nature genetics

Organ, organelle, organism

Physiology is the original systems biology. Presenting genetic discoveries for the benefit of clinicians specializing in individual organs and organ systems is likely to help produce integrated models of how genes function.

Although only a proportion of clinicians are engaged in research, and fewer are active in genetics, each is expert in an organ system and its perturbation. Some clinical organ experts are already collaborating with research geneticists in screening, phenotyping and making sense of genetic research. The rest constitute a receptive readership not only for transferring genetic results into medical practice, but also for integrating and making sense of puzzling findings by providing them with a context. This raises the question of whether genetics journals such as this one are doing all they can to ensure that the results of genetic research are properly described and presented. Is integration of genetic and genomic findings at the level of particular organs and current clinical specialties enough to achieve biological integration? Or, as David Valle and colleagues have suggested, does medical school training require more radical reorganization around new findings in genetics and genomics (*Annu. Rev. Genomics Hum. Genet.* **6**, 313–330; 2005)?

Clinician and geneticist alike can be hard pressed to define the normal function of a protein that, when mutant, causes multiple brain, liver, limb and kidney abnormalities. The best clues to the answer might be found in understanding the organellar functions of the protein and its role in just one of these organs, such as the kidney. Indeed, one of the phenotypes in humans with Meckel-Gruber syndrome and in the *wpk* rat—cystic kidney disease—may be key in revealing the relationship between organellar and organ-level functions. Two papers in this issue add to the growing body of evidence linking cilia to the organization of cell polarity and tissue patterning during development of many organs: Mira Kyttälä and colleagues identify *MKS1*, encoding a product related to components of the flagellar basal body proteome, and Ursula Smith, Mark Consugar and colleagues identify a new transmembrane protein encoded by *MKS3* that they speculate might act like the Fz family of receptors—key regulators of planar cell polarity (p 155, p 191, p 135).

This journal has been fortunate to publish many distinctive studies on mendelian loci underlying not only developmental kidney disorders but also adult physiological dysfunction. One way to help geneticists make sense of their results is to present the genetics for the attention of the broader community of clinical specialists who concentrate on organ function and disease. This is what we hope to do by providing selected research papers from this journal in a dedicated area of the ISN Nephrology Gateway (http://www.isn-online.org/isn/index.html). In the future, we hope to add insights into complex diseases such as hypertension, diabetic nephropathy and renal failure.

In return, an extended readership of clinicians might give advice on the quality of phenotypic information supplied and might suggest clinical features that can help the search for other contributory loci. A genetic research paper can thus contribute to an integrated functional view of an organ. This view might gain from extending the geneticist-clinician dialogue beyond the research collaboration that generated the original paper, perhaps even to specifically designed conferences. Likewise, there is no reason why genetic research should not be integrated with the help of the clinical communities engaged in research for the heart, lung and other organs. The same approach is likely to be successful even for less intensively researched organs such as skin.

Genomic information will be needed as well, because by itself, even a comprehensive description of genes perturbed by mutation will not be enough to construct an integrated model of organ function. In this issue, Renae Malek and colleagues (p 234, p 140) subdivide the physiological genomic space of the rat with axes representing the major environmental and genetic factors in cardiovascular disease. They provide transcriptome data for four major organs for normal and hypertensive rats of both sexes with genotypes that differ by one introgressed chromosome at a time under normal and hypoxic conditions. This resource should provide a starting point for organ-based genetics of complex diseases, allowing identification of genes in the lung that respond to hypoxia or pulmonary hypertension, and should also yield clues to the genetic influences on myocardial infarction and hypertension-induced renal dysfunction. Still, the phrase 'cardiovascular disease' is a reminder of the physiological interdependence of organ systems, including the heart, lung, blood vessels and kidney.

Although genetics provides an entry point for dissecting common complex diseases, we should also not underestimate the challenge of integrating the results. For some diseases, such as type 2 diabetes, even the major affected organ remains to be identified. ■