

ARIC Manuscript Proposal # 1130r

PC Reviewed: 3/21/05
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Priority: _____
Priority: _____

1.a. Full Title: Association of Peroxisome Proliferator-Activated Receptor α (PPAR α) Polymorphisms with Lipid Levels and Possible Effect Modification of Polyunsaturated Fatty Acid Intake

b. Abbreviated Title (Length 26 characters): PPAR α , Lipids and PUFA Intake

2. Writing Group: Writing group members: Kelly Volcik
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _KV_ [please confirm with your initials electronically or in writing]

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3. Timeline: Statistical Analyses: Feb – May 06
Manuscript Preparation: May – July 06
Manuscript Revision: August 06
Manuscript Submission: September 06

4. Rationale:

Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent nuclear transcription factors belonging to the nuclear receptor superfamily, with three subtypes expressed in humans and encoded by different genes (PPAR α , PPAR γ , and PPAR β/δ).¹⁻³ PPARs regulate target gene expression by binding to specific peroxisome

proliferator response elements (PPREs) in enhancer sites of regulated genes as a heterodimer with the retinoid X receptor (RXR).³ PPAR α regulates the expression of genes involved in lipid metabolism, and polyunsaturated fatty acids (PUFA) are natural ligands of PPAR α .⁴⁻⁵ Studies have shown that binding of PUFAs to PPAR α results in rapid changes in expression of genes involved in lipid oxidation.⁶⁻⁸

The most commonly studied variant of the PPAR α gene is a missense mutation (L162V) that has functional consequences on PPAR α activity.^{5,9-10} Previous studies have shown the L162V variant allele to be associated with higher levels of LDL cholesterol, total cholesterol, apolipoprotein B (apoB), apolipoprotein C-III (apoC-III) and triglycerides (TGs).^{2,9,11} A recent study by Tai and colleagues found the effect of the L162V polymorphism on TG and apoC-III concentrations to be dependent on PUFA intake, with high intake triggering lower apoC-III and TG levels in carriers of the 162V allele.⁵ The study by Tai was limited to ~2000 white individuals from a single geographic location. We propose to study the interaction of the PPAR α L162V polymorphism (rs1800206), along with two additional polymorphisms (rs3892755, rs6008259) within this gene, and PUFA intake in the large biethnic and multicenter ARIC study.

The 3 SNPs chosen for the analysis have been genotyped on the entire ARIC cohort (rs1800206 was recently completed as of mid-February 2006). There is one additional PPAR α SNP that has been genotyped in ARIC (rs9615784), but we will not be including this SNP in the proposed analysis due to it not being polymorphic in either whites or African-Americans (no heterozygotes nor homozygotes for the variant allele were identified). Therefore, the proposed study will be looking at the most commonly studied PPAR α SNP (rs1800206) from the literature/ previous studies, as well as 2 additional PPAR α SNPs (rs3892755, rs6008259). To our knowledge, there are no other commonly studied PPAR α SNPs that are not being included in the proposed analysis.

References

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11. Robitaille J, Brouillette C, Houde A, Lemieux S, Perusse L, Tchernof A, Gaudet D, Vohl MC. Association between the PPAR -L162V polymorphism and components of the metabolic syndrome. *J Hum Genet* 2004;49:482-489.

5. Main Hypothesis/Study Questions:

1. To estimate the frequency distribution of PPAR α gene variation in a population-based sample of whites and African-Americans.
2. In a race-specific manner, to evaluate the independent effect of PPAR α gene variation on LDL, HDL, HDL2, HDL3, apolipoprotein A-I, apolipoprotein B, triglyceride and total cholesterol levels. Age, gender, field center, BMI, smoking status, cholesterol-lowering medication use, total energy intake and total fat intake will be included as covariates.
3. In a race-specific manner, to evaluate whether PUFA intake modulates the independent effect of PPAR α gene variation on lipid levels. These analyses will be carried out taking into account age, gender, field center, BMI, smoking status, cholesterol-lowering medication use, total energy intake and total fat intake.

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

The usual DNA restriction, ethnic group and missing data exclusion criteria will be used. With regards to cholesterol medication use, those taking cholesterol-lowering medication (cholmd01, n=448) will be excluded from the analysis. In analysis models, the derived variable indicating medications that secondarily lower cholesterol (cholmd02) will be included as a covariate. ARIC nutrient intake data has two variables describing PUFA intake (g and %kcal). PUFA intake will be defined by 3 categories (low, medium and high) on the basis of the frequency distribution and range of PUFA intake in the ARIC population. Our initial plans are to categorize PUFA intake by calculating 1 standard deviation above and below the mean (preliminary results reveal this divides the groups into 15% low, 70% middle, 15% high; this distribution is similar to the approach taken in the Tai et al. paper). Further investigation of the data may lead to changes in the way we categorize PUFA intake (perhaps looking at tertiles instead).

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://www.csc.unc.edu/ARIC/search.php> ☒ 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)? None

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

11.b. If yes, is the proposal

 X **A. primarily the result of an ancillary study (list number* AS#1995.07)**

 **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.csc.unc.edu/aric/forms/>

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.