# ARIC Manuscript Proposal # 868

**PC Reviewed: 03/12/02** **Status: __A__** **Priority: __2__**
**SC Reviewed: 03/19/02** **Status: __A__** **Priority: __2__**

**1.a. Full Title:** Lipid-related genetic risk factors for decline in renal function in African-Americans in the ARIC Study

**b. Abbreviated Title (Length 26 characters):** Lipid genes & renal function decline

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

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## 3. Timeline:

The data for these analyses are already available as part of ARIC and the genotyping of Dr. Bray. We project that the analyses and writing will take place over the next six months.

## 4. Rationale:

End-stage renal disease (ESRD) incidence and prevalence have been increasing relentlessly as long as national statistics have been available. In 1998, there were more than 85,000 incident cases and more than 320,000 prevalent cases of ESRD in the United States [1, 2]. The incidence and prevalence of ESRD have doubled in the past 10 years and are expected to increase steadily [3]. Patients treated for ESRD experience a markedly higher risk of morbidity and mortality. Despite these statistics the etiology of ESRD is not fully understood. Kidney disease, especially associated with diabetes, is a significant cause of morbidity and mortality in the United States, particularly in African-Americans.

There is strong evidence that inherited factors contribute to renal failure susceptibility. Familial aggregation of nephropathy has been demonstrated in all major etiologies of end-stage renal disease (ESRD) and in every ethnic group evaluated [4]. With diabetes mellitus, epidemiological and family studies indicate genetic factors play an important role in the development of nephropathy [5-7]. There is especially compelling evidence in African-Americans for a genetic contribution to renal disease; evidence demonstrates that ESRD clusters independently from the systemic diseases of hypertension, diabetes mellitus, HIV infection, and systemic lupus erythematosus, furthermore disparate etiologies of ESRD exist within families from widely separated geographic regions of the US.

ARIC provides an excellent opportunity to study genetic risk factors for the early stages of the decline in renal function using the visit 1, 2, and 4 plasma creatinine measures.

The proposed study will examine specific lipid-related candidate genes and their association with decline in renal function. A prospective analysis of genetic risk factors for a rise in plasma creatinine during the 9 years of follow-up will be done. The primary outcome will be a combined incidence of a rise of at least 0.4 mg/dL in plasma creatinine above baseline (after accounting for laboratory differences between visit 4 and prior visits) or a

hospitalization for kidney disease. This definition has worked well in prior ARIC analyses [8, 9]. In addition, we will conduct analyses of the cross-sectional association of genotype with estimated GFR at the baseline visit. GFR will be estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation [3, 10]. Sensitivity analyses will explore a >=30% drop in estimated GFR as an alternative outcome. These parallel analytic approaches will ensure that results are robust to the specific outcome definition. This proposal will look at a number of genotypes which have already been typed. The study population will include approximately 3377 African Americans and an anticipated 272 cases with the primary outcome (197 from rise in plasma creatinine, 75 from hospitalization for kidney disease). Within ARIC, it has been shown that early renal function decline is 3 times more likely to develop in blacks than whites [9].

Dyslipidemia has been shown to play a role in the decline of renal function [8, 11, 12]. Several studies have focused on associations between the epsilon 2, 3,and 4 polymorphisms of apolipoprotein E (APOE) and development of renal disease. Carriers of apoE4 tend to have higher plasma levels of total and LDL cholesterol [13]. Though it has been associated with development of Alzheimer's disease [14] and CHD [15], carriers of apoE4 tend to be at lower risk for development of diabetic nephropathy [16]. The binding of apoE2 to lipoprotein receptors is defective in comparison with apoE3 or apoE4 and results in delayed clearance of triglyceride-rich lipoprotein [13]. There have been several studies that have demonstrated an association between the epsilon 2 allele and nephropathy associated with either IDDM [17] or NIDDM [18, 19]. However, there are also studies that have shown no association [20-22]. Most studies have been Japanese [18, 19], and the only U.S. study has been clinic-based [17]. As yet there has been no investigation of genetic variation of ApoE in a population-based study in the U.S. or in African-Americans. Also of interest are the paraoxonase genes; paraoxonase1 (PON1) is an enzyme bound to HDL which prevents the oxidation of LDL and HDL. PON polymorphisms have been associated with CHD [23] and with diabetic nephropathy [24]. The neuropeptide Y (NPY) 1128T-C polymorphism that results in substitution of leucine by proline at residue 7 in the signal peptide part of pre-pro-NPY has been associated with high serum total and LDL cholesterol levels [25] and diabetic retinopathy [26]. In animal studies, lipoprotein lipase (LpL) regulates lipoprotein-stimulated mesangial cell proliferation and gene expression, suggesting a role in glomerulosclerosis [27]. Clinical studies have also demonstrated possible roles for LpL [28-30] and hepatic lipase activity [30] in the development of diabetic nephropathy. We propose to examine polymorphisms in ApoE, PON1, NPY, LpL, hepatic lipase, and hormone sensitive lipase and their associations with decline in renal function.

The ability to examine gene-gene and gene-environment interactions will make this study especially interesting. The potential to examine causal pathways of lipid genes and nephropathy in a population-based sample that has been underrepresented in studies thus far will make this analysis particularly pertinent. Potential confounding by age, gender, socioeconomic factors, blood pressure, hypertension, diabetes, BMI and lipids will be controlled for. All analyses will be done stratified on diabetes, gender, and hypertension to avoid overlooking potential interactions.

## 5. Main Hypothesis/Study Questions:

The role of lipid-related candidate genes and their association with kidney disease in African-Americans.

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

Data analysis will be performed by C. Hsu and Dr. J. Coresh at the Johns Hopkins School of Hygiene & Public Health.

Variables needed (available at JHU): plasma creatinine and time of collection, center, age, gender, race, blood pressure, anthropometric data, medical history data (diabetes) and hospitalization for kidney disease. Genotypes (to be obtained from Dr. Bray) for ApoE, paraoxonase 1, neuropeptide Y, lipoprotein lipase, hepatic lipase, and hormone sensitive lipase.

## 7.a. Will the data be used for non-CVD analysis in this manuscript? __ 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?** **_✓_ 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?** **_✓_ 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"?** **_✓_ 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

_✓_ Yes _____ No

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