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# No Association of Type-2 Diabetes Risk Variants and Prostate Cancer Risk: The Multiethnic Cohort and PAGE

**Kevin M. Waters**[1,*], **Lynne R. Wilkens**[2], **Kristine R. Monroe**[1], **Daniel O. Stram**[1], **Laurence N. Kolonel**[2], **Brian E. Henderson**[1], **Loïc Le Marchand**[2], and **Christopher A. Haiman**[1]

[1]Department of Preventive Medicine, Keck School of Medicine, University of Southern California/ Norris Comprehensive Cancer Center, Los Angeles, California

[2]Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii

## Abstract

**Background—**Epidemiologic studies have found evidence of an inverse association between diabetes status and prostate cancer risk. We explored the hypothesis that common genetic variation may explain, in part, the inverse association between diabetes and prostate cancer.

**Methods—**We tested 17 diabetes risk variants for association with prostate cancer risk in a prostate cancer case-control study of 2,746 cases and 3,317 controls from five racial-ethnic groups in the Multiethnic Cohort.

**Results—**After adjustment for multiple testing none of the alleles were statistically significantly associated with prostate cancer risk. Aggregate scores that sum the risk alleles were also not significantly associated with risk.

**Conclusions—**We did not find evidence of association of this set of diabetes risk alleles with prostate cancer.

**Impact—**Resequencing and fine-mapping of the GWAS-identified loci for diabetes and prostate cancer is necessary to understand any genetic contribution for the inverse association between these common diseases.

### Keywords

Genitourinary cancer; prostate; type 2 diabetes; multiethnic; epidemiology

## Introduction

Epidemiologic studies provide support for type 2 diabetes (T2D) being protective for prostate cancer (PC) (1). Recently, three loci *(HNF1B, JAZF1, and THADA*) have been associated with the risk of both diseases, suggesting a genetic link (2).

Support for this hypothesis was recently provided in a PC study of 18 established T2D genetic risk variants, which reported a summary T2D genetic risk score (both with and without the *HNF1B* allele) to be associated with decreased PC risk in men of European ancestry (OR 0.96; 95%CI 0.92–0.99; P=0.02; without *HNF1B*) (3).

*Corresponding Author: Kevin M. Waters, Harlyne Norris Research Tower, 1450 Biggy Street, Room 1504, Los Angeles, CA 90033, Telephone: (323) 442-7755, Fax: (323) 442-7749, kwaters@usc.edu.

As part of the Population Architecture using Genomics and Epidemiology (PAGE) initiative, we tested established T2D risk alleles in a study of 2,746 incident PC cases and 3,317 controls among 5 populations from the Multiethnic Cohort (MEC).

## Methods

### Study population

The MEC is a prospective cohort of 215,251 subjects, previously described in detail (4). Incident cancer cases are identified annually through cohort linkage to population-based cancer Surveillance, Epidemiology, and End Results (SEER) registries in Hawaii and Los Angeles County as well as to the California State cancer registry.

The MEC PC case-control study includes 2,746 invasive cases and 2,288 controls, frequency matched by age (5 year groups) and race (5). We included 1,029 additional male controls with no PC history from a colorectal cancer MEC case-control study (6). Altogether, this study included 2,746 cases and 3,317 controls (European American (472/558), African American (721/954), Latino (668/704), Japanese American (753/936), and Native Hawaiian (132/165)). The Institutional Review Boards at the University of Southern California and University of Hawaii approved the study protocol.

### Genotyping

Genotyping of 17 T2D risk variants (Table 1) was performed using TaqMan. The variant in *SLC30A*8 (rs13266634) failed genotyping due to an adjacent SNP (rs16889462). The genotype completion rate for each SNP was >96.0% among both cases and controls in each racial/ethnic group. Of 90 Hardy-Weinberg Equilibrium (HWE) tests for each SNP in each racial/ethnic group, 2 were statistically significant ($p<0.05$, 4.5 expected).

### Statistical Analysis

Odds ratios (OR) and 95% confidence intervals (95% CI) for log-additive effects were estimated in unconditionallogistic regression models adjusted for age, diabetes self report, and BMI ($kg/m^2$). Subjects missing genotype information for more than 5 SNPs were excluded (n=62). Aggregate T2D risk scores (sum of total risk alleles - assigned based on OR>1 in published T2D GWAS) were used to test the hypothesis that overall T2D susceptibility is protective for PC risk. The risk score per allele ORs assumed independent effects of approximately the same magnitude for each allele. Individuals missing genotypes for a SNP were assigned the average number of risk alleles within each ethnicity.

## Results

On average, cases (mean 69.3 years) were slightly older than controls (68.6). After adjusting for multiple tests, we observed no statistically significant associations with PC risk. In racial/ethnic pooled analysis the *TSPAN8* variant (rs7961581) was nominally significantly associated with risk prior to adjustment for multiple tests (OR=0.90; 95% CI 0. 83–0.99; P=0.021). In racial-ethnic specific analysis we observed p values < 0.05 with variants in *IGF2BP2 CDC123* and *THADA* (HWE p value=$2.0\times10^{-4}$ for rs7578597 in Japanese Americans due to 2 rare homozygotes, 0.4 expected).

In the pooled sample, the mean risk allele count was 17.0 (range 8–25) and the per allele OR of the T2D risk score was 1.00 (95%CI 0.98–1.03; P=0.69). The ORs for the risk score ranged from 0.98 in Latinos to 1.03 in European Americans and were not statistically significant in any population (all P-values≥0.20).

## Discussion

In this multiethnic study, we found limited evidence that the known T2D risk variants are associated with PC risk independently or in combination. Our null findings with the summary risk score is different from a previous PC study of European Americans which found an inverse association (3). Aside from the *SLC30A*8 allele, the same variants were investigated in both studies (though for many SNPs highly correlated proxies to the index SNPs were used in the previous study). Discovered in European-ancestry populations, many of these markers may not be proxies of the functional alleles in other populations due to differences in LD and allele frequencies. However, we previously showed that the majority of these alleles were associated with T2D risk independently and in aggregate, in these populations (7). We also did not observe significant population heterogeneity in the associations of these variants. In the combined sample we had >77% power (adjusting for 17 tests) to detect an OR of 0.85 for common alleles (MAF≥0.25). We were underpowered, however, to detect modest associations in any single racial/ethnic group.

In conclusion, we did not find evidence for associations between validated T2D risk variants and PC risk in multiple populations. Once identified, the functional alleles at these loci, as well at other novel T2D risk loci, will need to be examined for a role in PC risk in these populations.

## Acknowledgments

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**Table 1**

The association of known T2D risk alleles with prostate cancer risk by race/ethnicity.*

| SNP/Allele Tested† | Chr./Nearest Gene | European Americans 472 cases 558 controls | African Americans 721 cases 954 controls | Latinos 668 cases 704 controls | Japanese Americans 753 cases 936 controls | Native Hawaiians 132 cases 165 controls | Pooled 2,746 cases 3,317 controls | Pooled P value (trend) | $P_{het}$‡ |
|---|---|---|---|---|---|---|---|---|---|
| rs10923931 T | 1 *NOTCH2* | 0.89(0.67–1.18) 0.11 | 0.91(0.78–1.05) 0.32 | 1.02(0.79–1.31) 0.10 | 1.05(0.65–1.68) 0.02 | 1.02(0.49–2.13) 0.05 | 0.93(0.84–1.04) 0.14 | 0.22 | 0.90 |
| rs7578597 T | 2 *THADA* | 0.97(0.73–1.29) 0.90 | 1.04(0.88–1.21) 0.75 | 1.31(0.97–1.77) 0.92 | 3.47(1.48–8.18) 0.99 | 0.99(0.47–2.08) 0.95 | 1.11(0.98–1.25) 0. 90 | 0.092 | 0.017 |
| rs1801282 C | 3 *PPARG* | 1.09(0.81–1.46) 0. 89 | 1.04(0.69–1.59) 0.97 | 1.02(0.78–1.33) 0.91 | 0.98(0.68–1.42) 0.96 | 1.53(0.76–3.10) 0.93 | 1.05(0.90–1.23) 0.94 | 0.51 | 0.90 |
| rs4607103 C | 3 *ADAMTS9* | 0.96(0.79–1.17) 0.74 | 1.06(0.91–1.23) 0.71 | 0.95(0.81–1.12) 0.69 | 1.02(0.88–1.17) 0.62 | 1.17(0.80–1.72) 0.73 | 1.01(0.93–1.09) 0.69 | 0.89 | 0.78 |
| rs4402960 T | 3 *IGF2BP2* | 1.26(1.05–1.52) 0.29 | 0.97(0.85–1.11) 0.52 | 0.99(0.84–1.18) 0.26 | 1.09(0.94–1.26) 0.30 | 0.81(0.55–1.18) 0.29 | 1.05(0.97–1.13) 0.35 | 0.26 | 0.097 |
| rs10010131 G | 4 *WFS1* | 1.02(0.85–1.22) 0.62 | 1.08(0.93–1.25) 0.64 | 1.11(0.93–1.31) 0.71 | 0.79(0.46–1.35) 0.99 | 1.46(0.93–2.31) 0. 81 | 1.07(0.98–1.17) 0.76 | 0.13 | 0.56 |
| rs7754840 C | 6 *CDKAL1* | 1.02(0.85–1.23) 0.31 | 1.14(1.00–1.32) 0.54 | 0.98(0.83–1.14) 0.32 | 0.99(0.86–1.13) 0.44 | 1.05(0.74–1.48) 0.56 | 1.04(0.96–1.12) 0.43 | 0.36 | 0.58 |
| rs864745 T | 7 *JAZF1* | 0.90(0.75–1.08) 0.51 | 0.96(0.83–1.12) 0.72 | 0.93(0.79–1.08) 0.62 | 1.16(0.98–1.38) 0.78 | 0.85(0.58–1.25) 0.77 | 0.98(0.90–1.06) 0.68 | 0.54 | 0.25 |
| rs2383208 A | 9 *CDKN2B* | 0.95(0.75–1.20) 0. 82 | 1.06(0.88–1.27) 0. 81 | 0.93(0.76–1.14) 0. 85 | 1.00(0.87–1.15) 0.56 | 0.95(0.63–1.42) 0.77 | 0.99(0.91–1.08) 0.75 | 0.85 | 0.91 |
| rs1111875 C | 10 *HHEX* | 1.11(0.92–1.32) 0.58 | 1.10(0.94–1.30) 0.74 | 1.03(0.89–1.20) 0.63 | 0.99(0.85–1.15) 0.28 | 1.03(0.72–1.48) 0.29 | 1.05(0.97–1.14) 0.54 | 0.22 | 0.86 |
| rs7903146 T | 10 *TCF7L2* | 0.98(0.81–1.18) 0.32 | 0.97(0.84–1.13) 0.29 | 1.06(0.88–1.26) 0.24 | 0.92(0.66–1.30) 0.05 | 1.02(0.64–1.64) 0.14 | 1.00(0.91–1.09) 0.21 | 0.91 | 0.93 |
| rs12779790 G | 10 *CDC123* | 1.30(1.03–1.64) 0.15 | 1.04(0.86–1.26) 0.15 | 0.91(0.75–1.11) 0.18 | 1.00(0.83–1.20) 0.17 | 0.92(0.61–1.38) 0.21 | 1.03(0.94–1.14) 0.16 | 0.53 | 0.23 |
| rs2237895§ C | 11 *KCNQ1* | 0.94(0.78–1.13) 0.42 | 0.96(0.81–1.14) 0. 21 | 0.92(0.77–1.09) 0.44 | 1.08(0.91–1.28) 0.34 | 0.86(0.59–1.27) 0.35 | 0.98(0.90–1.06) 0.34 | 0.55 | 0.32 |
| rs2237897§ C | 11 *KCNQ1* | 1.03(0.70–1.50) 0.95 | 0.92(0.72–1.18) 0.92 | 0.95(0.78–1.15) 0.78 | 1.05(0.88–1.24) 0.62 | 1.25(0.79–1.97) 0.78 | 1.02(0.92–1.13) 0. 80 | 0.76 | 0.45 |
| rs5219 T | 11 *KCNJ11* | 1.11(0.92–1.33) 0.36 | 0.97(0.77–1.22) 0.11 | 0.95(0.82–1.11) 0.38 | 0.97(0.84–1.11) 0.37 | 1.22(0.87–1.72) 0.36 | 1.00(0.93–1.09) 0.29 | 0.93 | 0.57 |
| rs7961581 C | 12 *TSPAN8* | 0.99(0.82–1.19) 0.30 | 0.92(0.78–1.08) 0.23 | 0.89(0.74–1.06) 0.23 | 0.87(0.73–1.03) 0.21 | 0.80(0.56–1.15) 0.32 | 0.90(0.83–0.99) 0.24 | 0.021 | 0.79 |

| SNP/Allele Tested[†] | Chr./Nearest Gene | European Americans 472 cases 558 controls | African Americans 721 cases 954 controls | Latinos 668 cases 704 controls | Japanese Americans 753 cases 936 controls | Native Hawaiians 132 cases 165 controls | Pooled 2,746 cases 3,317 controls | Pooled P value (trend) | $P_{het}$[‡] |
|---|---|---|---|---|---|---|---|---|---|
| rs8050136<br>A | 16<br>*FTO* | 1.05(0.88–1.25)<br>0.39 | 0.93(0.81–1.08)<br>0.44 | 1.07(0.90–1.26)<br>0.28 | 0. 88(0.74–1.04)<br>0.21 | 0.81(0.55–1.20)<br>0.24 | 0.97(0.89–1.05)<br>0.32 | 0.38 | 0.32 |

[*] In each cell is the odds ratio (and 95% confidence intervals) for allele dosage effects along with the risk allele frequency in controls. ORs adjusted for age (quartiles), BMI (quartiles), type 2 diabetes (self-report), and ethnicity (in pooled analysis)

[†] NCBI build 36 (forward strand)

[‡] $P_{het}$ = P value for heterogeneity of allelic effects across ethnic groups (4 df test)

[§] rs2237895 and rs2237897 adjusted for each other