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

Citation

Published Version
doi:10.2337/db08-1514

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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 885 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 (4.1 protein ezrin, radixin, moesin [FERM] domain containing 3) locus (odds ratio [OR] = 1.36, \( P = 5.0 \times 10^{-7} \)). 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...
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 nephropathy 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 \(\geq 300 \mu g/mg\) in two of the last three measurements taken at least 1 month apart, or ESRD (dialysis or renal transplant). Control subjects had type 1 diabetes for at least 15 years and no albuminuria, defined by an albumin-to-creatinine ratio <20 \(\mu g/mg\) in two of the last three measurements taken at least 1 month apart (if a third measurement was required, a value <10 \(\mu g/mg\) 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 survived and 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 GWU case subjects used in these experiments are 379 GWU case subjects (49 with proteinuria and 330 with ESRD), 413 GWU control subjects, 441 JDC case subjects (235 with proteinuria and 206 with ESRD), and 472 JDC control subjects. The measured genotypes for these individuals were augmented by imputation of ungenotyped SNPs using two major base pair regions flanking each of the lead SNPs in the GoKinD collection (where linkage disequilibrium, as measured by \(r^2\), is \(<0.20\) for all lead SNPs). A total of 8,245 imputed HapMap SNPs across these four loci were included in our association analysis. Further details of sample quality control and imputation procedures are available in the supplementary information and Supplementary Table 2.

**Statistical analysis.** Sample quality control and imputation procedures are available in the supplementary information. Further details of quality control procedures, software, statistical analysis and adjustments, and cluster plots are available in the supplementary information. Data from our analysis of the GoKinD collection are available for specific SNPs and/or genes upon request.

**Genotyping and analysis of the DCCT/EDIC data.** Genotypes of the DCCT/EDIC study participants were generated with the Illumina HumanM Beadchip. Briefly, quality control measures resulted in 840,354 SNPs suitable for statistical analysis. Population substructure was assessed to ensure that all included samples were of European ancestry. Multivariate Cox proportional hazard analyses were performed on data from 1,304 Caucasian subjects using time to onset of severe nephropathy, defined by an albumin excretion rate (AER) >300 mg/24 h or at least two consecutive examinations or dialysis/ renal transplant with prior persistent microalbuminuria (AERs >30 mg/24 h) as the outcome phenotype (\(n = 132\)). Among those with severe nephropathy, 116 subjects developed only proteinuria (AER >300 mg/24 h), whereas 16 progressed to ESRD. The DCCT cohort (primary prevention versus secondary intervention), treatment (intensive versus conventional), and interaction between cohort and treatment were used as covariates in the analysis of the effect of an independent additive SNP genetic factor. This model was examined for all associated loci in GoKinD and subsequently tested for both statistical significance and the same direction of effect for associated alleles (20–22).

**Gene expression.** The expression of candidate genes was examined in four primary human cell lines derived from cells that have been implicated in the pathogenesis of kidney complications (endothelial cells from the iliac artery, adult dermal fibroblasts, mesangial cells, and epithelial cells from proximal tubule) by 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 SNPs 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 (0.05/359,193 = \(1.4 \times 10^{-5}\)), the primary association analysis identified 11 SNPs representing four distinct chromosomal regions with \(P < 1 \times 10^{-5}\) (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 the original associations. Imputed SNP rs1888747 was more strongly associated with diabetic nephropathy than our lead genotyped SNPs. Imputed SNP rs1888747 was more strongly associated with diabetic nephropathy than the original associations.

Three additional genomic regions located on chromosomes 7p, 11p, and 13q were also associated with diabetic nephropathy. The rs39059 SNP (OR 1.39, P 5.0 \times 10^{-6}) localizes to the first intron of CHN2 (\beta-chimerin) isoform 2 and upstream of an alternatively spliced CPVL (serine carboxypeptidase vitellogenic-like) transcript on chromosome 7p. The rs451041 SNP (OR 1.36, P 3.1 \times 10^{-6}) is located on chromosome 11p in an intronic region of the CARS (cysteinyl-tRNA synthetase) gene. And, finally, the region bounded by rs451041/rs1742858 (OR 1.41, P 1.8 \times 10^{-6}) is located in a 42 kb intergenic region on chromosome 13q.

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). 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).

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 into tertiles of diabetes duration (at the onset of ESRD or at enrollment into GoKinD for patients and control subjects). The strength of the associations was consistent across these strata (data not shown).

![FIG. 1. Summary of genome-wide association scan results in the GoKinD collection. The –log_{10} P values calculated using the Cochran-Mantel-Haenszel method (adjusting for sex and GoKinD subcollection [JDC/GWU]) across the entire genome are shown for the combined GoKinD collection. The horizontal dashed line corresponds to a –log_{10} P value = 5.0 (P = 1 \times 10^{-5}). SNPs shown in green (n = 11) exceed this threshold because of the resolution of this image, some of the SNPs located on chromosome 13 (n = 7) appear indistinguishable.](image-url)
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></td>
<td></td>
<td></td>
<td>Control subjects</td>
<td>Case subjects</td>
</tr>
<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>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>rs39059</td>
<td>7p</td>
<td>29.2</td>
<td>CPVL/CHN2</td>
<td>A(G)</td>
</tr>
<tr>
<td>rs39075†</td>
<td>7p</td>
<td>29.2</td>
<td>CPVL/CHN2</td>
<td>G(A)</td>
</tr>
<tr>
<td>rs1888747†</td>
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<td>85.3</td>
<td>FRMD3</td>
<td>G(C)</td>
</tr>
<tr>
<td>rs10868025</td>
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<td>85.4</td>
<td>FRMD3</td>
<td>A(G)</td>
</tr>
<tr>
<td>rs1041466</td>
<td>11p</td>
<td>3.0</td>
<td>CARS</td>
<td>C(T)</td>
</tr>
<tr>
<td>rs451041</td>
<td>11p</td>
<td>3.0</td>
<td>CARS</td>
<td>A(G)</td>
</tr>
<tr>
<td>rs1411766/rs17412858‡</td>
<td>13q</td>
<td>109.1</td>
<td>No gene</td>
<td>A(G)/G(A)</td>
</tr>
<tr>
<td>rs6492208/rs2391777§</td>
<td>13q</td>
<td>109.1</td>
<td>No gene</td>
<td>T(C)/G(A)</td>
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<tr>
<td>rs7989848</td>
<td>13q</td>
<td>109.1</td>
<td>No gene</td>
<td>A(G)</td>
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<tr>
<td>rs9521445</td>
<td>13q</td>
<td>109.1</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 (r² = 1.0); §rs6492208 and rs2391777 were both genotyped on the Affymetrix array and are in complete linkage disequilibrium (r² = 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 rs5021445, were in strong linkage disequilibrium ($r^2 = 0.87$, respectively) with rs39075, 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
null
dria (a process facilitated by specialized mitochondria-specific and bifunctional ARSs). In the initial steps of protein translation, the function of these enzymes is to attach amino acids to their cognate tRNA molecules. To date, both autosomal dominant and recessive mutations in ARS-encoding genes have been identified only in neurodegenerative disease, including missense changes in glycylyl-tRNA synthetase (GARS) and both missense mutations and in-frame deletions in tyrosyl-tRNA synthetase (YARS) in Charcot-Marie-Tooth disease (32).

CARS has been implicated in cystinosis, an autosomal recessive renal tubule disorder caused by the accumulation of free cystine in cellular lysosomes (33,34). A recent study identified defects in lysosomal cystine transport as the primary cause of the disease (35). However, ESRD is prominent in this disorder, and such an outcome may be due to vulnerability of specific renal cells to damage by excess cystine. Interesting, in this light, is the observation that all of the associated SNPs, only those in the CARS locus were associated primarily with ESRD (supplementary Table 4). CARS is expressed in mesangial and proximal tubule cells. Further work is needed to characterize the role of CARS in the pathway that is involved in the development of ESRD in diabetes. Similar to the set of genes containing FERM domains, analysis of 21 ARS genes identified nominally significant associations with diabetic nephropathy for SNPs located in four members of this class of genes (supplementary Table 6), with the most significant association ($P = 9.1 \times 10^{-3}$) occurring at the TARS (threonyl-tRNA synthetase) locus.

Two additional loci were strongly associated with diabetic nephropathy in both panels of the GoKinD collection. Of the two genes located on chromosome 7p, CPVL, a carboxypeptidase that is highly expressed in the kidney and, more specifically, in proximal tubules, is a particularly interesting candidate gene. Other carboxypeptidases, such as ACE and bradykinin, are important regulators of renal hemodynamics and have previously been implicated in the pathogenesis of diabetic nephropathy (36,37). The last diabetic nephropathy–associated locus involves multiple SNPs within a 33 kb haplotype block on chromosome 13q. Previously, genomic deletions of this locus have been linked to congenital renal abnormalities (38). The two genes closest to the associated SNPs, MYO16 (myosin heavy-chain Myr 8) and IRS2 (insulin receptor substrate 2), 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 MYO16 or IRS2, the multiple signals identified in this region give credence to the association detected in our analysis. Additional experiments are needed to characterize the nature of these associations further.

The findings presented in our study contribute to understanding the genetic susceptibility of diabetic nephropathy in type 1 diabetes. As has been reported for other complex genetic disorders, no single major gene that contributes to an increased risk of disease emerged (20,39). However, given the incomplete coverage of the genome by the genotyping platform and the suboptimal study design (prevalent rather than incident cases of ESRD), detection of any existing major gene effect was not guaranteed. For example, because most of the case subjects with ESRD had survived many years on dialysis or with a kidney transplant, a disease allele that not only increased susceptibility to diabetic nephropathy but also increased mortality in patients with ESRD could go undetected. Appreciably, the SNPs that we identified in the GoKinD collection were mortality neutral (supplementary Table 4). The optimal study design for detecting 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 α-error in seeking replication for multiple SNPs in this dataset, our replication efforts refrained from considering SNPs less significant than $P = 1 \times 10^{-5}$. 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 FRMD3 and CARS loci require additional study to be certain of these findings. Third, although the locations of the variants confirmed in this study implicate both FRMD3 and 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 FRMD3 and 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.

ACKNOWLEDGMENTS

This work was supported by the following grants from the National Institutes of Health (NIH): DK77532 (to A.S.K.), DK68386 (to the Genetics Core of the Diabetes and Endocrinology Research Center at the JDC), DK-62204 (to A.D.P.), and DK-077510 (to A.D.P.) and from the Foundation for NIH (FNHI): 06GAIN0 (to J.H.W.). We acknowledge JDC NIH Training Grant T32 DK007260-31 (to M.G.P.) and a CIHR (Canadian Institutes of Health Research) scholarship (to L.M.) and senior investigator award (to S.B.B.). We also acknowledge support from the Canadian Network of Centres of Excellence in Mathematics (to S.B.B.). The GoKinD study was conducted by the GoKinD Investigators and supported by the Juvenile Diabetes Research Foundation (JDRF) and by funding from the Centers for Disease Control (CDC; PI 105-33, 106-554, and 107-360 administered by the National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]). The GoKinD collection of DNA was genotyped through the GAIN program, with the support of the FNHI and NIDDK. The GAIN database was accessed through the NCBI (National Center for Biotechnology Information). The DCCT/EDIC study is supported by contracts with the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institutes of Health (NIH): DK36836 (to the Genetics Core of the Diabetes and Endocrinology Research Center at the JDC), DK-62204 (to A.D.P.), and from the Foundation for NIH (FNHI): 06GAIN0 (to J.H.W.). We acknowledge JDC NIH Training Grant T32 DK007260-31 (to M.G.P.) and a CIHR (Canadian Institutes of Health Research) scholarship (to L.M.) and senior investigator award (to S.B.B.). We also acknowledge support from the Canadian Network of Centres of Excellence in Mathematics (to S.B.B.). The GoKinD study was conducted by the GoKinD Investigators and supported by the Juvenile Diabetes Research Foundation (JDRF) and by funding from the Centers for Disease Control (CDC; PI 105-33, 106-554, and 107-360 administered by the National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]). The GoKinD collection of DNA was genotyped through the GAIN program, with the support of the FNHI and NIDDK. The GAIN database was accessed through the NCBI (National Center for Biotechnology Information). The DCCT/EDIC study is supported by contracts with the Division of Diabetes, Endocrinology, and Metabolic Diseases of the NIDDK and the General Clinical Research Centers Program, National Center for Research Resources. The content and conclusions presented in this manuscript do not necessarily reflect the opinions or views of the JDRF, CDC, FNHI, NIDDK, or NCBI.

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