ARIC Manuscript Proposal # 1756

PC Reviewed: 3/8/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Meta-analyses of gene-environment interactions in smoking behavior

b. Abbreviated Title (Length 26 characters): **GxE in smoking**

2. Writing Group: (co-authors, in no particular order)
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SH__ **[please confirm with your initials electronically or in writing]**

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3. Timeline: Manuscript submission planned in Spring 2011

4. Rationale: Evaluate gene-environment interactions with heavy smoking

5. Main Hypothesis/Study Questions: Does genetic risk in loci previously associated with smoking vary across environment factors including age of onset of regular smoking, birth cohort, educational attainment, and gender.

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 subjects.
This study is a meta-analysis of 93,184 subjects from 44 datasets. Written informed consent was obtained from all subjects in the study populations from 9 countries (Australia, Denmark, Finland, Germany, Iceland, Italy, the Netherlands, the United States and the United Kingdom). Inclusion in the study required (1) ascertainment of cigarettes per day, and (2) the availability of genotyped or imputed data for rs1051730. All subjects were of European descent, age ≥ 25, and, within each sample, only unrelated individuals were included. The sample sizes for each of the samples used in the study are listed in Table 1.

Traits for analysis
The traits examined were smoking quantity (cigarettes per day), gender, birth cohort, age of onset of regular smoking, and educational attainment. Cigarettes per day (CPD) was coded as a four-level trait CPD ≤ 10, $10 <$ CPD ≤ 20, $20 <$ CPD ≤ 30, CPD > 30, coded 0, 1, 2, and 3 respectively. Birth cohort was divided into 20-year cohorts: 1920-1939, 1940-1959, and 1960-1979. Age of onset of regular smoking (AOS) was dichotomized: AOS ≤ 16, AOS > 16. Educational attainment was also dichotomized: terminal degree of high school or less, terminal degree greater than high school degree.

SNPs for analysis
We are interested in gene-environment interactions with known genetic associations with nicotine dependence. Our primary SNP of interest is rs1051730, a chromosome 15 SNP tagging the most replicated association with smoking quantity and nicotine dependence. In addition, we evaluated all SNPs found to be associated with nicotine dependence in a series of three large meta-analyses of smoking quantity GWAS [Liu et al. 2010; TAG 2010; Thorgeirsson et al. 2010]: rs6474412 (CHRNA6/B3 chr 8p11), rs1801272 &

rs3733829 (CYP2A6/2B6 chr 19q13), rs1329650 (chr 10q25), and rs6265 (BDNF chr 11).

Statistical analyses
To ensure uniform analyses, SAS (SAS Institute, Cary, NC) and R (www.r-project.org) scripts for genetic association analyses were developed centrally and then distributed. The scripts were executed by each participating site, and the results returned to the coordinating group.

Because the environmental factors may interact with one another, rather than conducting a meta-analysis of the interaction term or a 2-df test of interaction, each site ran the analysis of cpd=SNP within each environmental substrata (for example, running cpd=SNP in subjects with age of onset ≤ 16, and then >16), and within each environmental substrata (for example, running cpd=SNP in subjects with age of onset ≤ 16 and birth cohort 1920-1939, then in subjects with age of onset >16 and birth cohort 1920-1939, then in subjects with age of onset ≤ 16 and birth cohort 1940-1959, etc.). This was repeated for each two-way substrata (i.e. substrata of two environments), three-way substrata, and four-way substrata.

Meta-analysis
To test whether the association between smoking quantity and SNP varies across environmental strata, we combined the regression parameters from the stratified analyses in a meta-analysis. Using a mixed model with dataset as a random effect and environmental variable as fixed effect, we tested whether the association between smoking quantity and SNP varied based on environmental factor. This allows us to further test whether the environmental factors interact with one another in terms of the genetic effect of the SNP on cpd.

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)?

MS 1382: Genome-wide association study of smoking initiation, intensity, and cessation in African American and white ARIC participants, and meta-analysis of smoking within the Tobacco & Genetics (TAG) Consortium

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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TAG (2010), 'Genome-wide meta-analyses identify multiple loci associated with smoking behavior', *Nat Genet,* 42: 441-447.

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