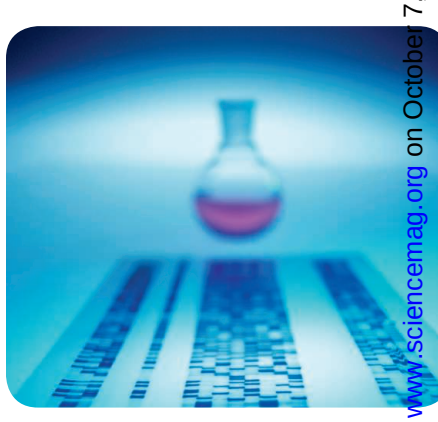
Aravinda Chakravarti is a professor at the McKusick-Nathans Institute of Genetic Medicine at the Johns Hopkins University of Medicine, Baltimore, MD. E-mail: aravinda@jhmi.edu.

Genomics Is Not Enough

NEXT WEEK, THE INTERNATIONAL CONGRESS OF HUMAN GENETICS CONVENES IN MONTREAL, WHERE genomic science, its technologies, genetic disease, and personalized medicine will be discussed. Translating current knowledge into medical practice is an important goal for the public who support medical research, and for the scientists and clinicians who articulate the critical research needs of our time. However, despite innumerable successful gene discoveries through genomics, a major impediment is our lack of knowledge of how these genes affect the fundamental biological mechanisms that are dysregulated in disease. If genomic medicine is to prosper, we need to turn our attention to this gaping hole.

Advances in biomedical research have raised high expectations for translating research into medical applications, including individualizing treatment and prevention. The concept of individualized medicine is not new to genetics. The identification of numerous inborn errors of metabolism and the discovery of their associated enzyme deficiencies paved the way for their specific genetic diagnosis and treatment. However, understanding their biological mechanisms was key. For example, severe mental retardation can arise from the effects of systemic phenylalanine accumulation on the brain, a condition called phenylketonuria. It was determining the underlying cause as a recessive genetic defect in the liver enzyme phenylalanine hydroxylase that led to individualized treatment and public health screening of newborns for the disorder.



Today, genomics technologies can routinely scan the human genome for genetic alterations in any disorder: More than 2000 single-gene Mendelian diseases have been elucidated in this way. Finding the genetic changes that cause the remaining 2000 Mendelian diseases appears within reach. But despite many efforts, attaining a similar understanding of common, chronic, complex diseases has been disappointing. Here, to bring major medical benefit, biomedical research must move beyond simple gene discovery by mapping, sequencing, or genome-wide association studies to focus on understanding human disease mechanisms. We need to answer not only which DNA variants in which genes lead to disease, but how they do so.

The lessons from genome biology are quite clear. Genes and their products almost never act alone, but in networks with other genes and proteins and in context of the environment. The corollary to this is that compromising the activity of one gene need not cripple an entire network. This is consistent with the observations that most traits involve multiple genes, common complex disorders arise from an accumulation of genetic defects in many genes, and Mendelian diseases are rare. Moreover, variation in the regulatory machinery of genes is much more frequent than that in the structure of gene products. Genome biology now needs to move to cell biology and physiology (systems biology) to understand how genetic perturbations lead to downstream dysregulation of proteins, their networks, and cells in disease.

Our evolving knowledge of genetic variation complicates this understanding. Each individual is genomically unique, with the DNA variation in our genomes serving as markers of our ancestries. Are each individual's biology and disease also unique? Or does the extensive sequence diversity in any disease coalesce into a smaller set of common functional deficiencies? By focusing on a mechanistic understanding of disease, genomic science has much to offer and can provide concrete suggestions about when medical treatment needs to be individualized and when made universal. These answers will themselves evolve as the science evolves. Consider the simple example of blood typing for everyday transfusions. This is individualized treatment that ignores widespread differences in type frequency between different populations because the focus of treatment is the individual, not the group. Recent research offers the future possibility of enzymatic treatment of any blood type to make it the universal type O, thus making a once successful individualized treatment universal. As this example shows, for genomic medicine there is no time with a more acute need for science than now.

– Aravinda Chakravarti

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