1.a. Full Title: A single nucleotide polymorphism on 8q22.1 and migraine risk: a possible link to breast cancer.

b. Abbreviated Title (Length 26 characters): A SNP on 8q22.1 and migraine risk

2. Writing Group:
   Writing group members: Seth Swanlund, Jim Pankow, Kristin Anderson, Anna Prizment, Kathy Rose, Kala Visvanathan, Aaron Folsom

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

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3. Timeline: The project will be started in March of 2011; first draft May 2011; submitted Summer 2011

4. Rationale: Migraine is 19th among all causes of years lived with disability according to the World Health Organization, making it a significant public health concern. Studies have shown that people who suffer from migraines may also become
predisposed to other illnesses including depression. Migraine is almost certain to have a genetic basis. The genetic basis of migraine is currently not well understood and greatly under-studied. Furthermore, a recent GWAS study in European populations implicated the first known common susceptibility variant on 8q22.1 (rs1835740) to be associated with migraines. The study ascertained cases from headache clinics and likely represents a more severe subgroup of migraine sufferers. Therefore, an attempt to replicate this novel single nucleotide polymorphism in a population-based cohort is warranted. In addition, recent studies have shown an inverse association between migraine and incident breast cancer. There is believed to be a common mechanism in the pathology of migraines and breast cancer involving female hormones. The susceptibility variant implicated in the migraine GWAS is thought to be a cis regulator of the MTDH gene, a well-established oncogene that is over-expressed in 40% of breast cancers. Therefore, investigating an association between migraine and breast cancer in the ARIC cohort may provide clues to understanding a possible relationship between MTDH, migraines, and breast cancer.

5. Main Hypothesis/Study Questions:

Question: Can an association between an implicated SNP and migraine be replicated in the ARIC cohort?

Question: Is migraine status independently associated with reduced risk of breast cancer in the ARIC cohort?

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 first question will be answered using a cross-sectional design to compare frequencies of SNP rs1835740 in migraine cases compared to non-cases. A personal history exam was administered during visit 3 (1993 to 1995). Cases will be ascertained based on their responses to the headache section of the questionnaire: a migraine will be defined using a modification of the International Headache Society (HIS) diagnostic criteria utilized by Carson et al in ARIC. The outcome will be categorized as 1) ‘all migraines’, irrespective of aura status; 2) migraine with aura; 3) migraine without aura; 4) headache with aura; 5) headache without aura. Only those with headache information and a measured imputed allele dosage for rs1835740 will be included, limiting the analysis to white subjects only.

The second question will be answered using a prospective cohort design. The cohort will consist of white and black women who participated in visit 3 and did not have missing data for the headache questions. Subjects will be excluded if they reported having any history of cancer at baseline (excluding non-melanoma skin cancer) or were diagnosed with cancer by the time of the questionnaire to give a cancer-free cohort. Subjects will be
followed from the time of the questionnaire (1993-1995) through the year 2006 and monitored for incident breast cancer. We will adjust for the potential confounders age, education, smoking, alcohol, BMI, menopausal status (at the time of questionnaire), use of contraceptive pill, hormone replacement therapy, number of live births, age at menarche and age at menopause. Information on aspirin and non-aspirin NSAID use will also be extracted from the questionnaire and adjusted for in the analysis. A Cox regression will be used to calculate hazard ratios and 95% CIs as measures of the association between migraine history and breast cancer risk. Time to event will be computed from the time of the questionnaire until date of diagnosis for those with breast cancer, and women with no incident breast cancer will be censored at death, loss to follow-up, or December 31,2006, whichever occurred first. The major limitation of this study is not having information on the histology (ductal or lobular) or the estrogen receptor (ER)/progesterone receptor (PR) status of the tumor; previous studies found differences in the hazard ratios by ER/PR status. Another limitation is the relatively small sample size of incident breast cancer in the cohort.

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.csec.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)?

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
   ___ A. primarily the result of an ancillary study (list number* __________)
   ___ X__ B. primarily based on ARIC data with ancillary data playing a minor role
   (usually control variables; list number(s)* _____ 1995.04  _______  ________
   ________)

*ancillary studies are listed by number at http://www.csecc.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

   (2010). Genome-wide association study of migraine implicates a common susceptibility
   variant on 8q22.1. Nature Genetics, 42(10), 869-+. doi:10.1038/ng.652

   of Clinical Oncology, 28(6), 1005-1010. doi:10.1200/JCO.2009.25.0423

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   premenopausal and postmenopausal women. Cancer Epidemiology Biomarkers &
   Prevention, 18(7), 2030-2034. doi:10.1158/1055-9965.EPI-09-0291
