The era of molecular biology has yielded rapid progress in understanding the pathophysiology of certain diseases by providing insights into the regulated production of specific proteins and mechanisms controlling enzyme pathways. Genetics takes advantage of molecular techniques by coupling them with detailed understanding of disease processes to assess the impact of a specific pattern of inheritance on the expression of a disease, i.e., the phenotype. This requires rigorous statistical analysis and a sufficient number of subjects at risk plus appropriate "control" subjects to evaluate whether a disease is linked to a specific gene. Understanding these techniques will be critical for medicine in the future because they will be used to identify patients at risk for developing disorders with complex pathologic processes as well as illnesses linked to specific genes. They also can determine if patients are likely to respond to specific therapies.

These issues are nicely illustrated by the exciting report of Yoshida et al. (1). They studied patients with biopsy-documented IgA nephropathy, the most common type of glomerulonephritis. First, they took advantage of experimental and clinical evidence that an activated renin system is involved in the pathogenesis of glomerular damage and that there is individual variability in angiotensin-converting enzyme (ACE) activity which is linked to a polymorphism in the ACE gene. They then used molecular techniques to evaluate whether there is a link between the genotype of ACE and progressive loss of creatinine clearance in IgA nephropathy. There was a higher frequency of the D allele of the ACE gene in patients with proteinuria and a progressive loss of renal function, and this association was present even in patients with a normal blood pressure.

What is the D allele? Rigat et al. (2) noted that the interindividual variation in plasma ACE activity was linked to an insertion/deletion polymorphism in an intron of the ACE gene; individuals homozygous for the shorter or deleted (DD) gene had the highest values of serum ACE activity compared with subjects with the longer or inserted (II) gene. Heterozygous individuals (ID) expressed intermediate serum ACE activities. It was reasoned that the D allele and a higher ACE activity could be associated with more extensive kidney damage. Although Yoshida et al. (1) did not measure ACE activity, they did examine whether any therapeutic benefit from an inhibitor of ACE activity was associated with the presence of the D allele. Again, this question arose because experimental and clinical studies have shown that proteinuria is usually linked to progression of renal failure and that drugs inhibiting ACE activity generally reduce the degree of proteinuria in a variety of kidney diseases (3). Moreover, captopril administration was shown to slow progression in patients with nephropathy from insulin-dependent diabetes mellitus (IDDM) (4).

Yoshida et al. (1) found that the D allele not only was more frequently found in subjects with progressive loss of renal function but also was associated with a more beneficial response to the ACE inhibitor, lisinopril. Lisinopril administration decreased proteinuria significantly but only in patients with the DD genotype. This group also did not have a significant decline in creatinine clearance over 48 wk even though they had been losing creatinine clearance before lisinopril therapy.

What mechanisms might explain these remarkable results? The ACE D polymorphism is due to a deletion of a microsatellite in an intron and, hence, would not influence the structure of ACE but might affect its expression (5). Since the ACE D genotype is associated with higher serum ACE activity, it could increase the risk of hypertension which would damage the kidney. Although activation of the renin system has been suspected as a major factor causing hypertension, the ACE D phenotype is not linked to essential hypertension (5).

Besides causing hypertension, an activated renin system might accentuate pathology in damaged organs. For example, the ACE D genotype has been linked to cardiac abnormalities including left ventricular hypertrophy, cardiomyopathy, and myocardial infarction in patients with coronary atherosclerosis (6–8). These associations suggest that the ACE D allele may be related to the development of organ damage; they also underscore the complexity of disease processes (5). In kidney diseases as well, the pathophysiology is complex, and an activated renin system could play an important role. For example, the associations among progression of renal failure, proteinuria, and an activated renin system in diabetic nephropathy suggest the ACE gene may be involved, but formal tests have produced mixed results (3, 4). Marre et al. (9) found an association between the frequency of the D allele and diabetic nephropathy in IDDM patients, but Schmidt et al. (10) could not confirm this result in patients with insulin- or non–insulin-dependent diabetes mellitus. Doria et al. (11) reported that the association between the D allele and nephropathy was weak in IDDM patients unless it was combined with another ACE gene polymorphism they detected in intron 7.

What are the practical implications of the report by Yoshida et al. (1)? Only guarded statements can be made because associations do not identify a cause–effect relationship between a higher frequency of the ACE D allele and progressive renal insufficiency in patients with IgA nephropathy. Still, proper care of patients with nephropathy requires careful monitoring of blood pressure and proteinuria because they are important risk factors for progressive nephropathy (3, 4). It is conceivable, therefore, that proteinuric patients with IgA nephropathy should also be screened for the ACE D genotype because its presence would suggest a propensity to develop progressive renal disease and a greater likelihood of responding to ACE inhibitor therapy.

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