Role of Renin-Angiotensin-Aldosterone System Gene Polymorphisms and Hypertension-induced End-stage Renal Disease in Autosomal Dominant Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited disease of the kidneys and is marked by progressive cyst growth and decline in kidney function, resulting in end-stage renal disease (ESRD). Hypertension is thought to be a significant modifying factor in the progression of renal failure in ADPKD. A number of genetic variations involved in renin-angiotensin-aldosterone system (RAAS) pathway genes have clinical or physiological impacts on pathogenesis of hypertension-induced ESRD in ADPKD. Information on RAAS pathway gene polymorphisms and their association with ESRD and ADPKD, published till March 2013, was collected using MEDLINE search. The present review deals with RAAS gene polymorphisms focused on hypertension-induced ESRD in ADPKD in different populations. The results were inconclusive and limited by heterogeneity in the study designs and the population stratification. In lieu of applying next generation sequencing technologies to study complex diseases, it is also possible to apply the same to unravel the complexity of ESRD in ADPKD.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a systemic disease with progressive development of fluid-filled cysts in both kidneys. It affects both genders in all races, with an estimated frequency of 1 in 400 to 1 in 1000 live births.¹ The heterozygous mutations in the polycystic kidney disease 1 and polycystic kidney disease 2 genes account for a vast majority of ADPKD cases.² It exhibits a prolonged nominal glomerular filtration rate, microalbuminuria, and hypertension, followed by a persistent decline in glomerular filtration rate, leading to end-stage renal disease (ESRD) in 50% of patients during the 5th to 6th decades of their life.³Autosomal dominant polycystic kidney disease patients also show a variety of other abnormalities that include aneurysms and cyst in the liver, pancreas, spleen, and lungs. In 60% of ADPKD patients, high blood pressure can be seen even before the impairment of kidney function, indicating hypertension as a significant factor in the progression of kidney failure.⁴

RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM
Renin-Angiotensin Aldosterone System Pathway and Hypertension

The renin-angiotensin aldosterone system (RAAS) has been strongly implicated as the susceptibility pathway in the pathogenesis of essential hypertension, cardiovascular disease, and progressive kidney disease.⁵ The RAAS
pathway includes 3 important components of renin, angiotensin, and aldosterone. Renin is secreted from kidney cells and stimulates formation of angiotensin, which consecutively stimulates the release of aldosterone from the adrenal cortex. Angiotensin I is formed by the action of renin on angiotensinogen. Angiotensin I is further converted to angiotensin II by the enzyme angiotensin-converting enzyme (ACE). Angiotensin II raises blood pressure by a number of actions, the most important ones being vasoconstriction and sympathetic nervous stimulation. In addition to the regulation of blood pressure, angiotensin II plays a major role in the sodium metabolism and renal hemodynamics.

**Autosomal Dominant Polycystic Kidney Disease and Renin-Angiotensin Aldosterone System Pathway**

In spite of comparable glomerular filtration rate in both normotensive and hypertensive patients of ADPKD, increased renal vascular resistance exhibited by hypertensive patients is the first demonstration of the involvement of RAAS in modulation of hypertension in ADPKD. Presence of elevated levels of renin in both renal tissues and cyst fluid of ADPKD kidneys indicates that the tubulocystic epithelium has the potential to synthesize renin. Furthermore, presence of RAAS components (angiotensinogen, ACE, angiotensin II, and angiotensin II type 1 receptor) within cysts and tubules and activation of RAAS during cyst expansion in ADPKD has also been demonstrated. Hence, the candidate genes involved in RAAS pathway are of immense interest to the researchers engaged in the study of a wide range of disorders modulated by hypertension. Polymorphic variants of many genes involved in components of RAAS pathway (renin, angiotensin I, angiotensin II, angiotensinogen, ACE, angiotensin II receptor type 1, angiotensin II receptor type 2, and CYP11B2) have been screened for clinical and physiological conditions of various kidney diseases. The aim of the present review is to summarize the knowledge about RAAS pathway gene polymorphisms investigated with regard to ADPKD.

**Information on RAAS pathway gene polymorphisms and their association with ADPKD**

Information on RAAS pathway gene polymorphisms and their association with ADPKD that has been published till March 2013 through MEDLINE search was collected. Further, the bibliographies of retrieved articles were reviewed for additional information. Details of the polymorphisms studied for ADPKD in different world populations have been documented in the Table.

**RENIN**

Renin is a proteolytic enzyme synthesized, stored, and secreted by the juxtaglomerular apparatus of the kidney and plays a key role in blood pressure homeostasis. Studies using animal models have clearly demonstrated the involvement of renin gene polymorphisms in development of hypertension. Variations in the plasma renin activity levels of the black men versus women, as well as their white counterparts showed a wide range of racial differences. Studies on biopsy, nephrectomy, and autopsy specimens have demonstrated abnormal distribution of renin-containing cells. Hyperplasia of these cells in the juxtaglomerular apparatus is also suggestive of the fact that these cells respond to different stimuli when compared to the normal kidney. Furthermore, increased levels of tubular immunoreactive renin and high intracystic renin concentrations in patients with ADPKD could be correlated with the expressions at both the protein and mRNA levels in ADPKD cyst-derived cells in culture. Although there is no direct evidence for RAAS in controlling blood pressure in ADPKD, increased renal vascular resistance found in hypertensive ADPKD patients as compared to the normotensive patients was indicative of renal structural abnormalities in early high incidence of hypertension in ADPKD. Hypertensive patients with polycystic kidney disease showed significantly higher plasma renin activity than patients with essential hypertension. The renin gene maps to chromosome 1q32, spans 12.5 kb in length and encodes 10 exons. Several polymorphisms within renin gene or near its promoter sequences that studied for hypertension yielded inconsistent results. However, no study has been conducted to ensure the association of these polymorphisms with hypertension in ADPKD.

**Angiotensinogen**

Renin acts on a single substrate, angiotensinogen, which is synthesized mainly by the liver and released into the circulation. The human angiotensinogen has a molecular mass of about 50 kD. Angiotensinogen is expressed in multiple tissues, including the liver, adipose tissue, heart, vessel wall, brain,
and kidney. Studies using immunohistochemical staining showed moderately strong angiotensinogen immunostaining in cyst-lining cells and in many proximal tubules of ADPKD kidneys. The gene

<table>
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<th>Study Name</th>
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<th>Country</th>
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*Studies on end-stage renal disease in autosomal dominant polycystic kidney disease patients.
Hypertension-induced Kidney Failure in Polycystic Kidney Disease—Ramanathan et al

coding for angiotensinogen (AGT) spans about 13 kb of genomic sequence and is located on 1q42.2 with 5 coding exons.50 To date, more than 20 AGT gene polymorphisms have been discovered and only 3 were found to be significantly associated with hypertension.51 A common variant of exon II (M268T:rs699 previously described as M235T) involves a change of the amino acid from methionine to threonine at position 268. Tests of promoter activity showed that this nucleotide substitution affects the basal transcription rate of the gene and thereby accounts for 15% to 40% of the variation in plasma angiotensinogen levels in Caucasians.52 Furthermore, a clear racial difference in the serum level of angiotensinogen has also been observed.53 The M268T has been reported as one of the strong candidates for hypertension in many populations.54-59 However, some studies have failed to confirm this association.60-66 The M268T polymorphism is in linkage disequilibrium with T174M and A(-6) polymorphisms of AGT that affects the basal transcription rate of the gene.52 A multi-ethnic study on atherosclerosis had shown correlations of the M268T polymorphism with kidney function.67 However, no interaction between age of onset of ESRD and AGT M268T polymorphism has been observed.9 In addition to this, M268T genotypes or alleles have not shown any association with creatinine, inverse creatinine, hypertension, or age at ESRD in ADPKD patients, indicating lack of the prognostic utility of this polymorphism.10 The homozygous TT genotype of M268T induced 2-fold increase in glomerular filtration rate decline in Spanish ADPKD patients.14 The individuals with ESRD due to various causes showed higher frequency of M268T T allele compared to the controls; however, M268T T allele showed no association with the kidney disease progression in dialysis patients of Polish origin.15 The prevalence of hypertension and the ages at the onset of ESRD were similar among the AGT M268T genotypes, indicating that this polymorphism is not associated with hypertension or the ESRD in ADPKD of Korean and Japanese patients.12,13

**Angiotensin-converting Enzyme**

Angiotensin-converting enzyme is a glycoprotein present in almost all mammalian tissues and body fluids.68 Angiotensin-converting enzyme occurs on the cell surface as ectoenzymes and also as soluble forms in serum and other body fluids.69,70 The main functions of ACE are conversion of angiotensin I to angiotensin II and the inactivation of bradykinin. In addition, it also cleaves many other oligopeptides.71 The ACE gene (26 exons) spans about 24 kb of genomic DNA and is located on 17q23. One of the important polymorphisms of ACE is insertion/deletion of a 287-bp alu repeat sequence in intron 16.72 The individuals carrying DD genotype exhibited the highest serum ACE activity than the carriers of II and ID genotype who showed low and intermediate activity levels of serum ACE.72 A meta-analysis of 46 studies revealed that the ID and DD genotypes showed higher plasma ACE activity than the II genotype.73 A recent study in elderly Chinese demonstrated the gender differences in serum ACE activity for subjects with DD genotype.74 This polymorphism accounts for nearly 50% of variation in the ACE serum activity in white population,75 but the role of this variant in black population is still uncertain.76 However, ACE ID polymorphism did not show any evidence for transcriptional regulation in vitro.77 This is further supported by allelic mRNA expression studies in human heart tissue.78 The ACE mRNA expression in human heart tissues correlated with the rs7213516, rs7214530, and rs4290 single-nucleotide polymorphisms residing in 2 kb to 3 kb upstream conserved regions of ACE gene.78 Studies using the animal models have revealed that ACE inhibitors improved the renal function and reduced the formation of cysts.79-81 The available literature has provided the most current evidence for pharmacological blockade of the RAS using ACE inhibitors to reduce progression of chronic kidney disease.82 Although no consistent evidence has been found for the association between serum ACE levels and ADPKD in patients with hypertension,21,28 numerous studies have been conducted to examine the association between ACE gene polymorphisms and ADPKD. Extrapolation of these results to examine the impact of the ACE gene ID polymorphism on ADPKD has rendered multiple studies reporting conflicting results. An association between D allele of ACE ID among ADPKD patients has been detected in different populations such as Australia,9 Netherland,18 Japan,12 Italy,20 Belgium,23 and Spain.27 On the contrary, no association has been found in Japan,16 Spain,17 Korea,19 United
Angiotensin II Type 1 Receptor

Angiotensin II is the major biologically active product of RAAS, formed from its original precursor, angiotensinogen by 2 successive enzymatic cleavages. Angiotensin II acts as a potent vasoconstrictor and exerts its effects through 2 structurally different receptor subtypes: angiotensin II type 1 receptor and angiotensin II type 2 receptor. Angiotensin II type 1 receptor mediates most of the known biological effects of angiotensin II. In humans, angiotensin II type 1 receptor is widely expressed in multiple tissues including kidney and vascular smooth muscle cells in the vasculature and is associated with increased blood pressure and progression of kidney disease. The gene coding for angiotensin II type 1 receptor is localized to chromosome 3q21q25, spans 45.123 kb and comprises 5 exons, the first 4 exons represent the 5′-UTR, whereas exon 5 harbored coding region. Several polymorphic sequence variants have been found on angiotensin II receptor type 1 (AGTR1) gene. The most well-studied polymorphism is A1166C (rs5186), a trans version at position 1166, is located in the 3′-UTR of the AGTR1 gene. Reporter silencing assays have demonstrated that the 1166C allele interrupts the base-pairing complementarity of miR-155 and reduces the ability of miR-155 to interact with the cis-regulatory site. This indicates that the hsa-miR-155 downregulates the expression of 1166A allele but not the 1166C allele. Thus, the likelihood of failure in the downregulation of ATR1 expression as the biological base is most plausible.

The AGT 1166-C allele has demonstrated increased risk for coronary artery disease, ischemic stroke, heart failure, ESRD, and hypertension. Although no evidence of linkage has been found between A1166C and hypertension in the French population, a significant increase in C allelic frequency has been observed in hypertensives than the normotensive individuals. Evidence suggestive of linkage of hypertension to the genetic area containing the AGTR1 gene has been confirmed with logarithm of the odds score of 2.9. Studies thus far have not shown a consistent evidence for association between AGTR1 gene polymorphisms and hypertension among different races. The AGTR1 polymorphism associated with hypertension has shown variation from population to population. The AGTR1 A44221G (rs5183) polymorphism located in exon 5 has been associated with hypertension in African-Americans, with the G allele increasing the risk of hypertension. Analysis of 7 AGTR1 tag single nucleotide polymorphisms along with the A1166C polymorphisms has revealed a significant association of rs12695895 with hypertension in Han Chinese. In Mexicans, the C573T (rs5182) polymorphism has been involved in the risk of developing hypertension.

The susceptibility to kidney disease is under tight genetic control and the proximal tubule salt and water reabsorption is mainly regulated by angiotensin II, mediated by AGTR1. Some of the studies have also indicated the upregulation of proximal tubule AGTR1 expression in the proximal tubule, regulated by ambient angiotensin II levels. The AGTR1 Ala163Thr (rs12721226) polymorphism has been significantly associated with the susceptibility to chronic kidney disease in Japanese individuals. The AGTR1 A1166C polymorphism has shown an increased frequency of the C allele and CC genotypes in renal damage among Egyptian children with ESRD. The AGTR1 1166CC genotype has been associated with glomerular filtration rate decline in ESRD caused by ADPKD in Argentinians. Polish individuals with ESRD due to various causes have shown a higher frequency of combined AC and CC genotypes of A1166C polymorphisms. Furthermore, patients with C allele have progressed to ESRD very quickly than the A allele. In contrast to this, no association between the age of onset of ESRD and AGTR1 A1166C polymorphism has been observed in polycystic kidney disease 1 gene families of United Kingdom and Australia. Furthermore, 2 independent studies in East Asian populations have also failed to show association between AGTR1 A1166C polymorphism and ADPKD.
type 2 (AGTR2) gene mRNA expression has been detected in the adult tissue of adrenal gland, heart, and brain. Renal angiotensin II type 2 receptor immunoreactivity has also been observed in the glomeruli of rat kidney. The AGTR2 expression in fetal life is high but substantially diminished after birth. The gene coding for human angiotensin II type 2 receptor is located on X chromosome and contains 3 exons spanning 5 kb of genomic DNA. The first 2 exons are untranslated and exon 3 only encodes the angiotensin II type 2 receptor protein. Studies on mice have demonstrated that angiotensin II type 2 receptor plays an important role in the regulation of blood pressure, water and electrolyte balance and exhibits vasodilation properties. Angiotensin II type 2 receptor activation has been linked to production of nitric oxide in autonomic neurons. The role of AGTR2 in regulation of blood pressure is evident in animal models; however, the association between AGTR2 gene polymorphisms and hypertension is contradictory. Analysis of tagging single nucleotide polymorphisms in AGTR2 gene have also failed to show significant association with hypertension. The AGTR2 A1332G genotypes have been associated with chronic kidney disease and scarring in posterior urethral valves of patients. Furthermore, several studies using animal models and cell lines have also indicated the importance of AGTR2 in the pathogenesis and remodeling of renal and cardiovascular diseases. However, no study has been conducted to ensure the association of AGTR2 polymorphisms with hypertension in ADPKD.

Aldosterone Synthase

Aldosterone synthase (18-hydroxylase or cytochrome P450 11B2) is the only enzyme involved in the production of aldosterone in humans. It is a mineralocorticoid synthesized from deoxycorticosterone in the zona golmerulosa of the adrenal cortex by a mitochondrial cytochrome P450 enzyme. Aldosterone synthase plays a major role in the regulation of sodium-water homeostasis, intravascular volume and blood pressure. Several lines of evidence have demonstrated the role of high plasma aldosterone level in hypertension and progression of kidney diseases. The gene coding for aldosterone synthase (CYP11B2) is located on chromosome 8q and contain 9 exons. Several polymorphic variants have been identified in the CYP11B2 gene. The promoter polymorphism (C-344T: rs1799998), which disrupts a putative steroidogenic factor-1 binding site, has been identified to alter aldosterone production, leading to sodium wasting and decreased excretion of potassium. Initial studies have reported a positive association between -344T allele and essential hypertension. Subsequent studies on C-344T polymorphism with hypertension and other cardiovascular parameters have proven to be inconclusive.

Higher levels of aldosterone have been noted in hypertensive ADPKD patients compared to the normotensive ADPKD patients; however, their extracellular volumes have been observed to be almost similar. No significant association has been found between CYP11B2-C-344T polymorphism with hypertension and other cardiovascular parameters. Nonetheless, this polymorphism showed significant association with diabetes-induced chronic renal insufficiency in Indian populations.

Endothelial Nitric Oxide Synthase Gene

Nitric oxide synthases (NOSs) are cytochrome P450-like hemoprotein enzymes that catalyze the conversion of L-arginine into l-citrulline and nitric oxide. The enzymatic synthesis of nitric oxide is accomplished by 3 NOS isoforms: the neuronal NOS (NOS1), inducible NOS (NOS2), and the endothelial NOS (NOS3). The endothelial NOS gene (NOS3) is composed of 26 exons, spans 21 kb, and is located on chromosome 7q35-36. Several polymorphic variants have been described in the NOS3 gene and some of them have been associated with altered nitric oxide synthesis. The Glu298Asp is a missense variant in exon 7 and 27-base pair (bp) variable number of tandem repeat in intron-4 of NOS3 are known to alter endothelial NOS expression, thereby leading to impaired nitric oxide synthesis. The promoter -786T > C polymorphism of the NOS3 gene, the -786 C allele binds a replication protein A1 that acts as a repressor of NOS3 transcription. On the contrary, bovine endothelial cells transfected with the (-786)T and (-786)C alleles have failed to show significant differences in the promoter activity.

Various studies have shown that nitric oxide
negatively regulates the renin-angiotensin system by inhibiting ACE activity and angiotensin II type 1 receptors.\textsuperscript{134} The release of nitric oxide by endothelial cells plays a major role in regulating the local hemodynamics and systematic blood pressure.\textsuperscript{135} Decreased production of nitric oxide plays a major role in the progression of renal disease.\textsuperscript{136} A significant decrease of different isoforms of nitric oxide synthase in the cystic epithelium has been observed during the growth of renal cyst in Han:Sprague-Dawley polycystic rats.\textsuperscript{137}

Direct analysis of $\text{NOS3}$ gene polymorphisms in ADPKD patients has also revealed inconclusive results from many populations. Although no direct association has observed between $\text{NOS3}$ 27 bp variable number of tandem repeat and ADPKD, patients with a 4a allele showed faster ESRD progression in the group of ADPKD.\textsuperscript{30,37,38,138} In contrast to this, Japanese ESRD patients have failed to show significant association with this allele.\textsuperscript{33} No consistent evidence has been found for association between the promoter -786T>C polymorphism and progression to ESRD in type 1 ADPKD patients.\textsuperscript{27,30} The relationship between Glu298Asp polymorphism and age of onset of ESRD in ADPKD patients has also been shown to be inconsistent.\textsuperscript{33-35}

**THERAPEUTIC IMPLICATIONS**

Effective intervention for uncontrolled hypertension in ADPKD is important to reduce the associated morbidity and mortality.\textsuperscript{139} Diuretics, $\beta$-blockers, ACE inhibitors, calcium channel blockers, and angiotensin receptor blockers have been used as potential antihypertensive drugs\textsuperscript{140}; however, there is no consensus about the type of antihypertensive therapy which is considered to be the most appropriate for ADPKD patients. The studies on ACE inhibitors in ADPKD are inconclusive because they have used small numbers of patients for shorter periods of time.\textsuperscript{1,80,141-144} In a meta-analysis of 11 randomized controlled trials including 1860 patients with nondiabetic kidney disease, the treatment of ACE inhibitors have shown effective control over the progression of kidney disease than the treatment without ACE inhibitors.\textsuperscript{145}

Although many researchers have hypothesized that polymorphisms involved in RAAS pathway genes have been known to alter the antihypertensive response, experimental results have remained inconclusive.\textsuperscript{146-149} The Genome-Wide Association Study has revealed that the rs4343, which is the tight linkage disequilibrium with $\text{ACE}$ I/D has reported strong association with blood pressure response to ACE inhibitors.\textsuperscript{150} However, the large randomized placebo controlled EUROPA trial failed to replicate this association.\textsuperscript{151} The 235T allele, rs7079 and rs26405430 of $\text{AGT}$ gene variants have shown association with blood pressure response to ACE inhibitors.\textsuperscript{152,153} However, further studies on larger samples failed to replicate these results.\textsuperscript{149,154,155} The A1166C polymorphism of $\text{AGTR1}$ gene has been widely studied, but the results are contradictory.\textsuperscript{149,154-158}

Only few studies have investigated the interaction between angiotensin receptor blockers and RAAS gene polymorphisms. In patients with heart failure, the impact of angiotensin receptor blockers along with ACE inhibitors in lowering the blood pressure and N-terminal pro-B-type natriuretic peptide has been altered by A1166C polymorphisms.\textsuperscript{159} On the contrary, $\text{AGTR1}$ A1166C and C573T polymorphisms have failed to modify the effect angiotensin receptor blockers.\textsuperscript{157,158} The $\text{ACE}$ (I/D), $\text{AGT}$ (M235T) and $\text{AT2}$ variants have failed to alter the blood pressure-lowering response of angiotensin receptor blockers.\textsuperscript{157,158}

**CONCLUSIONS**

The available literature on RAAS gene polymorphisms which have focused on hypertension-induced ESRD in ADPKD in different populations have been limited by heterogeneity in the study designs and the population stratification. The results have not been consistent in establishing strong association between the risk of ESRD and the polymorphisms involved in RAAS pathway. Although an individual’s physical exercise, nutrition, alcohol, stress, and smoking habits have been known to alter the blood pressure, earlier studies did not consider these factors. In lieu of applying next generation sequencing technologies to study complex diseases, it is also possible to apply the same to unravel the complexity of ESRD in ADPKD.

**CONFLICT OF INTEREST**

None declared.
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