Influence of ACE I/D gene polymorphism in the progression of renal failure in autosomal dominant polycystic kidney disease: a meta-analysis

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Abstract

Background. Autosomal dominant polycystic kidney disease (ADPKD) is a renal disease characterized by an important variability in clinical course, which cannot be fully explained by the genetic heterogeneity of the disease. Although the role for the angiotensin I-converting enzyme (ACE) insertion/deletion (I/D) polymorphism as a modifier factor in ADPKD renal deterioration has been suggested, direct evidence from genetic association studies remain inconclusive.

To provide a more robust estimate of the putative effect of the ACE I/D polymorphism on the renal progression in ADPKD, we performed a meta-analysis pooling data from all relevant studies in which the role of the ACE I/D variant in ADPKD clinical features was evaluated.

Methods. We applied a random-effects model to combine odds ratio and 95% confidence intervals. Q-statistic was used to evaluate the homogeneity and, both Egger's and Begg–Mazumdar tests were used to assess publication bias.

Results. Altogether, three distinct meta-analyses were generated using data from 13 studies. Despite the absence of publication bias and the presence of homogeneity among study results, the DD genotype failed to show an influence on risk of end-stage renal disease (ESRD), mean age at ESRD or risk of hypertension in ADPKD patients when compared with I-allele carriers (DD vs ID + II). Likewise, meta-analyses carried out separately for Caucasian and Asian studies showed no indication of an association between the DD genotype and a faster renal deterioration in ADPKD.

Conclusion. These findings do not support the hypothesis that the enhanced ACE activity associated with the D allele might promote a significantly worse prognosis in patients with ADPKD.

Keywords: ACE gene polymorphism; ADPKD; progression of renal failure; meta-analysis; autosomal dominant polycystic kidney disease

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenetic renal disorder characterized mainly by the growth of cysts in the kidneys [1]. According to epidemiological data, ADPKD occurs in one in 800–1000 individuals, typically resulting in renal failure during the fourth and fifth decades of life [2] and is responsible for up to 10% of chronic dialysis patients [1]. It is estimated that approximately 12.5 million people worldwide are affected by this renal pathology, making ADPKD a global public health burden [3]. Indeed, since around 50% of ADPKD patients require renal replacement therapy by the age of 60 years [4], ADPKD-related costs are calculated to reach billions of dollars each year worldwide [3].

Based on previous studies, mutations in at least three polycystin (PKD) genes can lead to ADPKD. Mutations in the PDK1 gene, which codes for the polycystin-1, represent around 85–90% of ADPKD cases [5]. Although to a lesser extent, the disease is also triggered by mutations in polycystin-2 (PKD2)
gene and putatively by undefined polycystin-3 (PKD3) loci, accounting for the remaining 10–15% of the ADPKD aetiology [6,7]. PKD products share sequence homology and are thought to play a role in cell–cell and cell–matrix interactions and in structures of a receptor–channel complex involved in regulating renal ion transport [7].

Despite the differences in renal progression among distinct mutated PKD genes and regions [5–7], one of the most striking aspects of ADPKD is the presence of an important variability in renal disease progression. Evidence from both mouse [8] and human [9] models suggests that disease-modifying loci may play a role in the variable renal progression found in ADPKD. In fact, recent studies in humans indicate the presence of considerable phenotypic variation even between patients harbouring identical mutations but with distinct genetic backgrounds. Importantly, inherited differences in genetic background were estimated to account for up to 59% of the phenotypic variability in PKD1 patients [9]. In this respect, a number of genes that are likely to influence the ADPKD progression have been investigated. However, among several candidates, the gene coding for the angiotensin I-converting enzyme (ACE) is by far the most studied.

The ACE gene has 26 exons and spans over 21 kb in the human chromosome 17 (17q23) [10]. Among several variants described so far, a diallelic insertion/deletion (I/D) polymorphism within intron 16 of the ACE gene has been the most investigated. This polymorphism was found to account for nearly 50% of the variation in the ACE serum activity in individuals defined as ‘white’ [10], while in black populations the role of the ACE I/D variant is still questionable [11]. Based on data from several reports [12], subjects of European descent harbouring the DD genotype have been consistently associated with a higher serum ACE activity when compared with I-allele carriers.

However, at this point, the direct biological mechanism by which ACE I/D polymorphism might influence serum ACE levels remains unclear. Nevertheless, the ACE I/D variant per se is not believed to have a direct effect on both ACE expression or function, and linkage disequilibrium with a nearby functional polymorphism is suggested as a probable explanation [10].

Once intrarenal renin/Ang II activation is associated with cyst expansion and renal progression in ADPKD [13], the DD genotype, yielding increased levels of ACE and consequently higher amounts of Ang II, attracts a great deal of attention as a potential modifier factor in ADPKD progression. However, data on the influence of ACE I/D polymorphism on ADPKD progression are derived from small underpowered studies and have yielded conflicting results. We, therefore, addressed more robustly the relevance of ACE I/D polymorphism in ADPKD progression by performing a comprehensive meta-analysis encompassing all relevant studies in which the effect of ACE I/D polymorphism on ADPKD was investigated.

Methods

Literature search and data extraction

We searched Biological Abstracts, Embase, Lilacs, Medline and Web of Science databases up to April 2006 for studies evaluating an association between ACE I/D gene polymorphism and clinical features in ADPKD. The studies were retrieved through an intensive combination of both MeSH terms and text words and titles. The following terms and the respective translations for German, Italian, Spanish and Portuguese were used: ‘ACE polymorphism’, ‘genotype’, ‘Polycystic Kidney’, ‘Autosomal Dominant’, ‘ADPKD’, ‘Disease Progression’, ‘Kidney Failure’, ‘Renal Failure’, ‘hypertension’, ‘end-stage renal disease’, ‘ESRD’, ‘PKD’, ‘DCP1’ and ‘Peptidyl-Dipeptidase’. In addition, the reference lists of identified papers and published reviews were checked and the abstracts from major nephrology meetings in the past seven years were screened. Furthermore, for each retrieved publication, an electronic ‘cited reference search’ was performed (Web of Science database) identifying all articles citing the index publication. Finally, authors of reviews in genetics of renal diseases and experts in ADPKD were contacted for additional papers or unpublished reports. The search and eligibility of the identified trials were carried out independently by two investigators (T.V.P and M.R.). The same authors extracted the data independently through a standardized protocol. Disagreements were resolved by discussion and re-analysis of the original data.

Selection criteria

Reports were included if they were in English, German, Italian, Portuguese or Spanish. Studies in other languages were excluded. Whenever data were incomplete, authors were contacted to obtain relevant information. When data could not be retrieved from original authors, incomplete studies were discharged.

Main outcomes and genetic model

The main outcome measures were the influence of ACE I/D polymorphism on both the risk of end-stage renal disease (ESRD) and hypertension and mean age (years) at ESRD in ADPKD patients. The odds ratio (OR) was used as the metric of choice for the evaluation of risk. The primary analysis compared ESRD ADPKD patients with non-ESRD ADPKD subjects for the contrast DD vs ID + II genotypes (recessive model). Likewise, hypertensive ADPKD patients were compared with normotensive ADPKD individuals for ACE I/D polymorphism distribution. Mean age at ESRD was also performed in a recessive model (DD vs ID + II). The choice of a recessive genetic model was based on a regression analysis as previously described [14].
**Statistical analysis**

For each study with binary outcomes, we calculated the OR and its 95% confidence intervals (CI). A random-effects model using the DerSimonian–Laird (DL) method [15] was employed to combine OR and 95% CI. For studies with continuous outcomes, mean age at ESRD was also combined by a random-effects model [15] using the unstandardized mean difference (UMD), defined here as the difference between the mean age at ESRD for DD genotype and the corresponding mean age at ESRD for I-allele carriers (ID + II). We applied this model because the random-effects approach more properly takes into account between-study heterogeneity such as differences in study design and patient enrolment [15]. Homogeneity among effect sizes was formally assessed through the Cochrane’s Q-statistic [15]. Evidence for publication bias was assessed using the Egger’s regression asymmetry statistics [16] and the Begg–Mazumdar adjusted-rank correlation test [17]. A P-value of <0.05 was judged significant, with the exception of the Q-statistic, in which a significance level of <0.1 was chosen. All analyses were performed with the Stata software (version 7; College Station, Texas).

**Results**

**Study selection and overview of the studies characteristics**

Our literature search identified 19 potentially relevant references describing studies in which associations between ACE I/D polymorphism and clinical features in ADPKD patients were evaluated. Of these, six were not eligible: four due to failure in obtaining relevant data from authors (lack of reported data), one evaluated other outcomes and one reported data in Japanese. A diagram flow summarising the process of study selection as well as further information concerning excluded studies are available online as supplementary material at the Nephrology Dialysis Transplantation Web site. Thus, a total of 13 studies fulfilled all inclusion criteria and provided sufficient data for meta-analysis: four were performed in Asian ADPKD populations [18–21], whereas nine were carried out in ADPKD populations of European descent [22–30]. Of these 13 studies, 11 were full-length reports in peer-reviewed journals [18,20–23, 25–29] and two were meeting abstracts [19,30]. Detailed characteristics of the studies eligible for the meta-analyses are shown in Table 1.

Does ACE I/D polymorphism influence the risk of ESRD in ADPKD?

For the meta-analysis about the association between ACE I/D polymorphism and risk of ESRD, data from nine subgroups from eight publications totalling 1420 individuals were combined: 398 ADPKD subjects at ESRD and 1022 ADPKD patients with normal renal function and/or lack of ESRD. Four studies investigated Asian patients (360 individuals: 135 ESRD and 225 non-ESRD) [18–21] and the other five subgroups from four publications [22,23,26,29] assessed individuals of European descent (1060 subjects: 263 ESRD and 797 non-ESRD). As ethnic heterogeneity of the ACE I/D polymorphism regarding both allele frequencies and the association between serum activity and I/D genotype is well known [11,31], summary ORs were also calculated considering separately each ethnic background to avoid population stratification.

By using a random-effect model [15], we found no evidence for an association between the DD genotype and an augmented risk for ESRD when compared with I-allele carriers considering all subgroups (DL common OR = 1.23; 95% CI = 0.89–1.68, P = 0.21). In addition, no evidence for heterogeneity among study results was observed (Q-statistic, \( \chi^2 = 9.63, \) df = 8, \( P = 0.29 \)). Likewise, separate analyses by ethnicity also failed to show a significant association between the DD genotype and a higher risk of ESRD in ADPKD patients: DL common OR for Asians: 1.56; 95% CI = 0.75–3.24, P = 0.23 and DL common OR for European-derived populations: 1.17; 95% CI = 0.76–1.80, P = 0.47. Q-statistic for these analyses also suggests homogeneity among study results for Asians (Q-statistic, \( \chi^2 = 1.05, \) df = 3, \( P = 0.79 \)), but mild heterogeneity among groups of European descent (\( \chi^2 = 8.06, \) df = 4, \( P = 0.09 \)). No evidence for publication bias was detected (all studies considered, Begg–Mazumdar test, \( P = 0.47 \); and Egger’s statistics, \( P = 0.48 \)). The forest plot regarding the ACE I/D polymorphism and risk of ESRD in ADPKD patients for all populations as well as pooled estimates by ethnicity is shown in Figure 1, which is available online as supplementary material at the NDT Web site.

**Influence of ACE I/D polymorphism on the age at ESRD in ADPKD**

Another approach to investigate the role of ACE I/D polymorphism in renal deterioration in ADPKD is to evaluate the mean age at ESRD. According to previous studies, mean age at ESRD is approximately normally distributed [9,28], which is adequate for the assumption of normality for combination of UMD.

The meta-analysis investigating the influence of ACE I/D polymorphism on mean age at ESRD in ADPKD patients included data from 12 subgroups from 11 reports, totalling 775 ADPKD patients at ESRD (206 harbouring the DD genotype and 569 carriers of the allele I; ID + II). Among the 12 subgroups, four consisted of Asian subjects (20 DD and 115 ID + II) [18–21], whereas eight from seven publications [22,24–28,30] were characterized by European descent (186 DD and 454 II + ID). By the random-effects model, we found no convincing evidence for a significant difference in mean age at ESRD for the DD genotype when compared with
### Table 1: Characteristics of studies included in the meta-analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Ethnicity</th>
<th>Sample size</th>
<th>Setting/Enrolment</th>
<th>Diagnosis of ADPKD</th>
<th>ADPKD type</th>
<th>Definition of Hypertension$^a$</th>
<th>Definition of ESRD</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uemasu et al. [18]</td>
<td>1997</td>
<td>Japan</td>
<td>Case-control</td>
<td>Asian</td>
<td>47</td>
<td>Hospital. Number of centres unclear</td>
<td>Familial history, medical history, abdominal echo-graphy and abdominal CT scan</td>
<td>Not defined</td>
<td>SBP &gt;140/DBP &gt; 90 mmHg</td>
<td>Patients undergoing dialysis</td>
<td>Lack of relevance of ACE I/D gene polymorphism in ADPKD</td>
</tr>
<tr>
<td>Hwang et al. [19]</td>
<td>1999</td>
<td>Korea</td>
<td>Cross-sectional</td>
<td>Asian</td>
<td>102</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>Lack of relevance of ACE I/D gene polymorphism in ADPKD</td>
</tr>
<tr>
<td>Lee et al. [20]</td>
<td>2000</td>
<td>Korea</td>
<td>Cross-sectional</td>
<td>Asian</td>
<td>108</td>
<td>10 centres in Korea</td>
<td>Family history, medical history and abdominal ultrasound</td>
<td>Not mentioned</td>
<td>DBP &gt; 90 mmHg or use of antihypertensive medication</td>
<td>Initiation of long-term renal replacement therapy</td>
<td>The mean age at ESRD was lower in patients with the DD genotype compared with the ID and II genotypes (DD, 45.0 ± 10.8 years; ID/II, 53.0 ± 11.1 years; $P = 0.05$). DD genotype associated with a higher risk of ESRD</td>
</tr>
<tr>
<td>Konoshita et al. [21]</td>
<td>2001</td>
<td>Japan</td>
<td>Cross-sectional</td>
<td>Asian</td>
<td>103</td>
<td>27 centres from Japan</td>
<td>Not mentioned</td>
<td>Not defined</td>
<td>Not evaluated</td>
<td>Initiation of long-term renal replacement therapy</td>
<td>DD genotype associated with a worse renal prognosis with significantly lower median renal survival time and significantly greater percentage of patients reaching ESRD before the age of 50 years.</td>
</tr>
<tr>
<td>Baboolal et al. [22]</td>
<td>1997</td>
<td>United Kingdom</td>
<td>Cross-sectional</td>
<td>Mainly European</td>
<td>189</td>
<td>Patients ascertained in South Wales, United Kingdom, and Victoria, Australia, Several centres from Spain.</td>
<td>Ultrasonography, tomography</td>
<td>Only PKD1</td>
<td>SBP &gt;95th percentile for age and sex, or use of antihypertensive medication</td>
<td>Initiation of long-term renal replacement therapy or death</td>
<td></td>
</tr>
<tr>
<td>Pérez-Oller et al. [23]</td>
<td>1999</td>
<td>Spain</td>
<td>Cross-sectional</td>
<td>European</td>
<td>155</td>
<td>Clinical and laboratorial findings, and Ultrasonography</td>
<td>Only PKD1</td>
<td>SBP &gt;95th percentile for age and sex without antihypertensive therapy</td>
<td>Initiation of long-term renal replacement therapy</td>
<td>DD genotype was associated with a worse renal prognosis with significantly lower median renal survival time and significantly greater percentage of patients reaching ESRD before the age of 50 years.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Country/Region</td>
<td>Design</td>
<td>Number of Centres</td>
<td>Recruitment</td>
<td>Clinical and laboratory findings, Ultrasonography</td>
<td>SBP, DBP, antihypertensive medication, renal replacement therapy</td>
<td>Initiation of long-term renal replacement therapy</td>
<td>Lack of relevance of ACE I/D gene polymorphism in ADPKD</td>
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</tr>
<tr>
<td>Saggar-Malik et al. [24]</td>
<td>2000</td>
<td>United Kingdom</td>
<td>Cross-sectional</td>
<td>33</td>
<td>Recruitment from the South West Thames region Database Centre from the South West Thames region Database</td>
<td>Clinical and laboratory findings, and ultrasonography</td>
<td>Not defined</td>
<td>SBP &gt; 160/DBP &gt; 90 mmHg, or antihypertensive medication</td>
<td>Serum creatinine ≥ 500 µmol/L or renal replacement therapy</td>
<td>Not mentioned in the provided information.</td>
<td></td>
</tr>
<tr>
<td>Magistroni et al. [25]</td>
<td>2001</td>
<td>Italy</td>
<td>Case-control</td>
<td>44</td>
<td>Recruitment from Dialysis and Transplantation Centre of Modena Centres from Australia, Bulgaria and Poland</td>
<td>Clinical and laboratory findings, ultrasonography</td>
<td>Not defined</td>
<td>SBP &gt; 140 and/or DBP &gt; 90 mmHg, use of antihypertensive medication</td>
<td>Initiation of long-term renal replacement therapy or kidney transplantation</td>
<td>Not mentioned in the provided information.</td>
<td></td>
</tr>
<tr>
<td>Schiavello et al. [26]</td>
<td>2001</td>
<td>Australia, Bulgaria and Poland</td>
<td>Cross-sectional</td>
<td>307</td>
<td>Ultrasonography only PKD1</td>
<td>Not evaluated</td>
<td>Not mentioned</td>
<td>Lack of relevance of ACE I/D gene polymorphism in ADPKD</td>
<td>Lack of relevance of ACE I/D gene polymorphism in ADPKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merta et al. [27]</td>
<td>2003</td>
<td>Czech Republic</td>
<td>Case-control</td>
<td>220</td>
<td>Ultrasonography only PKD1</td>
<td>Not evaluated</td>
<td>Not mentioned</td>
<td>Male patients with ADPKD harbouring the DD genotype had a statistically significant (5 years) lower mean age when compared with the ID+II ADPKD patients (P = 0.02)</td>
<td>Lack of influence of ACE I/D polymorphism on mean age at ESRD in ADPKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persu et al. [28]</td>
<td>2003</td>
<td>Belgium and France</td>
<td>Cross-sectional</td>
<td>191</td>
<td>Bilateral enlarged cystic kidneys and a positive family history</td>
<td>Not available</td>
<td>Not evaluated</td>
<td>Renal replacement therapy (dialysis or transplantation)</td>
<td>Lack of influence of ACE I/D polymorphism on mean age at ESRD in ADPKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecker et al. [29]</td>
<td>2003</td>
<td>USA</td>
<td>Cross-sectional</td>
<td>409</td>
<td>Not mentioned</td>
<td>Not defined</td>
<td>Not mentioned</td>
<td>Lack of relevance of ACE I/D gene polymorphism in ADPKD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of ADPKD patients included in the meta-analyses.

aSBP, systolic blood pressure; DBP, diastolic blood pressure.
Table 2. Summary estimates for the influence of the ACE I/D polymorphism on risk of ESRD, mean age at ESRD and risk of hypertension in ADPKD patients (DD vs ID + II)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
<th>Random-effects model</th>
<th>Q²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of ESRD</td>
<td>All</td>
<td>8</td>
<td>1420</td>
<td>1.23 (0.89, 1.80)</td>
<td>0.21</td>
<td>9.63</td>
</tr>
<tr>
<td></td>
<td>Asian studies</td>
<td>4</td>
<td>360</td>
<td>1.56 (0.75, 3.24)</td>
<td>0.23</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td>European-derived</td>
<td>4</td>
<td>1060</td>
<td>1.17 (0.76, 1.80)</td>
<td>0.47</td>
<td>8.06</td>
</tr>
<tr>
<td>Mean age at ESRD</td>
<td>All</td>
<td>11</td>
<td>775</td>
<td>-2.23 (-4.42, -0.05)</td>
<td>0.05</td>
<td>17.4²</td>
</tr>
<tr>
<td></td>
<td>Asian studies</td>
<td>4</td>
<td>135</td>
<td>-3.65 (-7.70, 0.40)</td>
<td>0.08</td>
<td>2.08</td>
</tr>
<tr>
<td></td>
<td>European-derived</td>
<td>7</td>
<td>640</td>
<td>-1.84 (-4.59, 0.92)</td>
<td>0.19</td>
<td>14.6²</td>
</tr>
<tr>
<td>Risk of hypertension</td>
<td>All</td>
<td>7</td>
<td>1299</td>
<td>1.13 (0.88, 1.46)</td>
<td>0.33</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>3</td>
<td>257</td>
<td>0.95 (0.46, 1.96)</td>
<td>0.89</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>European-derived</td>
<td>4</td>
<td>1042</td>
<td>1.16 (0.89, 1.52)</td>
<td>0.27</td>
<td>0.60</td>
</tr>
</tbody>
</table>

*p, effect size: odds ratio for both risk of ESRD and hypertension and unstandardized mean difference for mean age (years) at ESRD.

Q², Q-statistic.

Statistically significant, P < 0.10.

ID + II subjects: UMD: -2.23; 95% CI = -4.42 to -0.04, P=0.05. This analysis showed evidence for mild heterogeneity among study results (Q-statistic, χ² = 17.43, df = 11, P = 0.096). However, stratification by ethnicity also furnished evidence for a lack of association between the DD genotype and a lower risk of hypertension in ADPKD patients (DD common OR: 1.17; 95% CI = 0.76–1.80, P = 0.47) and ADPKD patients of European descent (DD common OR: 1.16; 95% CI = 0.89–1.52, P = 0.27). Evaluation of the study estimates suggests homogeneity among Asian studies (Q-statistic, χ² = 2.08, df = 3, P = 0.56) but considerable heterogeneity among the European subgroups (Q-statistic, χ² = 14.69, df = 7, P = 0.04). In these cases, meta-regression was not used to assess whether study-level covariates influence the magnitude of the UMD because relevant covariates were not always available for all subgroups and this type of analysis is unreliable when the number of combined studies is less than 10 [32]. Begg–Mazumdar test (P = 0.71) and Egger’s statistics (P = 0.92) showed no evidence for publication bias. The pooled UMD examining the influence of ACE I/D polymorphism on the age at ESRD in ADPKD patients for all studies as well as combined estimates by ethnicity are depicted in Figure 2, which is available online as supplementary material at the NDT website.

The insertion/deletion genotype and risk of hypertension in ADPKD

Activation of the renin–angiotensin system due to both cyst expansion and local renal ischaemia are suggested as major factors in the development of hypertension in ADPKD [13]. Hypertension, in turn, is very common among ADPKD subjects, occurring in up to 70% of the patients and being associated with a more rapid decline of renal function. Thus, a further approach to assess the role of ACE I/D polymorphism on the clinical course of ADPKD is to examine the prevalence of hypertension among the I/D genotypes.

The influence of ACE I/D polymorphism on the risk of hypertension in ADPKD was assessed by combining data from seven publications (eight subgroups) comprising a total of 1299 subjects (798 ADPKD hypertensives and 501 ADPKD patients classified as nonhypertensives). In this set of studies, three publications came from Asian patients (169 hypertensives and 88 normotensives) [18–20], while five subgroups from four studies [22,23,26,29] comprised European-derived ADPKD subjects (629 hypertensives and 413 normotensives).

Interestingly, no report showed evidence for an association between the DD genotype with a higher risk of hypertension. By combining all eight subgroups we also failed to find an association between ACE polymorphism and risk of hypertension in ADPKD subjects (DL common OR: 1.13; 95% CI = 0.88–1.46, P = 0.33). For this set, Q-statistic suggests strong homogeneity among study results, reinforcing the probable lack of involvement of the ACE polymorphism in ADPKD hypertension (Q-statistic, χ² = 1.33, df = 7, P = 0.99). Stratification by ethnical origin provides quite similar results. For Asians, the DL common OR was 0.95; 95% CI = 0.46–1.96, P = 0.89 and for European-derived groups, the DL common OR was 1.16; 95% CI = 0.89–1.52, P = 0.27 (Q-statistic, χ² = 0.47, df = 2, P = 0.79 and χ² = 0.60, df = 4, P = 0.96 for Asians and European-derived groups, respectively). Again, no evidence for publication bias was detected (eight subgroups, P = 0.17 and P = 0.26 for Begg–Mazumdar test and Egger’s statistics, respectively). Figure 3, which is available online as supplementary material at the NDT website, depicts graphically the summary OR for all studies as well as pooled estimates by ethnicity for the influence of ACE I/D polymorphism on the risk of hypertension in ADPKD patients. Table 2 summarizes the main results of the three meta-analyses considered here.
Discussion

One of the most striking aspects of ADPKD is the existence of an important variability in renal function deterioration [5,9]. In this respect, the identification of additional genetic risk factors for ADPKD is important as they may provide new insights into ADPKD pathogenesis as well as improve clinical therapy. However, genetic association studies of human diseases often lack power because of small sample size originated by inherent difficulties in both biological mechanism and patient recruitment. In order to derive a more robust and powered estimate of the putative influence of ACE I/D polymorphism on the clinical features in ADPKD, we pooled data from 13 independent studies in three distinct meta-analyses. For risk of ESRD, mean age at ESRD or risk of hypertension, our derived data provide no evidence of clinical relevance of ACE I/D polymorphism in ADPKD.

Nevertheless, these negative findings cannot completely rule out a role of the ACE I/D polymorphism in ADPKD progression and should be interpreted with caution. Indeed, the present meta-analyses have several limitations such as limited number, quality and size of available studies and evaluation of variables that cannot be the most appropriate outcomes to examine the role of ACE I/D polymorphism in renal progression in ADPKD [21]. Importantly, we extended our inclusion criteria to reports published in English, German, Italian, Portuguese and Spanish. Thus, although we made meticulous efforts to identify all relevant data and to contact experts in the field searching for unpublished reports, the available number of studies and subjects might be still too small to provide enough power to detect subtle effects of this common gene variant. In fact, recent evidence indicates that the variability of renal progression in ADPKD depends on multiple common modifier gene variants with modest effects acting in concert with environmental factors [9] and that sample sizes of thousands of subjects will be required to detect moderate increases in risk [33]. Hence, due to the limited number of studies available we cannot rule out a moderate to low effect of ACE I/D polymorphism in the renal progression of ADPKD subjects.

Perspectives and research priorities

Another possible explanation for the negative findings derived here would be that the proportion of patients who reached ESRD, mean age at ESRD or risk of hypertension are not parameters to properly examine renal progression in patients with ADPKD. In this respect, cumulative renal survival might be more informative [21]. Indeed, two [21,22] out of three studies [20] investigating the cumulative renal survival have suggested a significant lower renal survival for the DD genotype when compared with the I-allele carriers. Thus, well-designed, carefully conducted prospective cohort studies evaluating cumulative renal survival may provide an efficient tool to address this issue.

Another gap to be filled in the research of modifier genes in ADPKD, is the effect of gender and diet on renal progression. Previous evidence suggests that male ADPKD subjects have a worse prognosis when compared to female ADPKD patients [34], whereas both animal and human studies suggest that the rate of progression of renal insufficiency found in ADPKD
can be retarded with institution of a low-protein diet [35]. In the present meta-analysis, however, we were unable to stratify subgroups by gender due to lack of reported data. In addition, all studies failed to evaluate dietary aspects. Hence, studies with larger samples assessing both gene–gender and gene–nutrients interactions in ADPKD progression are warranted.

Finally, finding the causes of strong variability in renal progression will probably require a careful study of well-characterized and genetically homogeneous ADPKD subjects as well as meticulous analyses of gene–gene and gene–environment interactions. Additional genetic factors such as variants in NOS3 [5] and NPHS2 [38] are good candidates and may provide more informative and useful data for the ADPKD progression management than current available data.

In conclusion, current evidence fails to support the hypothesis that in ACE I/D polymorphism plays a major role in the risk of both ESRD and hypertension or in a reduced mean age at ESRD in ADPKD patients. However, lack of well-designed, adequately powered studies cannot entirely rule out a role for ACE I/D polymorphism in ADPKD progression. Future efforts in the research of modifier genes in ADPKD should focus on conducting larger studies in well-defined and genetically homogeneous ADPKD populations.

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