ARIC Manuscript Proposal #2148

PC Reviewed: 6/11/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Genetic Associations of Plasma Lactate

b. Abbreviated Title (Length 26 characters):
Genetics of Plasma Lactate

2. Writing Group:
Poojitha Balakrishnan, Adrienne Tin, James Pankow, Eric Boerwinkle, Ron Hoogeveen, J Hunter Young, WH Linda Kao , Others welcomed

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. PB **[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:
Start of analysis: April, 2013
Draft of manuscript: September, 2013

4. Rationale:

Plasma lactate is a measure of oxidative capacity, the ability to meet increased energy demand[1]. Recent studies have shown that increased plasma lactate levels are associated with insulin resistance and type 2 diabetes[2-4]. The heritability of change in lactate concentration is estimated to be 84% and the heritability of maximal lactate concentration is estimated to be 82%[5,6]

Yet, few genetic variants have been associated with plasma lactate[7]
. Some of the genes that have been implicated are involved in glycolysis substrate transportation into mitochondria and mitochondrial channels involved in establishing the ion potential gradient[7]
. And to our knowledge, no genome-wide study of plasma lactate has been conducted. Identifying common genetic variants associated with plasma lactate levels can inform possible pathogenesis of insulin resistance and other type 2 diabetes related traits.

5. Main Hypothesis/Study Questions:

Common genetic variants are associated with plasma lactate.

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
Genome-wide association study.

Inclusion criteria
All black and white ARIC participants from visit 4 with plasma lactate and genome-wide array data.

Outcome
Plasma lactate levels at visit 4 as a continuous outcome, log-transformed if right-skewed.

Covariates
Age at visit 4, Gender, Center, Body mass index, Waist circumference, Principal components associated with the outcome at $p<0.05$.

Predictor
Imputed genotype dosage using 1000 Genomes reference panels.

Statistical analysis
We will use linear regression to test for association with plasma lactate stratified by race group (5960 Whites, 1507 Blacks) in ARIC visit 4. Significant threshold is set at the genome-wide significance of 5e-8.

In order to elucidate the underlying biological mechanism, we will then test the association of the genome-wide significant variants with disease traits. Linear regressions

will be performed for continuous outcomes such as insulin resistance measured as HOMA-IR and logistic regressions will be performed for binary outcomes such as type 2 diabetes. Statistical significance will be determined by adjusting for the number of candidate genetic variants. By implementing mediation analysis with the above disease traits and plasma lactate, we can get closer to understanding the causal timeline.

We also aim to input the GWAS results from above to inform a gene set enrichment analysis. From the genome-wide significant genetic variants, we will define a priori a set of candidate genes to input into MAGENTA[8]. The results will indicate whether these candidate genes are enriched for statistical significance more than expected by chance.

We would like to replicate the findings from the above, proposed analyses in an independent cohort. We are currently working with the Beaver Dam Offspring Study for possible replication. Blood lactate was measured on 2556 Whites. Genotyping information is available from the ITMAT-Broad-CARE (IBC) array with 50,000 cardiovascular candidate variants with possibility of de novo genotyping[9].

Strengths and Limitations

This study proposes to investigate genetics of the plasma lactate phenotype, which has not been previously studied. A limitation is that there are a limited number of studies available for replication and only single measurements of plasma lactate are available in ARIC visit 4.

7.a. Will the data be used for non-CVD analysis in this manuscript? _X_ Yes __ 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? _X_ 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)?
No previous proposal in ARIC focus specifically on predicting ESRD using genetic information.

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

11.b. If yes, is the proposal

__ A. primarily the result of an ancillary study (list number*)

___ 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:

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3. Crawford SO, Hoogeveen RC, Brancati FL, et al. Association of blood lactate with type 2 diabetes: The atherosclerosis risk in communities carotid MRI study. *Int J Epidemiol*. 2010;39(6):1647-1655. Accessed 4/19/2013 4:23:40 PM.

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6. Lesage R, Simoneau J, Jobin J, Leblanc J, Bouchard C. Familial resemblance in maximal heart rate, blood lactate and aerobic power. *Hum Hered*. 2008;35(3):182-189. Accessed 4/19/2013 4:20:51 PM; 4/19/2013 4:20:51 PM.

7. Gerbitz K, Gempel K, Brdiczka D. Mitochondria and diabetes: Genetic, biochemical, and clinical implications of the cellular energy circuit. *Diabetes*. 1996;45(2):113-126. Accessed 4/22/2013 4:10:12 PM.

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