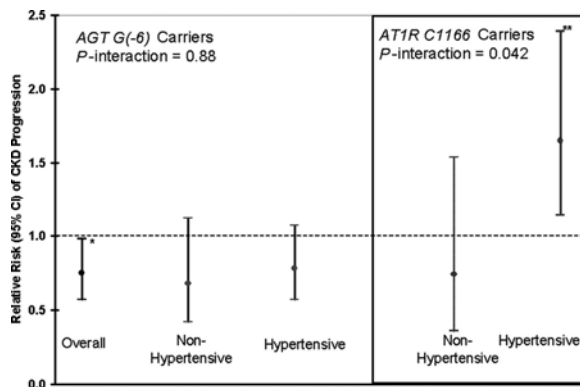


# Genetic Variation of the Renin-Angiotensin System and Chronic Kidney Disease Progression in Black Individuals in the Atherosclerosis Risk in Communities Study

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**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  $\mu\text{mol/L}$  [2.0 mg/dl] for men, 159  $\mu\text{mol/L}$  [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  $\mu\text{mol/L}$  (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.

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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.



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