Susceptibility Genes for Hypertension and Renal Failure

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Abstract. The incidence rates of ESRD are rapidly increasing worldwide. In the United States, the increasing incidence rates of ESRD have occurred coincident with overall reductions in death rates from heart disease and stroke. In the United States, the predominant causes of ESRD are reportedly high BP and diabetes mellitus. Minority populations, particularly African Americans, Native Americans and Hispanic Americans, are disproportionately affected relative to Caucasian Americans. There is mounting evidence that inherited factors, in addition to environmental exposure, contribute to the development of ESRD. This manuscript reviews the evidence in support of genetic factors that contribute to the common, complex causes of chronic renal failure.

In the United States, African-American individuals reportedly develop hypertension-associated ESRD seven times more often and all-cause ESRD four times more often, than white individuals (1). It remains unclear why only a small percentage of hypertensives and approximately 35% of Caucasian diabetics develop elevated serum creatinine concentrations and ultimately require renal replacement therapy. The majority of individuals with long-standing essential hypertension and diabetes do not develop kidney involvement.

A population-based analysis of incident dialysis patients residing in the southeastern United States revealed that more than 23% of African-American ESRD patients and 14% of white ESRD patients had additional first- or second-degree relatives on dialysis (2). Individuals with hypertension-, diabetes mellitus-, and glomerulonephritis-associated ESRD more often had relatives with ESRD than did those with younger age at ESRD onset and higher levels of education. These strikingly high rates confirmed prior reports in African-American (and Caucasian populations) demonstrating that 40% or more of patients with well-classified hypertensive or diabetic ESRD had relatives with advanced nephropathy (3–10). The original reports in African-American populations included control groups with members having long-standing hypertension, diabetes, systemic lupus erythematosus, and HIV infection, but lacking renal disease (3–9). Despite having a similar severity of their systemic disease (i.e., glycemic control in diabetics), the control group had significantly fewer relatives with ESRD. This familial aggregation of ESRD led to the concept that genes producing susceptibility to the initiation or progression of renal failure may explain the familial clustering of cases (11,12).

Inherited factors have been demonstrated to play major roles in the development of elevated BP. Essential hypertension, an idiopathic disorder, is commonly diagnosed within families. The heritability of elevated BP is controversial, but clearly has a significant genetic component (13). It has been suggested that several genes (perhaps as many as five) may have major effects on BP. The M235T polymorphism of the angiotensinogen gene was the first gene implicated in the causation of elevated BP and has been linked or associated with hypertension in European and American Caucasians, and in Asians (14–16). Although compelling evidence for causation exists, several studies have failed to support this association (17,18). Additionally, the deletion/deletion allele of the angiotensin converting enzyme gene is associated with higher circulating angiotensin converting enzyme levels and enhanced risk for myocardial infarction in low risk individuals (19). The deletion/deletion allele may possibly be associated with more rapid progression of diabetic and nondiabetic forms of nephropathy (20). However, conflicting data have been reported (21). Longitudinal studies in carefully phenotyped hypertensive populations should determine whether individuals with various genetic polymorphisms are at increased (or diminished) risk for developing the vascular complications of hypertension. A recent report suggests that carriers of an alpha adducin variant allele may have a reduced risk for heart attack and stroke when treated with diuretics, but not with other anti-hypertensive drug classes (22).

Recent developments in the etiology of ESRD center around genes and regions implicated in familial focal and segmental glomerulosclerosis (FSGS) and IgA nephropathy. These reports are from families clustering in a Mendelian pattern of autosomal dominant inheritance. Their applicability to individuals with sporadic variants of FSGS and IgA nephropathy remains uncertain. The α-actinin-4 gene on chromosome 19q13 (23) and additional loci on chromosomes 1q25–31 (24) and 11q21–22 (25) have been linked to nephropathy in familial FSGS. Gharavi et al. (26) identified a locus on chromosome 6q22–23 that is linked with familial IgA nephropathy.

Evidence in animal models suggests that BP and vascular damage may be under independent genetic control. The renin-
angiotensin system plays an important role in the regulation of renal sodium handling, maintenance of plasma volume, BP, and tissue fibrosis (via interactions between angiotensin II and TGF-β). Nonetheless, angiotensin II type 1 receptor-deficient mice develop vascular lesions typical of hypertensive (arteriolar) nephrosclerosis. The renal lesion (thickening of arterial walls, tubular atrophy, and interstitial fibrosis) is observed in the absence of hypertension and the growth-promoting effects of angiotensin II as mediated by the type 1 receptor (27). This animal model demonstrates that hypertension may not be necessary to initiate the renal histologic changes typically associated with arteriolar nephrosclerosis.

The fawn-haired rat is a model of early onset hypertension in animals prone to developing albuminuria and glomerulosclerosis. The renal lesion in this animal more closely resembles FSGS than hypertensive nephrosclerosis. In the fawn-haired rat, the genes regulating hypertension are clearly distinct from those that predict the development of albuminuria and renal insufficiency (28). The hypertension and renal failure promoting genes are located in different regions of rodent chromosome 1. The major loci producing proteinuria and renal failure are termed Rf-1 and Rf-2, with Bpfh1 labeled as the hypertension-promoting region. Rf-1 is located between markers D1Mit6 and D1Mgh12, and contributes 44% of the genetic variance for renal impairment. Rf-2 is located between markers D1Mit20 and Mt1pa. Bpfh1 is located between markers D1Mit4 and D1Mit14 and contributes 26% of the genetic component of variance in BP. This model suggests that a genetic background producing susceptibility to renal failure is more conducive to development of glomerulosclerosis than is absolute level of BP. This finding supports similar observations in humans (3).

The human syntenic region of the rodent renal failure -1 gene (Rf-1), an attractive candidate region for ESRD susceptibility, is located on chromosome 10q24-q26. Our group performed a linkage analysis in 356 African-American sib pairs concordant for ESRD in an attempt to assess for linkage between markers on human chromosome 10 and ESRD (29). These families contained 199 sib pairs concordant for hypertension-associated, chronic glomerulonephritis-associated, and unknown etiologies of ESRD, and 157 sib pairs concordant for diabetes mellitus-associated ESRD. Families containing members with Alport’s syndrome or polycystic kidney disease were excluded. Linkage was tested between 30 polymorphic markers spanning chromosome 10 and ESRD using GeneHunter software. The maximum likelihood ratio z-score (Zlr) occurred near locus D10S677 (Zlr = 3.33, P = 0.0004, lod 3.40), with a lesser peak near D10S1435 (Zlr = 1.77, P = 0.04, lod 1.42). The locus at D10S677 contributed significantly to diabetic (lod = 2.08, P = 0.008) and nondiabetic etiologies of ESRD (lod = 2.03, P = 0.009). D10S677 also contributed significantly to early-onset ESRD (≥50 yr) and late-onset ESRD (>50 yr).

These results were confirmed in 49 Utah kindreds selected for having multiple members with premature cardiovascular disease (30). These Caucasian families were followed longitudinally for 10 yr. Three separate 12-h timed urine collections were obtained at multiyear intervals to calculate creatinine clearance. The heritability of creatinine clearance was significant in all 3 exams (h² ranged from 0.33 in the first exam with 1360 participants to 0.53 in the third exam with 718 participants). The nonparametric lod score for creatinine clearance at the initial exam was 1.4 for marker D10S677. The second measure of creatinine clearance (2.5 yr later) yielded lod scores of 1.8 and 1.9 for the nearby markers D10S1239 and D10S1425, respectively. Creatinine clearance 10 yr after the initial exam revealed a lod score of 2.1 for the neighboring chromosome 10 marker D10S2470. Thus, there was consistent evidence of linkage to this region on human chromosome 10 from 3 different measurements of kidney function spanning a period of 10 yr. This result suggests that there may be a locus on chromosome 10 that leads to reduced renal function and can be detected while subjects are still healthy.

In conclusion, genes contributing to hypertension susceptibility have been identified. New genes are likely to be detected soon. Susceptibility to hypertensive nephrosclerosis may relate to the effects of additional, unrelated genes. Renal failure susceptibility genes may contribute to renal tubular and interstitial fibrosis, glomerulosclerosis, or arteriolar intimal-medial hyperplasia. Improved understanding of these inherited factors may yield information on the cause(s) of hypertensive renal failure, provide markers for identifying individuals at high risk during a preclinical stage of their illness, and lead to novel therapeutic strategies to inhibit hypertensive renal disease.

References


