**ARIC Manuscript Proposal # 1280**

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| **PC Reviewed: _8_/21_/07** | **Status: ___A_** | **Priority: _2__** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**:

Interactions between diabetes, diabetes genes, and the androgen receptor gene on risk of prostate cancer.

**b. Abbreviated Title (Length 26 characters)**:

Diabetes and Prostate Cancer

**2. Writing Group**:

Tamra E. Meyer, MPH, Eric Boerwinkle, PhD, Kelly Volcik, PhD, Alanna Morrison, PhD, Maureen Sanderson, PhD; Ann L. Coker, PhD, James S. Pankow, PhD, Aaron R. Folsom, MD, MPH

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _TEM__ **[please confirm with your initials electronically or in writing]**


F**irst author**: **Tamra E. Meyer, MPH**
Address: Human Genetics Center
UT School of Public Health
University of Texas Health Science Center at Houston
1200 Herman Pressler, Suite RAS-E435
Houston, TX 77030

Phone: 713-500-9897 Fax: 713-500-0900
E-mail: Tamra.E.Meyer@uth.tmc.edu

**Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author)**:

**Senior author: Eric Boerwinkle, PhD**
Address: Human Genetics Center
UT School of Public Health
University of Texas Health Science Center at Houston
1200 Herman Pressler, Suite RAS-E447
Houston, TX 77030

Phone: (713) 500-9816 Fax: 713-500-0900
E-mail: Eric.Boerwinkle@uth.tmc.edu

## 3. Timeline:

- Genotyping to be completed by October 1, 2007.
- Data cleaning to be completed by November 1, 2007.
- Data analysis to be completed by December 1, 2007.
- Manuscript draft to be completed by February 1, 2008.
- Manuscript submission by May 1, 2008.

## 4. Rationale:

### PROSTATE CANCER IS A SIGNIFICANT PUBLIC HEALTH PROBLEM

Prostate cancer is the leading cause of cancer incidence and the second leading cause of cancer mortality in men from the US.[1] Few consistent risk factors have been identified for prostate cancer except for age, race, and family history.[1] The association with family history indicates that genetic factors likely play an important role in the etiology of prostate cancer. The heritability of liability of prostate cancer is estimated to be about 42%.[2]

### GENES ASSOCIATED WITH DIABETES MAY INFLUENCE RISK OF PROSTATE CANCER

Genes associated with diabetes have been implicated as candidate genes for prostate cancer since several epidemiologic studies have reported associations between diabetes and prostate cancer. A meta-analysis of 19 studies published from 1971 to 2005 reported a negative association of 0.84 (95% CI: 0.76-0.93) between diabetes and prostate cancer.[3] Since 2005, one additional study found a negative association between diabetes and prostate cancer that approached statistical significance[4] while another study reported a null association with diabetes.[5]

Diabetes is a major risk factor for coronary heart disease in both blacks and whites.[6] As part of its regular contract mission, the ARIC study has genotyped polymorphisms in multiple diabetes susceptibility genes. For the most part, these studies have been in response to previous publications in smaller case-control studies. The overall objective of this manuscript proposal is to make opportunistic use of these data and examine the association between these candidate gene variations and prostate cancer in male participants in ARIC. The prostate cancer data are available as a result of ancillary study #1995.04, under the direction of Dr. Aaron Folsom at the University of Minnesota, who is a co-author on this proposal.

The genes of interest in this analysis include those recently replicated in genome-wide association studies of type 2 diabetes: TCF7L2, PPARG, KCNJ11, FTO, CDKAL1, HHEX, CDKN2A/B, SLC30A8, IGF2BP2, rs9300039[7-9], and genes identified with strong genetic or biological association in recent large case-control studies, reviews and meta-analyses: ADRB2, CAPN10, ENPP1, INS, IRS-1, PGC-1, IL-6, SLC2A2, ACDC, UCP2, UCP3, TCF1, and TCF2.[10-14] These genes are either previously genotyped or are in the process of being genotyped on the entire ARIC cohort as part of recent diabetes discovery.

## THE AR GENE MAY INTERACT WITH DIABETES AND GENES ASSOCIATED WITH DIABETES TO MODIFY RISK OF PROSTATE CANCER

Variation in the androgen receptor gene (AR) has been well studied as a risk factor for prostate cancer with inconsistent results.[15] However, it is generally recognized that shorter CAG repeat length is associated with an increased risk of prostate cancer.[15] Some recent studies have suggested that AR may interact biologically with several diabetes gene products.[16-17] Therefore, we will also test interactions between variation in diabetes genes and AR as well as interactions between measures of diabetes and AR. The AR gene is in the process of being genotyped on the entire ARIC cohort.

## REFERENCES


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17. Pelley RP, Chinnakannu K, Murthy S, et al. Calmodulin-androgen receptor (AR) interaction: Calcium-dependent, calpain-mediated breakdown of AR in LNCaP prostate cancer cells. *Cancer Res*. 2006;66:11754-11762.

## 5. Main Hypothesis/Study Questions:

- **Hypothesis 1:** The diabetes SNPs below, which are already or will be typed on the entire ARIC cohort, are independently associated with incident prostate cancer.

| Gene Name | Common SNP Name | dbSNP ID (if available) | Gene Name | Common SNP Name | dbSNP ID (if available) |
|---|---|---|---|---|---|
| | | rs9300039§ | IL6 | -174G/C | rs1800795§ |
| ACDC | – 11391G/A | rs17300539§ | INS | 5' VNTR§ | |
| ADRB2 | Gln27Glu | rs1042714† | IRS-1 | Gly972Arg | rs1801278§ |
| CAPN10 | SNP43 | rs3792267‡ | KCNJ11 | E23K | rs5219∞ |
| CDKAL1 | | rs7754840§ | PGC-1 | Gly482Ser | rs8192678§ |
| CDKN2A/B | | rs10811661‡ | PPARG | Pro12Ala | rs1801282∞ |
| ENPP1 | K121Q | rs1044498§ | SLC2A2 | Thr110Ile | rs5400∞ |
| FTO | | rs8050136§ | SLC30A8 | | rs13266634§ |
| HHEX | | rs1111875§ | TCF7L2* | | rs12255372∞ |
| HNF1a_TCF1 | I27L | rs1169294§ | TCF7L2* | | rs7903146∞ |
| HNF1b_TCF2 | | rs757210§ | UCP2 | -866G/A | rs659366§ |
| IGF2BP2 | | rs4402960§ | UCP3 | -55C/T | rs1800849§ |

*Since TCF7L2 polymorphisms and prostate cancer are currently being investigated in manuscript#1227, main effects for this gene will not be reported as a part of this paper, but will be included in interactions and in the risk score. †Listed in the online ARIC SNP database; ‡Submitted to ARIC Coordinating Center; ∞Genotyping complete but not yet reported to ARIC Coordinating Center; §Genotyping in progress in the laboratory

- **Hypothesis 2:** Diabetes candidate SNPs interact with the AR CAG VNTR (rs35025615) in a pairwise manner to modify risk of prostate cancer.
    - The main effect of AR and prostate cancer has not been previously evaluated and will be reported in this manuscript.
- **Hypothesis 3:** The risk of prostate cancer is modified according to a diabetes genetic risk score comprising scores for risk genotypes identified.
- **Hypothesis 4:** Diabetes interacts with AR CAG VNTR to modify risk of prostate cancer.
    - The main effect of diabetes on prostate cancer in ARIC has been previously reported.
- **Hypothesis 5:** Serum insulin and glucose interact with AR CAG VNTR to modify risk of prostate cancer.

**6. Data (variables, time window, source, inclusions/exclusions)**:

**Overview**

The analysis will be conducted by Tamra Meyer and supervised by Eric Boerwinkle. Both parties have signed the data distribution agreement. Cox proportional hazards models in Stata™ version 9.0 will be used for analyses. Prior to analysis, individuals will be excluded for female sex, race other than white or black, prevalent cancer at baseline (other than skin cancer), black race in Minnesota and Washington County and for restrictions on genetic analysis. Any SNPs with greater than 10% missing data or that are incompatible with Hardy-Weinberg equilibrium will be excluded. False discovery rate control will be used to determine appropriate significance levels adjusted for multiple testing. Associations will be evaluated for the population as a whole and the direction of associations will be confirmed separately among whites and blacks.

**Hypothesis-Specific Analysis Plan**

**Hypothesis 1:**

Main effects for each SNP on risk of prostate cancer through 2000 will be determined in Cox models adjusted for race. SNPs will be evaluated using an additive genetic model.

**Hypothesis 2:**

SNPs with main effects (Wald test $p<0.1$) using an additive model or those with literature suggesting biologically plausible interaction between the gene product and the AR will be evaluated by including an interaction term for each SNP and AR in the Cox model adjusted for race.

**Hypothesis 3:**

SNPs with main effects (Wald test $p<0.1$) using an additive model or those interacting with AR (likelihood ratio $p<0.1$) will be considered in a genetic risk score (GRS) calculated as follows for each individual:

1. SNP genotype value: 1 for the risk homozygote, 0 for the heterozygote, and -1 for the non-risk homozygote
2. For SNPs with main effects:
   SNP-specific GRS=SNP genotype value*SNP β-coefficient from a Cox model containing terms for the SNP and race
3. For SNPs that interact with AR:
   SNP-specific GRS=SNP genotype value*AR genotype value*interaction term β-coefficient from a Cox model that contains the interaction term, both lower order terms, and race
4. Total GRS= sum of SNP-specific GRS

For SNPs that differ in the direction of the association by race, a race-specific SNP genotype value and GRS will be used for that SNP. Continuous Total GRS will be included in a Cox model along with race to determine the Hazard Ratio for the association between GRS and time to prostate cancer.

**Hypothesis 4:**
Interaction between incident diabetes (DIABTS23 from visit 2, DIABTS34 from visit 3, and DIABTS42 from visit 4) or prevalent plus incident diabetes (DIABTS03 from visit 1, DIABTS23 from visit 2, DIABTS34 from visit 3, and DIABTS42 from visit 4) and AR as they combine to influence prostate cancer will be determined by including an interaction term for diabetes and prostate cancer in a Cox model. Potential confounders from the literature (such as race (RACEGRP from visit 1), body size (BMI01 from visit 1), age (V1AGE01 from visit 1), and frequency of routine physical exams (HHXB02 from visit 2)) will be included in the model if they change the OR for the association between diabetes and prostate cancer by at least 10%. Those missing on diabetes at all visits or those diagnosed with diabetes within one year of or after prostate cancer diagnosis will be excluded as appropriate.

**Hypothesis 5:**
The interaction between serum insulin (INSSIU01 from visit 1), serum glucose (GLUSIU01 from visit 1) and AR as they combine to influence prostate cancer will be evaluated. Insulin and glucose will be categorized into quartiles. Those missing on these variables, those who report using insulin to treat their diabetes, or those with information collected only after prostate cancer diagnosis will be excluded. Confounders will be considered as for hypothesis 4. In addition, models will be adjusted for diabetes treatment. Since serum insulin in particular is prone to measurement error, we will interpret these results with caution.

**7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ No**

**b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? _X__ Yes ____ No**
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

**8.a. Will the DNA data be used in this manuscript? __X__ Yes ____ No**

**8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?**
**__X__ Yes ____ No**

**9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.**
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X____ Yes _____ No

**10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

1. **Proposal #1078-Metabolic Syndrome and Prostate Cancer Incidence; SC Reviewed _5/13/05; Published AJE 2006;164:1094-1102**
2. **Proposal #785-Testosterone, Androgen Receptor Polymorphism and the QT Prolongation Index**
3. **Proposal #1227-TCF7L2 Variants and Cancer Risk**

**11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No**

**11.b. If yes, is the proposal**

**_X__ A. primarily the result of an ancillary study (list number*_1995.07, 1995.04_)**

**___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)**

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

**12. Manuscript preparation is expected to be completed in one to two years. If a manuscript is not submitted for ARIC review at the end of the 2-years from the date of the approval, the manuscript proposal will expire.**