ARIC Manuscript Proposal # 1343 and 1988 r

PC Reviewed: 11/08/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Addendum to MP #1343 and 1988:** Next Generation Sequencing to Identify Susceptibility Variants for Uric Acid Levels and Gout

2. Writing Group:
Writing group members: Adrienne Tin, Anna Kottgen, Eric Boerwinkle, Josef Coresh, others welcome.

ARIC author: **Adrienne Tin**
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3. Timeline: Data analysis to start immediately, completion of data analysis and drafting of the manuscript over the next year.

4. Rationale:

This is an addendum to the ARIC MP #1343 and 1988 (Next Generation Sequencing to Identify Susceptibility Variants for Uric Acid Levels and Gout).

Serum urate is an established major risk factor for gout.[1] However, the role of uric acid in relation to other chronic diseases is controversial, including chronic kidney disease, cardiovascular disease, and dementia.[2-5] It has been proposed that uric acid may be an antioxidant in an extracellular context and has an pro-inflammatory role in an intercellular context.[6] If uric acid levels indeed influence cell function, the consequence can be observed in the levels of DNA methylation in immune cells, which express *SLC2A9*,[7] a uric acid transporter, and have important roles in oxidative stress response and inflammation. Recently measures of DNA methylation (DNAm) in whole blood are available in the African American cohort in the ARIC study. The inclusion of genomic data, such as DNAm in the study of uric acid can yield additional insight of uric acid metabolism and its influence on chronic diseases, including gout.

5. Main Hypothesis/Study Questions:

Serum urate levels will be associated with DNA methylation levels at some CpG sites.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary

of data analysis, and any anticipated methodologic limitations or challenges if present).

1. Inclusion criteria: Participants with HM450K data passing quality control (n=2802),[8] with data in measures of serum urate at visit 2.

Outcomes:
Inverse normalized beta value of DNA methylation at 473,788 CpG sites passing quality control[8]

Predictor: serum urate levels.

Other variable of interest at visit 2: age, gender, BMI, center.

Data analysis:

The quality filtering criteria of the methylation data will be the same as those reported in Demerath et al.[8] To control for batch effect, we will use chip number as random effect and plate and chip row as fixed effect in a linear mixed effect model with inverse normalized DNAm beta value as outcome. Imputed white blood cell count will be included as fixed effect covariates to control for differences in DNAm levels due to cell type distribution.

Model:

Normalized DNAm beta value ~ serum urate + age + sex + BMI + plate + chip row + imputed neutrophils, lymphocytes, monocytes and eosinophils cell count + random_effect (chip number)

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

b. If Yes, is the author aware that the file ICTDER03 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 ICTDER03 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 ICTDER03 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; this is an extension of approved proposals _____ 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)?

#1343: "Stage II of a Genome-Wide Association Study for Genetic Variants Associated with Uric Acid Levels and Gout" (approved addendum to conduct consortium-wide meta-analyses, 1343A)

#1379, "Genome-wide Association Study of Single Nucleotide Polymorphisms with Kidney Disease and Kidney Disease Related Traits"

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* 2006.03, 2007.02**)**

___ 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/

References

1. Bardin, T. & Richette, P. Definition of hyperuricemia and gouty conditions. *Curr Opin Rheumatol* **26**, 186-91 (2014).
2. Borghi, C. & Desideri, G. Urate-Lowering Drugs and Prevention of Cardiovascular Disease: The Emerging Role of Xanthine Oxidase Inhibition. *Hypertension* **67**, 496-8 (2016).
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8. Demerath, E.W. *et al.* Epigenome-wide association study (EWAS) of BMI, BMI change and waist circumference in African American adults identifies multiple replicated loci. *Hum Mol Genet* (2015).

ARIC Manuscript Proposal #1343

PC Reviewed: 2/12/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Stage II of a Genome-Wide Association Study for Genetic Variants Associated with Uric Acid Levels and Gout

b. Abbreviated Title (Length 26 characters): **uric acid and gout genetics**

2. Writing Group:

Writing group members: Anna Kottgen, Linda Kao, Eric Boerwinkle, Qiong Yang, Shih-Jen Hwang, Emelia Benjamin, Daniel Levy, Rotterdam investigators to be named, Jacqueline Witteman, Caroline Fox, Josef Coresh

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

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3. Timeline: Data analysis to start as soon as genotyping completed, draft of manuscript within 1 month of completion of genotyping

4. Rationale:

Uric acid levels are associated with cardiovascular disease, hypertension, the metabolic syndrome, renal disease, and gout.[1] While elevated uric acid levels lead to the development of gout in susceptible individuals, it is unclear whether the association of uric acid with cardiovascular disease is causal.[2] Uric acid levels have been shown to be heritable.[3, 4] Several monogenetic causes of gout exist, but the common forms of hyperuricemia and gout are believed to have a polygenic component.[5] The elucidation of genetic risk factors for elevated uric acid levels may provide further insight into the pathophysiologic processes involved in uric acid metabolism, the relationship of hyperuricemia to gout and cardiovascular disease, and ultimately the identification of potential treatment targets.

Over the past year, genome-wide association studies (GWAS) successfully identified novel genetic loci influencing serum uric acid levels.[6, 7] None of these reports investigated the association of these genetic variants with gout as a complication of hyperuricemia. This is an interesting area for further research as not all individuals with hyperuricemia develop gout.[5] Genetic variants contributing to variation in serum urate levels therefore might or might not be associated with the development of gout.

In 2007, the NHLBI genotyped 500,000 single nucleotide polymorphisms (SNPs) in ~9,000 related and unrelated participants of the population-based Framingham Heart Study (FHS) using the Affymetrix GeneChip Human Mapping 500K array. Serum uric acid level was analyzed as a quantitative trait on multivariable-adjusted sex-specific residuals using both PBAT[8] and GEE models to account for relatedness among study persons. Covariates included in the generation of the sex-specific residuals were age, body mass index, hypertension treatment, and number of alcoholic drinks/week. Three SNPs that reached genome-wide significance, i.e. were significantly associated with serum uric acid levels after correcting for the 500,000 tests conducted (p-values between 10^{-9} and 10^{-78}), were selected by FHS investigators to be followed up for replication in additional population-based studies, the ARIC Study and the Rotterdam Study.

Replication of initial findings from GWAS is essential in order to reduce the type I error rate, and a conclusive GWAS should contain stage I, the discovery stage, as well as stage II, a replication stage of initial findings in one or more independent samples.[9] Here we propose to conduct stage II of a GWAS to identify genetic variants associated with serum uric acid levels and gout in the ARIC Study.

5. Main Hypothesis/Study Questions:

Main hypothesis: The three SNPs that were significantly associated with uric acid levels and/or gout in the FHS Study will also be significantly associated with these traits in Caucasian ARIC participants.

Study questions:

Primary study question:

1. Will the association between these SNPs and uric acid levels and gout replicate in Caucasian ARIC participants?

Secondary study questions:

2. Will this association also be present in black ARIC participants? If so, will it provide additional insight into the localization of a putative causal genetic variant

due to the different patters of linkage disequilibrium? Furthermore, do differences in frequencies of such genetic variants between white and black ARIC participants contribute to the higher levels of uric acid in blacks compared to whites?

3. Will any replicating genetic variants lie in annotated genes, and if so, in those with a known pathophysiological role in urate metabolism? Can new hypotheses for the cause of elevated uric acid levels, gout, or their association with other cardiovascular risk factors be generated?
4. Applying the concept of Mendelian randomization,[10] can new insights into a potential causal role of uric acid levels in the development of cardiovascular disease, renal disease, or the metabolic syndrome be generated?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design:
Three SNPs were selected by FHS investigators based on the most statistically significantly associated SNPs with serum uric acid levels in the FHS 500K GWAS. These 3 SNPs will be genotyped in the entire ARIC cohort using TaqMan assay at the ARIC DNA lab in Houston (E. Boerwinkle).
Inclusions/Exclusion: Individuals who did not consent to DNA research as well as those reporting race other than "black" or "white" will be excluded. Inclusion and exclusion criteria as well as statistical models will be harmonized with the use in FHS in order to increase comparability across the studies and to minimize the number of tests conducted. In secondary analyses, individuals reporting the intake of medications influencing uric acid levels such as thiazides, allupurinol, and uricosuric medications will be excluded. Genotyping quality control will be performed and SNPs not meeting the standards (see analysis section) will be excluded.
Outcome: In primary analyses, uric acid levels will be evaluated cross-sectionally at ARIC visit 1. Gout will be evaluated by combining all cases detected on the questionnaire at ARIC visit 4 or having had a hospitalization with a gout code. The combined definition should increase the sensitivity among cases who may have died or were lost to follow-up before visit 4. On the questionnaire, cases will be defined as individuals reporting ever having been told they had gout.

In secondary analyses, uric acid levels at ARIC visit 2 will be evaluated cross-sectionally, as well as uric acid levels at ARIC visit 1 and ARIC visit 2 with correlation taken into account using generalized estimating equations. The difference in uric acid levels between ARIC visits 1 and 2 will be evaluated but the short follow-up (median 3 years) will likely result in very limited power to detect changes. Further, the age at the first time cases were told they had gout will be examined as a function of genotype. The association of genotype with gout will be stratified by whether gout was reported on questionnaire, hospitalization, or both as well as stratified on the reported age at gout diagnosis using the median age at diagnosis to categorize this outcome.

Other variables of interest: Visit 1 age, gender, study center; and additionally visit 1, 2, and 4 blood pressure, antihypertensive medication incl. use of thiazide diuretics, diabetes mellitus, smoking, triglycerides, HDL cholesterol, BMI, alcohol intake, and serum creatinine.

Data analysis:

Quality control: SNPs with call rates <90%, a p-value for the test of Hardy-Weinberg equilibrium of $<10^{-4}$, and a minor allele frequency of <5% will be dismissed from analyses.

Genetic model and statistical significance: According with the analyses conducted in FHS, an additive genetic model will be assumed in order to limit the number of tests conducted. Statistical significance in ARIC will be set at an alpha of 0.0167, which corresponds to an alpha of 0.05 after the application of a Bonferroni correction for the investigation of 3 SNPs. All analyses will be carried out stratified by race. Moreover, overall statistical significance for each SNP will be evaluated in a meta-analysis across studies.

Primary analyses: The distribution of baseline characteristics in the study population by genotype as well as by outcome (gout status) will be computed using t-tests, chi-square tests and ANOVA as applicable. Generalized linear models will be used to examine the association of genotypes with uric acid and gout. Analogous to the analyses in FHS, the regression models will be adjusted for age, sex, BMI, hypertension treatment, and alcohol consumption.

Secondary analyses: Regression analyses will be repeated for uric acid levels at visit 2, and the difference between uric acid levels between visits 1 and 2 will be computed and used as the independent variable in additional regression analyses. Individuals using medications known to influence uric acid levels such as allopurinol, thiazides, and high concentrations of salicylates will be excluded from these analyses. Gout cases will be stratified by the median age of first gout, and logistic regression analyses will be repeated to investigate whether the genetic contribution is larger in younger individuals. Finally, the hazard ratios of a hospitalization for gout will be evaluated using multivariable-adjusted Cox Proportional Hazards regression as a function of genotypes.

Power: Making the reasonable assumption that the SNP allele frequencies in white ARIC participants will be similar to the ones observed in FHS participants, the power in ARIC to replicate the observed associations will be high. Although the effect size in the general population is typically overestimated in the stage I sample of a GWAS, the large sample size of ~12,000 white ARIC participants as well as the highly significant association in FHS should allow for the detection of an effect even if the magnitude of the association will likely be lower.

Limitations: In our analyses among white ARIC participants, we will not be able to correct for the presence of underlying population stratification. We will adjust for population stratification among black ARIC participants using a set of 1,536 ancestry informative markers genotyped previously. With only 3 SNPs genotyped, we may be limited in out ability to fine-map associations using both black and white study samples (see study question 2). Finally, we may be limited in our inferences for study question 4 if the genotyped SNPs are not the causal SNPs.

7.a. Will the data be used for non-CVD analysis in this manuscript?__ Yes _X__ No

b. If Yes, is the author aware that the file ICTDER03 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 ICTDER03 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 ICTDER03 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. #759 - Serum uric acid and risk of stroke: the ARIC study; published
2. #1077r - Uric Acid and Hypertension; published
3. #1229 - Uric Acid & Metabolic Syndrome
4. #1311 - Serum uric acid, lung function and chronic obstructive pulminary disease in adults
5. #525 1. Elevated uric acid as a risk factor for coronary heart disease: the ARIC study; published
6. #313 1. Association between serum uric acid and asymptomatic carotid atherosclerosis: the ARIC study; published

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* _AS #2006.16)
__ 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 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.**

References

1. Kutzing MK, Firestein BL. Altered uric acid levels and disease states. *J Pharmacol Exp Ther*. 2008;324:1-7.

2. Viazzi F, Leoncini G, Ratto E, Pontremoli R. Serum uric acid as a risk factor for cardiovascular and renal disease: An old controversy revived. *J Clin Hypertens (Greenwich)*. 2006;8:510-518.

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ARIC Manuscript Proposal #1988

PC Reviewed: 9/11/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Addendum to MP #1343:** "Next Generation Sequencing to Identify Susceptibility Variants for Uric Acid Levels and Gout"

b. Abbreviated Title (Length 26 characters): **Sequence analysis of urate**

2. Writing Group:

Writing group members: Adrienne Tin, Lawrence Shimmin, Anna Kottgen, Jim Hixson, Eric Boerwinkle, Linda Kao, Josef Coresh

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Data analysis to start immediately, completion of data analysis and drafting of the manuscript over the next year.

4. Rationale: Recent genome-wide association studies (GWAS) have identified multiple loci for serum uric acid levels and gout.[1, 2] Many of the index GWAS SNPs identified are either in intronic or intergenic regions with unknown function. Moreover, together, the SNPs at these loci explain only a small proportion of the variance in serum

urate, suggesting that additional variants, including rare variants, at these known loci, and new loci remain to be identified. Thus, sequencing approaches are necessary in order to further characterize variants at known loci and to identify novel, rare variants that may account for the "missing heritability."

Therefore, we propose to use next generation sequencing to identify additional variants and analyze their association with serum uric acid and gout. This will be a multi-layer project, beginning with the sequencing of exons, promoters, and flanking regions of candidate genes identified from previous GWAS of urate (Hixon's ancillary proposal). Subsequently, we will analyze the exome chip and exome and whole genome data generated from CHARGE-S for association with serum urate and gout. Results from the aforementioned analyses will be combined with other cohorts from either the CHARGE Consortium or other collaborators from the Global Urate Genetics Consortium for meta-analysis.

5. Main Hypothesis/Study Questions:
Common and rare SNP are associated with serum urate levels and gout. In addition to the known GWAS loci, novel loci will be identified through sequencing.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

The design of the sequence study are case-control (Hixson's ancillary study) and case-cohort (CHARGE-S). In the case-control, cases were defined as those with self-reported gout and controls were those with serum urate $<5^{th}$ race-specific percentile and reported no gout.

We will exclude individuals without genetic consent, has no genotype data, or has no serum urate data.

A brief description of the statistical analysis plan is provided below:

- Single SNP (MAF>1%) analyses: we will perform linear (urate) or logistic (gout) regression for each outcome on additive coding of SNP genotype. Additional exact p-value or permutation p-value will be provided for rare variants (MAF<5%). Number of replicates in the permutation should >1/pval from regression.
- Secondary analyses of aggregated effects of multiple nonsynonymous SNPs in each gene.
    - Weighted sum approach by Madsen and Browning (A Groupwise Association Test for Rare Mutations Using a Weighted Sum Statistic, PloS Genetics.[3]

- Fixed threshold test (T1, T5) and variable threshold test by Price et al.[4] Software for all methods can be downloaded from http://genetics.bwh.harvard.edu/rare_variants
- Kernel-based association test which is more powerful than the above tests when a region contain protective, deleterious and null variants and can incorporate covariates.[5]

- General approach following up a SNP of interest. We will apply the following criteria to narrow down our list of SNPs for follow up: 1) non-syn coding SNPs; 2) SNPs observed in cases but not controls; 3) SNPs identified in controls but not cases; 4) SNPs with high statistical significance even in analyses of the sequenced individuals; 5) novel SNPs (not in any public databases); 6) SNPs associated with a splice site; 7) SNPs predicted to be functional; 8) SNPs that are in LD with the initial GWAS index SNP but have predicted functional significance; 9) SNPs in regulatory regions of the gene.
- When using CHARGE-S data, we will apply the appropriate sampling weight in our analysis of the continuous serum urate trait.

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

b. If Yes, is the author aware that the file ICTDER03 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
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_X_ Yes ____ No

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__X Yes _____ No

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#1343: "Stage II of a Genome-Wide Association Study for Genetic Variants Associated with Uric Acid Levels and Gout"

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* 2006.03, 2007.02**)**

___ 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 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.

References

1. Yang Q, Kottgen A, Dehghan A, *et al.* Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet* 2010; **3:** 523-530.

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5. Wu MC, Lee S, Cai T, *et al.* Rare-variant association testing for sequencing data with the sequence kernel association test. *Am J Hum Genet* 2011; **89:** 82-93.