Genome-Wide Association Scan for Diabetic Nephropathy Susceptibility Genes in Type 1 Diabetes

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Genome-Wide Association Scan for Diabetic Nephropathy Susceptibility Genes in Type 1 Diabetes

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OBJECTIVE—Despite extensive evidence for genetic susceptibility to diabetic nephropathy, the identification of susceptibility genes and their variants has had limited success. To search for genes that contribute to diabetic nephropathy, a genome-wide association scan was implemented on the Genetics of Kidneys in Diabetes collection.

RESEARCH DESIGN AND METHODS—We genotyped ~360,000 single nucleotide polymorphisms (SNPs) in 820 case subjects (284 with proteinuria and 536 with end-stage renal disease) and 865 control subjects with type 1 diabetes. Confirmation of implicated SNPs was sought in 1,304 participants of the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study, a long-term, prospective investigation of the development of diabetes-associated complications.

RESULTS—A total of 13 SNPs located in four genomic loci were associated with diabetic nephropathy with $P < 1 \times 10^{-5}$. The strongest association was at the FRMD3 locus (4.1 protein ezrin, radixin, moesin [FERM] domain containing 3) locus (odds ratio [OR] = 1.45, $P = 5.0 \times 10^{-5}$). A strong association was also identified at the CARS (cysteinyl-tRNA synthetase) locus (OR = 1.36, $P = 3.1 \times 10^{-5}$). Associations between both loci and time to onset of diabetic nephropathy were supported in the DCCT/EDIC study (hazard ratio [HR] = 1.33, $P = 0.02$, and HR = 1.32, $P = 0.01$, respectively). We demonstrated expression of both FRMD3 and CARS in human kidney.

CONCLUSIONS—We identified genetic associations for susceptibility to diabetic nephropathy at two novel candidate loci near the FRMD3 and CARS genes. Their identification implicates previously unsuspected pathways in the pathogenesis of this important late complication of type 1 diabetes. *Diabetes 58: 1403–1410, 2009

Diabetic nephropathy is the leading contributor to end-stage renal disease (ESRD) in the U.S. (1). Clinically, diabetic nephropathy is manifest as a progressive disease process that advances through characteristic stages. It begins with microalbuminuria (leakage of small amounts of albumin into the urine) and progresses to overt proteinuria. In a large proportion of these patients, renal function declines and continues to deteriorate until ESRD is reached, and replacement therapy is indicated (2–4). Overall, ESRD develops in ~20% of all patients with type 1 diabetes (5,6).

Despite evidence that genetic susceptibility plays a role in the development of diabetic nephropathy in type 1 diabetes (7–9), success in identifying the responsible genetic variants has been limited (10,11). This has been attributable, in part, to the small size of the DNA collections available to individual research groups and the narrow focus of the searches on candidate genes. Another challenge that has received little attention in previous studies is the possibility that successive stages of diabetic nephropathy are influenced by different genetic factors (12,13).

To conduct a statistically robust study that provides genome-wide coverage for detection of common variants that may have relatively small, but pathogenically significant, effect on risk of diabetic nephropathy in type 1 diabetes, the Genetics of Kidneys in Diabetes (GoKinD) collection was established (14). A genome-wide scan of this collection was supported by the Genetic Association Information Network (GAIN) initiative (15). This report presents 1) results of this genome-wide association scan in the GoKinD collection, 2) replication of the significant associations in this scan with time to onset of diabetes-associated complications (severe nephropathy) in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study, and 3) characterization of expression of the

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identified candidate diabetic nephropathy genes in normal human cell lines.

**RESEARCH DESIGN AND METHODS**

Subjects for the GoKinD collection were recruited through two centers with different methods of ascertainment and recruitment (14). The George Washington University (GWU) Biostatistics Center coordinated the recruitment of volunteers (through mass media advertisement) living throughout the U.S. (excluding New England) and Canada to 1 of 27 clinical centers located across the U.S. and Canada. The Section of Genetics and Epidemiology at the Joslin Diabetes Center (JDC) recruited and examined patients of the Joslin Clinic from New England who were already enrolled in the Joslin Kidney Study on the Genetics of Diabetic Nephropathy, a clinic-based cohort study in which case subjects with diabetic nephrpathy and a random sampling of eligible control subjects were identified and recruited (16).

A detailed description of the GoKinD collection has been published (14). Briefly, subjects enrolled in GoKinD had type 1 diabetes diagnosed before age 31, began insulin treatment within 1 year of their diagnosis, and were between 18 and 59 years of age at the time of enrollment. Participation in the DCCT/EDIC study was an exclusion criterion so that the two study populations would be independent. Case subjects with diabetic nephropathy had either persistent proteinuria, defined by a urinary albumin-to-creatinine ratio ≥300 μg/mg in two of the last three measurements taken at least 1 month apart, or ESRD (diagnosis or renal transplant). Control subjects had type 1 diabetes for at least 15 years and normoalbuminuria, defined by an albumin-to-creatinine ratio <20 μg/mg in two of the last three measurements taken at least 1 month apart (if a third measurement was required, a value <10 μg/mg was necessary for inclusion), without ever having been treated with ACE inhibitors or angiotensin receptor blockers, and they were not being treated with antihypertensive medication at the time of recruitment into the study. For additional information regarding the definition of case and control subjects used in this analysis, refer to the report by Mueller et al. (14). In total, 1,879 subjects (935 case and 944 control subjects) were recruited into GoKinD. The GWU panel included 437 case subjects with diabetic nephropathy (58 with proteinuria and 379 with ESRD) and 446 control subjects; the JDC panel included 498 case subjects with diabetic nephropathy (268 with proteinuria and 230 with ESRD) and 498 control subjects. Further details are also provided in the supplementary information, which is available in an online appendix at http://diabetes.diabetesjournals.org/cgi/content/full/db08-1514/DC1.

Confirmation of our findings in the GoKinD collection was sought in genome-wide association data from the DCCT/EDIC study, a long-term, prospective investigation of the development of diabetes-associated complications (17,18). Of the original DCCT cohort recruited between 1983 and 1989, 1,575 subjects were retained in the EDIC follow-up study. Participants in EDIC underwent baseline examinations between 1994 and 1995 and have since participated in annual follow-up examinations to assess the development or progression of complications. As of EDIC year 12 (2005), this cohort had 16–22 years of follow-up, and 132 cases of severe nephropathy (proteinuria or ESRD) had been documented in 1,304 Caucasian DCCT/EDIC participants. The closest genetic association with quantitative real-time PCR. Sources of these cells, cell culture conditions, and protocols used in these experiments are available in the supplementary information.

**RESULTS**

Genome-wide association scans for genes associated with diabetic nephropathy in type 1 diabetes. The application of metrics for SNP and sample quality resulted in the analysis of 359,193 autosomal SNPs and 1,705 GoKinD samples of European ancestry (885 control subjects and 820 case subjects) (see Research Design and Methods and the supplementary information). Clinical characteristics of the JDC and GWU panels are summarized in Table 1. Because different ascertainment protocols were used by the JDC and GWU, the resulting data were found to exhibit significant stratification. As a result, the primary association analyses were conducted using a stratified test of association.

Although no SNP achieved genome-wide significance \( (P < 5 \times 10^{-8}) \), the primary association analysis identified 11 SNPs representing four distinct chromosomal regions with \( P < 1 \times 10^{-4} \) (Fig. 1 and Table...
Finally, the region bounded by rs1411766/rs1742858 (OR = 1.41, \( P = 5.0 \times 10^{-7} \)) was more strongly associated with diabetic nephropathy than our lead genotyped SNPs. Imputed SNP rs1888747 were more strongly associated with diabetic nephropathy than the original SNP in that region (rs39059) (Fig. 2A). Both imputed SNPs were genotyped in the GoKinD samples, and the associations with the imputed data were confirmed (rs39075, \( P = 6.5 \times 10^{-7} \); and rs1888747, \( P = 6.3 \times 10^{-7} \) (Table 2). Analyses of the imputed SNPs in our lead loci identified 11 additional SNPs that were highly correlated with the original associations (\( P < 1 \times 10^{-5} \)). Of these, two were more strongly associated with diabetic nephropathy than our lead genotyped SNPs. Imputed SNP rs1888747 (chromosome 9q), which is in partial linkage disequilibrium (\( r^2 = 0.81 \)) with rs10868025, was more strongly associated with diabetic nephropathy than the original SNP (\( P = 4.7 \times 10^{-7} \)) (Fig. 2B). Similarly, two imputed SNPs in the 7p region (rs39075 and rs39076) were also more strongly associated than the original SNP in that region (rs39059) (Fig. 2A). If the etiology of diabetic nephropathy involves the interaction of a locus with the cumulative effect of hyperglycemia, the association of the locus with diabetic nephropathy can vary according to diabetes duration at diabetic nephropathy onset, such that it is strongest in early-appearing case subjects and diminishes in later ones, even reversing in direction in very late-appearing case subjects (23). We examined the SNPs in Table 2 according to diabetes duration by stratifying case and control subjects across tertiles of diabetes duration (at the onset of ESRD or at enrollment into GoKinD for proteinuria patients and control subjects). The strength of the associations was consistent across these strata (data not shown).
**TABLE 2**

Summary of SNPs associated with diabetic nephropathy in the GoKinD collection

<table>
<thead>
<tr>
<th>Locus</th>
<th>Risk allele frequencies and ( P ) values for control and case subjects by panel</th>
<th>GWU GoKinD</th>
<th>JDC GoKinD</th>
<th>( P ) values and ORs for combined analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP</td>
<td>Chromosome</td>
<td>Position (Mb)</td>
<td>Nearest gene(s)</td>
<td>Risk allele (non-risk allele)</td>
</tr>
<tr>
<td>n</td>
<td>7p</td>
<td>29.2</td>
<td>\textit{CPVL/CHN2}</td>
<td>A(G)</td>
</tr>
<tr>
<td>rs39059</td>
<td>7p</td>
<td>29.2</td>
<td>\textit{CPVL/CHN2}</td>
<td>G(A)</td>
</tr>
<tr>
<td>rs39075†</td>
<td>9q</td>
<td>85.3</td>
<td>\textit{FRMD3}</td>
<td>G(A)</td>
</tr>
<tr>
<td>rs1888747†</td>
<td>9q</td>
<td>85.4</td>
<td>\textit{FRMD3}</td>
<td>A(G)</td>
</tr>
<tr>
<td>rs10868025</td>
<td>11p</td>
<td>3.0</td>
<td>\textit{CARS}</td>
<td>C(T)</td>
</tr>
<tr>
<td>rs739401</td>
<td>11p</td>
<td>3.0</td>
<td>\textit{CARS}</td>
<td>A(G)</td>
</tr>
<tr>
<td>rs451041</td>
<td>13q</td>
<td>109.0</td>
<td>No gene</td>
<td>G(A)</td>
</tr>
<tr>
<td>rs1041466</td>
<td>13q</td>
<td>109.1</td>
<td>No gene</td>
<td>A(G)/G(A)</td>
</tr>
<tr>
<td>rs1411766‡rs17412858§</td>
<td>13q</td>
<td>109.1</td>
<td>No gene</td>
<td>T(C)/G(A)</td>
</tr>
<tr>
<td>rs6492208‡rs2391777§</td>
<td>13q</td>
<td>109.1</td>
<td>No gene</td>
<td>A(G)</td>
</tr>
<tr>
<td>rs7989848</td>
<td>13q</td>
<td>109.0</td>
<td>No gene</td>
<td>A(C)</td>
</tr>
</tbody>
</table>

The most strongly associated SNPs from the combined analysis of the GWU and JDC GoKinD panels are presented along with the risk allele frequencies and \( P \) values (calculated using the Cochran-Mantel-Haenszel method, adjusting for sex, between case and control subjects within each collection) for each separate collection. Combined \( P \) values and ORs were calculated using the Cochran-Mantel-Haenszel method. Chromosomal locations, SNP positions, and gene annotations are in reference to NCBI Build 36.1. A summary of the genotype frequencies for the most strongly associated SNPs in the GoKinD collection are presented in supplementary Table 3. †rs39075 and rs1888747 were identified through imputation and genotyped using Taqman assays in the GoKinD collection; ‡rs1411766 and rs17412858 were both genotyped on the Affymetrix array and are in complete linkage disequilibrium \((r^2 = 1.0)\); §rs6492208 and rs2391777 were both genotyped on the Affymetrix array and are in complete linkage disequilibrium \((r^2 = 1.0)\).
Additionally, if a locus influences mortality risk, the high mortality experienced by patients with ESRD would alter its association with diabetic nephropathy according to the duration of survival with ESRD and may mask the effect of a diabetic nephropathy risk allele or produce a false association. For this reason, we also analyzed the lead SNPs in Table 2 according to duration of ESRD. For each of these SNPs, the ORs were consistent across tertiles of ESRD duration (supplementary Table 4), a pattern consistent with the absence of survival bias. However, the current study is underpowered to formally exclude the presence of such effects.

Confirmation of associated type 1 diabetic nephropathy SNPs in the DCCT/EDIC study. Data from a genome-wide association scan of the DCCT/EDIC study were used to assess whether genome regions identified in the GoKinD collection were associated with advanced diabetic nephropathy in an independent collection. Among the 11 SNPs identified in GoKinD, eight were included on the Illumina array used in the DCCT/EDIC study (Table 3). The three SNPs not included on this platform, rs39059, rs739401, and rs451041, were in strong linkage disequilibrium (r² ≥ 0.87) with rs90755, rs451041, and rs7989848, respectively. Analysis of time to onset of severe nephropathy confirmed the significant associations with diabetic nephropathy in GoKinD for rs1888746 (FRMD3, P = 0.02), rs13289150 (FRMD3, P = 0.05), and rs451041 (CARS, P = 0.01).

Analysis of candidate diabetic nephropathy gene expression. Previous studies, as well as publicly available gene expression data (www.ncbi.nlm.nih.gov/geo), have shown that genes closest to the lead SNPs identified in GoKinD are expressed in a variety of human tissues, including kidney (24–26). To further test whether these candidate genes may be involved in the development of diabetic nephropathy, we examined their expression in cell lines relevant to this disease. The expression of CHN2, CPVL, FRMD3, and CARS was examined in four primary...
human cell lines: iliac artery endothelial cells, adult dermal fibroblasts, mesangial cells, and renal proximal tubule cells. Our data show that CARS expression was high in all four of the cell lines that we examined (Table 4). FRMD3 expression was also detected in each cell type, with its highest expression being observed in renal proximal tubule cells. Of the two candidate diabetic nephropathy genes located in chromosome 7p region, neither was detected in mesangial cells, whereas CPVL expression was greatest in proximal tubule cells.

**DISCUSSION**

In this report, we describe the results of a genome-wide association scan in the GoKinD collection to identify loci associated with risk of diabetic nephropathy in type 1 diabetes. The most significant associations were identified with variants located within four distinct chromosomal regions. Although the biology underlying these associations remains to be elucidated, they implicate CHN2/CPVL, FRMD3, CARS, and an intergenic region on chromosome 13q as novel genes/genetic regions involved in the pathogenesis of diabetic nephropathy. None of these loci overlap with previously reported associations between candidate genes and the development of any stage of diabetic nephropathy (10,11). Importantly, replication in a Cox proportional hazard analysis of the associations at the FRMD3 and CARS loci with time to the onset of severe nephropathy in the DCCT/EDIC study bolsters the significance of these two findings; that two studies having such different designs (one a case-control study and the other a prospective cohort study) yielded similar ORs strengthens confidence in this conclusion.

FRMD3 encodes the 4.1O protein, a structural protein with unknown function and a member of the 4.1 family of proteins (26). Members of the 4.1 protein family have well-characterized roles as cytoskeletal proteins, maintaining both cellular shape and form, in a variety of cell types, including mouse nephron (27,28). Although membership of the 4.10 protein in this family has recently been questioned, it does contain a FERM domain, which is a module that is integral in maintaining cell integrity through its interactions with transmembrane proteins and actin filaments (29,30). FRMD3 is detectable in adult ovaries as well as in fetal skeletal muscle, brain, and thymus (26). Our data extend the expression profile of FRMD3 to specifically include mesangial and proximal tubular cells. Interestingly, among 18 genes that contain FERM domains, as well as in fetal skeletal muscle, brain, and thymus (26). Our data extend the expression profile of FRMD3 to specifically include mesangial and proximal tubular cells. Interestingly, among 18 genes that contain FERM domains, we identified nominally significant associations with diabetic nephropathy for SNPs located in eight of these genes (supplementary Table 5), including FARLP (FERM, Rho-GEF and pleckstrin domain protein 2; \( P = 3.0 \times 10^{-4} \)) and EPB41L2 (erythrocyte membrane protein band 4.1-like 2; \( P = 2.3 \times 10^{-4} \)). Although these findings require further study, including replication in additional collections, it is interesting to speculate that these data may point to the involvement of new, previously unsuspected pathways in the pathogenesis of diabetic nephropathy.

**TABLE 4**

Relative gene expression of novel candidate diabetic nephropathy susceptibility genes in primary human cell lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>CPVL ( C_i ) values</th>
<th>CHN2 ( C_i ) values</th>
<th>FRMD3 ( C_i ) values</th>
<th>CARS ( C_i ) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial cells, iliac</td>
<td>17.3 ± 0.7</td>
<td>12.5 ± 0.1</td>
<td>12.5 ± 0.3</td>
<td>8.4 ± 0.4</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>15.7 ± 0.1</td>
<td>n.e.</td>
<td>11.9 ± 0.7</td>
<td>6.5 ± 0.4</td>
</tr>
<tr>
<td>Mesangial cells</td>
<td>n.e.</td>
<td>n.e.</td>
<td>12.9 ± 0.5</td>
<td>7.2 ± 0.1</td>
</tr>
<tr>
<td>Proximal tubules</td>
<td>8.6 ± 0.1</td>
<td>13.1 ± 0.1</td>
<td>10.2 ± 0.2</td>
<td>8.0 ± 0.1</td>
</tr>
</tbody>
</table>

The relative gene expression of CPVL, CHN2, FRMD3, and CARS was determined in four primary human cell lines using real-time PCR. Relative gene expression of each gene was calculated in reference to a normalization control (\( \beta\)-actin) and is presented as the mean \( \Delta C_i \) (\( C_i \) value from each gene minus \( C_i \) value from the normalization control) and SD from three separate experiments. Mean \( \Delta C_i = 0 \) equals high relative gene expression (i.e., expression similar to \( \beta\)-actin), n.e., not expressed (mean \( \Delta C_i > 40.0 \)).
the role of microtubule cells. Further work is needed to characterize the role of all the associated SNPs, only those in the vicinity of either \( \text{CARS} \) or \( \text{FRMD3} \), are located 384 kb centromeric and 120 kb telomeric of this region, respectively. Although there is little linkage disequilibrium between the variants within this block and those in the vicinity of either \( \text{MYO16} \) or \( \text{IRS2} \), the multiple signals identified in this region so far to detect all disease loci, regardless of their effect on mortality, would be a large cohort of incident ESRD case subjects. Such a data set is currently unavailable.

There are other limitations to this study as well. The GoKinD collection is heavily weighted with case subjects with ESRD; thus, the small number of case subjects with proteinuria limited our ability to detect variants primarily associated with the risk of proteinuria. Second, because of the limited power of the DCCT/EDIC study and the need to contain inflation of the \( \alpha \)-error in seeking replication for multiple SNPs in this dataset, our replication efforts renounced from considering SNPs less significant than \( P = 1 \times 10^{-3} \). It is certainly possible that additional variants among those not meeting this threshold may truly be associated with diabetic nephropathy; however, given these limitations, these variants remain to be identified. Similarly, despite replication in the DCCT/EDIC cohort, we acknowledge that positive associations at both the \( \text{FRMD3} \) and \( \text{CARS} \) loci require additional study to be certain of these findings. Third, although the locations of the variants confirmed in this study implicate both \( \text{FRMD3} \) and \( \text{CARS} \) as novel genes involved in the pathogenesis of diabetic nephropathy, the underlying mechanisms of disease of these associations need to be elucidated. And, finally, although confirmation in DCCT/EDIC has been achieved for variations near \( \text{FRMD3} \) and \( \text{CARS} \), additional cohorts, particularly non-Caucasian, would be useful to further characterize the pathogenic role of these, and other, candidate genes identified in the GoKinD collection.

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No potential conflicts of interest relevant to this article were reported.
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