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

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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 (CAKUT) [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 discuss the possibility that these polymorphisms may be used as prognostic markers for renal failure.
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 controls). 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 for the contingency table. Data were combined using a random-effects model of meta-analysis also. The characteristics of all studies are shown in Table 2A and numbers of patients and controls included in each meta-analysis are shown in Table 1.

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, 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 I² >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 trend was observed (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.

| 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| A1138T | 1 | |
| CKD     | AGTR1| A1166C/rs5186 | 812/4252 | 8 |
| CKD     | AGTR1| C573T | 1 | |
| CKD     | AGTR1| C521T | 2 | |
| CKD     | AGTR1| A1138T | 1 | |
| CKD     | AGTR1| A1138T | 1 | |
| IgAN    | AGTR1| A1166C/rs5186 | 785/1373 | 5 |
| VUR     | AGTR1| A1166C/rs5186 | 174/216 | 3 |
| VUR     | AGTR2| A1132G/rs5194 | 352/790 | 3 |
Association of CKD and A1166C polymorphism of AGTR1 gene could not be found neither with per allele contrast nor with genotype contrasts. The ORs were 1.16 (95% CI: 0.83–1.64) for the per allele contrast (C vs A), 1.06 (95% CI: 0.50–2.25) for the CC vs AA + AC contrast and 1.16 (95% CI: 0.82–1.63) for the CC + AC vs AA contrast. Excluding one study of which the population was not in HWE did not grant significance to the association (data not shown). Heterogeneity was rather low in all cases with p-values >0.05 and I² < 50% (Table 3), with no publication bias (p-value >0.05 for all tests, data not shown). No time trend was observed in any of the contrasts (Table 4). No individual study was found to influence the effect estimate of the remaining of the studies at an influential meta-analysis (data not shown).

Afterwards, IgA Nephropathy was investigated for its association with the A1166C polymorphism of AGTR1. 36 studies were found from the literature search, however, only five fulfilled all the appropriate criteria and were used in the meta-analysis [31,37,38,47,48]. In total, they contained 785 patients and 1373 controls (Tables 2C and S3) and all populations were in HWE. Meta-analysis for the allele contrast (C vs A) produced an OR of 1.00 (95% CI: 0.84–1.17) indicating the absence of any association of the A1166C polymorphism with IgA Nephropathy. Likewise, no association was found in the other two genotype contrasts (CC vs AA + AC and CC + AC vs AA) as shown in Table 3. Heterogeneity was very low in all contrasts with p-values >0.05 and I² < 50% (Table 3) and no publication bias (p-value >0.05 for all tests, data not shown) was observed. Proteus phenomenon was observed in the CC vs AA and the CC + AC vs AA contrast while in the CC vs AA + AC contrast no time trend was observed (Table 4). According to the influential meta-analysis performed, there was no study to influence the ORs of the remaining studies (data not shown).

Subsequently, we wished to analyze the association of A1166C polymorphism of AGTR1 gene with Vesicoureteral Reflux (VUR). From the literature search 14 studies were initially retrieved, but only three could be used in the meta-analyses [40,49–51]. Altogether they included 174 patients and 216 healthy controls (Tables 2D and S4). However, the

### Table 2A
Characteristics of studies included in the meta-analysis for the association of AGTR1 A1166C polymorphism with ESRD.

| Study | Year | Country | Race | Cases | Diagnostic criteria | Controls | Diagnostic criteria |
|-------|------|---------|------|-------|---------------------|----------|---------------------|
| Zsom M | 2011 | Hungary | Caucasian | 134 | ESRD with primary glomerulonephritis interstitial nephritis, hypertension related CKD | 200 | Healthy and age-matched controls |
| Elshamaa MF | 2011 | Egypt | Other | 44 | Pediatric patients with ESRD based on e GFR on MHD | 70 | Healthy control subjects with no clinical signs of vascular or renal disease and no family history |
| Huang HD | 2010 | China | Asian | 47 | ESRD patients a) mainly on MHD, b) transplant recipients c) IgA Nephropathy | 120 | Healthy subjects |
| Ayed Kh | 2006 | Tunisia | African | 131 | Renal transplant recipients | 50 | Normotensive healthy subjects with clear yearly examinations and negative hypertension history |
| Tabel Y | 2005 | Turkey | Other | 13 | Children with end-stage renal insufficiency | 287 | Healthy adult subjects |
| Buraczynska M | 2006 | Poland | Caucasians | 745 | Hemodialysis (n = 687) and peritoneal dialysis (n = 58) patients | 520 | Healthy control subjects with no clinical signs of vascular or renal disease and no family history of renal disease |
| Lau YK | 2004 | Singapore | Asian | 32 | Biopsy-proven primary IgAN-ESRD on MHD | 94 | Healthy subjects |
| Liu KP | 2004 | Taiwan | Asian | 16 | Children with VUR progressing to ESRD | 117 | Unrelated healthy adults without renal disease |
| Lee KB | 2003 | Korea | Asian | 24 | ADPKD-ESRD patients | 105 | Normotensive controls |
| Coll E | 2003 | Spain | Caucasian | 104 | Dialysis patients | 131 | Healthy subjects with absence of nephropathy, renal failure, diabetes mellitus, or cardiovascular diseases |
| Papp F | 2003 | Hungary | Caucasian | 70 | ESRD patients (20 pediatric, 50 adult) | 150 | Normotensive healthy subjects (130 adults, 20 children) |
| Losito A | 2002 | Italy | Caucasian | 160 | Hemodialysis patients | 169 | Healthy blood donors and hospital staff |
| Buraczynska M | 2002 | Poland | Caucasian | 430 | Hemodialysis (n = 407) and peritoneal dialysis (n = 23) patients | 260 | Healthy control subjects, with no clinical signs of vascular or renal disease and no family history of renal disease |
| Basset et-EA | 2002 | France | Caucasian | 294 | Transplant recipients | 181 | Gender matched normal local subjects |
| Filler G | 2001 | Germany | Caucasian | 100 | Pedictric transplant recipients | 100 | Healthy consecutive newborns |
| Frimat L | 2000 | France | Caucasian | 76 | IgA-ESRD patients | 960 | Healthy Caucasian men in the Stanislas cohort |
| Gumprecht J | 2000 | Poland | Caucasian | 176 | ESRD patients | 352 | Not reported |

MHD: hemodialysis, ADPKD: Autosomal dominant polycystic kidney disease.

### Table 2B
Characteristics of studies included in the meta-analysis for the association of AGTR1 A1166C polymorphism with CKD.

| Study | Year | Country | Race | Cases | Diagnostic criteria | Controls | Diagnostic criteria |
|-------|------|---------|------|-------|---------------------|----------|---------------------|
| Su SL | 2012 | Taiwan | Asian | 135 | Patients with stages 3–5 CKD according to US National Kidney Foundation [1], modified | 270 | Healthy subjects age- and sex-matched |
| Zsom M | 2011 | Hungary | Caucasian | 61 | CKD patients with primary glomerulonephritis, interstitial nephritis, Hypertension related CKD | 200 | Healthy and age-matched controls |
| Elshamaa MF | 2011 | Egypt | Egyptian | 32 | Pediatric patients with advanced CKD (stage 4) based on e GFR under CT | 70 | Healthy subjects with no clinical signs of vascular or renal disease and no family history |
| Huang HD | 2010 | China | Asian | 83 | IgAN-non-ESRD patients | 120 | Healthy subjects |
| Hsu CC | 2006 | US | African Americans | 307 | CKD progression defined as a) increase in SCR ≥ 35 μmol, b) hospitalization discharge, c) death coded for chronic renal disease [ICD-9] codes 581 to 583 or 585 to 588 | 3331 | Not reported |
| Peruzzi L | 2005 | Italy | Caucasian | 50 | Patients with renal hypodysplasia | 50 | Healthy subjects matched for sex, age and origin |
| Lau YK | 2004 | Singapore | Asian | 86 | Biopsy-proven primary IgAN-non-ESRD | 94 | Healthy subjects |
| Liu KP | 2004 | Taiwan | Asian | 58 | VUR patients diagnosed by voiding cystourethoradiography and graded as ≤V | 117 | Unrelated healthy adult volunteers without renal disease |

e GFR: estimated glomerular filtration rate, CT: conservative treatment, ICD-9: international classification of diseases, ninth revision, SCR: serum creatinine.
study of Liu and coworkers [40] could be used only for allele contrasts since no genotype data was presented. As shown in Table 3, meta-analysis under the C vs A allele contrast illustrated an OR 1.07 (95% CI: 0.68–1.67) suggesting no statistical significant association. Likewise, the genotype contrasts did not give any evidence for a significant association of AGTR1 A1166C polymorphism with VUR (Table 3).

Between study heterogeneity was very low in all contrasts since p-values > 0.05 and I² < 50% (Table 3). No publication bias was observed with p-value > 0.05 for all tests (data not shown). Trend time was observed (Proteus phenomenon) for the C vs A contrast (Table 4), while for the other two contrasts calculations could not be performed since only two studies were included. In an influential meta-analysis no individual study was found to influence the ORs of the rest (data not shown).

3.2. A1332G polymorphism of AGTR2 gene

Finally, another polymorphism, A1332G of the AGTR2 gene was also analyzed for its association with VUR. Initially 14 studies were retrieved from the literature search, yet, only three abided with the selection criteria and were used in the meta-analysis [50,52,53]. Altogether, they comprised 352 patients, 790 controls. All studies included Caucasian populations (Tables 2E and 5). Because AGTR2 gene is on X chromosome, one study [53] gave data for males and females separately, and thus two cohorts were included in the initial meta-analysis. One study [50] presented data only for males, and data from [52] was on mixed population. Meta-analysis for the allele contrast on mixed populations revealed no association of AGTR2 A1332G polymorphism since OR was 1.13 with 96% CI 0.66–1.92. No publication bias was observed (p-value > 0.05 for all tests, data not shown) and significant heterogeneity appeared (p-value 0.041 and I² = 63.8%; Table 3). Time trend (Proteus phenomenon) was also observed (Table 4). Meta-analysis for male populations was additionally carried out, but did not present any significant association (Table 3). Thus, association of AGTR2 A1332G polymorphism in males with VUR could not be proven (Table 3).

3.3. AGTR1 A1166C and hypertension in ESRD patients

From the 17 studies we recruited in the meta-analysis for the association of AGTR1 A1166C with ESRD, three of them were found to test the association of AGTR1 A1166C polymorphism with IgA Nephropathy. Three of them were found to test the association of AGTR1 A1166C polymorphism with IgA Nephropathy. Data was presented for the AA vs CC + AC contrast and thus we were able to perform a meta-analysis concerning this contrast. The OR was found equal to 0.98 with 95% CI: 0.68, 1.42 suggesting no association of A1166C polymorphism with hypertension in ESRD patients. According to Begg and Egger tests there was no publication bias and heterogeneity was very low (data not shown).

3.4. Multivariate meta-analyses for the association of AGTR1 A1166C polymorphism with renal disease phenotypes

To validate the above results, multivariate meta-analyses were performed. The analysis that was performed revealed no evidence for the association of AGTR1 A1166C polymorphism with ESRD, since the AC vs AA yields a p-value = 0.181 and OR: 1.14 (95% CI: 0.94, 1.37) and the CC vs AA, an OR: 1.29 (95% CI: 0.78, 2.15) and p-value = 0.319 (Table 5). Likewise, multivariate meta-analysis did not detect any significance for the association of this polymorphism with CKD. No association of AGTR1 A1166C polymorphism with IgA Nephropathy could be proven since the ORs were 1.01 (95% CI: 0.81, 1.25) and 0.95 (95% CI: 0.61, 1.47) for the AC vs AA and CC vs AA contrasts respectively. Similarly, multivariate meta-analysis suggested no significant association with VUR for either dominant AC vs AA [OR: 1.29 (95% CI: 0.73, 2.29)] or the recessive contrast [CC vs AA [OR: 0.16 (95% CI: 0.02, 1.39)] (Table 5). Nevertheless, these findings were expected since the majority of the univariate tests were unable to show an association. Multivariate meta-analysis could help in avoiding an inflation of the Type I error rate (i.e. reduce false positive findings), but it does not offer greater statistical power.

4. Discussion

The Renin–Angiotensin System plays a pivotal role in the physiology of the kidneys. In non-dialyzed CKD patients, ACE inhibitors and AGTR blockers are used as the treatment of choice since they grant greater survival [10,54]. It has been recently shown [55] that AGT M235T gene polymorphism is associated with ESRD susceptibility in Caucasians. In addition, a meta-analysis [56] demonstrated genetic association of ACE I/D polymorphism with ESRD risk which actually correlates well with findings that increased circulating ACE levels in plasma are related with ACE I/D polymorphism [57].

Both A1166C of AGTR1 and A1332G of AGTR2 are within the 3′ untranslated regions of the genes. Though these polymorphisms do not lead to amino acid substitutions, these 3′ untranslated regions may play a pivotal role in the genomic context of the genes and may influence their expression levels, since they could result in defects in

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**Table 2C** Characteristics of studies included in the meta-analysis for the association of AGTR1 A1166C polymorphism with IgA Nephropathy.

| Study     | Year | Country | Race   | Cases | Diagnostic criteria                          | Controls                     | Diagnostic criteria          |
|-----------|------|---------|--------|-------|---------------------------------------------|------------------------------|-----------------------------|
| Huang HD  | 2010 | China   | Asian  | 130   | IgAN by renal biopsy                        | 120                          | Healthy subjects            |
| Lau YK    | 2004 | Singapore | Asian  | 118   | IgAN patients                               | 94                           | Not reported                |
| Maruyama K| 2001 | Japan   | Asian  | 95    | IgAN patients                               | 99                           | Healthy adult volunteers with no history of renal disease or abnormal urinary findings | Healthy subjects in the Stanislas cohort |
| Frimat L  | 2000 | France  | Caucasian | 274  | IgAN defined as glomerulo-nephritis with predominantly IgA deposits in the mesangium of all glomeruli | 960                          |                             |
| Pei Y     | 1997 | Canada  | Caucasian | 168  | IgA by renal biopsy                         | 100                          | Healthy subjects with no history of renal disease or hypertension |

VCUG: voiding cysto-urethrography.

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**Table 2D** Characteristics of studies included in the meta-analysis for the association of AGTR1 A1166C polymorphism with VUR.

| Study     | Year | Country | Race | Cases | Diagnostic criteria                          | Controls                     | Diagnostic criteria          |
|-----------|------|---------|------|-------|---------------------------------------------|------------------------------|-----------------------------|
| Liu KP    | 2004 | Taiwan  | Asian| 74    | VUR diagnosed by VCUG and graded as I-V     | 117                          | Unrelated healthy adult volunteers without renal disease |
| Haszoon I | 2002 | Hungary | Caucasian | 77  | VUR graded as I-V                           | 80                           | Healthy blood donors         |
| Hohenfellner K | 1999 | Germany | Caucasian | 23  | VUR diagnosed by radiological investigations including VCUG and graded as I-V | 19                           | boys with absence of any disorder of the urinary tract |
messenger RNA (mRNA) processing, mRNA half-life, or affect the function of regulatory elements such enhancers and insulators [2, 58]. The deletion/insertion polymorphism in intron 16 of the ACE gene is an example of such non-coding sequence polymorphisms that influence gene function. Moreover, Sethupathy et al. [59] have shown that there is a microRNA from chromosome 21, namely miR155, that downregulates the expression of the 1166A allele but not of the 1166C. They hypothesize that the 1166C allele is associated with hypertension just because miR155 cannot negatively control the expression levels of AGTR1.

In view of the above data, considering the fact that AGT, ACE and AGTRs perform in the same biochemical pathways, and taken the number of case-control studies investigating relationship of AGTR1 and AGTR2 gene variants with kidney diseases, we set out to explore putative genetic associations of AGTR1 and AGTR2 gene polymorphisms with renal diseases. We investigated these associations for sub-group renal diseases such as ESRD, CKD, IgA Nephropathy and VUR.

Table 3

Univariate meta-analysis for all contrasts performed for both AGTR1 (A1166C) and AGTR2 (A1332G) polymorphisms for its association with diseases as indicated.

| SNP | Contrast | Disease | Number of studies | Odds ratio (random effects) | 95% confidence interval (Cohran's Q) | p-value for heterogeneity | F (%) | Between studies variance (I2) |
|-----|----------|---------|-------------------|-----------------------------|-------------------------------------|--------------------------|-------|-----------------------------|
| A1166C/AGTR1 | A vs C | ESRD | 16 | 1.10 | 0.91 | 1.34 | 53.06 | 0.000 | 71.7% | 0.097 |
| | | CKD | 7 | 1.16 | 0.83 | 1.64 | 10.41 | 0.109 | 42.3% | 0.087 |
| | | IgAN | 5 | 0.99 | 0.84 | 1.17 | 2.31 | 0.678 | 0.0% | 0.000 |
| | | VUR | 3 | 1.07 | 0.68 | 1.67 | 2.29 | 0.318 | 12.8% | 0.022 |
| | CC vs AA + AC | ESRD | 14 | 1.31 | 0.83 | 2.07 | 30.80 | 0.004 | 57.8% | 0.370 |
| | | CKD | 6 | 1.06 | 0.50 | 2.25 | 3.16 | 0.675 | 0.0% | 0.000 |
| | | IgAN | 5 | 0.94 | 0.62 | 1.45 | 0.51 | 0.000 | 0.0% | 0.000 |
| | | VUR | 2 | 0.41 | 0.02 | 1.22 | 0.10 | 0.749 | 0.0% | 0.000 |
| | CC + AC vs AA | ESRD | 15 | 1.15 | 0.52 | 1.44 | 38.42 | 0.000 | 63.6% | 0.108 |
| | | CKD | 7 | 1.16 | 0.82 | 1.63 | 11.03 | 0.087 | 45.6% | 0.091 |
| | | IgAN | 5 | 1.00 | 0.81 | 1.23 | 3.05 | 0.550 | 0.0% | 0.000 |
| | | VUR | 2 | 1.15 | 0.66 | 2.01 | 0.36 | 0.551 | 0.0% | 0.000 |
| A1332G/AGTR2 | A vs C | VUR | 4 (mixed) | 1.13 | 0.66 | 1.92 | 8.28 | 0.041 | 63.8% | 0.649 |
| | | VUR | 2 | 0.67 | 0.41 | 1.10 | 0.61 | 0.433 | 0.0% | 0.000 |

reinforcing the absence of association of AGTR1 A1166C with CKD. Besides, due to low heterogeneity and according to our calculation (needing four to 1500 times more subjects to reach significance) based on the Barrowman et al. method [60], we believe that the absence of association of AGTR1 A1166C polymorphism with CKD is rather factual.

Similarly, no association was found between AGTR1 A1166C polymorphism and IgA Nephropathy and VUR, under all contrasts (allele and genotypes) tested. While for the association with IgAN the absence of association was pretty clear, the ORs for the association with VUR were fluctuating between various contrasts, due to the very small number of studies (three for allele contrast and two for the genotypes contrasts). Further evaluations suggested very low heterogeneity of the studies and no publication bias. Time-trend related bias (Proteus phenomenon) detected in these meta-analyses denote that more studies will improve the significance of our results. Additional multivariate meta-analyses that we performed confirmed the lack of association of AGTR1 A1166C polymorphism with IgAN and VUR.

Furthermore, we attempted to investigate the involvement of the A1332G polymorphism of the AGTR2 gene, located in the X chromosome, in the pathogenesis of VUR. Meta-analysis of the available data
from three studies including both male and female populations showed no association under the allele contrast. It should be mentioned that the absence of any association of the two aforementioned polymorphisms was relatively unexpected, considering the fact that polymorphisms of the other two RAS proteins genes (AGT and ACE) do associate with renal diseases. Nevertheless, no Genome Wide Association Study (GWAS) revealed ATRs polymorphisms as putative markers for renal disease progression. However, considering the fact that polymorphisms of the other two RAS proteins were associated with diabetic nephropathy in a meta-analysis[62], but not with diabetes (to the best of our knowledge). On the other hand, and in support of our results, a publication came during the preparation of the present manuscript showing lack of association of ATR1 A1166C polymorphism with the risk for ESRD [63], though including only eight studies as compared to 17 that we included in the present study. Taken together our data suggest that neither ATR1 A1166C nor AGTR2 A1332G polymorphisms can be used as reliable markers to predict the risk for CKD, ESRD, IgAN or VUR.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.csbj.2014.05.006.

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