ The lawsuit filed against MCH and Dr. Matalon includes a claim for breach of informed consent.⁸ If there is a possibility that the researcher or sponsor of a study is going to exploit the study for commercial gain and not share the profits with participants, it is widely accepted that the participants in the study should be informed of that possibility and consent to it in writing.⁹ For their part, NTSAD and others providing grants to Dr. Matalon could have required an assignment of rights to discoveries (as MCH did and other patient groups have done), but failed to do so.^{2,9}

Unlike the CD case, most research involves a diffuse group of subjects, none of whom individually is in a position to protect their philanthropic interests. Some have argued that, in order to serve the philanthropic desires of research participants,

particularly in genetic research, there should be an institutional mechanism by which a single body negotiates with research sponsors on behalf of all participants (and the community as a whole) to ensure that some portion of the fruits of the study (in the form of money or technology) is dedicated to a philanthropic purpose.^{9,10,11}

Restrictive Licensing Policy. The plaintiffs in the lawsuit against MCH also object to the restrictive licensing strategy of MCH. MCH was willing to grant labs licenses to perform only a limited number of CD tests. The plaintiffs argue that their philanthropic purpose in aiding Dr. Matalon will be thwarted if the CD test is not made widely available.⁶ A possible broader concern not expressed by the plaintiffs is that, because the Patent covers the ASPA gene and protein, MCH is in a position to limit research on ASPA as a drug or gene therapy target.⁷ MCH's expressed rationale for granting only limited licenses was that it hoped to make the Patent technology attractive to a single master licensee with a nationwide, unlimited license.^{2,3}

This issue boils down to an argument over the wisdom of granting a patent in this situation. The primary benefit of a patent lies in being able to prevent others from selling the patented product, so that the patentee can charge monopoly prices.^{12,13} Here, MCH was not in a position to sell CD tests itself, so it wanted its master licensee to be able to charge monopoly prices (and to pay MCH for the privilege of doing so). The existence of competition from a number of other labs with unlimited licenses would prevent the master licensee from raising prices for the CD test. If those who finance research are not allowed to benefit, either directly or indirectly from the pricing power associated with patents, their incentive and ability to finance research will diminish.^{12,13}

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