



THE ANGIOTENSIN CONVERTING ENZYME (ACE) GENE INSERTION/DELETION (I/D) POLYMORPHISM IS ASSOCIATED WITH RENAL FUNCTION IN CHILDREN FOLLOWING KIDNEY TRANSPLANTATION (SA-PO432)



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Background

- Prevention of a stable allograft function in children following renal transplantation (RTx) depends on various factors including underlying diagnosis, blood pressure, age of donor/recipient as well as episodes of acute and chronic allograft rejection.
- There is increasing evidence that also genetic factors influencing blood pressure regulation, vascular proliferation or immune response play an important role for the course of renal function following RTx.
- Due to their impact on blood pressure regulation we have studied polymorphisms of the renin-angiotensin-aldosterone system in 91 children following RTx and associated genotypes with loss of glomerular filtration rate (GFR, ml/min/1.73m²) and blood pressure (mean observation time 5.4 years [0.5 – 16 years]).
- The following polymorphisms were studied: Angiotensinogen (AGT) Met235Thr, Renin Mbol G/A, Angiotensin I converting enzyme (ACE) Insertion/Deletion (I/D) and Angiotensin II receptor type-1 (AT1R) A1166C.

Characteristics of 91 patients

	living donor	cadaveric
n	24	67
gender (m/f)	15/9	45/22
age at RTx (years)	9.04 ± 1.06	8.89 ± 0.65
waiting time (years)	1.0 ± 1.2	2.5 ± 2.7
preemptive	3/24	1/67
cold ischemia (h)	3.1 ± 0.3	16.6 ± 4.8
initial non function	0/24	11/67
cyclosporine A	22/24	47/67
tacrolimus	2/24	20/67
antihypertensive agents	0.75 ± 0.22	0.67 ± 0.14

Genotyping (RFLP analysis or direct sequencing)

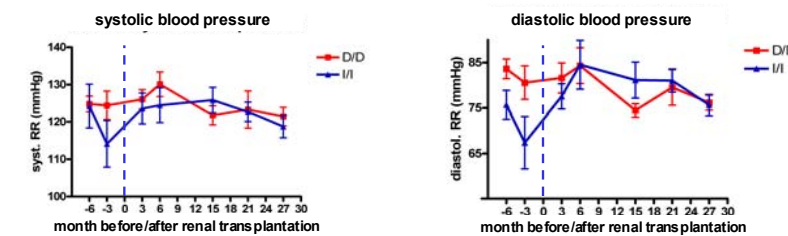
polymorphism	allelic frequency
Angiotensinogen 235Met/Thr	Met/Met=19 (21%); Met/Th=50 (55%); Thr/Thr=22 (24%) Met 235=0.48 vs. Thr=0.52 (literature: Met=0.58 vs. Thr=0.52)
Renin (Mbol G/A)	Mbol G=35 (38%); Mbol G/A=48 (53%); Mbol A=8 (9%) Mbol G=0.65 vs. Mbol A=0.35 (literature: G=0.7 vs. A=0.3)
ACE Insertion/Deletion	D/D=29 (32%); D/I=41 (45%); I/I=21 (23%) Deletion=0.54 vs. Insertion=0.46 (literature: D=0.58 vs. I=0.42)
Angioten. II-Rezeptor 1166A/C	A/A=47 (52%); A/C=37 (41%); C/C=7 (8%) 1166 A=0.72 vs. 1166 C=0.28 (literature: A=0.71 vs. C=0.29)

Course of GFR (ml/min/1.73m²), calculated from individual slopes

polymorphism	slope
Angiotensinogen 235Met/Thr	Met/Met -3.5±1.7 vs. Thr/Thr -5.9±1.8 (p=0.347)
Renin Mbol G/A	G/G -6.2±1.8 vs. A/A -6.7±4.2 (p=0.914)
Angiotensin I converting enzyme I/D	D/D -4.3±0.8 vs. I/I -1.3±1.1 (p=0.035)*
Angiotensin II-receptor 1166A/C	A/A -5.5±1.2 vs. C/C -2.8±1.9 (p=0.345)

*p<0.05 = significant, linear regression analysis

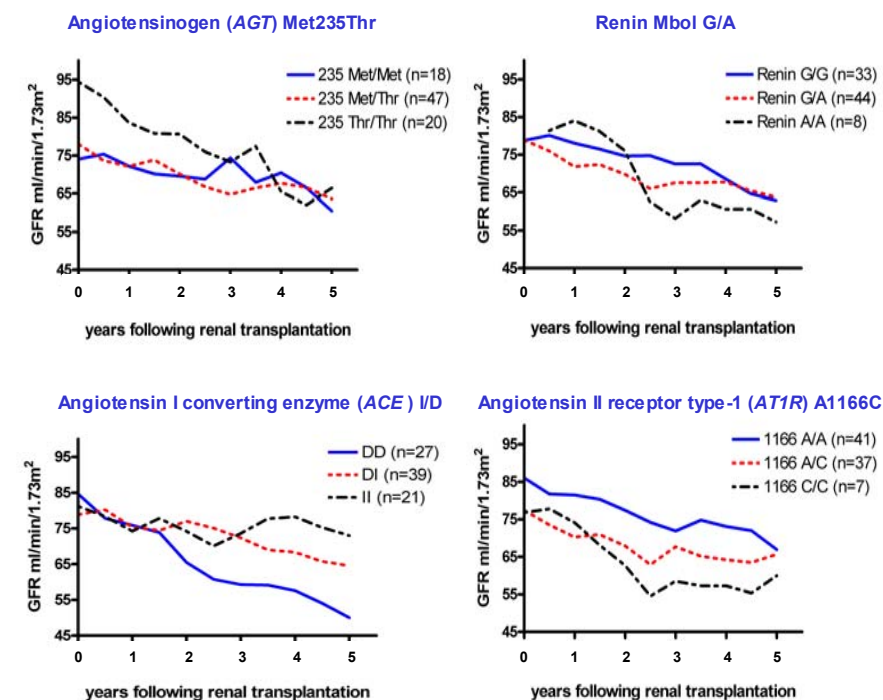
The ACE D/D genotype is associated with higher systolic and diastolic blood pressure before renal transplantation



Results

- Allelic frequencies of all investigated polymorphisms were not significantly different from healthy controls.
- While there was no significant correlation of the AGT Met235Thr, Renin G/A and AT1R 1166A/C polymorphism with the slope of GFR, homozygous carriers of the ACE D-allele showed a significantly higher decline of GFR when compared to carriers of the I-allele (-4.3±0.8 vs. -1.3±1.1, p=0.035)
- Homozygous carriers of the ACE D-allele showed a significantly higher systolic and diastolic blood pressure before renal transplantation (DD-allele-carriers with increased left ventricular hypertrophy? Schunkert et al. 1996, *N Engl J Med* 330:1634-1638).

Course of GFR (ml/min/1.73m²) in five years following renal transplantation



Conclusions

- The ACE DD-genotype may contribute to a faster, non immunological renal allograft failure and needs to be investigated in prospective studies.
- The influence of the donor genotype on long-term renal allograft function needs to be considered, too.