Members of the Family Investigation of Nephropathy and Diabetes Research Group

Genetic Analysis and Data Coordinating Center, Case Western Reserve University, Cleveland, Ohio: RC Elston**, SK Iyengar*, KAB Goddard**, JM Olson** (deceased), RP Igo, Jr., S Ialacci[#], C Fondran, J Fondran, A Horvath, G Jun, K Kramp, SRE Quade, M Slaughter, E Zaletel.

Participating Investigator Centers:

Case Western Reserve University, Cleveland, OH: JR Sedor*, J Schelling**, A Sehgal**, A Pickens[#], L Humbert[#], L Getz-Fradley[#].

Harbor-University of California Los Angeles Medical Center: S Adler*, HE Collins-Schramm** [§], E Ipp**, H Li** [§], M Pahl**[†], MF Seldin** [§], J LaPage[#], B Walker[#], C Garcia[#], J Gonzalez[#], L Ingram-Drake[#].

Johns Hopkins University, Baltimore, MD: M. Klag*, R. Parekh*, L Kao**, L Mead**, T Whitehead[#], J Chester[#].

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Phoenix, AZ: WC Knowler*, RL Hanson**, RG Nelson**, A Malhotra**, L Jones[#], R Juan[#], R Lovelace[#], C Luethe[#], LM Phillips[#], J Sewemaenewa[#], I Sili[#], B Waseta[#].

University of California, Los Angeles, CA: MF Saad*, SB Nicholas*, X Guo**, J Rotter**, K Taylor**, M Budgett[#], F Hariri[#].

University of New Mexico, Albuquerque, NM: P Zager*, V Shah**, M Scavini[#], A Bobelu[#].

University of Texas Health Science Center at San Antonio, San Antonio, TX: H Abboud*, N Arar**, R Duggirala**, BS Kasinath**, R Plaetke**, M Stern**, C Jenkinson[**], C Goyes[#], V Sartorio[#], T Abboud[#], L Hernandez[#].

Wake-Forest University, Winston-Salem, NC: BI Freedman* [‡], DW Bowden**, SC Satko**, SS Rich**, S Warren[#], S Viverette[#], G Brooks[#], R Young[#], M Spainhour[#].

Laboratory of Genomic Diversity, National Cancer Institute, Frederick MD: C Winkler*, MW Smith**, M Thompson[#], R Hanson[#], B Kessing[#].

NIDDK Program Office: JP Briggs, PL Kimmel, R Rasooly.

External Advisory Committee: D Warnock (chair), R Chakraborty, GM Dunston, SJ O'Brien (ad hoc), R Spielman (deceased).

*Principal Investigator
**Co-investigator

[#]Program Coordinator
[§]University of California, Davis, CA
[†]University of California, Irvine, CA
[‡]Study Chair

Supplementary Methods

Phenotypes. DM was diagnosed in participants currently or previously treated with insulin and/or oral hypoglycemic medicines. Subjects reporting DM but not treated with these medicines, and those without a history of DM, had HbA1c and fasting plasma glucose concentration measured at study entry. HbA1c concentrations ≥ 6.0% were considered suggestive of DM and fasting plasma glucose and/or oral glucose tolerance testing was then performed. American Diabetes Association 1997 criteria [1] were used to define diabetes in previously undiagnosed cases. Subjects with either type 1 or type 2 DM were eligible. Subjects were considered to have overt proteinuria in the presence of a historical 24 hour urine collection with ≥ 500 mg protein/24h or ≥ 300 mg albumin/24h, random urine protein:creatinine ratio (PCR) ≥ 0.5 g/g, or random urine ACR ≥ 0.3 g/g. ESRD was defined as the need for chronic renal replacement therapy with dialysis or renal transplantation.

Two laboratories independently measured urine albumin and creatinine, and the two ACR values were averaged to obtain the quantitative urine ACR phenotype.

Genotypes, marker maps and data cleaning. The Center for Inherited Disease Research (CIDR) carried out a genome-wide scan on 4918 FIND DNA samples using the Illumina Linkage IVb panel (http://www.illumina.com/products/snp/snp_linkage_analysis.ilmn) of approximately 6000 SNPs.

Computer programs from the S.A.G.E. software package [2] were employed for data cleaning and the primary linkage analysis. Pedigree errors and Mendelian errors in marker genotypes were resolved by alternating relationship error detection using RELTEST and Mendelian error detection using MARKERINFO. When necessary, a second relationship testing program, RELPAIR version 2.0.1 [3], was enlisted to resolve relationship errors involving complex relationships and verify ambiguous results from

RELTEST. A total of 52 individuals in 50 pedigrees were dropped from the analyses after being reclassified as unrelated and 245 individuals in 191 pedigrees were reclassified as half-sibs and retained. Six true monozygotic (MZ) twin pairs were identified and one person from each twin pair was randomly dropped. Ten additional putative MZ twin pairs could not be resolved with available relationship information and both members of all ten pairs were excluded. Additionally, nine small pedigrees or parts of larger pedigrees were dropped because complex reclassifications were suggested by RELTEST and/or RELPAIR. After data cleaning, two pedigrees with fewer than four individuals (including untyped founders) were removed because the pedigree structure was not informative for linkage analysis.

A total of 4780 samples (97.2%) genotyped successfully, for which CIDR released data. Of the 138 samples that did not genotype successfully, 4 were dropped for insufficient DNA and 134 due to poor performance. Of the 30,811,200 genotypes released, 75,847 (0.25%) were scored as missing (not including the chromosome Y markers), including all genotypes with a GenCall quality score [4] below 0.25. The reproducibility rate was 99.996% based on 1,277,217 blind duplicate genotypes (i.e., 45 discrepancies were noted).

The Illumina SNP marker data provided by CIDR were screened for several quality criteria [5]. CIDR excluded 128 SNPs from the data release with a call rate of less than 90% (these SNPs did not contribute to the statistics above for missing genotypes). Prior to receiving the data, it was decided to discard any SNP with 50 Mendelian errors after pedigree cleaning (see below), or whose median GenCall score over all typed individuals was less than 0.5. However, all released markers met both criteria.

Subsequent screening was performed separately for each ethnic group (see Supplementary Table S1 for a summary of autosomal markers contributing to genetic analyses). A large deviation from Hardy-Weinberg proportions (dHWP) with excess

homozygosity may indicate a common deletion polymorphism in our sample [6]. Consequently, for each marker we sampled unrelated individuals from the dataset (one per pedigree), performed an exact test for HWP [7], and excluded the marker if HWP was rejected with $p < 0.001$. Uninformative SNPs, with a minor allele frequency (MAF) in the ethnic-group-specific sample of less than 0.05, were also removed from consideration. Markers that passed these quality control tests composed the genome-wide scan for studies of allelic association (Supplementary Table S2).

Linkage disequilibrium (LD) between neighboring single-nucleotide polymorphism (SNP) markers may create bias in estimates of *ibd* sharing among relatives, and hence in results from model-free linkage analyses [8-10]. Pairwise LD was measured in our data among SNP markers within individual ethnic groups using Haploview [11]. To save computational burden, only pairs of markers within 5 cM of each other were tested for LD. Pairs or larger groups of markers in perfect LD (i.e., $r^2 = 1$) were identified, and redundant markers omitted from the marker set. In addition, clusters of SNPs with $| D' | > 0.5$ for all pairs of consecutive markers within the cluster, as measured by Haploview, were thinned to a single marker each by retaining the marker with the greatest MAF and removing the rest. Large inversion polymorphisms may affect both apparent map order and recombination frequencies. Most polymorphic genomic rearrangements are rare and span less than 50 kb [12-14], but two known inversion polymorphisms are large enough and common enough to warrant concern regarding our linkage panel. We examined the physical map of the CIDR panel for SNPs that fall within the 4.7-Mb inversion polymorphism on chromosome 8p23 [15] with an estimated frequency of 21% in Caucasians [16], and an 0.9-Mb polymorphism on chromosome 17q21.31 with an inversion frequency of about 20% in Caucasians but much lower in AA and AI populations [17]. Fourteen markers were typed within the 8p23 polymorphism: all but the most central one were removed to prevent inaccuracies in map estimation due to variation in marker order. Only one Illumina IVb marker fell

within the inversion polymorphism on 17q21.31, and hence, no thinning was necessary in this region.

In linkage analyses, the genetic map that Illumina constructed for its Linkage IVb panel by linear interpolation of physical map distances (based on Build 35 of the human genome) between microsatellite markers in the deCODE linkage map was used [18].

Linkage analysis. This analysis is based on the concept that sib pairs identical-by-descent (IBD) for marker locus alleles will be phenotypically similar for traits influenced by a nearby linked gene. Marker allele frequencies were estimated using FREQ, and multipoint estimates of IBD sharing were obtained using GENIBD. In the estimation of empirical *p* values, IBD sharing is randomly permuted within sibships and across sibships of the same size. The empirical *p* value is the proportion of permuted samples that yield an asymptotic *p* value smaller than that observed from the original data. Suitable numbers of permutations were performed to estimate the empirical *p* value to within 10% of its true value with 95% confidence (i.e., approximately 100/*p* replicates). We converted *p* values to LOD scores using a one-sided alternative hypothesis for linkage.

Association analysis. Briefly, ASSOC fits a linear mixed model in which the SNP genotype is included as a fixed effect. Various types of familial correlations may also be incorporated as random effects (i.e., as variance components), including polygenic, marital and sibship effects. SNPs were encoded, under an additive model, as the number of copies—0, 1 or 2—of a particular allele, selected arbitrarily for each marker. Because the FIND families were ascertained on strict criteria for probands and diabetic siblings favoring discordant relatives, the overall correlation for both DN and urine ACR in sib pairs was negative in all ethnic groups. This caused the estimate of the polygenic variance component to converge to the lower bound of zero. In this situation, a more valid model may be obtained by switching the trait response and SNP

predictor variables and was employed. Although the effect estimates necessarily differ, regressing the genotype on the trait value remained valid under the model assumptions.

We generated uniform quantile-quantile plots to examine the association results from each ethnic group (Supplementary Figs. S1-S2), and tested the results for inflation of type I error due to population stratification using the method of genomic control [19].

References

1 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-1197.

2 S.A.G.E.: Statistical Analysis for Genetic Epidemiology, version 6.0, 2009,

3 Epstein MP, Duren WL, Boehnke M: Improved inference of relationships for pairs of individuals. Am J Hum Genet 2000;67:1219-1231.

4 Oliphant A, Barker DL, Stuelpnagel JR, Chee MS: BeadArray™ technology: enabling an accurate, cost-effective approach to high-throughput genotyping. BioTechniques 2002;32:S56-S61.

5 Schaid DJ: Evaluating associations of haplotypes with traits. Genet Epidemiol 2004;27:348-364.

6 McCarroll SA, Hadnott TN, Perry GH, Sabeti PC, Zody MC, Barrett JC, Dallaire S, Gabriel SB, Lee C, Daly MJ, et al.: Common deletion polymorphisms in the human genome. Nat Genet 2005;38:86-92.

7 Wigginton JE, Abecasis GR: PEDSTATS: descriptive statistics, graphics and quality assissment for gene mapping data. Bioinformatics 2005;21:3445-3447.

8 Schaid DJ, Guenther JC, Christensen GB, Hebbring S, Rosenow C, Hilker CA, McDonnell SK, Cunningham JM, Slager SL, Blute ML, et al.: Comparison of

microsatellites versus single-nucleotide polymorphisms in a genome linkage screen for prostate cancer-susceptibility loci. Am J Hum Genet 2004;75:948-965.

9 Huang Q, Shete S, Amos CI: Ignoring linkage disequilibrium among tightly linked markers induces false-positive evidence of linkage for affected sib pair analysis. Am J Hum Genet 2004;75:1106-1112.

10 Boyles AL, Scott WK, Martin ER, Schmidt S, Li Y-J, Ashley-Koch A, Bass MP, Schmidt M, Pericak-Vance MA, Speer MC, et al.: Linkage disequilibrium inflates type I error rates in multipoint linkage analysis when parental genotypes are missing. Hum Hered 2005;59:220-227.

11 Barrett JC, Fry B, Maller J, Daly MJ: Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005;21:263-265.

12 Conrad DF, Andrews TD, Carter NP, Hurles ME, Pritchard JK: A high-resolution survey of deletion polymorphism in the human genome. Nat Genet 2006;38:75-81.

13 Matise TC, Sachidanandam R, Clark AG, Kruglyak L, Wijsman EM, Kakol J, Buyske S, Chui B, Cohen P, de Toma C, et al.: A 3.9-centimorgan-resolution human single-nucleotide polymorphism linkage map and screening set. Am J Hum Genet 2003;73:271-284.

14 Tuzun E, Sharp AJ, Bailery JA, Kaul R, Morrison VA, Pertz LM, Haugen E, Hayden H, Albertson D, Pinkel D, et al.: Fine-scale structural variation of the human genome. Nat Genet 2005;37:727-732.

15 Sugarawa H, Harada N, Ida T, Ishida T, Ledbetter DH, Yoshiura K, Ohta T, Kishino T, Niikawa N, Matsumoto N: Complex low-copy repeats associated with a common polymorphic inversion at human chromosome 8p23. Genomics 2003;82:238-244.

16 Jorgenson E, Tang H, Gadde M, Province M, Leppert M, Kardia S, Schork N, Cooper R, Rao DC, Boerwinkle E, et al.: Ethnicity and human genetic linkage maps. Am J Hum Genet 2005;76:276-290.

17 Stefansson H, Helgason A, Thorleifsson G, Steinsthorsdottir V, Masson G, Barnard J, Baker A, Jonasdottir A, Ingason A, Gudnadottir VG, et al.: A common inversion under selection in Europeans. Nat Genet 2005;37:129-137.

18 Kong A, Gudbjartsson DF, Sainz J, Jonsdottir GM, Gudjonsson SA, Richardsson B, Sigurdardottir S, Barnard J, Hallbeck B, Masson G, et al.: A high-resolution recombination map of the human genome. Nat Genet 2002;31:241-247.

19 Devlin B, Roeder K: Genomic control for association studies. Biometrics 1999;55:997-1004.

20 Imperatore G, Hanson RL, Pettitt DJ, Kobes S, Bennett PH, Knowler WC, the Pima Diabetes Genes Group: Sib-pair linkage analysis for susceptibility genes for microvascular complications among Pima Indians with type 2 diabetes. Diabetes 1998;47:821-830.

21 Moczulski DK, Rogus JJ, Antonellis A, Warram JH, Krolewski AS: Major susceptibility locus for nephropathy in type 1 diabetes on chromosome 3q: results of novel discordant sib-pair analysis. Diabetes 1998;47:1164-1169.

22 Bowden DW, Colicigno CJ, Langefeld CD, Sale MM, Williams A, Anderson PJ, Rich SS, Freedman BI: A genome scan for diabetic nephropathy in African Americans. Kidney Int 2004;66:1517-1526.

23 Placha G, Poznik GD, Dunn J, Smiles A, Krolewski B, Glew T, Puppala S, Schneider J, Rogus JJ, Rich SS, et al.: A genome-wide linkage scan for genes controlling variation in renal function estimated by serum cystatin C levels in extended families with type 2 diabetes. Diabetes 2006;55:3358-3365.

24 Österholm A-M, He B, Pitkämiemi J, Albinsson L, Berg T, Sarti C, Tuomilehto J, Tryggvason K: Genome-wide scan for type 1 diabetic nephropathy in the Finnish population reveals suggestive linkage to a single locus on chromosome 3q. Kidney Int 2007;71:140-145.

25 Chen G, Adeyemo AA, Zhou J, Chen Y, Doumatey A, Lashley K, Huang H, Amoah A, Agyenim-Boateng K, Eghan BA, et al.: A genome-wide search for linkage to renal function phenotypes in West Africans with type 2 diabetes. Am J Kidney Dis 2007;49:394-400.

26 Krolewski AS, Poznik GD, Placha G, Canani L, Dunn J, Walker W, Smiles A, Krolewski B, Fogarty DG, Moczulski D, et al.: A genome-wide linkage scan for genes controlling variation in urinary albumin excretion in type II diabetes. Kidney Int 2006;69:129-136.

27 Iyengar SK, Abboud HE, Goddard KAB, Saad MF, Adler SG, Arar NH, Bowden DW, Duggirala R, Elston RC, Hanson RL, et al.: Genome-wide scans for diabetic nephropathy and albuminuria in multiethnic populations: The Family Investigation of Nephropathy and Diabetes. Diabetes 2007;56:1577-1585.

28 Schelling JR, Abboud HE, Nicholas SB, Pahl MV, Sedor JR, Adler SG, Arar NH, Bowden DW, Elston RC, Freedman BI, et al.: Genome-wide scan for estimated GFR in multi-ethnic diabetic populations: The Family Investigation of Nephropathy and Diabetes. Diabetes 2008;57:235-243.

29 Freedman BI, Bowden DW, Rich SS, Xu J, Wagenknecht LE, Ziegler J, Hicks PJ, Lange CD: Genome-wide linkage scans for renal function and albuminuria in Type 2 diabetes mellitus: the Diabetes Heart Study. Diabetic Med 2008;24:268-276.

30 Rogus JJ, Poznik GD, Pezzolesi MG, Smiles AM, Dunn J, Walker W, Wanic K, Moczulski D, Canani L, Araki S, et al.: High-density single nucleotidepolymorphism genome-wide linkage scan for susceptibility genes for diabetic nephropathy in type 1 diabetes. Diabetes 2008;57:2519-2526.

31 Vardarli I, Baier LJ, Hanson RL, Akkoyun I, Fischer C, Rohmeiss P, Basci A, Bartram CR, van der Woude FJ, Janssen B: Gene for susceptibility to diabetic nephropathy in type 2 diabetes maps to 18q22.3-23. Kidney Int 2002;62:2176-2183.

Supplementary Figures

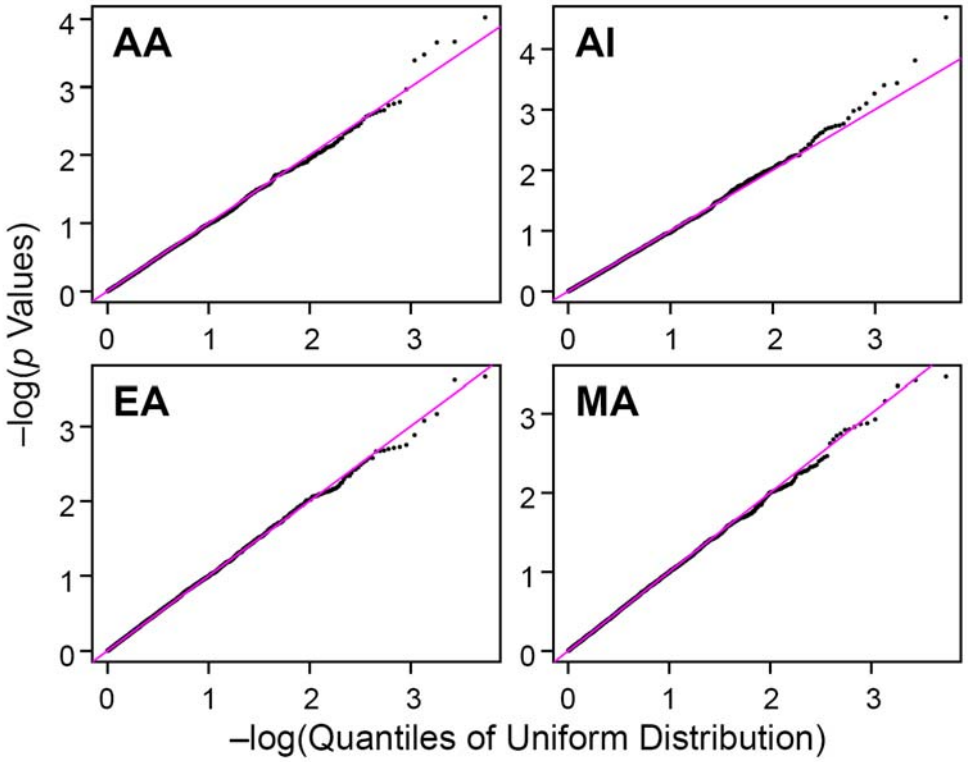

Fig. S1. Uniform quantile-quantile plots from association analyses for diabetic nephropathy. Results from each study population are plotted separately, as indicated. A diagonal line in each panel indicates the expected ordered *p* values under the null hypothesis. Values of the genomic control parameter λ, given at lower right within each panel, suggest that no genomewide inflation of test statistics occurred because of population stratification or of cryptic relatedness in the sample.

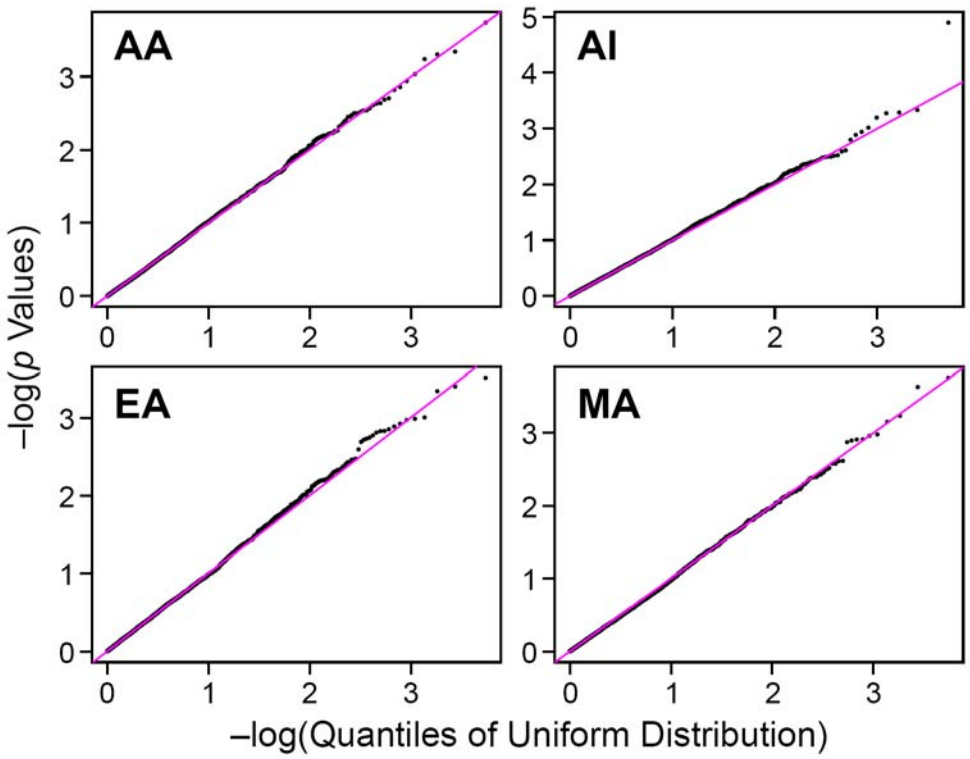

Fig. S2. Uniform quantile-quantile plots from association analyses for urine ACR. See legend to Supplementary Fig. S1 for explanation. Values of the genomic control parameter λ suggest that no genomewide inflation of test statistics occurred because of population stratification or of cryptic relatedness in the sample.

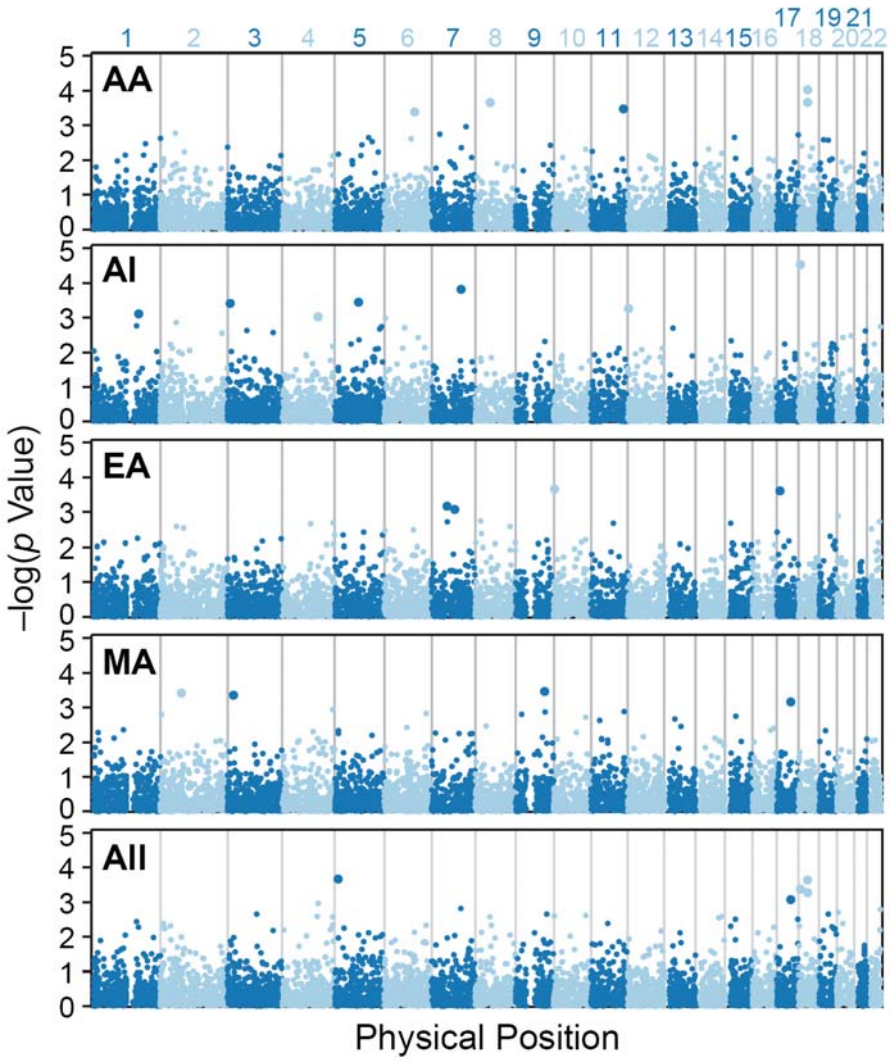

Fig. S3. Results of genomewide sparse association analyses for diabetic nephropathy, adjusted for sex. Horizontal and vertical axes are physical position (genome build 36.2) and negative logarithm of *p* values. Panels, from top to bottom, display results for the African American, American Indian, European American, Mexican American samples, and pooled Fisher *p* values from all study samples. Large dots signify $p < 0.001$. Vertical dashed lines show chromosomal boundaries. Chromosome numbers appear above the top panel.

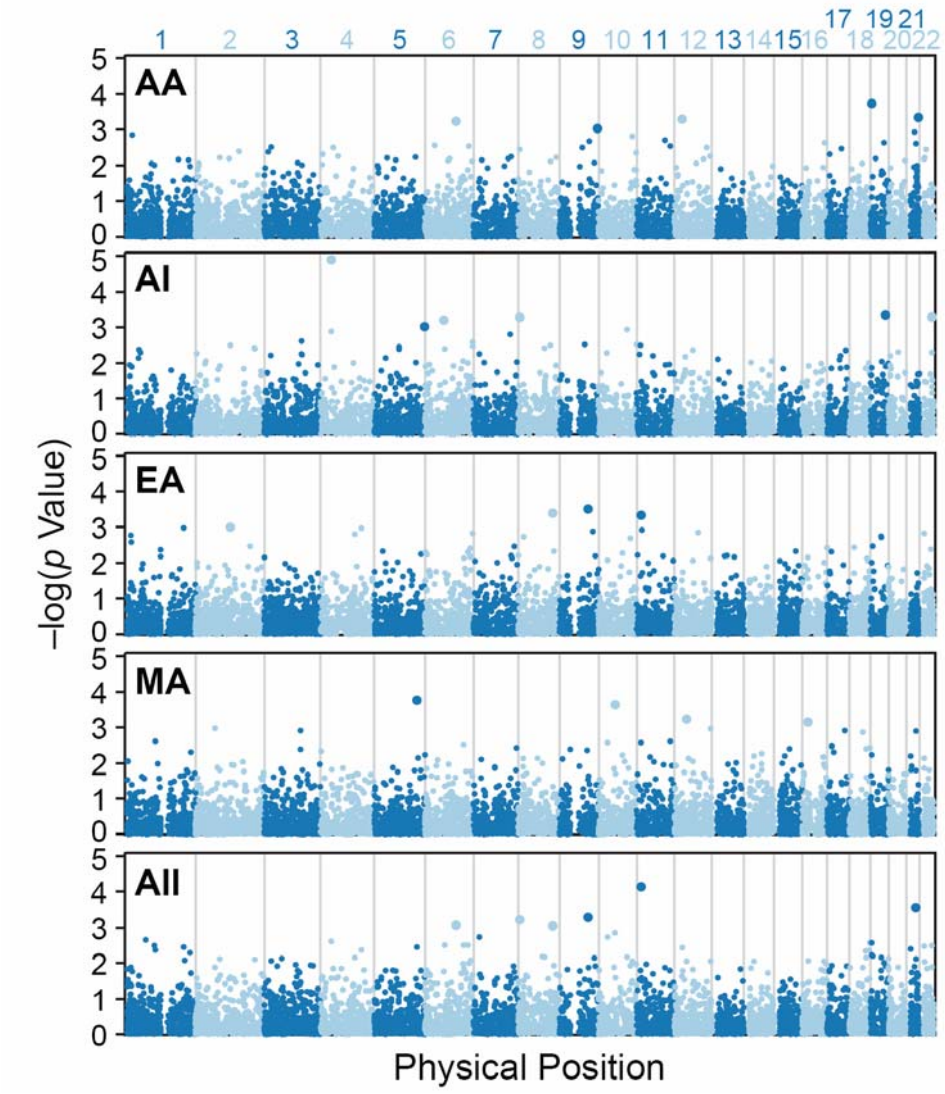

Fig. S4. Results of sparse association analyses for urine ACR. See legend of Supplementary Fig. 3 for explanation.

Supplementary Tables

Supplementary Table S1. Summary of chromosomal regions implicated in multiple genomewide linkage scans for diabetic nephropathy.

Chr.	Sample	Type	Trait	LOD	cM	Reference
3q	98 AI ASPs	2	DN	1.48	181	Imperatore et al., 1998 [20]
	66 EA DSPs	1	DN	3.1	165	Moczulski et al., 1998 [21]
	206 AA sib pairs	2	DN	4.35	135	Bowden et al., 2004 [22]
	63 Caucasian extended families (Joslin Study)	2	GFR	2.2	161	Placha et al., 2006 [23]
	88 Finnish DSPs	1	DN	2.67	149	Österholm et al., 2007 [24]
	321 West African ASPs	2	SCr	2.21	216	Chen et al., 2007 [25]
7p	206 AA sib pairs	2	DN	3.59	33	Bowden et al., 2004 [22]
	63 Caucasian extended families, with non-DM relatives (Joslin Study)	2	GFR	4.0	23	Placha et al., 2006 [23]
7q	98 AI ASPs	2	DN	2.04	144	Imperatore et al., 1998 [20]
	63 Caucasian extended families (Joslin Study)	2	ACR	3.1	172	Krolewski et al., 2006 [26]
	96 AA pedigrees (80 sib pairs) (FIND Study)	2	DN	3.21	104	Iyengar et al., 2007 [27]
	196 MA pedigrees (521 sib pairs) (FIND Study)	2	GFR	4.23	170	Schelling et al., 2008 [28]
	348 EA + 68 AA families (Diabetes Heart Study)	2	GFR	2.32	108	Freedman et al., 2008 [29]
10q	63 Caucasian extended families (Joslin Study)	2	GFR	3.6	114	Placha et al., 2006 [23]
	321 West African ASPs	2	SCr	2.53	93	Chen et al., 2007 [25]
	348 EA families (Diabetes Heart Study)	2	SCr	2.07	104	Freedman et al., 2008 [29]
	100 DSPs	1	DN	2.4	142	Rogus et al., 2008 [30]
18q	18 large Turkish families	2	DN	6.1	110	Vardarli et al., 2002 [31]
	206 AA sib pairs	2	DN	3.72	100	Bowden et al., 2004 [22]
	Multiethnic sample (FIND Study)	2	DN	1.88	116	Iyengar et al., 2007 [27]
	196 MA pedigrees (521 sib pairs) (FIND Study)	2	GFR	1.55	120	Schelling et al., 2008 [28]

Chr., chromosome arm; Type, type of diabetes; Trait, DN = binary diabetes nephropathy phenotype, GFR = glomerular filtration rate, ACR = urine albumin:creatinine ratio, SCr = serum creatinine; LOD, logarithm of the backwards odds; Location, genetic map location at peak significance; ASPs, DN affected sib pairs; DSPs, sib pairs discordant for DN; EA, European American; AA, African American; MA, Mexican American; AI, American Indian. Some LOD scores were derived from *p* values assuming a "one-sided" χ^2 distribution. Genetic maps may differ across studies.

Supplementary Table S2. Selection of Illumina IVb markers for linkage and association analyses.

	AA	**AI**	**EA**	**MA**
Original No. Autosomal SNPs	5548	5548	5548	5548
Monomorphic	2	7	9	2
Low MAF ($0 < MAF < 0.05$)	66	599	45	42
dHWP ($p < 0.001$)	12	10	8	8
Total for Association Scans	**5468**	**4932**	**5486**	**5496**
Chr. 8p inversion polymorphism	12	8	11	11
Thinned for LD	754	1094	913	939
Total for Linkage Scans	**4702**	**3830**	**4562**	**4546**

MAF, minor allele frequency; dHWP, deviation from Hardy-Weinberg proportions. Only the most central marker in the 4.7-Mb chromosome 8p inversion polymorphism was retained. For linkage scans, SNPs were thinned such that $| D' | < 0.5$ between adjacent SNPs.

Supplementary Table S3. Overall FIND sample size for the binary trait DN.

		Full Sib Pairs				Half Sib Pairs			
Group	Pedigrees	CA	D	CU	Total	CA	D	CU	Total
AA	346	185	124	9	318	26	41	3	[70]
AI	212	202	94	16	312	39	34	3	76
EA	199	59	129	22	210	2	3	0	[5]
MA	478	289	266	40	595	18	18	1	37
Total	**1235**	**735**	**613**	**87**	**1435**	**85**	**96**	**7**	**188** (113 used)

CA, concordant affected; D, discordant; CU, concordant unaffected. Numbers in square brackets indicate sets of half-sib pairs not used in the SIBPAL analysis because of numerical instability in the H-E regression.

Supplementary Table S4. Summary of pedigrees/genotyped individuals used in analyses for urine ACR.

Ethnic Group	Pedigrees	Individuals	Full-Sib Pairs	Half-Sib Pairs
African American	346	745	444	99
American Indian	212	598	434	85
European American	199	430	327	[14]
Mexican American	478	1316	996	84
Total	**1235**	**3089**	**2201**	**282** (268 used)

Numbers in square brackets indicate sets of half-sib pairs not used in the SIBPAL analysis because of numerical instability in the H-E regression.

Supplementary Table S5. Major association peaks for DN ($p < 0.001$).

Chr.	Marker	Mb	cM	Group	p
1	rs767707	164.29	169.2	AI	7.9×10^{-4}
2	rs1015645	75.78	100.4	MA	3.8×10^{-4}
3	rs892605	10.68	28.4	AI	3.9×10^{-4}
3	rs1449900	22.52	43.6	MA	4.5×10^{-4}
4	rs318539	130.19	127.8	AI	9.6×10^{-4}
5	rs187609	86.05	102.1	AI	3.6×10^{-4}
				All	2.2×10^{-4}
6	rs2050042	108.42	112.2	AA	4.1×10^{-4}
7	rs1532083	56.37	77.8	EA	6.8×10^{-4}
7	rs917089	83.38	97.8	EA	8.4×10^{-4}
7	rs1476878	106.29	116.7	AI	1.5×10^{-4}
8	rs1837630	53.55	65.6	AA	2.2×10^{-4}
9	rs6477450	105.52	108.4	MA	3.4×10^{-4}
10	rs4328141	2.88	8.5	EA	2.2×10^{-4}
11	rs658922	118.51	121.1	AA	3.3×10^{-4}
12	rs1420725	2.62	5.6	AI	5.5×10^{-4}
17	rs2193112	11.38	32.3	EA	2.4×10^{-4}
17	rs1025905	50.06	80.4	MA	6.9×10^{-4}
				All	8.5×10^{-4}
18	**rs1241983**	**6.87**	**22.6**	**AI**	$\mathbf{3.0 \times 10^{-5}}$
				All	4.2×10^{-4}
18	rs1662910	33.10	58.0	AA	2.2×10^{-4}
				All	5.4×10^{-4}
18	**rs948438**	**33.11**	**58.0**	**AA**	$\mathbf{9.5 \times 10^{-5}}$
				All	2.3×10^{-4}

Chr., chromosomes; cM, centimorgans on the deCODE linkage map; Mb, megabasepairs (Build 35); Group, ethnic group (AA = African American, AI = American Indian, EA = European American, MA = Mexican American, All = Fisher p value from combined analysis). Reported p values are from the Wald test; p values < 10^{-4} are in boldface.

Supplementary Table S6. Major association peaks for urine ACR ($p < 0.001$).

Chr.	Marker	Mb	cM	Group	*P*
2	rs6714807	122.79	134.6	EA	9.9×10^{-4}
4	**rs1039559**	**38.65**	**58.0**	**AI**	$\mathbf{1.3 \times 10^{-5}}$
5	rs357608	150.82	157.0	MA	1.8×10^{-4}
5	rs1544926	177.60	199.8	AI	9.7×10^{-4}
6	rs1555224	65.02	81.2	AI	6.4×10^{-4}
6	rs2050042	108.42	112.2	AA	5.8×10^{-4}
				All	8.7×10^{-4}
8	rs1920469	5.82	13.4	AI	5.3×10^{-4}
				All	6.1×10^{-4}
8	rs1433396	122.07	122.1	EA	4.0×10^{-4}
				All	9.0×10^{-4}
9	rs1329088	100.96	103.7	EA	3.1×10^{-4}
				All	5.3×10^{-4}
9	rs877954	134.55	151.7	AA	9.2×10^{-4}
10	rs1904764	58.81	75.3	MA	2.3×10^{-4}
11	rs722317	15.88	24.3	EA	4.6×10^{-4}
				All	$\mathbf{7.3 \times 10^{-5}}$
12	rs1151048	26.98	49.2	AA	5.5×10^{-4}
12	rs871880	42.01	58.3	MA	5.8×10^{-4}
16	rs741720	21.15	43.4	MA	7.0×10^{-4}
19	rs1715093	3.51	12.2	AA	2.2×10^{-4}
19	rs1012003	52.85	75.9	AI	4.6×10^{-4}
21	rs2250226	42.36	59.3	All	2.8×10^{-4}
22	rs1540327	43.42	56.0	AI	5.2×10^{-4}

Chr., chromosomes; cM, centimorgans on the deCODE linkage map; Mb, megabasepairs (Build 35); Group, ethnic group (AA = African American, AI = American Indian, EA = European American, MA = Mexican American, All = Fisher *p* value from combined analysis). Reported *p* values are from the Wald test; *p* values < 10^{-4} are in boldface.