Estimated glomerular filtration rate and its association with the retinol-binding protein 4 (RBP4) locus on human chromosome 10q23

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Abstract

Background. We tested for associations between estimated glomerular filtration rate (eGFR) and retinol-binding protein 4 (RBP4) haplotypes found on human chromosome 10q23. This locus had been linked to eGFR in a previous linkage scan in patients with Type 2 diabetes mellitus.

Methods. We analysed 469 patients with Type 2 diabetes and 174 normoalbuminuric controls for associations between RBP4 haplotypes and eGFR. For comparison with controls, 295 cases with proteinuria/end-stage renal disease were tested for associations with advanced diabetic nephropathy. Genotyping was performed using high-resolution DNA melting assays. Data analysis was performed using the haplo.stats package.

Results. Genetic variations in RBP4 were not associated with advanced diabetic nephropathy. Compared with the common A/G/G/C haplotype, C/A/A/C carriers among the normoalbuminuric controls had higher eGFR values among younger patients but lower eGFRs among the older patients (effect size = 2.2, $P = 3.3 	imes 10^{-7}$). Furthermore, while eGFR values were fairly consistent over the range of systolic blood pressure (SBP) values for the common haplotype, eGFR in C/A/A/C carriers increased with SBP (effect size = 3.6, $P = 1.5 	imes 10^{-7}$). There was a significant interaction between the C/A/A/C haplotype and HbA1c as they affect eGFR compared to the common haplotype (effect size = 2.1, $P = 2.1 	imes 10^{-3}$). Power calculations demonstrated that our study had >90% power to detect the
observed interactions even while performing multiple hypotheses testing. The interaction between SBP and the C/A/A/C haplotype remained significant ($p = 2.8 \times 10^{-2}$) even when these three haplotype–environment interactions were simultaneously estimated.

**Conclusion.** RBP4 haplotypes may be important in genetically modulating renal function in response to environmental challenges among patients with Type 2 diabetes.

**Keywords:** estimated glomerular filtration rate; haplotypes; interaction; multiple hypothesis testing; retinol-binding protein 4

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### Introduction

While urinary albumin excretion is an important criterion for diagnosing and tracking the progression of diabetic nephropathy, it is increasingly recognized that there may be early renal function changes, even in the normoalbuminuric patient, which may subsequently develop into renal insufficiency [1–3]. Despite their potential clinical importance, little is known about the factors that influence renal function in these patients [4]. Among the environmental factors, raised triglyceride levels were associated with low estimated glomerular filtration rate (eGFR) in a study of 660 normoalbuminuric Type 2 diabetic Brazilian patients [2]. An association between dyslipidaemia and eGFR has also been demonstrated in non-proteinuric Type 1 diabetic patients at the Joslin Clinic, where low eGFR was associated with a higher prevalence of lipid-lowering treatment [5]. Increased blood pressure may also be associated with low eGFR, whereas poor glycaemic control has surprisingly not yet been linked with eGFR levels [2, 5].

In normoalbuminuric patients with diabetes mellitus, the influence of genetics on renal function remains largely unexplored. A previous genome-wide linkage scan in extended families with Type 2 diabetes mellitus for genes controlling renal function revealed potential major susceptibility gene loci. Analysis of the relatives of diabetics who were predominantly normoalbuminuric revealed a small number of linkage peaks, including one on human chromosome 10q23 [6]. This linkage peak had an LOD score of 3.1 and was most closely associated with microsatellites D10S2470 and D10S677 [6]. Interestingly, these microsatellites flanked a 3.6-Mb chromosomal region harbouring the gene for retinol-binding protein 4 (RBP4) (Supplementary figure 1). While initial reports suggested that the adipokine RBP4 may be involved in the development of insulin resistance and Type 2 diabetes mellitus [7, 8], more recent studies indicated that it is more likely linked with renal function rather than to Type 2 diabetes mellitus itself [9–15]. Raised circulating levels of RBP4 have been strongly associated with lower eGFR, whereas its association with albuminuria has been conflicting [9–11, 14, 15].

Since RBP4 has been associated with low eGFR in Type 2 diabetes mellitus, we investigated potential associations between eGFR and RBP4 haplotypes on human chromosome 10q23. Given that the original genetic linkage was observed among Type 2 diabetic patients, the majority of whom were normoalbuminuric [6], the primary focus of our study centred on patients with diabetes mellitus for a substantial period of time but who had remained normoalbuminuric during repeated measurements. We also tested for the presence of genetic associations with the more advanced stages of diabetic nephropathy, namely, proteinuria and chronic renal failure/end-stage renal disease (CRF/ESRD).

### Materials and methods

#### Patient groups

Patients in this study were recruited from the Joslin Clinic in Boston and had been involved in earlier studies reporting on the genes for angiotensin-converting enzyme and interleukin-6 [16, 17]. Since 1998, individuals with Type 2 diabetes mellitus have been recruited for studies examining the genetics of nephropathy from among patients attending the Joslin Clinic in Boston, Massachusetts. Diabetes mellitus was classified as Type 2 if it was diagnosed between ages 35 and 64 years and was treated for at least 2 years with diet or oral hypoglycaemic agents. Only patients <75 years of age at enrolment were included in the study.

#### Diagnosis of diabetic nephropathy

Diabetic nephropathy was determined on the basis of medical records from the Joslin Clinic (supplemented with records from other physicians, if necessary) and results from routine urinary analyses, including measurements of the albumin to creatinine ratio (ACR) [18]. Because the diagnosis of Type 2 diabetes mellitus is generally established many years after the onset of hyperglycaemia, patients were classified as normoalbuminuric controls if they had Type 2 diabetes mellitus with a known duration of at least 7 years and an ACR (in milligrams/grams) of <17 in men or <25 in women from at least two of the last three urine specimens spanning at least a 2-year interval. Patients with microalbuminuria or intermittent proteinuria were not included in this study. Patients were classified as cases if they had persistent proteinuria or if they had ESRD due to diabetic nephropathy. Persistent proteinuria was defined as two of three successive positive urinalyses by either reagent strip (greater than 2+ on Multistix; Bayer Corporation, Diagnostics Division, Elkhart, IN) or an ACR (in milligrams/grams) >250 in men or >355 in women. Patients with persistent proteinuria and serum creatinine >2.0 mg/dL were classified as cases with CRF. At the time of this study, genomic DNA was available for 295 cases with advanced diabetic nephropathy and 174 persistently normoalbuminuric controls. Renal function was estimated by the simplified Modification of Diet in Renal Disease equation where the estimated GFR (eGFR, mL/min/1.73m<sup>2</sup>) = 186.3 × (plasma creatinine in mg/dL<sup>−1.144</sup>) × (age in years<sup>−0.203</sup>) × (0.742 for women) × (1.21 if subject is black) [19]. Only Caucasians were included in this study.

#### Examination of study participants

All patients selected for the genetic studies were examined at the clinic or at their homes. After consenting to participate in the study, each subject was given a standardized physical examination and provided a diabetes history that included diagnosis, treatment and complications. Each individual provided a blood sample for biochemical measurements and DNA extraction. Medical records were thoroughly reviewed to minimize the possibility of including patients with non-diabetic kidney disease. Patients were also directly questioned by a physician to determine whether they were ever diagnosed with non-diabetic kidney disease. The Committee on Human Subjects of the Joslin Diabetes Center approved the protocols and obtained informed consent for these studies.

#### Selection of RBP4 tagging SNPs

Tagging single nucleotide polymorphisms (SNPs) were selected using the International Hapmap Caucasian CEU SNP genotypes (www.hapmap.org). A total of five tagging SNPs (rs3758538, rs10882278, rs7094671, rs7079946 and rs12766992) were chosen with minor allele frequencies ≥0.05 and $r^2 ≤ 0.8$.

#### Genotyping

The five tagging SNPs were genotyped using short amplicon-based high-resolution DNA melting assays. Each primer pair was designed using Primer 3 software (http://frodo.wi.mit.edu/primer3/) (Supplementary table 1). The polymerase chain reaction conditions were: initial denaturation and was performed at 95°C for 2 min, followed by 40–60 cycles of...
denaturation at 98°C for 20 s, annealing at respective temperature for 15 s, extension at 68°C for 30 s and final extension at 68°C for 5 min. To maximize the incorporation of dsDNA-binding dye, LC-green Plus (Idaho Technology Inc., Salt Lake City, UT), all samples were subjected to denaturation at 95°C for 30 s and annealing at 25°C for 30 s. Fluorescence monitoring during thermal denaturation from 45 to 98°C was done immediately using LightScanner (Idaho Technology Inc.).

**Statistical analysis**

Basic and descriptive analyses for comparing cases and control characteristics were conducted using two-sample t-tests for continuous characteristics [e.g. high-density lipoprotein (HDL), body mass index (BMI)] and Fisher’s exact test for binary characteristics (e.g. gender). Hardy–Weinberg equilibrium (HWE) tests were performed using Fisher’s exact test as implemented in the ‘genetics’ package of R version 2.9.1 (www.r-project.org). Linkage disequilibrium (LD) maps for SNPs that conform to HWE were produced using Haploview version 4.2 (http://www.broadinstitute.org/). SNP association analyses for eGFR trait were performed using analysis of variance. Furthermore, SNP association analyses for advanced diabetic nephropathy were performed using logistic regression with log-additive genetic effects assumed. The haplotype analyses were performed using the haplo.glm function in R package haplo.stats. The posterior probabilities of pairs of haplotypes for each subject were estimated using the maximum likelihood method and the estimated probabilities were subsequently used as weight in the regression model with eGFR as the dependent variable and the haplotypes and environmental variables (e.g. age at examination) by using the normal QQ plot to examine the normality of the eGFR data, four outlier individuals were identified and removed to ensure that the normality assumption was met. Interactions between the haplotypes and the environmental variables were investigated and significant interactions were retained in the regression model. Effects of statistically significant confounders were adjusted for by including the confounders in the regression model. For all statistical analyses, Type I error was set to 5%. Bonferroni adjustment was made when multiple SNPs/haplotypes were simultaneously tested.

**Power calculation**

With a sample size of 180 normoalbuminuric controls, we would have at least 90% power to detect a haplotype × environment interaction effect size of ≥1.4. This assumed that five haplotypes were tested simultaneously, that Bonferroni adjustment was used and that overall Type 1 error = 0.05; furthermore, the major haplotype was assumed to have a population frequency of ~70% and the minor haplotype to have a population frequency of at least 5%. The effect size in this power calculation was defined as differences in gradient between the two haplotypes relative to their pooled standard deviation. This is the standard definition according to Cohen [20].

**Results**

**Patient characteristics**

A total of 469 patients were analysed in this study. They included 174 normoalbuminuric controls among whom associations between RBP4 haplotypes and eGFR were investigated. An additional group of 295 cases with proteinuria (PROT, n = 138) and CRF/ESRD (n = 157) were used for comparison with the controls for testing associations between RBP4 haplotypes and advanced diabetic nephropathy. Both controls and cases were similar in terms of gender composition, age at diabetes mellitus diagnosis, BMI, HDL and glycaemic control (HbA1c, values (Table 1). Cases were slightly older, had higher triglyceride levels and had a longer known diabetes mellitus duration (all P < 0.0001) than controls. They also had higher systolic blood pressure (SBP) (P < 0.0001) but slightly lower diastolic blood pressure compared to controls (P < 0.001) (Table 1). Cases were more likely to have been on anti-hypertensive medication compared to controls (P < 0.0001). eGFR was lower in cases than in normoalbuminuric controls (P < 0.0001).

**Table 1. Clinical characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Cases</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>174</td>
<td>295</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>99/75</td>
<td>179/116</td>
<td>0.438</td>
</tr>
<tr>
<td>Age at DM diagnosis</td>
<td>43.5 (8.5)</td>
<td>43.8 (7.8)</td>
<td>0.763</td>
</tr>
<tr>
<td>At enrolment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.4 (7.7)</td>
<td>61.1 (7.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.9 (15.6)</td>
<td>31.8 (6.9)</td>
<td>0.147</td>
</tr>
<tr>
<td>Known duration of DM (years)</td>
<td>14.3 (6.5)</td>
<td>17.4 (7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin A1c (%)</td>
<td>8.2 (1.4)</td>
<td>8.2 (1.6)</td>
<td>0.882</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>129.1 (14.6)</td>
<td>139.5 (20.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>89.1 (23.4)</td>
<td>80.9 (18.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-hypertensive medication (yes/no)</td>
<td>73/65</td>
<td>31/215</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>78.6 (17.4)</td>
<td>44.2 (30.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>127.9 (88.9)</td>
<td>242.5 (151.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>50.6 (17.7)</td>
<td>46.1 (13.7)</td>
<td>0.057</td>
</tr>
<tr>
<td>Cases with CRF/ESRD (n)</td>
<td>NA</td>
<td>157</td>
<td></td>
</tr>
</tbody>
</table>

*DM, diabetes mellitus.*

**Hardy–Weinberg equilibrium and linkage disequilibrium**

The genotype distribution of rs7079946 deviated significantly from that expected under HWE (Supplementary table 2). Consequently, this SNP was discarded from further analyses. The remaining four SNPs (rs3758538, rs10882278, rs7094671 and rs12766992) had high D’ values (>0.8) with their immediate neighbouring SNP and thus formed a haplotype block as proposed by Gabriel et al. [21] (Supplementary table 3).

**Associations with advanced diabetic nephropathy**

There were no significant associations between RBP4 SNPs and haplotypes with advanced stages of diabetic nephropathy. This remained true whether or not cases with proteinuria and CRF/ESRD were considered together or separately (Supplementary tables 4 and 5).

**Associations with eGFR in normoalbuminuric controls**

Whereas direct haplotype and single SNP analyses failed to reveal evidence for associations with eGFR in the normoalbuminuric controls (Supplementary tables 6 and 7), statistical analyses that incorporated potential haplotype interactions with individual patient clinical characteristics revealed several salient associations. These associations persisted even after adjustment for other clinical covariates as potential confounders. For all haplotypes, there were significant negative slopes of eGFR over age (Supplementary figure 2). Compared with the common A/G/G/C haplotype, carriers of the C/A/A/C haplotype had higher eGFR values among younger patients but had lower eGFRs among the older patients (Supplementary figure 2). This difference in the slopes of eGFR over age at examination between the two haplotypes was highly significant (effect size = 2.2, P = 3.3 × 10⁻³) and was consistent with a haplotype–age interaction (Table 2).

In addition to age at examination, we observed potential haplotype–environment interactions with SBP and HbA1c.
While the eGFR values were fairly consistent over the range of SBP values for the common A/G/G/C haplotype, carriers of the C/A/A/C haplotype had eGFR values that increased with SBP (effect size = 3.6, \( P = 1.5 \times 10^{-5} \)) (Table 3, Supplementary figure 3). There was also a highly significant interaction between the C/A/A/C haplotype and HbA1c affecting eGFR compared to the A/G/G/C haplotype (effect size = 2.1, \( P = 2.1 \times 10^{-3} \)) (Table 4). Specifically, while the eGFR values associated with the common A/G/G/C haplotype were mostly unchanged over the range of HbA1c values, carriers of the C/A/A/C haplotype had markedly lower eGFR values with increasing HbA1c (Supplementary figure 4). Aside from age, SBP and HbA1c, there was no evidence for interactions between the RBP4 haplotypes and BMI, triglyceride, HDL levels, diastolic blood pressure or diabetes duration and eGFR (data not shown). We also investigated whether these three haplotype–environment interactions were independent of each other. In a statistical model where the three haplotype–environment interactions were simultaneously estimated, only the interaction between SBP and the C/A/A/C haplotype remained statistically significant (\( P = 2.8 \times 10^{-2} \)).

**Table 2.** Association between RBP4 haplotypes and slopes of GFR over age (years) at examination

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequency (%)</th>
<th>Slope/unit age (years)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/G/G/C</td>
<td>67.4</td>
<td>0.58</td>
<td>-1.00 to -0.17</td>
<td>(Ref category)</td>
</tr>
<tr>
<td>A/G/A/T</td>
<td>14.5</td>
<td>-1.01</td>
<td>-1.82 to -0.20</td>
<td>( 3.8 \times 10^{-1} )</td>
</tr>
<tr>
<td>C/G/G/C</td>
<td>7.3</td>
<td>-0.20</td>
<td>-0.92 to 0.52</td>
<td>( 9.2 \times 10^{-2} )</td>
</tr>
<tr>
<td>C/A/A/C</td>
<td>5.8</td>
<td>-1.13</td>
<td>-1.66 to -0.60</td>
<td>( 3.3 \times 10^{-7} )</td>
</tr>
<tr>
<td>Rare</td>
<td>N/A</td>
<td>-0.64</td>
<td>-1.07 to -0.20</td>
<td>( 5.2 \times 10^{-1} )</td>
</tr>
</tbody>
</table>

*Adjusted for sex and anti-hypertensive medication. Subsequent adjustment for BMI, HbA1c, SBP, cholesterol, HDL, triglyceride and diabetes duration was not significant.

**Table 3.** Association between RBP4 haplotypes and slopes of eGFR over SBP (mmHg)

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequency (%)</th>
<th>Slope/unit SBP (mmHg)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/G/G/C</td>
<td>67.0</td>
<td>0.06</td>
<td>-0.10 to 0.23</td>
<td>(Ref category)</td>
</tr>
<tr>
<td>A/G/A/T</td>
<td>14.6</td>
<td>-0.08</td>
<td>-0.48 to 0.31</td>
<td>( 4.5 \times 10^{-1} )</td>
</tr>
<tr>
<td>C/G/G/C</td>
<td>7.2</td>
<td>0.17</td>
<td>-0.24 to 0.59</td>
<td>( 5.5 \times 10^{-1} )</td>
</tr>
<tr>
<td>C/A/A/C</td>
<td>6.0</td>
<td>0.49</td>
<td>0.10 to 0.87</td>
<td>( 1.5 \times 10^{-2} )</td>
</tr>
<tr>
<td>Rare</td>
<td>N/A</td>
<td>0.10</td>
<td>-0.30 to 0.51</td>
<td>( 8.4 \times 10^{-1} )</td>
</tr>
</tbody>
</table>

*Adjusted for age at examination, sex and use of anti-hypertensive medication. Subsequent adjustment for BMI, SBP, cholesterol, HDL, triglyceride and diabetes duration was not significant.

We observed several potential haplotype–environment interactions with eGFR, especially between the C/A/A/C haplotype and age, HbA1c and SBP. Relative to the common haplotype, young carriers of the C/A/A/C haplotype had higher eGFR values but had a more negative slope with increasing age. In this context, it is interesting that glomerular hyperfiltration in early diabetes has been proposed to predict the more advanced stages of diabetic nephropathy, including microalbuminuria, proteinuria and a steeper loss of eGFR with time; however, these findings have not always been consistent [22–25]. A caveat to our findings was that the high eGFR among the young carriers did not exceed 120 mL/min and thus did not meet the threshold normally associated with hyperfiltration. The other interactions involving HbA1c and SBP are intriguing from a clinical standpoint since both are potentially modifiable and successful interventions may help to ameliorate any deleterious effects linked to the RBP4 haplotypes. This may be especially important for SBP since statistical modelling that simultaneously estimated the three haplotype–environment interactions revealed that only the interaction between SBP and C/A/A/C haplotype remained statistically significant.

In contrast to the findings among normoalbuminuric patients, we did not detect any associations between RBP4 SNPs and haplotypes having advanced stages of diabetic nephropathy, such as those having proteinuria and CRF/ESRD. While this finding suggests that genetic variations in RBP4 were unlikely to confer a major risk for advanced diabetic nephropathy, it remains possible that minor effects were present given the modest number of cases in our study.

There were a few limitations in the present study. Firstly, because of the cross-sectional design of our study, our conclusions were limited to differences in slopes between haplotypes rather than to actual changes in eGFR as seen in cohort studies. Secondly, our study used eGFR as a surrogate measure of renal function. Although eGFR is widely used in the literature, it may be impacted by poor nutritional status of certain patients and particularly those with significant renal impairment. Although it is preferable to use actual GFR measurements, this would have required invasive techniques that are logistically challenging to achieve in our patient population. Thirdly, our main findings were based on analyses from 174 normoalbuminuric controls. Despite this limited number of controls, formal power calculations demonstrated that we had adequate power (>90%) to detect the observed interactions, even while performing multiple

**Table 4.** Association between RBP4 haplotypes and slopes of eGFR over HbA1c (%)

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequency (%)</th>
<th>Slope/unit HbA1c (%)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/G/G/C</td>
<td>65.7</td>
<td>0.78</td>
<td>-2.07 to 3.64</td>
<td>(Ref category)</td>
</tr>
<tr>
<td>A/G/A/T</td>
<td>15.5</td>
<td>1.68</td>
<td>-1.43 to 4.78</td>
<td>( 6.6 \times 10^{-1} )</td>
</tr>
<tr>
<td>C/G/G/C</td>
<td>7.3</td>
<td>-0.29</td>
<td>-5.65 to 5.07</td>
<td>( 7.2 \times 10^{-1} )</td>
</tr>
<tr>
<td>C/A/A/C</td>
<td>5.9</td>
<td>-3.14</td>
<td>-7.97 to 1.70</td>
<td>( 2.9 \times 10^{-3} )</td>
</tr>
<tr>
<td>Rare</td>
<td>N/A</td>
<td>-0.53</td>
<td>-7.18 to 6.13</td>
<td>( 7.0 \times 10^{-1} )</td>
</tr>
</tbody>
</table>

*Adjusted for age at examination, sex and usage of anti-hypertensive medication. Subsequent adjustment for BMI, SBP, cholesterol, HDL, triglyceride and diabetes duration was not significant.

**Discussion**

It has been increasingly recognized that loss of renal function can occur in a subset of diabetic patients even in the absence of albuminuria [1–3]. Because little is known about the risk factors responsible for this loss of renal function, we investigated a potential involvement of RBP4 in conferring genetic susceptibility to loss of eGFR in normoalbuminuric patients.
hypotheses testing (see Power Calculations under Materials and methods). Finally, the impact of RBP4 haplotypes on the circulating levels of this adipokine was not assessed. This represented a potential limitation of our study since others have proposed that plasma RBP4 may be correlated with renal dysfunction [15]. Nevertheless, the lack of this information does not affect the validity of the genetic associations between the RBP4 haplotypes and eGFR.

A strength of our study included access to a carefully phenotyped case-control collection of patients attending the Joslin Clinic. In addition, our positive findings were highly significant as indicated by small P-values. While this gave us reassurance that the present findings were most likely true positives, we are cognizant that follow-up studies from other independent patient populations will be necessary to confirm a genetic effect of RBP4 in modulating renal function.

In conclusion, while there were no direct associations between RBP4 genetic variations and eGFR or with advanced diabetic nephropathy, our study documented a specific gene–environment interaction involving eGFR in normoalbuminuric diabetic patients. From a clinical standpoint, these patients have traditionally been considered to have low risk for chronic kidney disease. Our observation that RBP4 resided directly within the physical chromosomal region on 10q23, which had previously been linked to variations in eGFR, added to enthusiasm for the present discovery. However, a potential involvement of other genes in this region remains to be investigated.

Supplementary data

Supplementary Figures 1–4 and Tables 1–7 are available online at http://ndt.oxfordjournals.org.

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Conflicts of interest statement. None declared.

References


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