Richard S. Spielman 1946–2009

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Richard S. Spielman was a leader and innovator in statistical genetics, perhaps best known for developing the first family-based association test, the transmission disequilibrium test (TDT). Richard Spielman died on April 25, 2009, at the age of 63. He was the Thomas and Evelyn Butterworth Professor of Genetics at the University of Pennsylvania. He received his BS degree in biology from Harvard College in 1967 and his MS and PhD degrees in human genetics from the University of Michigan before moving to the University of Pennsylvania in 1974.

Spielman's scientific publications, totaling over 100, attest to his prolificacy as well as a rarely found breadth across a range of disciplines in statistical, population and human genetics. Spielman began his career examining the population genetics of indigenous people of the Americas as a graduate student with James Neel. He found a correlation between linguistic divergence and the pattern of genetic variation as measured by the divergence in gene frequencies in seven language areas among 50 South American Yanomamo villages. Working with a relatively isolated study group presented an unusual opportunity to determine the tempo of biological divergence and the degree to which it parallels one aspect of cultural divergence. As the first work to demonstrate the ability to define language groups by genetic variation, Spielman's graduate studies reflected his early and profound interest in drawing new connections between genetic and phenotypic variation.

In the 1980s, Spielman began working with Warren Ewens, in a partnership that developed into a close and fruitful life-long collaboration. Their early studies focused on developing formal theories for the population genetics of variation at the DNA level. Although general mathematical theories were available, there had been limited genetic data with which to test these models. When a technology for genome-wide genetic mapping by RFLP was proposed in 1980, Spielman and Ewens seized this opportunity to develop the first population genetic models for RFLP data. Here, Spielman again showed his interest in characterizing genetic variation, and his productive combination of statistical models with these early genetic datasets moved the field to a new level of resolution.

Spielman in the 1990s became increasingly interested in phenotypic variation and in resolving genetic associations to disease, devoting much of his efforts to type 1 diabetes and the role of HLA. Although at this time association studies were becoming both feasible and popular in the human genetics community, analysis of these studies began to raise concerns that population stratification might significantly inflate the false positive rate, contributing to many of the false-positive association reports of this time period. Spielman recognized the urgent need to develop new statistical methods and analysis strategies, which led to his most recognized and lauded work, the development of the TDT. Technically, this is a test for linkage in the presence of association, but in practice, most researchers considered it an association test and used it as such. The test requires a family-based study design, including the collection of data from parents and one or more offspring affected with a heritable trait. For each parent heterozygous for a specific marker allele, the TDT tests whether the frequency with which that allele is inherited by affected offspring is significantly different from 50%. Conditioning on heterozygous parents allows the analysis of multiple affected offspring while also rendering the TDT insensitive to population heterogeneity. The TDT was considered seminal as the first statistical test for associating genetic variation to phenotypes in family data. This advance came at a time when the human genetics community sorely needed such a method to bring order to the increasing number of genetic association studies, and the TDT remains widely used today.

Some ten years ago, together with his wife and collaborator, Vivian Cheung, a professor and Howard Hughes Investigator at the University of Pennsylvania, Spielman began developing statistical approaches in several new areas. One such approach involved considering the expression level of a gene as a heritable quantitative trait, known as eQTL mapping. Over the past five years, Spielman and Cheung reported eQTL maps for a large range of expression phenotypes. This work is of tremendous importance for the genetic mapping of heritable traits because it allows researchers to focus on expressed genes rather than genetic variants.

From these eQTL studies, Spielman and Cheung moved into several more clinical applications, including the identification of carriers of a recessive disease via their expression phenotype. For example, heterozygous carriers of ataxia telangiectasia (*ATM*) mutations are not clinically distinct from noncarriers but are at increased risk for several diseases. Spielman and Cheung demonstrated that *ATM* mutation carriers show a distinguishable gene expression pattern, which shed a completely new light on recessive traits and may lead to a better understanding of the etiology of these traits. Similar findings were obtained for heterozygous carriers of Nijmegen breakage syndrome mutations. In another outshoot of their eQTL studies, Spielman and Cheung applied these methods to identify regulators of expression levels of radiation-response genes.

Spielman was the founding chair of the Genomics and Computational Biology graduate group at the University of Pennsylvania and was a gifted and highly motivated teacher within this program as well as across the community. He was an editorial board member of the *American Journal of Human Genetics*, *Genome Research* and the *Journal of Clinical Investigation*. Richard Spielman was a highly respected leader in the fields of statistical genetics and biology. Throughout his career, he was a driver in bringing precise statistical methods and standards to a range of biological problems, efforts that were well appreciated by his colleagues across many disciplines. ■

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