Association of Adiponectin Gene Polymorphisms With Type 2 Diabetes in an African American Population Enriched for Nephropathy

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OBJECTIVE—Polymorphisms in the adiponectin gene (ADIPOQ) have been associated with type 2 diabetes and diabetic nephropathy in type 1 diabetes, in mostly European-derived populations.

RESEARCH DESIGN AND METHODS—A comprehensive association analysis of 24 single-nucleotide polymorphisms (SNPs) in the adiponectin gene was performed for type 2 diabetes and diabetic nephropathy in African Americans.

RESULTS—The minor allele (A) in a single SNP in intron 1 (rs182052) was associated with diabetic nephropathy (P = 0.0015, odds ratio [OR] 1.37, CI 1.13–1.67, dominant model) in an African American sample of 851 case subjects with diabetic nephropathy and 871 nondiabetic control subjects in analyses incorporating adjustment for varying levels of racial admixture. This association remained significant after adjustment of the data for BMI, age, and sex (P = 0.0013–0.0004). We further tested this SNP for association with longstanding type 2 diabetes without nephropathy (n = 317), and evidence of association was also significant (P = 0.0054, OR 1.46, CI 1.12–1.91, dominant model) when compared with the same set of 871 nondiabetic control subjects. Combining the type 2 diabetes and diabetic nephropathy samples into a single group of case subjects (n = 1,168) resulted in the most significant evidence of association (P = 0.0003, OR 1.40, CI 1.17–1.67, dominant model). Association tests between age at onset of type 2 diabetes and the rs182052 genotypes also revealed significant association between the presence of the minor allele (A/A or A/G) and earlier onset of type 2 diabetes.

CONCLUSIONS—The SNP rs182052 in intron 1 of the adiponectin gene is associated with type 2 diabetes in African Americans. Diabetes 58:499–504, 2009

RESEARCH DESIGN AND METHODS

Case subjects included 851 unrelated African Americans with type 2 diabetes—associated end-stage renal disease (ESRD) from dialysis centers in Winston-Salem, Greensboro, and Hickory, NC. All diabetic nephropathy case subjects had ESRD and were on dialysis at the time of recruitment. Diabetes was considered to be the primary cause of nephropathy if subjects developed diabetes after the age of 35 years and diabetes was present ≥5 years before initiation of renal replacement therapy and/or in the presence of diabetic retinopathy or proteinuria exceeding 500 mg/24 h. An additional 317 unrelated African Americans with type 2 diabetes and no renal disease, and 871 nondiabetic unrelated control subjects were recruited from medical clinics.
chances, and health fairs in North Carolina. Diabetic subjects lacking nephropathy had diabetes for >10 years with a spot urine albumin-to-creatinine ratio <30 mg/dl and serum creatinine concentration <1.5 mg/dl in men or <1.3 mg/dl in women. Individuals were actively receiving treatment with oral hypoglycemic agents and/or insulin. Nondiabetic control subjects were self-reported African Americans born in the southeast, age ≥18 years, who denied a personal history of diabetes or a personal or family history of kidney disease in first-degree relatives. Each participant provided 40 ml blood for DNA isolation. DNA was isolated using an AutoPure LS automated DNA extraction robot (Genta Systems, Minneapolis, MN). Recruitment and sample collection procedures were approved by the Institutional Review Board at Wake Forest University, and all subjects provided written informed consent.

SNP genotyping. A total of 24 SNPs were genotyped in 1,168 African American case subjects (851 with diabetic nephropathy and 317 with type 2 diabetes lacking nephropathy) and 871 nondiabetic control subjects. SNPs were chosen based on their ability to capture genetic information for African (Yoruban) and European (CEU) populations in Hapmap (www.hapmap.org) using Tagger (Haplovew [16]). Tagged SNPs had a minor allele frequency >0.05 and captured an inter-SNP \( r^2 \) value >0.8 for known polymorphisms in the region. Three SNPs, rs17300539, rs4632532, and rs266729, were included based on previous association with type 1 diabetic nephropathy or insulin resistance syndrome phenotypes (13,17). A total of 34 SNPs were initially chosen for analysis. Two SNPs failed design, six SNPs could not be incorporated into a multiplex, and two SNPs were eliminated because of low genotyping efficiency. The genotyped SNPs captured at least 64% of the variation in the Yoruban HAPMAP sample. SNPs were genotyped using the MassARRAY genotyping system (Sequenom, San Diego, CA). PCR primers were designed using the MassARRAY Assay Design 3.4 Software (Sequenom). All case and control subjects were genotyped at 70 admixture informative markers (AIMs) to estimate the percentage of African ancestry for each individual (18,19).

DNA sequencing. The associated SNP rs182052 was sequenced in 175 African Americans with diabetic nephropathy to verify the accuracy of the genotype calls. The region was PCR amplified and products were purified and directly sequenced using Big Dye Ready Reaction Mix on an ABI3730xl sequencer (Applied Biosystems, Foster City, CA). Sequence data were visualized using Sequencher Software version 4.6 (GeneCodes Corporation, Ann Arbor, MI).

Statistical analysis. Biometric data were compared using a Kruskal-Wallis one-way ANOVA on Ranks (SigmaStat; Statsoft Software, San Jose, CA) with a Dunn’s method multiple comparison test. Age at onset of type 2 diabetes in the diabetic nephropathy and type 2 diabetic case subjects was compared using a Mann-Whitney rank-sum test (SigmaStat). Each SNP was tested for deviations from Hardy-Weinberg equilibrium using the \( \chi^2 \) goodness-of-fit test in the statistical analysis program SNPGenome (www.phs.wufbmc.edu) (20). Tests for genotypic association were performed on each SNP individually using SNPGenome-ADMIX, a component of the SNPGenome program that includes the capability to perform association calculations adjusting for covariates. Genotypic association reported here is for analyses incorporating adjustment for ancestry proportions. The primary inference is based on the 2 d.f. global test of genotypic association. If significant, then the individual genetic models (dominant, additive, and recessive) were examined for context. This is consistent with the Fisher’s protected least significant difference multiple comparisons procedure. Percentage of African ancestry was computed from 70 admixture informative markers using the program Frappe (18,19). The influence of other possible covariates (age, BMI, and sex) on evidence of association was tested using SNPGenome-ADMIX. Two-SNP haplotype analysis was completed using the program Dandelion (www.phs.wufbmc.edu). Linkage disequilibrium was calculated as defined by Gabriel et al. (21) with the program Haplovew (22).

We computed a series of Cox proportional hazards models and the corresponding likelihood ratio statistics to test for associations between adiponectin polymorphisms and age at type 2 diabetes onset for 1) diabetic nephropathy case subjects, 2) type 2 diabetic (no nephropathy) case subjects, and 3) type 2 diabetic and diabetic nephropathy case subjects combined.

RESULTS

Descriptive data for participants are summarized in Table 1. Diabetic nephropathy and type 2 diabetic case subjects were older and more were female compared with the nondiabetic control subjects. Type 2 diabetic case subjects had increased BMI compared with diabetic nephropathy case subjects and nondiabetic control subjects. The average age at type 2 diabetes onset for case subjects with diabetic nephropathy was less than that of case subjects with type 2 diabetes without nephropathy.

A total of 24 SNPs in the adiponectin gene were successfully genotyped in diabetic nephropathy case subjects and nondiabetic control subjects. None of the SNPs departed from the Hardy-Weinberg equilibrium after correction for multiple comparisons. Two SNPs, rs182052 and rs3821799, showed evidence of association with diabetic nephropathy (Supplemental Table 1, found in an online appendix at http://dx.doi.org/10.2337/db08-0598). SNP rs182052 was associated with diabetic nephropathy in the 2 d.f. test (\( P = 0.002 \)) and under the dominant model (\( P = 0.002, \) odds ratio [OR] 1.37; 95% CI 1.13–1.67) (Table 2). SNP genotype calls for rs182052 were verified by direct DNA sequence analysis in 175 case subjects with diabetic nephropathy to ensure that the slight departure from Hardy-Weinberg equilibrium in the case subjects was not the result of erroneous genotyping. Genotypes observed from DNA sequencing were 100% concordant with genotypes generated from the Sequenom MassArray system. The SNP rs3821799 was also associated (\( P = 0.039 \)) but did not retain statistical significance after adjusting for multiple comparisons.

SNP rs182052 was associated with BMI and waist measures in Hispanic Americans in the Insulin Resistance and Atherosclerosis (IRAS) Family Study (22). To ascertain whether the association of rs182052 with diabetic nephropathy reflected an association with BMI or other phenotypes known to be associated with increased risk of type 2 diabetes or diabetic nephropathy, genotypic association was evaluated with individual adjustments for BMI, sex, and age at exam (Table 2) and showed little effect on the evidence of association. We also tested association after simultaneously adjusting for admixture, BMI, sex, and age. Evidence of association between rs182052 and

### Table 1

Demographic characteristics of African American cohort

| n  | Age | BMI | % female | Age at onset of type 2 diabetes | Age at onset of ESRD |
|----|-----|-----|----------|--------------------------------|---------------------|
| Non diabetic control subjects | 871 | 50.9 ± 11.6 | 52.9 ± 7.0 | 55.1 | 41.0 ± 12.0 | 58.5 ± 10.2 |
| Diabetic nephropathy | 851 | 61.8 ± 10.0* | 29.4 ± 6.8 | 62.7 | 43.8 ± 12.0* |
| Type 2 diabetes (no nephropathy) | 317 | 58.6 ± 11.5* | 32.9 ± 7.1* | 65.5 | — |

*Mean is significantly different from nondiabetic subjects (\( P < 0.05 \)). †Mean is significantly different (\( P < 0.05 \)) from the type 2 diabetes (no nephropathy) case subjects.
The linkage disequilibrium structure for the adiponectin gene in African American nondiabetic control subjects is shown in Supplemental Fig. 1. African Americans have one large block at the 3’ end of the gene and four smaller blocks surrounding it. The associated SNP, rs182052, is located in a small linkage disequilibrium block containing one other known SNP, rs266729, and covering the promoter.

A Cox proportional hazards model was used to determine the relative risk (RR) for early age at onset of type 2 diabetes for genotypes at the associated SNP, rs182052 (Table 3). Significant risk for earlier onset of type 2 diabetes was detected under the dominant model ($P = 0.0031 - 0.0002$; RR $1.26 - 1.41$) for the diabetic nephropathy and type 2 diabetic case groups individually and when the two groups were combined (diabetic nephropathy + type 2 diabetes). Significant risk was also found with age at onset of ESRD under the dominant model ($P = 0.0113$; RR $1.20$), RR increased when the data were adjusted for sex, BMI, and admixture ($P = 0.0084$; RR $1.21$). Pearson’s correlation coefficient ($r = 0.56$; $P < 0.001$) indicated a positive correlation between the age at onset of type 2 diabetes and the age at onset of ESRD, suggesting that early age of onset of ESRD may depend on an early age of onset of type 2 diabetes. We confirmed this by calculating the RR of age at onset of ESRD after adjustment for age at onset of type 2 diabetes and saw no significant risk (Table 3). When the survival distribution function is plotted versus the age at onset of type 2 diabetes (Fig. 1), individuals with the minor allele A (A/A or A/G genotypes) have an earlier age at onset of type 2 diabetes compared with individuals who are homozygous for the G allele (G/G genotype).

**DISCUSSION**

We have evaluated association between adiponectin gene polymorphisms and type 2 diabetes and diabetic nephropathy in a large sample of African Americans. We observed evidence of association between the rs182052 polymorphism in intron 1 in African Americans with type 2 diabetes. This evidence of association remained significant after adjustment for African ancestry, age, BMI, and sex. In the fully adjusted models, the $P$ value for association of rs182052 with type 2 diabetes was 0.0005, a level of significance that survives even stringent Bonferroni adjustment. Survival analysis revealed association between the minor allele and earlier age at onset of type 2 diabetes. Previous studies of association between adiponectin poly-

**TABLE 2**

| Hardy-Weinberg equilibrium | Genotypic association | 2 d.f. | Dominant | Additive | Recessive |
|-----------------------------|-----------------------|--------|-----------|----------|-----------|
| Case subjects | Control subjects | | | | |
| Admixture  | 0.024 | 0.060 | 0.0019 | 0.0015 | 1.37 | 1.13–1.67 | 0.0393 | 1.16 | 1.01–1.34 | 0.6442 | 0.94 | 0.71–1.24 |
| Age | 0.0032 | 0.0009 | 1.49 | 1.18–1.89 | 0.0081 | 1.26 | 1.06–1.49 | 0.6225 | 1.09 | 0.78–1.53 |
| BMI | 0.0008 | 0.0004 | 1.46 | 1.19–1.80 | 0.0110 | 1.22 | 1.05–1.42 | 0.9334 | 0.99 | 0.73–1.34 |
| Sex | 0.0017 | 0.0013 | 1.38 | 1.13–1.67 | 0.0378 | 1.16 | 1.01–1.34 | 0.6330 | 0.93 | 0.70–1.24 |
| Combined | 0.0019 | 1.46 | 1.15–1.86 | 0.0114 | 1.25 | 1.05–1.49 | 0.5593 | 1.11 | 0.79–1.56 |
| Type 2 diabetes + diabetic nephropathy vs. nondiabetic | Admixture | 0.003 | 0.061 | 0.0003 | 0.0003 | 1.40 | 1.17–1.67 | 0.0196 | 1.17 | 1.03–1.33 | 0.5549 | 0.92 | 0.71–1.20 |
| Age | 0.0006 | 0.0002 | 1.50 | 1.21–1.86 | 0.0058 | 1.25 | 1.07–1.46 | 0.8796 | 1.02 | 0.75–1.40 |
| BMI | 0.0001 | 0.0001 | 1.47 | 1.21–1.79 | 0.0075 | 1.22 | 1.05–1.41 | 0.7473 | 0.95 | 0.72–1.27 |
| Sex | 0.0002 | 0.0002 | 1.41 | 1.17–1.69 | 0.0187 | 1.17 | 1.03–1.34 | 0.5110 | 0.92 | 0.70–1.19 |
| Combined | 0.0005 | 1.48 | 1.19–1.84 | 0.0088 | 1.24 | 1.06–1.45 | 0.8408 | 1.03 | 0.75–1.42 |

Genotypic association for rs182052 after individual adjustment for admixture, age, BMI, and sex in 851 type 2 diabetes + diabetic nephropathy case subjects versus 871 nondiabetic control subjects and type 2 diabetes + diabetic nephropathy case subjects plus an additional 317 type 2 diabetic (no nephropathy) subjects (total cases = 1,168) versus the same 871 nondiabetic control subjects. Genotypic association is also shown for all four covariates simultaneously (combined).
morphisms and type 2 diabetes or diabetic nephropathy have evaluated European-derived or Asian populations, with only one study in non-European South Africans (14) and one study with a small number of African Americans (15). To our knowledge, this is the first study that has addressed adiponectin gene polymorphism associations with type 2 diabetes and diabetic nephropathy in African Americans.

In our case samples, allele frequencies of rs182052 deviated slightly from the Hardy-Weinberg equilibrium. This may be the result of differing allele frequencies in the European and African ancestral populations. In HapMap (www.hapmap.org), the Yoruban population has a minor allele frequency of 0.395 at this SNP, whereas the European population has a minor allele frequency of 0.353. This difference underscores the importance of including adjustment for African Ancestry in analyses of African American populations. In our case subjects and control subjects, the percentage of African ancestry was between the two groups of case subjects and the control subjects (80 ± 10 to 82 ± 10).

This study was well powered to detect associations consistent with complex genetic traits with over 1,168 (combined) type 2 diabetes and diabetic nephropathy case subjects and more than 871 nondiabetic control subjects. With this large sample size, we had >80% power to detect an odds ratio of 1.3–1.5 under the dominant model of association within a range of minor allele frequencies (0.1–0.3). While a number of the genotyped SNPs had low minor allele frequencies (<0.05) and would contribute to a reduction in power, the associated SNP was relatively common (minor allele frequency = 0.348 in control subjects) and the low P value contributes a high level of confidence in this association.

Previous studies have reported association between adiponectin polymorphisms and type 2 diabetes (14,15,23–26) and diabetic nephropathy (13). These studies have primarily detected association with SNPs in the promoter region (rs17300539 and rs206729) or in exons (rs22517766 and rs1501289). With our African American sample, we have the ability to detect association with both type 2 diabetes and diabetic nephropathy. We tested three of these SNPs (rs17300539, rs206729, and rs1501289) and found no significant evidence for association. That the association in our African American collection is at a different SNP is not unexpected. This may reflect ethnic differences in adiponectin gene structure, as discussed by Ukkola et al. (15) in their evaluation of African Americans from the HERITAGE study. The lack of two distinct linkage disequilibrium blocks in the adiponectin gene in our African American sample, compared with that previously demonstrated in European-derived samples (27), also supports this conclusion. In addition, Woo et al. (28) identified nine SNPs in the adiponectin gene that had significantly different minor allele frequencies (P < 0.001) between African Americans and European Americans. These genetic data are further supported by evidence that African Americans have reduced plasma adiponectin concentrations than other ethnic groups (Europeans, Japanese, and Pima Indians) (29). The potential for ethnic differences in the adiponectin gene emphasizes the need to study genetic associations in multiple populations, particularly African Americans.

Whereas association with type 2 diabetes has not been previously reported with rs182052, this SNP has been associated with BMI and waist measures in Hispanic Americans in the Insulin Resistance and Atherosclerosis Family Study (22). To ascertain whether the association we observed was the result of type 2 diabetes and not increased BMI, we adjusted for BMI in the association analysis. The evidence of association remained significant after BMI adjustment, indicating that the difference in adiposity between case subjects and control subjects is not driving the association and that the mechanism is via some other pathway. In addition, rs182052 is in the same haplotype block as rs206729 (Supplementary Fig. 1) in African Americans, an SNP with prior reports of association with type 2 diabetes (11). Haplotype analysis of these two SNPs revealed no association with type 2 diabetes or diabetic nephropathy (Supplementary Table 3).

Woo et al. (28) and Heid et al. (27) have demonstrated association between the minor allele of rs182052 (A) and reduced levels of plasma adiponectin in European-derived American adolescents and healthy Europeans, respectively. In our study, individuals with the minor allele (A/A or A/G genotypes) had earlier onset of type 2 diabetes. If the minor allele is contributing to type 2 diabetes in our samples by reduced levels of plasma adiponectin, this

| Age at onset of type 2 diabetes | Dominant RR | Dominant P | Recessive RR | Recessive P | Additive RR | Additive P |
|---------------------------------|-------------|------------|-------------|-------------|------------|------------|
| Diabetic nephropathy            | 1.29        | 0.0003     | 1.00        | 0.0102      | 1.14       | 0.0358     |
| Type 2 diabetes                 | 1.41        | 0.0031     | 0.9714      | 0.0638      | 1.19       | 0.0088     |
| Diabetic nephropathy + type 2 diabetes | 1.26 | 0.0002 | 0.9217 | 0.0663 | 1.13 |

After adjustment

| Age at onset of ESRD | Dominant RR | Dominant P | Recessive RR | Recessive P | Additive RR | Additive P |
|----------------------|-------------|------------|-------------|-------------|------------|------------|
| Diabetic nephropathy | 1.27        | 0.0011     | 0.9391      | 0.0192      | 1.13       | 0.0651     |
| Type 2 diabetes      | 1.42        | 0.0034     | 0.7143      | 0.0507      | 1.17       | 0.0651     |
| Diabetic nephropathy + type 2 diabetes | 1.25 | 0.0004 | 0.9878 | 0.0091 | 1.12 |

After adjustment for sex, BMI, and admixture

| Age at onset of type 2 diabetes | Dominant RR | Dominant P | Recessive RR | Recessive P | Additive RR | Additive P |
|---------------------------------|-------------|------------|-------------|-------------|------------|------------|
| Diabetic nephropathy            | 1.20        | 0.0113     | 1.14        | 0.0098      | 1.14       | 0.0098     |
| Type 2 diabetes                 | 1.21        | 0.0084     | 1.18        | 0.0063      | 1.16       | 0.0063     |
| Diabetic nephropathy + type 2 diabetes | 0.99 | 0.86 | 1.11 | 0.73 | 1.03 |

P values and RRs are reported for the dominant, additive, and recessive models both before and after adjustment for sex, BMI, and admixture proportions. Analysis of age at onset of ESRD is also adjusted for age at onset of type 2 diabetes.
would be consistent with previous studies that have demonstrated an association between hypoadiponectinemia and increased risk of type 2 diabetes (24,30). We do not have serum adiponectin concentrations for the subjects in our study; however, it would be interesting to determine whether rs182052 contributes to plasma adiponectin concentrations in our collection of African Americans. It should be noted that Woo et al. (28) detected no association between rs182052 and plasma adiponectin levels in a comparably sized sample of African American adolescents.

A primary issue with the observations we have made is whether the observed association reflects an association between rs182052 and type 2 diabetes, diabetic nephropathy, or both. We have sampled a relatively large number of African American subjects with diabetic nephropathy and a smaller collection with type 2 diabetes and no nephropathy to attempt to ascertain whether this gene is associated with nephropathy or diabetes. As the SNP was associated in subjects with diabetic nephropathy and subjects with type 2 diabetes lacking nephropathy, we believe that the data are most consistent with the rs182052 variant contributing to type 2 diabetes susceptibility in African Americans. This is supported by the Cox model’s RR, which indicated increased risk for earlier age at onset of type 2 diabetes. Additionally, we compared allele frequencies of rs182052 between the diabetic nephropathy case subjects (n = 851) and the type 2 diabetic (no nephropathy) case subjects (n = 317) and observed no evidence of association. Although this analysis has less power than the initial case-control analysis, it does support our conclusion that rs182052 is associated with type 2 diabetes in African Americans.

We observed association between a variant in the adiponectin gene and type 2 diabetes in African Americans. This SNP, rs182052, has not previously been associated with diabetes or diabetic nephropathy in other populations, although it has been associated with plasma adiponectin levels. That other variants previously associated with diabetes or diabetic nephropathy in Europeans were not associated in our African American population emphasizes the potential that there are likely ethnic differences in the linkage disequilibrium structure of the adiponectin gene.

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

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