Genome scan of glomerular filtration rate and albuminuria: the HyperGEN study

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Abstract

Background. Albuminuria and reduced glomerular filtration rate (GFR) are markers of renal dysfunction associated with hypertension. We performed genome-wide scans to detect loci impacting these parameters in 1251 African American (AAs) and 1129 European American (EAs) hypertensive siblings from the Hypertension Genetic Epidemiology Network study.

Methods. GFR, estimated by the Modification of Diet in Renal Disease equation, and albuminuria, measured as albumin to creatinine ratio (ACR), were adjusted for gender, age, centre, mean blood pressure, anti-hypertensive medication class and diabetes status using SOLAR. Since albuminuria and abnormal GFR often coexist, we conducted bivariate linkage analyses to investigate the presence of pleiotropy.

Results. The phenotypic correlation between ACR and GFR was not significant in EAs (r = 0.04) and significantly negative in AAs (r = -0.17). Univariate analyses of ACR showed suggestive evidence of linkage on chromosomes 8, 16 and 17 (LOD: 2–2.8) in AAs, on chromosomes 18 and 19 (LOD = 2) in EAs, and on chromosome 19 (LOD = 2.6) when combining AAs and EAs. For GFR, suggestive linkage was found on chromosomes 7, 14 and 19 (LOD: 2.2–2.9) in AAs and on chromosomes 14, 15 and 16 (LOD: 2.1–3.3) in the combined group. Also, bivariate analyses showed a LOD score of 3.4 at 133 cM on chromosome 7 in AAs.

Conclusions. Suggestive evidence for linkage to GFR and ACR was observed at many loci. The findings are consistent with previous studies. Also, indication of a pleiotropic locus was detected in chromosome 7 in AAs.

Keywords: albumin to creatinine ratio; albuminuria; genome scan; glomerular filtration rate; hypertension; renal function

Introduction

There are many pathways through which hypertension may develop, and genetic effects are believed to play an important role in its development and progression. Primary hypertension is one of the most important risk factors associated with progressive loss of renal function [1,2]. More than 80% of patients with chronic renal failure have a history of hypertension. Additionally, hypertension may also be caused by renal disease [1].

Nephrosclerosis is an important renal lesion related to hypertension. Its final stages include progressive arterio- and arteriolonephrosclerosis with interstitial fibrosis, ischaemic glomerular collapse and glomerulosclerosis. Elevated glomerular capillary pressure from compensatory hyperfiltration increases the flux of proteins, including albumin, into the urinary space and accelerates glomerulosclerosis [1,3]. As a consequence, elevated urinary albumin levels and reduced glomerular filtration rate (GFR) often coexist. Albuminuria and low GFR are indicators of renal dysfunction [1]. Based on these observations, we expected to observe a negative correlation between albuminuria and GFR, a portion of which may be due to common genetic factors.
Janssen et al. [4] found elevated levels of urinary albumin in normotensive offspring of hypertensive parents, supporting a genetic contribution to the relationship between hypertension and renal disease. Some studies have reported a marked familial aggregation of hypertensive renal disease and albuminuria [2,5]. To determine whether unique and/or common loci (or loci) regulate urinary albumin excretion and GFR in the presence of hypertension, we performed univariate and bivariate variance components linkage analyses of urinary albumin excretion and GFR in Hypertension Genetic Epidemiology Network (HyperGEN) families.

Materials and methods

Population

The study subjects were participants in the HyperGEN study, part of the NHLBI-sponsored Family Blood Pressure Program (FBPP) [6]. HyperGEN is a multi-centre cross-sectional family study with five field centres: Framingham (MA), Minneapolis (MN), Salt Lake City (UT), Forsyth County (NC) and Birmingham (AL). The main goal of HyperGEN is to identify and characterize genes that contribute to hypertension. Variables assessed included blood pressure, serum and urine chemistries, anthropometrics, echocardiographic measurements and basic demographic information including questions about family and personal history of hypertension, medication, diet, physical activity and lifestyle. DNA extraction and genotyping were also performed.

HyperGEN collected race-specific data from three groups of subjects: (i) severe and mild hypertensive sibships selected from families with two or more hypertensive siblings diagnosed before 60 years of age, (ii) adult offspring not on anti-hypertensive medication, (iii) an age-matched random sample from the source population. Analyses performed in this report were restricted to hypertensive sibships (the first of the three groups) since genotyping data were not yet available for the majority of the offspring.

Clinical data were collected from 2407 individuals in 917 sibships with mild and severe primary hypertension [1262 African Americans (AAs) and 1145 European Americans (EAs)]. Mild hypertension was defined as systolic blood pressure (SBP) between 140 and 160 mmHg or diastolic blood pressure (DBP) between 90 and 100 mmHg, or using only one anti-hypertensive medication. Severe (or stage 2) hypertension was defined as having SBP >160 or DBP >100 mmHg, or using two or more anti-hypertensive medications.

Phenotypes

The two phenotypes of interest were albumin to creatinine ratio (ACR) and GFR. ACR was measured from an overnight urine collection and GFR was estimated by the abbreviated Modification of Diet in Renal Disease (MDRD) equation [7,8].

GFR was approximately normally distributed, but the distribution of ACR was markedly positively skewed and leptokurtic, especially for EAs (Table 1). To attempt to remedy this, we log-transformed ACR. However, even after such transformation, the distribution of ACR was still leptokurtic. Because at least one trait was not normally distributed, empirically derived P-values were used to assess the statistical significance of all our linkage results.

Phenotypes were adjusted for gender, age, field centre, mean blood pressure [estimated by DBP + 1/3(SBP)], class of anti-hypertensive medication used and type 2 diabetes status. Our data include information about type and number of medications that were being taken by participants at the time of the study. The classes of anti-hypertensive medication were calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), β-blockers, diuretics, and others that included α-β blockers and adrenolytic anti-hypertensives.

Genotypes

Three hundred and ninety-one microsatellite markers were typed by the NHLBI Mammalian Genotyping Service (MGS) in Marshfield (WI), with an average marker density of 9.5 cM. As a measure of quality control, the HyperGEN Data Coordinating Center, Washington University in Saint Louis, MO compared select individuals’ DNA samples with blinded duplicates that were sent to the genotyping laboratory with a different identification number as ‘extra siblings’. There was >98% agreement between these ‘paired’ samples. More information about the MGS, including laboratory methods (gel preparation, PCR conditions) is available at the Marshfield Clinic Center web page [9].

The software ASPEX [10], MERLIN [11,12], GRR [13], PedCheck [14] and MAPMAKER [15] were used to verify whether the marker assignments were consistent with the reported familial relationship and had no Mendelian or other inconsistencies. The marker data were set to missing or the marker deleted depending on how many inconsistencies individuals had.

Analytical methods

Multi-point variance components linkage analysis was conducted as implemented in SOLAR [16]. This method assumes multivariate normal distribution for the phenotype of interest and allows the estimation and hypothesis testing of locus-specific effects, residual polygenic effects, covariate effects and environmental effects [17].

Covariate adjustment was performed using SOLAR, which takes into account the familial relationship to calculate the multivariate regression coefficients. Univariate and bivariate variance components linkage analyses were conducted across the genome.

Table 1. Statistics of phenotypes by race

<table>
<thead>
<tr>
<th>Statistic</th>
<th>European American</th>
<th>African American</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR ACR log(ACR)*10</td>
<td>74.31 247.47 36.56</td>
<td>89.93 913.42 43.17</td>
</tr>
<tr>
<td>Median</td>
<td>73.19 42.98 37.61</td>
<td>88.44 55.88 40.23</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.16 12.69 −1.10</td>
<td>0.06 9.37 −0.21</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.65 181.76 3.52</td>
<td>1.17 106.75 2.78</td>
</tr>
</tbody>
</table>

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[9] European American African American
[8] Median 73.19 42.98 37.61 88.44 55.88 40.23
For the univariate analysis, LOD scores and heritabilities can be obtained. For the bivariate analysis [18,19], which can be used when two traits are correlated, phenotype specific heritabilities and LOD scores as well as genetic and environmental correlations can be calculated. Also, we tested the hypotheses that genetic correlations of the major genes were either 0 (no pleiotropy) or 1 (complete pleiotropy) as proposed by Williams et al. [20]. The identity by descent (IBD) matrix was computed in MERLIN using the Lander–Green exact algorithm [21].

To derive empirical P-values, we generated 10 000 replicate data sets with the same phenotypes as the original data but with a single completely polymorphic marker locus and genetic transmission under the null model [22]. For each replicate, a LOD score was computed and stored. It was then possible to compute an empirical P-value for any of our observed LOD scores by counting the number of simulated null LOD scores that equaled or exceeded the observed LOD. The empirical P-values so produced are single-point, which reveal the probability, if there were no genetic effect, of finding a LOD at a single predetermined chromosomal location that is as high or higher than the one observed. A single-point P-value of $10^{-4}$ corresponds to a genome-wide P-value of 0.05. A genome-wide P-value, if the null hypothesis were true, is the probability that the highest LOD in a genome scan is as high or higher than the one observed. That is, the genome-wide P-value is corrected for multiple testing.

Results

Our analyses included 2254 individuals with data on GFR (1129 AA and 1125 EA) and 2274 individuals with data on ACR (1234 AA and 1040 EA); 1251 AA and 1036 EA had both traits. Individuals who were not AA or EA ($n=10$), monozygotic twins ($n=10$) and members of inter-racial families ($n=7$) were excluded from the analyses. Table 2 includes the number of pairs of siblings, half siblings, parent–child and avuncular, by race and trait.

EAs were, on average, 10 years older than AAs. Mean GFR was $\sim$16 ml/min higher in AAs. Mean ACR in AAs was considerably higher than in EAs (913.4 compared with 247.5 mg/g). Forty-seven percent of the EA sample was male, compared with 31% of the AA sample. The prevalence of diabetes was 20% in EAs compared with 27% in AAs. The majority of the participants were taking anti-hypertensive medication (84% of EAs and 74.5% of AAs). Additionally, anti-hypertensive medication patterns differed by race: 29% of EAs compared with 42% of AAs were taking calcium channel blockers; 41% of EAs compared with 30% of AAs were taking ACE inhibitors or ARB; and 30% of EAs were taking $\beta$-blockers compared with 14% of AAs (Table 3). All participant characteristics were significantly different by race with the exception of the percentage intake of medications other than the ones discussed above (last row on Table 3).

There was a small but significant negative phenotypic correlation between ACR and GFR in AAs ($r=-0.17$, $P$-value <0.0001). The estimate for the genotypic correlation was $-0.002$ and the environmental correlation was $-0.23$. In EAs, there was no significant phenotypic correlation ($r=0.04$, $P$-value = 0.2).

Heritability estimates for GFR were 0.26 (SE = 0.08) and 0.38 (SE = 0.08) in AAs and EAs, respectively. For ACR, the heritability estimates were 0.39 (SE = 0.08) and 0.29 (SE = 0.08) in AAs and EAs, respectively. Those moderate values indicate that there may be genes influencing the phenotypes of interest.

Table 4 shows the highest LOD scores for adjusted models and their respective empirical $P$-values. An empirical $P$-value of 0.0027 (for locus 56 of chromosome 8 in ACR for AAs), for example, means that only 27 out of 10 000 LOD scores generated under the null hypothesis were as high or higher than the observed LOD of 2.84. The univariate analyses showed suggestive evidence of linkage (LOD $\geq 2$).

### Table 2. Number of pairs for each trait by race and familial degree

<table>
<thead>
<tr>
<th>Familial relationship</th>
<th>European American GFR</th>
<th>European American ACR</th>
<th>African American GFR</th>
<th>African American ACR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siblings</td>
<td>965</td>
<td>778</td>
<td>648</td>
<td>661</td>
</tr>
<tr>
<td>Half siblings</td>
<td>21</td>
<td>17</td>
<td>140</td>
<td>138</td>
</tr>
<tr>
<td>Parent–child</td>
<td>36</td>
<td>31</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Avuncular</td>
<td>80</td>
<td>66</td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

*a* Mean comparison t-test was used.

*b* Chi-square test was used.

*c* $P$-value from mean comparison test of ACR on the log scale.

### Table 3. Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>European American</th>
<th>African American</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>60.84 (9.39)</td>
<td>50.97 (10.72)</td>
<td>&lt;0.0001<em>a</em></td>
</tr>
<tr>
<td>GFR in ml/min, mean (SD)</td>
<td>74.31 (16.83)</td>
<td>89.93 (23.40)</td>
<td>&lt;0.0001<em>a</em></td>
</tr>
<tr>
<td>ACR in mg/g, mean (SD)</td>
<td>247.47 (1460.85)</td>
<td>913.42 (4490.47)</td>
<td>&lt;0.0001<em>a</em>c*</td>
</tr>
<tr>
<td>Mean blood pressure in mmHg (SD)</td>
<td>113.13 (16.09)</td>
<td>120.86 (17.80)</td>
<td>&lt;0.0001<em>a</em></td>
</tr>
<tr>
<td>Male (%)</td>
<td>47%</td>
<td>31%</td>
<td>&lt;0.0001<em>b</em></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20%</td>
<td>27%</td>
<td>&lt;0.0001<em>b</em></td>
</tr>
<tr>
<td>Severe hypertension (%)</td>
<td>53%</td>
<td>59%</td>
<td>0.0023<em>b</em></td>
</tr>
<tr>
<td>Anti-hypertensive drug (%)</td>
<td>85%</td>
<td>74%</td>
<td>&lt;0.0001<em>b</em></td>
</tr>
<tr>
<td>Calcium channel blockers (%)</td>
<td>29%</td>
<td>42%</td>
<td>&lt;0.0001<em>b</em></td>
</tr>
<tr>
<td>ACE inhibitors or ARB (%)</td>
<td>41%</td>
<td>30%</td>
<td>&lt;0.0001<em>b</em></td>
</tr>
<tr>
<td>$\beta$-blockers (%)</td>
<td>30%</td>
<td>14%</td>
<td>&lt;0.0001<em>b</em></td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>32%</td>
<td>37%</td>
<td>0.0099<em>b</em></td>
</tr>
<tr>
<td>Other medications (%)</td>
<td>3%</td>
<td>3%</td>
<td>0.4005<em>b</em></td>
</tr>
</tbody>
</table>
on chromosomes 7, 14 and 19 for GFR, and on chromosomes 8, 16 and 17 for ACR in AA s and on chromosomes 18 and 19 for ACR in EAs. Race specific plots of LOD score distributions by chromosome can be found in Figures 1 and 2. Despite ethnic differences in the linkage results, we also investigated whether the use of both racial groups would increase the power to detect linkage for those two phenotypes. We observed more pronounced results for ACR on chromosome 19 and evidence for linkage for GFR on chromosomes 14, 15 and 16, not previously detected in ethnic specific analyses. Table 5 shows the highest LOD scores for the combined analysis as well as the corresponding LOD scores for AA s and EAs at those specific locations.

In the bivariate analysis of GFR and ACR, we observed a LOD score of 3.37 at 133 cM on chromosome 7 in AA s suggesting the presence of a pleiotropic effect with respect to the two traits in this racial group. At the same location, the univariate analyses showed maximum LOD scores of 2.52 for GFR and 1.12 for ACR (Figure 3). No LOD scores above 2 were observed in EAs, and when combining both racial groups we obtained LOD scores of 2.98 at 138 cM for chromosome 7, 2.66 at 93 cM for chromosome 14 and 2.21 at 17cM for chromosome 15 (Table 6). We tested whether the genetic correlation in such loci was 0 or 1, and none of the tests was statistically significant at α = 0.05.

Discussion

A fully adjusted genome scan of ACR showed suggestive evidence of linkage on chromosomes 8, 16 and 17 in AA s and on chromosomes 18 and 19 in EAs. The results for GFR suggested evidence of linkage on chromosomes 7, 14 and 19 in AA s. When both racial groups were included, we observed more pronounced results on chromosome 19 for ACR and suggestive evidence for linkage for GFR on chromosomes 14, 15 and 16.

Our only genome-wide significant results were on chromosomes 14 (LOD = 3.29 at 94 cM) and 15 (LOD = 3.13 at 16 cM) for GFR, observed when we combined data from both racial groups. The chromosome 14 results are clearly driven by the AA s. To the best of our knowledge, chromosome 14 has not been linked to GFR or ACR. Consistent with our results on chromosome 15, linkage for albuminuria near the intragenic marker GABRB3 has been reported in diabetic Mexican Americans (LOD scores of 3.3 and 2.6 for two-point and multi-point analyses, respectively) [23].

Another important finding of our study regards chromosome 18 for ACR in EAs (LOD = 2.10 at locus 105). Significant linkage for proteinuria and for proteinuria with microalbuminuria have also been found in a partial genome scan on 18 extended Turkish families with type 2 diabetes and diabetic nephropathy (LOD = 2.2 at 110 cM and 6.6 at 110 cM assuming dominance) [24]. Those results have been replicated in an affected sib-pair analysis on Pima Indians [24]. A large ordered subset analysis (OSA) by age of diagnosis of diabetes, conducted by Bowden et al. [25], in AA end-stage renal disease (ESRD) families also revealed a maximized LOD score of 3.72 on chromosome 18 at 100.5 cM. Near this region, in a recent study of 135 diabetic nephropathy cases and 107 diabetics without nephropathy, Janssen et al. [26], found the carnosinase (CNDP1) gene, located on locus 18q22.3–q23, to be associated with susceptibility for diabetic nephropathy in type 1 and type 2 diabetic patients.

Bowden et al. [25] also found a LOD score of 3.13 on chromosome 19 at 21 cM in AA s, which is consistent with our results in EAs (LOD = 2.12 at 10 cM) and in the AA s and EAs combined group (LOD = 2.60 at 12 cM). Our results also confirm a prior analysis [27] of ACR using a subgroup of HyperGEN participants (LOD = 2.73 at 9 cM), since many of these participants were also used in the present analysis. This prior HyperGEN analysis included 1727 phenotyped individuals (834 AA s and 893 EAs), 547 less individuals than in the current sample.

Our results for chromosome 7 (LOD = 2.93 at 137 cM for GFR in AA s) were similar to the findings from a study of 93 diabetic Pima Indian sib-pairs concordant for overt proteinuria that revealed a LOD score of 2 at 144 cM on chromosome 7 for microvascular complications [28].

We also found suggestive linkage on chromosome 8 (LOD = 2.84 at 56 cM for ACR in AA s), which replicates the findings of Freedman et al. [29] (LOD = 3.37 at locus 29.73) in a non-parametric OSA of ESRD by age at diagnosis in 296 hypertension-associated ESRD-affected sib-pairs.

Finally, the chromosome 16q23.3 region has been linked to renal disease susceptibility in Native Americans [30]. In AA s we found suggestive linkage on chromosome 16 for ACR (LOD = 2.02 at 48 cM and 2.17 at 129 cM) and in the combined analysis the highest LOD on this chromosome was found for GFR.

### Table 4. Highest ethnic-specific LOD scores from adjusted univariate analyses of ACR and GFR

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Chromosome</th>
<th>Locus (cM)</th>
<th>LOD score</th>
<th>Empirical P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>African Americans</td>
<td>8</td>
<td>56</td>
<td>2.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>48</td>
<td>2.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>129</td>
<td>2.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17</td>
<td>122</td>
<td>2.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>137</td>
<td>2.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>95</td>
<td>2.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19</td>
<td>49</td>
<td>2.21</td>
</tr>
<tr>
<td>GFR</td>
<td>European Americans</td>
<td>18</td>
<td>105</td>
<td>2.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19</td>
<td>10</td>
<td>2.12</td>
</tr>
</tbody>
</table>

Age, gender, centre, mean blood pressure, diabetes status and anti-hypertensive medication use were included as covariates.
Fig. 1. Univariate multi-point linkage results for GFR and log(ACR) in EAs (adjusted for gender, age, field centre, mean blood pressure, class of anti-hypertensive medication used and diabetes status).
Fig. 2. Univariate multi-point linkage results for GFR and log(ACR) in AAs (adjusted for gender, age, field centre, mean blood pressure, class of anti-hypertensive medication used and diabetes status).
Results for ACR in the combined analysis were not significant (highest peaks LOD = 1.70 at 46 cM and 0.23 at 100 cM). The interpretation of such findings is not straightforward and the suggestion of a pleiotropic locus on chromosome 16 seems to be possible although not confirmed by our bivariate analyses results (LOD = 1.82 at 100 cM, and 1.13 at 46 cM for the combined analysis).

Overall, many of our univariate results were consistent with findings of other studies, but there are many regions previously linked to renal function traits that were not detected in our study. Among those, we would like to mention a prior genome scan of creatinine clearance [31,32] in HyperGEN participants that revealed a LOD score of 4.66 on chromosome 3 at 66 cM. In our analyses using MDRD GFR, the highest LOD score for chromosome 3 was 1.00 at locus 26 cM. Clearly, estimation of creatinine clearance using timed urine collections and the MDRD equation may differ. Each method has inherent biases when contrasted with the gold standard of either inulin or iothalamate clearance. Neither of these methods was employed in HyperGEN. Also, Bowden et al. [25] reported a maximized LOD score of 2.65 on chromosome 10 at 161.1 cM. This region is near the human orthologous region of the rodent Rf-1 locus for hypertensive nephropathy in the fawn hooded rat [33]. These findings have been replicated in AA sib-pairs concordant for ESRD [34,35], hypertensive EA pedigrees from Utah [36], AA and EA families with diabetic nephropathy [37], but not in our study.
Although it seems that there is an increase in power to detect linkage in some chromosomes when we included both races, our results suggest the existence of racial differences in genetic susceptibility of ACR and GFR. Those differences could be caused by a number of effects including gene by environment interactions, differences in allele frequencies, differences in sample size and family structure that could affect power, population differences in environmental risk factors related to renal function, and chance. AAs have a higher prevalence of hypertension and renal disease compared with EAs. Ethnic disparities in renal disease may result from differences in socio-economic status, medication compliance, diabetes prevalence, anatomical differences, abnormal renal haemodynamic control, endothelin-1 plasma concentration, or a combination of these factors [38]. Genetic factors may also contribute to the enhanced susceptibility to hypertension and renal disease among AAs, through differences in these factors or through other mechanisms [5].

The LOD scores detected in ethnic-specific analyses were not genome-wide significant, especially in EAs. One possible explanation is the effect of anti-hypertension treatment and control rates. Hypertension control may inhibit renal disease progression [1], weakening a potential genetic signal, especially in EAs for whom blood pressure lowering has been shown to delay progression of nephropathy. In HyperGEN, EAs were better controlled in terms of blood pressure than AAs. AAs with hypertensive nephrosclerosis derive less renal protection from improvements in blood pressure control. The majority of the participants were taking anti-hypertensive medication (84% of EAs and 74.5% of AAs). This could have diluted the genetic effects and decreased the power to detect linkage. Compared with EAs, AAs have a higher prevalence of hypertension and renal disease. In our sample, a greater proportion of AA subjects were diabetic (27% of AAs compared with 20% of EAs). AAs have an earlier age of onset of hypertension, and more severe hypertension than their EAs counterparts [39]. In our analysis, slightly more AAs had severe hypertension, and mean blood pressure was higher than in EAs. Therefore, if the renal susceptibility locus is dependent on hypertension severity, it may only be apparent in the group with more extreme exposure to high blood pressure. The distribution of anti-hypertensive medication classes differed between EAs and AAs (Table 3). Finally, since diabetic participants were included, if there are different loci functioning in the renal impairment of this condition than for hypertension, our results could be biased towards the null.

The bivariate analyses revealed interesting results for chromosome 7. We observed a LOD score of 3.37 at 133 cM in AAs and of 2.98 at 138 cM for the combined population, suggesting the presence of a pleiotropic effect with respect to the two phenotypes. Interestingly, the peak for the bivariate analysis in the combined population was smaller than in AAs, which could indicate that the pleiotropic effect is smaller or inexistent in EAs. We also observed bivariate LOD scores above 2 for chromosomes 14 and 15, but those seem to be driven by GFR as observed in Table 6. The results obtained in the bivariate analyses could not be confirmed by the pleiotropy tests.

Our results suggest that there may be a common genetic locus involved in the relationship between altered GFR and ACR in these families enriched for members with essential hypertension, but there are probably many other genes that regulate exclusively one of the phenotypes. Placha et al. [40] suggest that albuminuria and renal function appear to be under independent genetic control in diabetic subjects with nephropathy. This should not be surprising in hypertensive individuals, since albuminuria appears to be a much stronger risk factor for CVD morbidity and mortality than progressive nephropathy. Calcified atherosclerotic plaque has recently been shown to strongly correlate with ACR, as well [41].

This large linkage analysis of ACR and GFR in AA and EA HyperGEN families demonstrated multiple loci that appeared to be linked with these traits within each racial group. Some of these regions replicate linkage to GFR and ACR in other family sets. Moreover, suggestive evidence for a shared genetic effect was detected. The identification of genes independently regulating ACR and GFR as well as a possible gene co-regulating both traits located within linkage peaks that replicate between multiple studies are needed.

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Conflict of interest statement. None declared.


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