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GENE-GENE INTERACTION IN RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM CONTRIBUTES TO END-STAGE RENAL DISEASE SUSCEPTIBILITY IN A HAN CHINESE POPULATION

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OBJECTIVES

Several renin-angiotensin-aldosterone system (RAAS) gene polymorphisms are associated with ESRD. However, the influence of genetic interactions among these RAAS genes on ESRD susceptibility remains unknown.

We investigated whether RAAS gene single nucleotide polymorphisms (SNPs) and their interactions were associated with ESRD.

METHODS

This was a case-control study for 647 ESRD cases and 644 controls. Angiotensinogen (AGT) [M235T (rs699) and T174M (rs4762)], angiotensin II type I receptor (AGTR1) [A1166C (rs5186) and C573T (rs5182)], angiotensin-converting enzyme (ACE) [I/D (rs1799752) and G2350A (rs4343)], and aldosterone synthase (CYP11B2) [C-344T (rs1799998)] were selected and genotyped and compared between cases and controls to identify SNPs associated with ESRD susceptibility.

Gene-gene interactions among the loci were evaluated using multiple dimensionality reduction (MDR) and MDR-permutation testing software (version 1.0 beta).

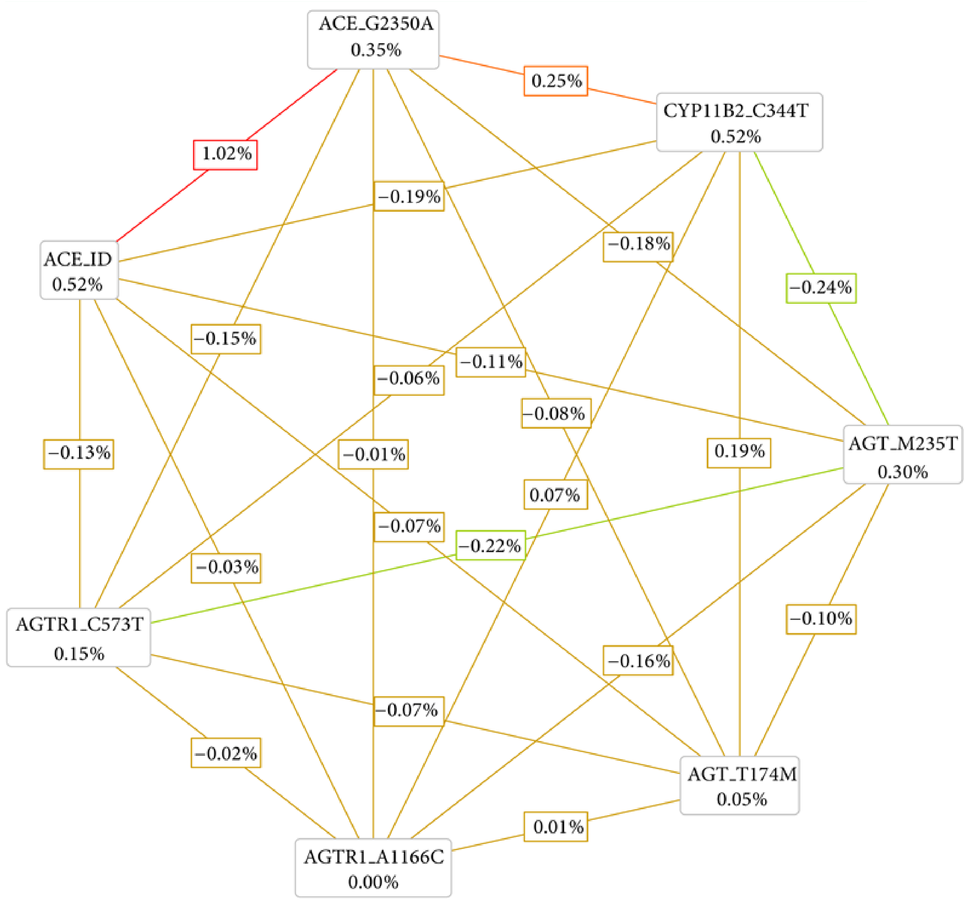
RESULTS

Best gene-gene interaction models identified by the MDR method

Locus no.	Best model	Testing Bal. Acc. (%)	CVC†	P-value*
1	ACE I/D	0.5179	6/10	0.6520
2	ACE I/D, ACE G2350A	0.5537	10/10	0.0280
3	ACE I/D, ACE G2350A, CYP11B2 C-344T	0.5608	9/10	0.0060
4	AGTR1 C573T, ACE I/D, ACE G2350A, CYP11B2 C-344T	0.5499	7/10	0.0560
5	AGT M235T, AGTR1 C573T, ACE I/D, ACE G2350A, CYP11B2 C-344T	0.5568	7/10	0.0150
6	AGT M235T, AGT T174M, AGTR1 C573T, ACE I/D, ACE G2350A, CYP11B2 C-344T	0.5290	6/10	0.4100
7	AGT M235T, AGT T174M, AGTR1 A1166C, AGTR1 C573T, ACE I/D, ACE G2350A, CYP11B2 C-344T	0.5227	10/10	0.5500

*Interactions were validated based on 1000 permutations; †CVC: cross-validation consistency.

Interaction map for ESRD risk evaluated by MDR



AGT, AGTR1, ACE, and CYP11B2 gene polymorphisms with risk of different cause of ESRD

	Diabetic nephropathy (n = 256) adjusted# OR (95% CI)	Hypertensive nephropathy (n = 84) adjusted# OR (95% CI)	Glomerulonephritis (n = 174) adjusted# OR (95% CI)	Systemic nephropathy (n = 66) adjusted# OR (95% CI)	Other& (n = 67) adjusted# OR (95% CI)
AGT					
M235T					
CT/CC	0.75 (0.52–1.09)	1.07 (0.58–1.98)	0.51 (0.31–0.85)*	0.97 (0.5–1.89)	1.08 (0.59–1.99)
TT/CC	0.33 (0.09–1.14)	—	0.18 (0.02–1.41)	—	0.46 (0.06–3.55)
T174M					
CT/CC	1.26 (0.84–1.88)	1.10 (0.54–2.24)	1.07 (0.66–1.75)	0.79 (0.35–1.77)	1.17 (0.58–2.36)
TT/CC	0.94 (0.17–5.07)	—	0.94 (0.10–8.55)	2.58 (0.29–23.17)	2.13 (0.23–19.54)
AGTR1					
A1166C					
AC/AA	0.79 (0.42–1.47)	0.96 (0.37–2.51)	1.49 (0.81–2.74)	0.72 (0.22–2.43)	1.59 (0.68–3.74)
CC/AA	—	—	—	—	—
C573T					
CT/CC	1.30 (0.92–1.83)	0.96 (0.54–1.70)	1.32 (0.87–1.98)	1.31 (0.69–2.49)	1.00 (0.54–1.84)
TT/CC	0.68 (0.33–1.39)	0.76 (0.26–2.25)	0.59 (0.24–1.46)	1.62 (0.61–4.35)	1.4 (0.55–3.58)
ACE					
ID					
ID/II	1.89 (1.31–2.71)*	1.16 (0.64–2.11)	1.35 (0.89–2.05)	0.83 (0.42–1.61)	1.22 (0.66–2.26)
DD/II	1.71 (0.97–3.00)	2.21 (1.01–4.83)*	1.03 (0.5–2.13)	2.07 (0.93–4.64)	1.99 (0.85–4.65)
G2350A					
GA/GG	1.65 (1.14–2.40)*	1.93 (1.02–3.63)*	1.02 (0.66–1.56)	1.92 (0.97–3.77)	0.91 (0.49–1.68)
AA/GG	2.04 (1.28–3.28)*	2.41 (1.11–5.22)*	1.13 (0.63–2.04)	2.17 (0.9–5.25)	1.12 (0.5–2.53)
CYP11B2					
C-344T					
TC/TT	0.75 (0.52–1.07)	0.58 (0.32–1.04)	0.73 (0.48–1.12)	0.50 (0.25–0.99)*	0.82 (0.44–1.55)
CC/TT	1.11 (0.61–2.00)	0.53 (0.16–1.78)	0.75 (0.34–1.68)	1.55 (0.62–3.85)	2.26 (0.99–5.15)

*$P < 0.05$, #adjusted for gender, age, BMI, and smoking status; &Others: for example, kidney stone, polycystic kidney disease, and so forth.

CONCLUSIONS

Our results suggest that AGT, ACE, and CYP11B2 gene polymorphisms are associated with ESRD and that an interaction effect of ACE I/D, ACE G2350A, and CYP11B2 C-344T polymorphisms may play a more important role than individual factors for ESRD development. A higher ESRD risk was found for the simultaneous occurrence of ACE DD-ACE AA. This investigation was done with Han Chinese patients. The applicability of our results to other ethnic groups is uncertain and warrants further study.

REFERENCES:

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