Genetic Variation of the Renin-Angiotensin System and Chronic Kidney Disease Progression in Black Individuals in the Atherosclerosis Risk in Communities Study

Charles Chia-chuen Hsu, Molly S. Bray, W. H. Linda Kao, James S. Pankow, Eric Boerwinkle and Josef Coresh

ABSTRACT: The renin-angiotensin system (RAS) regulates BP and may affect chronic kidney disease (CKD) through induction of tissue growth and fibrosis. The angiotensinogen (AGT) promoter G(–6) allele lowers transcription and is inversely associated with hypertension. In white individuals, the A1166C 3'-UTR variant of angiotensin II type 1 receptor (AT1R) has been associated with CKD. CKD associations with these RAS genes are uncertain in high-risk black populations. A prospective population-based study of CKD risk was conducted among 3706 black individuals without severe renal dysfunction at baseline (serum creatinine 177 µmol/L [2.0 mg/dl] for men, 159 µmol/L [1.8 mg/dl] for women) to examine associations with AGT and AT1R. Incident CKD progression was defined as kidney disease hospitalization or increase in serum creatinine level 35 µmol/L (0.4 mg/dl) above baseline. During mean follow-up of 10.2 yr, CKD progression incidence rate (per 1000 person-years) was 8.2 (n = 312 cases). Risk was lower for AGT G(–6) carriers compared with A(–6) (incidence 6.9 versus 9.0; log-rank P = 0.03) and nonsignificantly higher among AT1R C1166 carriers. Adjusting for hypertension and major CKD risk factors, AGT G(–6) decreased risk (relative risk 0.75; 95% confidence interval 0.57 to 0.98). AT1R C1166 increased risk only among those with hypertension (relative risk 1.65; 95% confidence interval 1.14 to 2.39). The AGT G(–6)A polymorphism may play a role in CKD progression in black individuals, consistent with in vitro effects on AGT levels and renal remodeling but independent of BP. The AT1R C1166 allele may increase susceptibility but only in the presence of hypertension.

J Am Soc Nephrol. 2006; 17(2): 504-12

Relative risk (RR) for CKD progression by AGT and AT1R genetic variation, stratified by hypertensive status. The effect of AGT on CKD progression was not significantly modified by hypertension (P = 0.88 for interaction). There was a significant interaction on risk for CKD progression between AT1R C1166 carrier status and hypertension (P = 0.042). Statistical significance: *P < 0.05; **P < 0.01.

Consistency of the findings supports the hypothesis that much of CKD is multifactorial with significant inherited components in black individuals.