Genotype-Phenotype Correlations: Assessing the Influence of Sequence Variants on the Clinical Phenotype

It used to be simple. Physicians observed patients, asked questions, examined them, and established a defined clinical phenotype. Sometimes a laboratory analyte, with a sufficient and significant correlation with the observed clinical phenotype, could be measured to provide a basis for hypothesis-driven approaches to disease pathogenesis. Two classic examples of diseases are cystic fibrosis (CF), which is associated with increased sweat chloride concentrations, and diabetes mellitus, which is associated with increased glucose. The road to gene discovery has been considered tractable for CF because of its inheritance pattern, whereas diabetes has been considered a polygenic disorder quite intractable to such approaches.

Over the past few years, however, as mutations for a variety of disorders have been uncovered, things have become both simplified and complicated. For example, the discovery of mutations in the CFTR gene was a major breakthrough in the understanding and diagnosis of the “monogenic disorder” CF. It soon became clear, after careful genotype-phenotype correlations, that CF behaves in many ways like a multifactorial (or polygenic) disorder (1). Some of the genes underlying this clinical variability have been uncovered after careful phenotypic (i.e., clinical) analysis, correlations with other distinct genetic disorders, and candidate gene analysis. This does not negate the importance of mutations in CFTR in disease pathogenesis and the characteristic diagnostic phenotype (i.e., increased sweat chloride), but instead highlights the role of genetic modifiers in clinical presentation and the importance of carefully generated distinct phenotypes in enabling their identification.

Conversely, perhaps an approach similar to that for a polygenic disorder can provide insight into potential “monogenic” contributors to a complicated phenotype such as type 2 diabetes. A case in point is the article by Stevens et al. in this issue of Clinical Chemistry (2), in which a carefully defined population of patients with type 2 diabetes was studied for mutations in the apolipoprotein (APOE) gene in the hopes of uncovering mutations thought to play a pivotal role in lipoprotein metabolism. The notion here was the idea that the base phenotype, i.e., hyperglycemia, would help to uncover mutations that may be deleterious in such patients and may otherwise go unnoticed in nondiabetic individuals. Indeed, using heteroduplex analysis and subsequently verifying the identified changes by DNA sequencing, the authors discovered APOE sequence variants in 3 of 765 patients, a frequency that was considerably higher than in nondiabetic patients.

Thus, we have a model for studies of multifactorial disorders—extensive and careful selection criteria based on thorough clinical analyses, scanning of candidate genes for sequence variants, confirmation by sequencing, protein analysis, and subsequent corroboration with biochemical data related to specific pathway perturbations that are further associated with a specific clinical disorder (in this case, dyslipoproteinemia). Although it is not clear in this case whether these variants had any significant effect on the lipid profile or clinical outcome, the investigative approach is one that merits consideration and represents, in this age of single-nucleotide polymorphism analysis, a rational step in the attempt to discover significant contributors to clinical outcome in common complex disorders such as type 2 diabetes.

References

Lawrence M. Silverman*
Mani S. Mahadevan

Department of Pathology
University of Virginia Health Sciences Center
Charlottesville, VA 22908

*Author for correspondence. Fax 434-924-8307; e-mail lms7r@virginia.edu.

DOI: 10.1373/clinchem.2004.042762