ARIC Manuscript Proposal # 1534

PC Reviewed: 7/14/09   Status: <u>A</u>   Priority: <u>2</u>
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: *Interactions between whole grain intake and genotype with respect to fasting glucose concentrations in multiple cohorts within the CHARGE & MAGIC consortia*

 b. Abbreviated Title (Length 26 characters): *whole grain x SNPs— glucose*

2. Writing Group:
    Writing group members:
Jennifer Nettleton & Jim Pankow (ARIC)
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Paul Franks (GLACIER)
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _**JN**_ **[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**: *Cohort-specific data analyses: August 15, 2009*
Meta-analysis: September 15, 2009
Manuscript drafting complete: November 15, 2009

4. **Rationale**:

We propose to test the interaction of whole grain intake with MAGIC-discovered gene variants on fasting glucose concentrations using data from 4 CHARGE cohorts (including ARIC, as well as FHS, CHS, and Rotterdam) and 5 MAGIC cohorts (European cohorts, not part of CHARGE, including GLACIER, ULSAM, PIVUS, GENDAI, and GHRAS). MAGIC has brought to light many SNPs associated with fasting and 2hr glucose and insulin at GWA significance; we will focus on 16 of these SNPs. We will use an additive genetic model, and adjust for confounding variables (age, sex, total Caloric intake, and field center or family/population substructure, as necessary). The results of cohort-specific analyses will be meta-analyzed. If interactions are identified, we will explore models that also adjust for BMI or other measure of adiposity—a potential causal pathway intermediate.

We expect that our analyses will bring to light how the dietary exposures might modulate genetic predisposition to type 2 diabetes. We have selected the approach outlined above for reasons of practicality and, importantly, clinical relevance. We believe that an approach that focuses on SNPs known to be associated with the dependent phenotype (here, fasting glucose) will provide us the opportunity to evaluate diet x gene interactions in several large cohorts on a manageable scale, which is an important consideration at this stage in the development of gene x environment research. By focusing on candidate genes we can clarify our approach to gene x environment analysis and explore interactions with loci for which we have begun to gain better understanding. After we have honed our analytic approach, we can then begin to address these questions on a larger scale, i.e., diet x GWAS.

Our approach also allows us to address an important clinical question, "how (if at all) would our current dietary recommendations change, given our empirical knowledge of genetic risk?" Three recent nested case-controls studies highlight the current direction of the field and the reality of the interactive role of diet and genetic factors with respect to diabetes risk [1-3]. Two of these studies reported significant interactions between *TCF7L2* variation and whole grain intake [1] or other measures of carbohydrate quality [2] in determining diabetes risk. The third study, considered the interactions between Western and Prudent dietary patterns and a diabetes genetic risk score in prediction of diabetes [3]. In that study, investigators noted significant synergy between genetic risk and a Western diet, where those with high Western dietary pattern scores and high genetic risk scores showed a significantly magnified risk of diabetes. Due, in part, to differences in characterization of dietary exposures and genetic risk (scores vs. specific SNPs), each study reached a somewhat unique conclusion. However, the unifying conclusion of the three studies is that yes, diet, perhaps carbohydrate quality in particular, appears to influence the impact of genetics in determining risk of diabetes [2] (or vice versa, genetics does influence the impact of diet in determining risk of diabetes [1]).

References
1. Fisher E, Boeing H, Fritsche A, Doering F, Joost HG, Schulze MB. Whole-grain consumption and transcription factor-7-like 2 (TCF7L2) rs7903146: gene-diet interaction in modulating type 2 diabetes risk. *Br J Nutr.* 2009;101(4):478-481.
2. Cornelis MC, Qi L, Kraft P, Hu FB. TCF7L2, dietary carbohydrate, and risk of type 2 diabetes in US women. *Am J Clin Nutr.* 2009;89(4):1256-1262.
3. Qi L, Cornelis MC, Zhang C, van Dam RM, Hu FB. Genetic predisposition, Western dietary pattern, and the risk of type 2 diabetes in men. *Am J Clin Nutr.* 2009;89(5):1453-1458.

5.   Main Hypothesis/Study Questions:

Ho: association between whole grain intake and fasting glucose does not differ by SNP genotype (SNPs of interest listed below)

6. Design and analysis

ENVIRONMENTAL EXPOSURE:

Whole grain intake (servings/day, modeled as a continuous variable)

The composite variable— "whole grain intake"— comprises the following (-line items from each cohort are shown)

CHARGE/MAGIC COHORTS	MAGIC ONLY COHORTS
ARIC *whole grains = sum of (3)…*	GHRAS *whole grains = sum of (1)…*
-dark or whole grain bread	-whole grain bread
-cooked cereals	
-cold cereal (high-fiber/whole grain or "variety")*	
FHS *whole grains = sum of (8)…*	GENDAI *whole grains = sum of (7)…*
-dark bread	whole wheat (or rye) bread (1 slice)
-cooked oatmeal	whole wheat (or rye) Melba toast (toasted bread) (2 pieces)
-cold cereal (whole grain)*	whole wheat or barley rusk (1 rusk)
-brown rice	high fiber cold cereals (1 cup)
-bulgar/kasha/couscous	whole wheat or high fiber pasta (1/2 cup)
-popcorn	brown rice (1/2 cup)
-wheat germ	whole wheat crackers (2 pieces)
-added bran	
CHS *whole grains = sum of (3)…*	GLACIER *whole grains = sum of (4)…*
-whole wheat/rye/pumpernickel breads	-porridge oat, graham, rye, barley
-cooked cereals	-high-fiber cold cereals
-high-fiber/bran/granola cereals*	-coarse bread (whole grain)
	-crisp bread (mostly rye/whole grain varieties)
ROTTERDAM *whole grains = sum of (9)…*	ULSAM & PIVUS *whole grains*
-brown bread (wheat)	data from 7-day diet records… definitions pending…
-brown bread (wholemeal)	
-rye bread dark	
-rye bread light	
-porridge oatmeal	
-muesli without sugar	
-rice brown boiled	
-wheat germ	
-wheat bran	

*based on coded and categorized self-reported brand of cold cereal most commonly consumed

OUTCOMES:

Fasting glucose

EXCLUSIONS:

Prevalent diabetes

Non-fasting status

Non-white race

Inadequate (failed QC) dietary data

INTERACTION TEST:

A regression coefficient (β±SE) for the interaction term whole grains*SNP will be calculated in each cohort and values meta-analyzed.

Note: whole grain intake will modeled continuously [servings/d], and an additive genetic model will be used [estimated copies of risk allele]

Likelihood ratio test for the interaction term will be used to generate p-values

MODEL COVARIATES:

sex, age *(continuous: years),* total daily energy intake *(continuous: kcal/day),*cohort and/or population substructure as needed

+BMI, if interactions reach a priori significance level (see below)

i.e., main model:

fasting glucose = SNP (estimated copies of risk allele), WHOLE GRAINS (servings per day, continuous),
SNP*WHOLE GRAINS + model covariates listed above

SIGNIFICANCE: $p \leq 0.003$* for the interaction term in each meta-analysis, although we will also focus on consistency of results, given the lower power for these GxE analyses.

*0.016667 = 0.05/16 SNPs (Bonferroni correction)

7.a. Will the data be used for non-CVD analysis in this manuscript?
Fasting glucose is the primary outcome

   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*
(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?   *Yes*

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"? *Yes*

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 *Yes*

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)?

#1407: Interaction between FTO and dietary patterns in relation to diabetes and obesity in the Atherosclerosis Risk in Communities (ARIC) Study

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? *Yes*
Interactions between Diet and Genes Related to Risk of Type II Diabetes, #2007.12

11.b. If yes--the proposal
Is primarily the result of an ancillary study (number* 2007.12)
ARIC is one of 9 cohort studies contributing data to the CHARGE/MAGIC-based meta-analysis.

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.

The lead author is aware of, and will comply with, this stipulation.