# Variants of the Transcription Factor 7-Like 2 (TCF7L2) Gene Are Associated With Type 2 Diabetes in an African-American Population Enriched for Nephropathy

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**OBJECTIVE—**Recently, variants in the TCF7L2 gene have been reported to be associated with type 2 diabetes across multiple Europid populations, but only one small sample of African-American type 2 diabetic patients has been examined. Our objective was to investigate the importance of TCF7L2 in a larger African-American case-control population.

**RESEARCH DESIGN AND METHODS—**We investigated single nucleotide polymorphisms (SNPs) in six known type 2 diabetes genes in 577 African-American case subjects with type 2 diabetes enriched for nephropathy and 596 African-American control subjects. Additionally, we genotyped 70 ancestry-informative markers (AIMs) to apply adjustments for differences in ancestral proportions.

**RESULTS—**The most significant associations were observed with TCF7L2 intron 3 SNPs rs7903146 (additive $P = 4.10 \times 10^{-6}$, odds ratio [OR] 1.51; admixture-adjusted $P_a = 3.77 \times 10^{-6}$) and rs7901695 ($P = 0.001$, OR 1.30; $P_a = 0.003$). The 2-SNP haplotype containing these SNPs was also associated with type 2 diabetes ($P = 3 \times 10^{-5}$). Modest associations were also seen with TCF7L2 intron 4 SNPs rs7895340, rs11196205, and rs12255372 ($0.01 < P < 0.05$; $0.03 < P_a < 0.08$), as well as with ATP-sensitive inwardly rectifying potassium channel subunit Kir6.2 (KCNJ11) and hepatocyte nuclear factor 4-α (HNF4A) SNPs ($0.01 < P < 0.05$; $0.01 < P_a < 0.41$). No significant associations were detected with genotyped calpain 10 (CAPN10), peroxisome proliferator–activated receptor γ (PPARG), and transcription factor 1 (TCF1) SNPs.

**CONCLUSIONS—**This study indicates that variants in the TCF7L2 gene significantly contribute to diabetes susceptibility in African-American populations. ***Diabetes*** **56:2638–2642, 2007**

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AIM, ancestry-informative marker; HWE, Hardy-Weinberg equilibrium; SNP, single nucleotide polymorphism.



Few genetic variants have shown association with type 2 diabetes across populations. These include polymorphisms in calpain 10 (CAPN10) (1), peroxisome proliferator–activated receptor γ (PPARG) (2), ATP-sensitive inwardly rectifying potassium channel subunit Kir6.2 (KCNJ11) (3), hepatocyte nuclear factor 4-α (HNF4A) (4), and hepatic transcription factor 1 (TCF1) (5) genes. Several reports have confirmed associations between intron 3 and intron 4 polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes (6–13).

Three studies of TCF7L2 have included African-American or U.K. Afro-Caribbean individuals. In the Diabetes Prevention Program (14), incident diabetes occurred in 139 of 605 African-American participants, and results for the two TCF7L2 SNPs genotyped (rs12255372 and rs7903146) were not significant in African Americans. A case-control study that included U.K. Europids, Indian Asians, and Afro-Caribbeans did not find significant heterogeneity between groups, although associations did not reach significance in the Afro-Caribbean group ($n = 385$) (13). A study of 118 nondiabetic female African-American subjects found a significant association between rs1255372 and lower disposition index (15).

To investigate reported TCF7L2 SNPs in a larger African-American type 2 diabetic case-control population and to place results in the context of other type 2 diabetes loci, we genotyped 13 SNPs in six known diabetes genes. Additionally, we estimated ancestral proportions for study subjects using ancestry informative markers (AIMs) to take into account the impact of admixture on association results.

## RESEARCH DESIGN AND METHODS

This study was conducted under institutional review board approval from Wake Forest University School of Medicine and adhered to the tenets of the Declaration of Helsinki. Recruitment of African-American and European-American patients and control subjects has previously been described (16). Briefly, 577 unrelated African-American patients with type 2 diabetes, born in North Carolina, South Carolina, Georgia, Tennessee, or Virginia, were recruited from dialysis facilities. Presumed type 1 diabetic patients were excluded on the basis of a history of diabetic ketoacidosis or diabetes diagnosis before age 25 years with continuous insulin therapy since diagnosis. A diagnosis of type 2 diabetes was based on participants reporting an initial diagnosis of diabetes after age 35 years, receiving oral hypoglycemic agents or dietary therapy without insulin for at least 1 year after initial diagnosis, and active treatment with diabetes medications. Case subjects had type 2 diabetes diagnosed at least 5 years before initiating renal replacement therapy, background or greater diabetic retinopathy, and/or >3+ proteinuria on urinalysis in the absence of other causes of nephropathy. A total of 596 African-American and 36 European-American control subjects, born in North

TABLE 1
Characteristics of African-American subjects

| Trait | Type 2 diabetes–ESRD case subjects | | Control subjects | |
|---|---|---|---|---|
| | *n** | Mean ± SD | *n** | Mean ± SD |
| Male/female | 225/352 | — | 292/304 | — |
| Age at exam (years) | 541 | 62.2 ± 10.3 | 448 | 49.3 ± 9.8 |
| Age at type 2 diabetes diagnosis (years) | 544 | 41.8 ± 11.6 | — | NA |
| Age at ESRD diagnosis (years) | 560 | 59.0 ± 10.5 | — | NA |

*Number with data available. All case subjects were diagnosed with type 2 diabetes and ESRD (end-stage renal disease). NA, not applicable.

Carolina, South Carolina, Georiga, Tennessee, or Virginia, without a current diagnosis of type 2 diabetes or renal disease were recruited from community sources. DNA extraction was performed using the PureGene system (Gentra Systems, Minneapolis, MN). DNA was obtained from 44 Yoruba Nigerians from the National Institute of General Medical Sciences Human Variation Collection (Coriell Cell Repositories, Camden, NJ).

**Diabetes candidate gene genotyping.** SNPs CAPN10 rs3792267; PPARG rs1801282; TCF7L2 rs7901695, rs7903146, rs7895340, rs11196205, and rs12255372; and HNF4A rs1884613 and rs2144908 were genotyped by Illumina's Custom Genotyping Service (San Diego, CA). SNPs genotyped using iPlex methodology (Sequenom, San Diego, CA) (17) were CAPN10 rs2975760, KCNJ11 rs5219, TCF1 rs1800574, and HNF4A rs4810424. Primer sequences are available on request. CAPN10 SNP rs5030952 (UCSNP-63) was unable to be genotyped successfully on either platform. Genotyping success rates for candidate SNPs were >97.7% in case subjects and >96.5% in control subjects. TCF7L2 SNP genotyping success rates were 100% in case subjects and >99.8% in control subjects. Concordance rates for 50 replicate pairs were 100% for all SNPs except rs4810424, where there were two discordant alleles among 96 chromosomes.

**Genotyping for admixture analyses.** A total of 70 AIMs were genotyped by Illumina's Custom Genotyping Service or using a MassARRAY system (Sequenom) (17) in 577 African-American case subjects, 596 African-American control subjects, 44 Yoruba Nigerians, and 39 European Americans (Supplementary Table 1 [available in an online appendix at http://dx.doi.org/10.2337/db07-0012]). Primer sequences are available on request. Genotyping success rates for AIMS were >97.4% in African-American case subjects and >95.6% in African-American control subjects.

**Statistical analyses.** Haplotype block structure was established using Haploview 3.2 (18), with the block definition from Gabriel et al. (19). Unadjusted genotypic association tests were assessed by a $\chi^2$ statistic using $2 \times 2$ and $2 \times 3$ contingency tables.

Tests of haplotypic association were performed using the score test (Haplo.score) implemented in the Haplo.stats package (20). Analyses were initially performed using 1,000 permutations. Where association tests indicated possible significance (empirical global $P$ value $< 0.10$), permutations were increased (10,000–1,000,000). Haplotypes with <2% overall frequency were removed from analyses. Estimates of case and control haplotype frequencies were obtained using Dandelion 1.26 (21).

Individual ancestral proportions were estimated using an EM algorithm (FRAPPE) (22) under a two-population model. Logistic regression tests of additive (or dominant) genetic models included adjustments for individual estimates of African ancestry (23).

**Sequencing.** SNPs were tested for departures from Hardy-Weinberg equilibrium (HWE). SNPs that deviated from HWE were sequenced in 23 African-American case and 23 African-American control subjects using BigDye Terminator Cycle Sequencing Kits (version 1.1; Applied Biosystems, Foster City, CA) and a 3730xl DNA Analyzer (Applied Biosystems). Data were viewed using Sequencher (version 4.1.4; Gene Codes Corporation, Ann Arbor, MI).

## RESULTS

Population characteristics are shown in Table 1. Control subjects were significantly younger than case subjects ($P < 0.0001$) but older than mean age at type 2 diabetes diagnosis ($P < 0.0001$). Age data were unavailable for 25% of control subjects. BMI data are not presented because measures reflected weight on dialysis in case subjects and were unavailable for the majority of control subjects. A higher proportion of females (61%) was observed in the case than in the control subjects (51%), possibly due to a combination of higher prevalence of type 2 diabetes in women, as well as participation and survival bias.

In African-American case subjects, the mean ± SD proportion of African ancestry was estimated to be 0.817 ± 0.133, while in African-American control subjects it was 0.791 ± 0.131. Distributions are shown in Supplementary Fig. 1.

HNF4A SNP rs1884613 was inconsistent with HWE in African-American control subjects ($P = 0.01$). PPARG rs1801282 ($P = 0.007$) and KCNJ11 rs5219 ($P = 0.0009$) deviated from HWE proportions in African-American case subjects most likely because the minor alleles for these SNPs are rare (0.014 and 0.056, respectively) (Table 2). Additionally, rs5219 minor allele frequency estimates for "ancestral" African ($n = 44$) and European-American populations ($n = 39$) are at the extremes (0 in Africans and 0.408 in European Americans), suggesting that genotype frequencies will be greatly influenced by admixture. Two SNPs were inconsistent with HWE in both case and control subjects: *1*) TCF7L2 rs7903146, where $P = 0.016$ (due to heterozygote excess) in case subjects and $P = 0.015$ (homozygote excess) in control subjects and *2*) HNF4A rs4810424, where $P < 0.0001$ in both case and control subjects, with heterozygotes fewer than expected in both samples. Sequencing results from 23 case and 23 control subjects for these five SNPs were 100% concordant with Illumina or Sequenom calls, except for HNF4A rs4810424, which had one discordant allele call from 92 chromosomes.

Linkage disequilibrium metrics between the two CAPN10 SNPs were $D' = 1.00$ ($r^2 = 0.006$). The TCF7L2 SNPs fell into two blocks of linkage disequilibrium (Fig. 1), with the first block containing intron 3 SNPs rs7901695 and rs7903146 and the second block containing intron 4 SNPs rs7895340, rs11196205, and rs12255372. The three HNF4A SNPs were in high linkage disequilibrium, with pairwise values of $D' = 0.95$ ($r^2 = 0.66$) between rs4810424 and rs1884613, $D' = 0.97$ ($r^2 = 0.85$) between rs1884613 and rs2144908, and $D' = 0.84$ ($r^2 = 0.58$) between rs4810424 and rs2144908.

Single SNP association results are presented in Table 2. Genotype frequencies and counts for each SNP are shown in Supplementary Table 2. The most significant associations were seen with TCF7L2 intron 3 SNPs rs7903146 (additive $P = 4.10 \times 10^{-6}$; admixture-adjusted $P_a = 3.77 \times 10^{-6}$) and rs7901695 ($P = 0.001$; $P_a = 0.003$). The recessive association with TCF7L2 rs7895340 ($P = 0.011$) (Table 2) is based on relatively few homozygous individuals (Supplementary Table 2). Other SNPs that showed modest evidence of association included TCF7L2 intron 4 SNPs rs11196205 and rs12255372; HNF4A SNPs rs4810424, rs1884613, and rs2144908; and KCNJ11 rs5219 (Table 2).

Haplotype analysis of the two CAPN10 SNPs did not exhibit a significant association with type 2 diabetes ($P = 0.96$; data not shown). TCF7L2 haplotype block one, containing rs7901695 and rs7903146, was significantly as-

TABLE 2
Single SNP genotypic tests of association with type 2 diabetes and end-stage renal disease

| Gene | SNP | Major/minor alleles* | Minor allele frequency controls | Minor allele frequency cases | Dominant $P$† | OR (95% CI) | Additive $P$ | OR (95% CI) | Recessive $P$ | OR (95% CI) | Admixture-adjusted additive $P$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CAPN10 | rs2975760 | T/**C** | 0.037 | 0.036 | 0.689 | 0.91 (0.59-1.42) | — | — | — | — | — |
| CAPN10 | rs3792267 | **G**/A | 0.155 | 0.156 | 0.589 | 1.07 (0.83-1.38) | 0.960 | 1.01 (0.80-1.26) | 0.153 | 0.57 (0.26-1.24) | — |
| PPARG | rs1801282 | **C**/G | 0.020 | 0.014 | 0.185 | 0.65 (0.34-1.23) | — | — | — | — | — |
| TCF7L2 | rs7901695 | T/**C** | 0.455 | 0.477 | **0.004** | **1.47 (1.14–1.91)** | **0.001** | **1.30 (1.11–1.53)** | **0.023** | **1.37 (1.04–1.79)** | **0.003** |
| TCF7L2 | rs7903146 | C/**T** | 0.276 | 0.366 | **$1.79 \times 10^{-8}$** | **1.95 (1.54–2.46)** | **$4.10 \times 10^{-6}$** | **1.51 (1.27–1.80)** | **0.444** | **1.16 (0.79–1.69)** | **$3.77 \times 10^{-6}$** |
| TCF7L2 | rs7895340 | **A**/G | 0.226 | 0.188 | 0.100 | 0.82 (0.65-1.04) | **0.022** | **0.79 (0.65–0.97)** | **0.011** | **0.45 (0.24–0.85)** | 0.071 |
| TCF7L2 | rs11196205 | **C**/G | 0.224 | 0.186 | 0.091 | 0.81 (0.64-1.03) | **0.026** | **0.79 (0.65–0.97)** | **0.022** | **0.49 (0.26–0.91)** | 0.078 |
| TCF7L2 | rs12255372 | G/**T** | 0.282 | 0.320 | **0.020** | **1.31 (1.04–1.65)** | **0.044** | **1.20 (1.00–1.43)** | 0.630 | 1.10 (0.74-1.66) | **0.037** |
| KCNJ11 | rs5219 | G/**A** | 0.071 | 0.056 | **0.045** | **0.69 (0.49–0.99)** | — | — | — | — | 0.173‡ |
| TCF1 | rs1800574 | C/**T** | 0.004 | 0.004 | 0.959 | 1.03 (0.33–3.21) | — | — | — | — | — |
| HNF4A | rs4810424 | C/**G** | 0.107 | 0.147 | **0.032** | **1.39 (1.03–1.88)** | **0.018** | **1.28 (1.04–1.57)** | **0.038** | **1.63 (1.02–2.61)** | **0.014** |
| HNF4A | rs1884613 | C/**G** | 0.091 | 0.116 | **0.019** | **1.42 (1.06–1.90)** | 0.042 | 1.31 (1.01-1.70) | 0.837 | 0.93 (0.37-2.30) | **0.026** |
| HNF4A | rs2144908 | G/**A** | 0.097 | 0.126 | **0.018** | **1.41 (1.06–1.87)** | — | — | — | — | 0.408‡ |

*Major allele is defined as most common allele in controls. †Only the dominant model was considered where the minor allele homozygote count for either case or control subjects was <10. Test models refer to the minor allele. ‡Dominant model. Boldface: reported risk allele and $P < 0.05$.

sociated with type 2 diabetes ($P = 3 \times 10^{-5}$; empirical $P = 1 \times 10^{-5}$) (Table 3); however, haplotype block 2—containing rs7895340, rs11196205, and rs12255372—did not reach significance ($P = 0.056$; empirical $P = 0.051$; data not shown). The HNF4A 2-SNP haplotype containing rs4810424 and rs1884613 showed nominal evidence of association with type 2 diabetes, as did the 3-SNP haplotype containing all HNF4A SNPs genotyped (Supplementary Table 3).

## DISCUSSION

We investigated SNPs in six known type 2 diabetes candidate genes for association with type 2 diabetes in an African-American population. The strongest associations with type 2 diabetes were TCF7L2 intron 3 SNPs rs7901695 and rs7903146. Recently, Helgason et al. (24) reported rs7903146 to be the type 2 diabetes risk variant in West Africans. The frequency of the rs7903146 T (risk)-allele was similar in Africans (0.284), African-American control subjects (0.275), European Americans (0.269), and the previously reported African-American sample (0.31) (14). In contrast, the rs7901695 C (risk)-allele was present at a higher frequency in Africans (0.466), African-American control subjects (0.455), and the Amish (0.40) (10) than in European-American (0.295) and other Europid populations (0.22–0.30) (6,7) and was the major allele in African-American case subjects (0.501). For rs7903146, there was a significant increase in relative frequency of heterozygotes in case subjects compared with that in control subjects (+15%), with a comparatively small change in TT homozygotes (+1%). Calculations using a range of allele frequencies bounded by 0.276 (control subjects) to 0.366 (case subjects) suggest that the TT genotype relative risk is smaller than that for heterozygotes; hence, risk is best described by an overdominant model. This is also reflected in the increased OR for the dominant (1.95) versus the additive (1.51) test.

The TCF7L2 SNPs fell within two haplotype blocks (Fig. 1), consistent with the low linkage disequilibrium between rs7903146 and rs12255372 in other African-American populations (14,15). It is possible that the higher linkage disequilibrium observed in Europids has obscured the primary region of association; our results suggest that it may be productive to focus future type 2 diabetes analyses on TCF7L2 intron 3.

Reported associations of type 2 diabetes with SNPs in CAPN10 (25), TCF1 (5), and PPARG (2) were not detected (Table 2). Although nonsignificant, the trend for PPARG P12 risk is in the expected direction and the OR close to reported values (2).

Borderline association with KCNJ11 E23K ($P = 0.044$) (Table 2) is in the direction opposite that in previous reports (3). HNF4A associations with type 2 diabetes (Table 2 and Supplementary Table 3) are in the expected directions (4). However, concordance rates for HNF4A rs4810424 are below 100% for genotyping (97.9%) and sequencing (98.9%), and this SNP shows substantial deviations from HWE estimates ($P < 0.0001$), suggesting that results should be viewed with caution.

Our ascertainment scheme did not distinguish whether associations were with type 2 diabetes or diabetic nephropathy. However, all SNPs in candidate genes were selected on the basis of previous associations with type 2 diabetes. It remains unknown whether TCF7L2 is independently associated with diabetic nephropathy. The majority

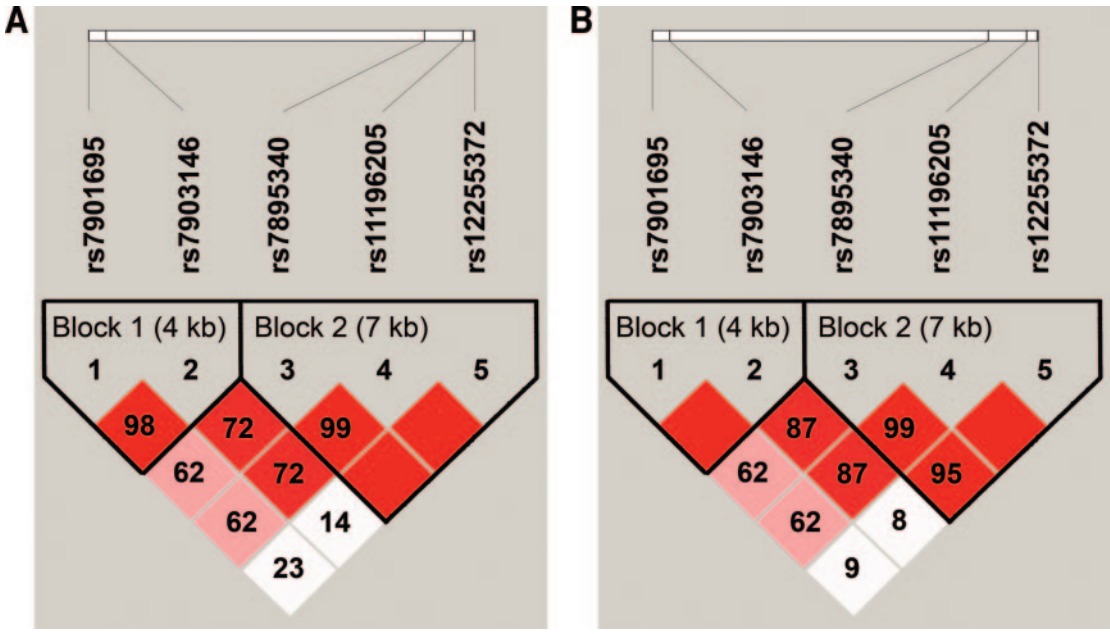


**FIG. 1. Linkage disequilibrium structure of the TCF7L2 gene in African-American case ($n = 577$) (*A*) and control ($n = 596$) (*B*) subjects, with haplotype blocks based on the definition of Gabriel et al. (19) implemented in Haploview. D′ values are displayed in the squares. Empty squares represent a pairwise D′ = 1; red squares represent high pairwise linkage disequilibrium, coloring down to white squares of low pairwise linkage disequilibrium.**

of control subjects were not tested for diabetes, and none were tested for renal impairment; thus, the control sample probably contains a small proportion of undiagnosed type 2 diabetic case subjects and individuals with renal dysfunction. While this has not affected our ability to detect positive associations with TCF7L2, it likely reduced our power to detect more subtle influences of variants in other genes investigated and led to underestimation of ORs.

While adjustment for admixture reduced the strength of the majority of observed associations (Table 2), associations with TCF7L2 SNPs rs7903146 and rs7901695 remained significant. Five self-identified African-American case and four African-American control subjects had estimates of African ancestry below 5%. Removing these individuals from analyses does not substantially change any of our conclusions (data not shown).

This study demonstrates that TCF7L2 is an important diabetes gene in African-American populations. Our results place the strong associations with TCF7L2 SNPs within the context of modest or nonsignificant effects in this population of previously reported type 2 diabetes loci and, more precisely, localize the region associated with disease to intron 3. Further investigations of the mechanism of TCF7L2 risk should be a priority.

TABLE 3
Association analysis for TCF7L2 haplotype containing rs7901695 and rs7903146

| Haplotype | Case frequency | Control frequency | Haplotype score | *P* | Empirical *P* |
|---|---|---|---|---|---|
| Global | — | — | — | $3 \times 10^{-5}$ | $1 \times 10^{-5}$ |
| TC | 0.467 | 0.506 | −3.34 | 0.0009 | 0.0008 |
| CC | 0.169 | 0.219 | −1.37 | 0.17 | 0.18 |
| CT | 0.345 | 0.268 | 4.61 | $<1 \times 10^{-5}$ | $1 \times 10^{-5}$ |


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