ARIC Manuscript Proposal # 785

1.a. Full Title: Testosterone, Androgen Receptor Polymorphism and the QT Prolongation Index

b. Abbreviated Title (Length 26 characters):
AR Polymorphism & QTI

2. Writing Group (list individual with lead responsibility first):

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3. Timeline: We are currently preparing a research project grant application (R01) for submission on June 1, 2001 based on an ancillary study proposal which was approved by the ARIC Executive Committee at its February 28, 2001 meeting in San Antonio, TX. The proposal will be reviewed by the ARIC Laboratory Committee at its upcoming meeting. Our timeline therefore depends on input from key ARIC collaborators and ability to compete successfully for R01 funding. At this point, however, we anticipate completing our line of investigation in a three-stage process. In Stage 1, we will test the first of three major hypotheses (see below). In Stage 2, we will test our second and third hypotheses, and in Stage 3, we will expand our focus from the prediction of QT prolongation to the prediction of relevant clinical endpoints.

4. Rationale: The congenital long QT syndrome (LQTS) is a rare genetic disease characterized by life-threatening ventricular tachyarrhythmias, prolonged ventricular repolarization, and as its eponym implies, a long QT interval. At least 177 mutations in five genes encoding potassium or sodium channel proteins have been implicated in the pathogenesis of congenital LQTS. Despite provocative evidence suggesting that polymorphism of the androgen receptor, a ligand-dependent transcription factor present in atrial and ventricular myocardium, also may be an important predictor of the duration of ventricular repolarization, the putative association has not been directly evaluated. This albeit indirect evidence includes findings that the duration of ventricular repolarization is shortened by testosterone (the androgen receptor ligand), that it is longer among
women than men, and as compared with relatively healthy controls, that it is longer in hypogonadal men and shorter in virilized women. These findings are consistent with the marked decrease in the QT prolongation index (QTI) during puberty in males, but not females, the gradual return of QTI toward pre-pubertal levels during development of a relatively hypogonadal state among aging men, and the striking predominance of women with acquired and congenital LQTS.

The trinucleotide repeat ([CAG]$_n$) in exon 1 of the androgen receptor gene varies in length among the normal population. Abnormal expansion of [CAG]$_n$ causes X-linked, recessive spinal and bulbar muscular atrophy (SBMA, Kennedy’s disease), a rare, adult-onset neurodegenerative disease characterized by androgen insensitivity and in some cases, left ventricular hypertrophy or frank cardiomyopathy. Because fertility, benign prostatic hyperplasia and prostate cancer (androgen-related health states) have been inversely associated with [CAG]$_n$, we plan to address the relationship between [CAG]$_n$, bioavailable testosterone concentration and QTI.

5. **Main Hypothesis/Study Questions:** This ancillary study is designed to answer three main questions: 1) Is the duration of ventricular repolarization associated with a functional polymorphism of the androgen receptor? 2) Is the duration of ventricular repolarization associated with androgen levels? 3) Do androgen levels modify the association between duration of ventricular repolarization and this functional polymorphism? In answering these and related questions, the ancillary study will give practitioners who are treating patients with hypogonadism and survivors of ventricular tachyarrhythmia with increasing regularity insight into the potential cardiovascular consequences of androgen deficiency and testosterone replacement therapy.

6. **Data (variables, time window, source, inclusions/exclusions):**
Our study population will include a race, gender and QTI-stratified random sample of participants aged 51-70 years at Visit 3. We will base eligibility of participants on absence of conditions associated with acquired QT prolongation. We will measure QTI from the resting, twelve-lead electrocardiogram and [CAG]$_n$ from extracted DNA using the polymerase chain reaction and automated fluorescence technology or direct DNA sequencing. We also will genotype a panel of unlinked genetic markers and measure bioavailable testosterone from stored sera. We will rely on stratified, weighted, multi-variable logistic regression and analysis of variance models of QTI on [CAG]$_n$ to measure strength of the QTI-[CAG]$_n$ association and to determine whether bioavailable testosterone modifies this association. We will use the average $\chi^2$ square statistic for associations between QTI and unlinked genetic markers to adjust for latent population stratification.

7a. **Will the data be used for non-CVD analysis in this manuscript?** ____ Yes  __X__ No
As described above, the data collected by this ancillary study will not be used for non-CVD analyses. However, based on conversations with other ARIC investigators, future analyses could logically focus on non-CVD, androgen-related health states (e.g. male-pattern baldness or prostate cancer).

7b. **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 response to consent updates related to stored sample use for research.)
8a. Will the DNA data be used in this manuscript?  __X__ Yes  ____ No

8b. 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

  __X__ Yes  _____ No