1. a. **Full Title**: The Frequency of an Amyloidogenic Allele of Transthyretin (V122I) Decreases with Increasing Age in Community Samples of African-Americans

b. **Abbreviated Title (Length 26 characters)**: TTR V122I Decreases with Age

2. **Writing Group**: Writing group members: Joel Buxbaum, Alice Alexander, Daniel Jacobson, Clement Tagoe, Dalane Kitzmann, James Koziol, Tom Mosely, Ervin Fox

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

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3. **Timeline**: Immediate

4. **Rationale**: Genotyping for the amyloidogenic transthyretin allele TTR V122I of the African-American cohorts of both ARIC (under 65) and the Cardiovascular Health Study
(CHS)(over 65) has been performed. Analysis of the data indicate that the prevalence of the allele decreases with increasing age, suggesting a mortality effect consistent with the role of the allele in imparting an absolute anatomic risk for cardiac amyloid deposition after age 60. It can be argued that the two African-American populations can be different genetically or have different genetic substructures. Both populations have been typed for alleles in the α-adducin gene (Chromosome: 4; Location: 4p16.3) and that encoding the G-protein beta3 subunit (Chromosome: 12; Location: 12p13) and have identical allele frequencies, suggesting that the two cohorts are part of the same population genetically. Their widely dispersed locations in the genome support that conclusion. Recently Blair et al have published the results of genotyping 1632 of the ARIC African-American cohort for the ApoE 2, 3 and 4 alleles. We have compared the frequency of those alleles with those found in the CHS African-American participants and found significant differences in both ApoE 3 and 4, i.e. the frequency of ApoE 3 being higher and that of ApoE4 lower. These data are consistent with the previously demonstrated age-associated decrement in ApoE4 found in the CEPH cohort and represent a positive age control for our TTR V122I data. Hence we are confident that the significant association of TTR V122I with mortality is genuine. Nonetheless it can be argued that the ARIC and CHS cohorts represent different genetic strata of the entire African-American population.

The CHS cohort has also been genotyped for a set of neutral markers in an attempt to define both the degree of admixture and stratification among CHS African-Americans. If such genotyping has been performed in the ARIC African-American cohort the results of those analyses would be even more useful.

These studies comparing the frequencies of the amyloidogenic TTR V122I allele in community-based African-American cohorts representing a continuum of ages from 44 to 90 as well as those of other non-disease associated alleles will establish whether the allele, and presumably the consequent cardiac amyloidosis, has a significant effect on mortality in elderly African-Americans and reinforce the notion that prophylactic therapy, when available, could have a significant health benefit by reducing or eliminating this cause of heart failure in the affected population.

5. Main Hypothesis/Study Questions:

a. The ARIC and CHS African-American cohorts are sufficiently similar genetically so that the decrease in the frequency of the amyloidogenic TTR V122I allele seen across the two groups, i.e. younger(ARIC) older(CHS), can be interpreted as a mortality effect of the allele.

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

The CHS African-American cohort has already been genotyped for alleles at 24 ancestry-informative biallelic SNP’s spanning the entire genome (rs2814778, rs930072, rs7349, rs723632, rs 722098, rs 146026, rs 6003, rs 1985080, rs 518116, rs 3287, rs 1989486, rs 7041, rs 994174, rs 1800498, rs 2816, rs 2891, ra 3188520, rs 1042602, rs 326946, rs 20778863, rs 3188519, rs 594689, rs 2228478, rs 584059), the common Arg16Gly and Gln27Glu polymorphisms of the β2-adrenergic receptor (Chromosome: 5; Location: 5q31-q32), the angiotensin II type I receptor A1166C snp (Chromosome: 3; Location: 3q21-q25), C-reactive protein (Chromosome: 1; Location: 1q21-q23), and the Il-6 promoter Chromosome: 1; Location: 1q21. If the allele frequencies in the African-American cohort of ARIC of any of
these SNP’s are available for comparison with those determined in CHS and are similar, they would confirm our existing evidence that the CHS and ARIC African-American cohorts are derived from the same genetic universe with little significant stratification and that the differences in allele frequencies of TTR V122I and the ApoE alleles are a function of the age-related disease-associated mortality effects of those alleles. Allele frequencies at the identified loci will be compared between the two populations using Fisher’s exact test correcting for multiple comparisons using the method of Bonferroni.

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?  __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.csec.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)?

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* 1995.05)
   ____  B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________  __________)


12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.