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The role of genetic polymorphisms of the Renin–Angiotensin System in renal diseases: A meta-analysis

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ABSTRACT

Renal failure has a complex phenotype resulting from an underlying kidney disease as well as environmental and genetic factors. In the present study we performed a systematic review and meta-analyses to evaluate the association of the A1166C polymorphism of Angiotensin II type 1 Receptor gene (AGTR1) with Chronic Kidney Disease (CKD), End Stage Renal Disease (ESRD), IgA Nephropathy (IgAN) and Vesicoureteral Reflux (VUR) as well as the association of A1332G polymorphism of Angiotensin II type 2 Receptor (AGTR2) gene with Vesicoureteral Reflux (VUR). We found that neither AGTR1 A1166C, nor AGTR2 A1332G polymorphisms were significantly associated with any of the aforementioned renal diseases, suggesting that they cannot be used as predictive markers in either general or subgroup ethnic populations.

1. Introduction

Chronic Kidney Disease (CKD) is a global public health problem reaching high prevalence and demanding elevated health costs. It is characterized by a slow, progressive and irreversible decline of renal function; it is usually asymptomatic and thus untreated [1]. National Kidney Foundation guidelines classify the severity of Chronic Kidney Disease in five stages. Stage 5 CKD is often called End Stage Renal Disease (ESRD) and is characterized by severe illness with poor life expectancy if untreated. However, ESRD is a complex disorder with a variety of phenotypes emanating from a variety of underlying kidney disorders in conjunction with genetic and environmental factors as well as other preexisting or secondary clinical entities [2]. Treatment in ESRD is renal replacement which encounters dialysis or kidney transplantation [3]. Persons at high risk predominantly suffer from diabetes mellitus or hypertension [4]. Nevertheless, many common adult-onset kidney disorders may be due to various risk-alleles and to interactions between various genes and gene–environment interactions [5].

Immunoglobulin A Nephropathy (IgAN), where IgA deposits are found in the glomerular mesangial area, is the most common form of glomerulonephritis world-wide and leads to ESRD in about 20% of the cases [6,7]. Vesicoureteral Reflux (VUR) is a form of Congenital Anomaly of the Kidney and Urinary Tract (CACUT) [8]. It is a very common urological cause of renal insufficiency in children, culminating to ESRD in children, adolescents, and young adults, which is potentially preventable [9].

The Renin–Angiotensin System (RAS) influences sodium balance, extracellular fluid (ECF) volume, and renal and systemic vascular resistance. Thus, the RAS serves as one of the most powerful regulators of arterial blood pressure [10]. The primary effector molecule of this system is angiotensin II (ANG II) and is formed after two cleavage steps by Renin and Angiotensin Converting Enzyme (ACE). The ANG II mediates its actions via two G protein-coupled receptors, the Angiotensin II type 1 Receptor (AGTR1) and Angiotensin II type 2 Receptor (AGTR2) [10,11].

ANG II binds to AGTR1 and induces systemic vasoconstriction, a situation that leads to elevated peripheral resistance, and ultimately increases blood pressure. Arterial hypertension (HT) is frequently associated with chronic renal failure, and it is the most important risk factor for the progression of renal failure. In summary, RAS proteins convey the response of the kidneys to effective circulating volume thus regulating salt and water handling by the kidney. This fine-tuned molecular balance may be adversely influenced by a genetically mediated variability of RAS protein variants, leading to early damage of the cardiovascular or renal organ systems [10].

Although yet quite complex, there is strong evidence of genetic susceptibility in renal failure [5,10,12]. In the present study, we attempted to clarify the genetic association of polymorphisms of the angiotensin receptors with renal diseases and discus the possibility that these polymorphisms may be used as prognostic markers for renal failure.

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2. Materials and methods

2.1. Literature search

A comprehensive literature search until November 2012 was performed and 30 independent studies were retrieved that could fulfill all the eligible criteria. The keywords that were used for the search were: AGTR, AGTR1, AGTR1B, AGTR2, 'ANGIOTENSIN RECEPTOR', 'ANGIOTENSIN II RECEPTOR', GENE, VARIANT, POLYMORPHISM, MUTANT, MUTATION, ALLELE, 'CHRONIC KIDNEY DISEASE', 'KIDNEY FAILURE' 'END-STAGE KIDNEY DISEASE', 'END-STAGE RENAL DISEASE', 'END-STAGE RENAL FAILURE', DIALYSIS, 'IgA GLOMERULONEPHRITIS', 'IgA NEPHROPATHY', 'VESICOURETERAL REFLUX', VUR and combinations of them. To enrich the investigation, references of published studies were incorporated.

2.2. Data extraction

Data extraction from each study was performed by two reviewers according to the eligibility criteria. All problems of poor agreement, when they occurred, were resolved after discussion with a third investigator and the necessary data were stratified in spreadsheet. The following data were extracted from each study: Pubmed ID, first author's name, year of publication, geographical location and ethnicity of population studied, and total number of the subjects (cases and control groups). The distributions of alleles and genotypes were calculated in cases and controls for each study and are shown in Tables S1–S5. When a case–control study was designed according to a family based model, the family-trio model was encountered that distinguishes between affected offspring and non-affected parents (controls) and analysis was performed according to the transmission disequilibrium test (TDT) [13].

2.3. Statistical analysis

Odds ratio (OR) was used as the effect size of choice to test the association between the mutant alleles or genotypes (as defined in each polymorphism case), and the disease phenotypes. In case of a zero cell, a continuity correction was applied by adding 0.5 to all cells of the contingency table. Data were combined using a random-effects method [14] with inverse-variance weights, and ORs were calculated along with their 95% CIs for each genotype or allele contrast. The between study heterogeneity was evaluated using the chi-square based Cochran's Q statistic and the consistency index (I^2) [15].

The multivariate random-effects method of meta-analysis was also applied as a more advanced method for testing gene–disease associations. In this framework, the two summary log-odds ratios related to the risk allele, e.g. the log-odds ratio of heterozygotes vs. homozygotes (AB vs. AA) and the log-odds ratio of homozygotes for the risk allele vs. homozygotes for the wild type allele (BB vs. AA), are modeled simultaneously as a bivariate response. This method has several important properties, since it can infer and quantify the genetic model of inheritance directly, by estimating the ratio λ of the two log-odds ratios [16–19]. This way, we avoid multiple testing and thus the inflation of the Type I error rate. Stata 10 (StataCorp) was the statistical package that was used for all the analyses. Results with p-value <0.05 were considered statistically significant.

To estimate possible publication bias, the rank correlation method of Begg and Mazumdar [20] was used. Additionally, the fixed effects regression method of Egger was also recruited [21]. Influential meta-analysis was further performed, by removing an individual study each time, and re-calculating the effects estimates (ORs) and heterogeneity. In order to identify a possible trend of the combined estimate over years, a condition that often introduces a special kind of bias ("Proteus phenomenon"), cumulative meta-analysis was also performed. Time-trend was detected using two methods: the standard cumulative meta-analysis [22–24] approach, where we visually inspect the plot, and a more recently proposed regression-based method [25].

3. Results

A literature search was performed to identify all studies assessing the association of *Angiotensin II type 1 Receptor* (*AGTR1*) and *Angiotensin II type 2 Receptor* (*AGTR2*) gene polymorphisms with renal diseases. Meta-analyses were performed for the polymorphisms for which at least three studies were found. Polymorphisms of both genes related to disease phenotypes along with the number of studies identified and numbers of patients and controls included in each meta-analysis are shown in Table 1.

3.1. A1166C polymorphism of AGTR1 gene

In a meta-analysis to test the putative association of the A1166C (rs5186) polymorphism of the *AGTR1* gene with ESRD 109 studies were retrieved. Nevertheless, only 17 studies were included [26–42] that fulfilled the selection criteria and comprised of 2596 patients and 3866 controls. One study [32] had a family based design, (trio), and it was analyzed with the transmission disequilibrium test (TDT) according to the method presented in [13].

The characteristics of each study are shown in Table 2A, while details about alleles and genotypes are shown in Table S1. No statistical significant association was found for the per-allele contrast since OR was 1.10 with 95% CI: 0.91–1.34. Similarly, non-significant association was found when dominant and recessive models were analyzed (CC + AC vs AA: OR 1.15, 95% CI: 0.92–1.44 and CC vs AA + AC: OR 1.31, 95% CI: 0.83–2.07, Table 3). Meta-analysis in subgroups according to race did not yield any significant association (data not shown). Similarly, when meta-analysis was restricted to studies in Hardy–Weinberg Equilibrium (HWE) no significant associations were found (data not shown).

In all three meta-analyses heterogeneity was high since p-value <0.05 and I^2 > 50% (Table 3), while no publication bias was observed (p-value >0.05 for all tests). Furthermore, Proteus phenomenon was not detected in cumulative meta-analysis for the AA vs AC + CC contrast, while for the A vs C and the CC vs AA + AC contrasts a time trend was obvious (Table 4). Influential meta-analysis was also performed and showed that no individual study influenced the effect estimate (data not shown).

After that, a meta-analysis was carried out to test the association of the same polymorphism (*AGTR1* A1166C) with Chronic Kidney Disease (CKD). From the 109 studies only eight were found eligible to provide data for 812 patients and 4252 healthy subjects [36–38,40,42,44–46]. The characteristics of all studies are shown in Table 2B and numbers of alleles and genotypes in Table S2.

Table 1
Polymorphisms of *AGTR1* and *AGTR2* genes studied for their association with renal diseases.

Disease	Gene	SNP	Patients/controls	Number of studies
ESRD	AGTR1	A1166C/rs5186	2596/3866	17
ESRD	AGTR1	C521T		1
ESRD	AGTR1	A1138T		1
ESRD	AGTR1	AG214CC		1
CKD	AGTR1	A1166C/rs5186	812/4252	8
CKD	AGTR1	C573T		1
CKD	AGTR1	C521T		2
CKD	AGTR1	A1138T		1
CKD	AGTR1	AG214CC		1
CKD	AGTR1	G163A		2
CKD	AGTR2	A1332G/rs5194		1
IgAN	AGTR1	A1166C/rs5186	785/1373	5
VUR	AGTR1	A1166C/rs5186	174/216	3
VUR	AGTR2	A1332G/rs5194	352/790	3