ARIC Manuscript Proposal #2343

PC Reviewed: 4/8/14    Status: A    Priority: 2
SC Reviewed: _________    Status: _____    Priority: ____

1.a. Full Title: Genetic Epidemiology of Pelvic Organ Prolapse

b. Abbreviated Title (Length 26 characters): Genetic Epi of Prolapse

2. Writing Group:
   Writing group members:

Jennifer M. Wu, MD, MPH
Christy Avery, PhD
Jeannette Bensen, PhD
Anna Kucharska-Newton, PhD
Digna R Velez Edwards, PhD
Todd L. Edwards, PhD
Amy Park, MD
Kari North, PhD

1 Department of Obstetrics and Gynecology, UNC-Chapel Hill, Chapel Hill, NC
2 Department of Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, NC
3 Vanderbilt Epidemiology Center, Center for Human Genetics Research, Department of Obstetrics and Gynecology, Vanderbilt University, Nashville, TN
4 Center for Human Genetics Research, Institute for Medicine and Public Health, Division of Epidemiology, Department of Medicine, Nashville, TN
5 Department of Obstetrics and Gynecology and Urology, Georgetown University School of Medicine, Medstar Washington Hospital Center, Washington, D.C.

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

First author: Jennifer Wu
Address: University of North Carolina at Chapel Hill
CB#7570, Dept of Obstetrics and Gynecology
3032 Old Clinic Building
Chapel Hill, NC 27517
Phone: (919) 966-0014  Fax: (919) 843-9952
E-mail: jennifer_wu@med.unc.edu
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).

Name: Kari North, PhD  
Address: CB#7435, 137 E. Franklin St. Suite 306  
Chapel Hill, NC 27599  
Phone: (919) 966-2148  
Fax: (919) 966-9800  
E-mail: kari_north@unc.edu

3. Timeline:  
Preliminary work will begin once we receive approval, noting that a grant to support the analysis and interpretation of results will be submitted in June, 2014. However, the work will move ahead with or without dedicated funding.

4. Rationale:  
Pelvic organ prolapse, which affects 40% of postmenopausal women, impairs quality of life due to pelvic pain and bladder and bowel dysfunction.\(^1\) Prolapse is the herniation of the bladder, uterus, or rectum, into, and often beyond, the vaginal opening. Currently, one in eight women will undergo surgery for prolapse during her lifetime.\(^2\) Unfortunately, these surgeries are costly,\(^3\) can lead to serious complications,\(^4\) and are not durable, as 30% of women develop recurrent disease.\(^5\) A critical barrier to progress in disease prevention is our limited understanding of the etiology of the underlying disease. Without a better understanding of the fundamental causes of prolapse, effective preventive measures cannot be developed and treatments focus on end-stage disease.

While epidemiologic studies have identified factors associated with prolapse, we do not understand the underlying mechanisms which lead to disease. Risk factors include age,\(^1,6\) race,\(^1,\)\(^5-9\) obesity,\(^1,7\) vaginal delivery,\(^8,9\) and genetics.\(^10,11\) Several studies suggest that prolapse is highly heritable, with 40% of the risk explained by genetic factors.\(^7-10\) Thus, the identification of genetic markers associated with prolapse may provide insight into its etiology. Our R03-funded work and other preliminary investigations have detected several single nucleotide polymorphisms (SNPs) associated with advanced prolapse.\(^11-19\) These studies focused on candidate genes in extracellular matrix (ECM) pathways,\(^12,16,20,2413-17\) as abnormalities in collagen and elastin may lead to prolapse.\(^18,25-27\) Although encouraging, these studies were conducted in a small number of women (i.e. < 250 cases of prolapse and < 250 controls) and focused on a limited number of genetic variants.\(^12,13,28\) While one genome-wide association study (GWAS) has been conducted, it evaluated a small cohort of women and used a less dense GWAS platform.\(^19\) Thus, in order to accomplish our long-term goal of understanding the etiology of prolapse, a substantially larger, more robust and comprehensive genetic epidemiologic investigation is critically needed.

For this application, we are planning to establish a unique consortium of the largest collection of women with and without prolapse who have existing DNA samples and detailed clinical data. We will capitalize on a large sample of comprehensively phenotyped women from the Women’s Health Initiative (WHI) and from two established biorepositories at
Duke and UNC. We also hope to include ARIC female participants in this large collaborative effort.

**IMPACT:** Pelvic organ prolapse is a prevalent, heritable, morbid, and costly condition. Its poorly understood etiology and lack of predictive biomarkers hinders the provision of care for its prevention and treatment. Findings from this novel and robust study could transform science, as our results will represent the initial steps in ascertaining potential causal variants which can lead to mechanistic studies to understand the genesis of prolapse. Without this knowledge, effective preventive strategies cannot be developed and treatments will remain focused on advanced disease. Ultimately, understanding the etiology of pelvic organ prolapse will advance scientific knowledge and address a critical barrier to progress in women’s health.

5. **Main Hypothesis/Study Questions:**

**HYPOTHESIS:** Genetic variants influence pelvic organ prolapse risk. To test this hypothesis, we propose the following specific aims:

**AIM 1:** Identify common SNPs associated with pelvic organ prolapse in a population-based, two-stage GWAS.

**AIM 2:** Identify low frequency SNPs associated with pelvic organ prolapse using a two-stage approach.

To achieve our aims, we will capitalize on our pelvic organ prolapse (POP) consortium, which includes data from the Women’s Health Initiative, as well as existing biorepository samples from UNC, Duke University and Vanderbilt University. Based on a preliminary review of the ARIC data, we conservatively estimate that approximately 500 women, among 7,014 women from whom CMS Medicare claims care available, will have developed a prolapse. The total sample size in the proposed POP consortium, including the ARIC cases and controls, will be 4,000 cases and 11,000 controls.

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).**

6.A. **Study Design**

We will use association analysis to identify common and low frequency SNPs (allele frequency (MAF) 1-5%) associated among women with pelvic organ prolapse and women without prolapse.

6.B. **Inclusion and Exclusion Criteria:**

- **Cases of women with pelvic organ prolapse:** The CMS Medicare claims linked to data for ARIC cohort participants will be used to identify women with prolapse based on International Classification of Disease (ICD)-9 diagnosis codes as well as Current Procedural Terminology
(CCPT) codes for surgeries for prolapse. A priori defined ICD-9 and CPT codes for prolapse (listed below) will be obtained from annual inpatient records (MedPAR files) and outpatient claims (Carrier and Outpatient files) for the years 1991-2012.

Identification of women with prolapse using ICD-9 and CPT codes has been well-documented by numerous studies, including several investigations of prolapse in the Medicare population. In addition, ICD-9 and CPT codes have been used to evaluate pelvic organ prolapse in large healthcare claims databases and national databases including the National Hospital Discharge Survey, the Nationwide Inpatient Sample, and National Survey of Ambulatory Surgery.

- The following ICD-9 diagnosis codes and CPT codes will be utilized to identify women with pelvic organ prolapse:

**ICD-9 Diagnosis Codes for Pelvic Organ Prolapse = 618.X**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>618.0</td>
<td>Prolapse of vaginal walls without mention of uterine prolapse</td>
</tr>
<tr>
<td>618.00</td>
<td>Unspecified prolapse of vaginal walls</td>
</tr>
<tr>
<td>618.01</td>
<td>Cystocele midline</td>
</tr>
<tr>
<td>618.02</td>
<td>Cystocele lateral</td>
</tr>
<tr>
<td>618.03</td>
<td>Urethrocele</td>
</tr>
<tr>
<td>618.04</td>
<td>Rectocele</td>
</tr>
<tr>
<td>618.05</td>
<td>Perineocele</td>
</tr>
<tr>
<td>618.09</td>
<td>Other uterine prolapse without mention of uterine prolapse/cystourethrocele</td>
</tr>
<tr>
<td>618.1</td>
<td>Uterine prolapse without mention of vaginal wall prolapse</td>
</tr>
<tr>
<td>618.2</td>
<td>Uterovaginal prolapse, incomplete</td>
</tr>
<tr>
<td>618.3</td>
<td>Uterovaginal prolapse, complete</td>
</tr>
<tr>
<td>618.4</td>
<td>Uterovaginal prolapse, unspecified</td>
</tr>
<tr>
<td>618.5</td>
<td>Prolapse of vaginal vault after hysterectomy</td>
</tr>
<tr>
<td>618.6</td>
<td>Vaginal enterocele, congenital or acquired</td>
</tr>
<tr>
<td>618.7</td>
<td>Old laceration of muscles of pelvic floor</td>
</tr>
<tr>
<td>618.8</td>
<td>Other specified genital prolapse</td>
</tr>
<tr>
<td>618.81</td>
<td>Incompetence or weakening of pubocervical tissue</td>
</tr>
<tr>
<td>618.82</td>
<td>Incompetence or weakening of rectovaginal tissue</td>
</tr>
<tr>
<td>618.83</td>
<td>Pelvic muscle wasting</td>
</tr>
<tr>
<td>618.84</td>
<td>Cervical stump prolapse</td>
</tr>
<tr>
<td>618.89</td>
<td>Other specified genital prolapse</td>
</tr>
<tr>
<td>618.9</td>
<td>Unspecified genital prolapse</td>
</tr>
</tbody>
</table>

**CPT codes for Pelvic Organ Prolapse Surgeries**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>57106</td>
<td>Vaginectomy (Partial, vaginal apex revision)</td>
</tr>
<tr>
<td>57107</td>
<td>Vaginectomy (partial removal of vaginal wall; with removal of paravaginal tissue (radical vaginectomy))</td>
</tr>
<tr>
<td>57109</td>
<td>Vaginectomy, partial removal of vaginal wall; with removal of paravaginal tissue (radical vaginectomy) with bilateral total pelvic lymphadenectomy and para-aortic lymph node sampling (biopsy)</td>
</tr>
<tr>
<td>57110</td>
<td>Vaginectomy (Complete)</td>
</tr>
<tr>
<td>57111</td>
<td>Vaginectomy, complete removal of vaginal wall; with removal of paravaginal tissue (radical vaginectomy)</td>
</tr>
</tbody>
</table>
57112 Vaginectomy, complete removal of vaginal wall; with removal of paravaginal tissue (radical vaginectomy) with bilateral total pelvic lymphadenectomy and para-aortic lymph node sampling (biopsy)
57120 Colpocleisis
57200 Colporrhaphy, suture of injury of vagina (nonobstetrical)
57210 Colpoperineorrhaphy, suture of injury of vagina and/or perineum (nonobstetrical)
57240 Anterior colporrhaphy, repair of cystocele with or without repair of urethrocele
57250 Posterior colporrhaphy, repair of rectocele with or without perineorrhaphy
57260 Combined anteroposterior colporrhaphy;
57265 Combined anteroposterior colporrhaphy; with enterocele repair
57267 Insertion of mesh or other prosthesis for repair of pelvic floor defect, each site (anterior, posterior compartment), vaginal approach (List separately in addition to code for primary procedure)
57268 Repair of enterocele, vaginal approach (separate procedure)
57270 Repair of enterocele, abdominal approach (separate procedure)
57280 Colpopexy, abdominal approach
57282 Colpopexy, vaginal; extra-peritoneal approach (sacrospinous, iliococcygeus)
57283 Colpopexy, vaginal; intra-peritoneal approach (uterosacral, levator myorrhaphy)
57284 Paravaginal defect repair; open approach
57285 Paravaginal defect repair; vaginal approach
57423 Laparoscopic paravaginal defect repair
57425 Laparoscopy, surgical, colpopexy (suspension of vaginal apex)

**Controls (women without pelvic organ prolapse):** Women without a prolapse ICD-9 diagnosis code of 618.X or a CPT code representing a pelvic organ prolapse surgery during the entire study will be considered a control.

6.C. Other variables of interest:

- We are also interested in evaluating the following variables obtained from cohort examinations to describe the study population.
  1. Age
  2. Number of pregnancies / gravidity
  3. Number of liveborn children / parity
  4. Uterus removed / hysterectomy
  5. Menopause
  6. Current smoking
  7. Height and weight / BMI

6.D. Summary of data analysis:

**Genetic data:** We will analyze the 1,000 Genomes imputed data (extant) as well as the exome chip data (extant).

**Statistical analysis:** For the association analyses, we will employ an additive model of inheritance. The odds of prolapse will be modeled using a generalized linear model and logit link.
**Covariates:** For the analysis, there are few variables that will be true confounders (must be associated with both the exposure and the outcome); thus, minimal model adjusting will be performed for the effects of age, parity, and ancestral principal components.

**Replication:** Replication of findings adds confidence regarding truly significant results and helps weed out false positives. Validation of significant results in one or more independent samples offers further population-based statistical support for the specific genes influencing susceptibility for pelvic organ prolapse. For both Aims 1 and 2, stage 1 discovery analyses will be conducted in an independent cohort of 4,000 cases of women with prolapse and 11,000 controls of women without prolapse. In stage 2 for discovery, SNPs significant at p-value $\leq 5 \times 10^{-6}$ will be taken forward and meta-analyzed with an independent sample of 2,000 cases and 2,000 controls. SNPs that achieve Bonferroni corrected critical value of $< 5 \times 10^{-8}$ in the meta-analysis of the stage 1 and stage 2 results will be considered statistically significant at the genome-wide level for Aims 1 and 2.

**Power analyses.** Power is evaluated using a two-sided $\alpha=5 \times 10^{-8}$, an additive genetic model, MAF of 1-20%, estimated sample size of 4,000 cases and 11,000 controls, and ORs ranging 1.15-1.45. For $K$ independent SNPs detectable at powers $P_0$, $P_1, \ldots, P_N$, the probability of detecting $\geq 1$ is $1-(1-P_0)(1-P_1)\ldots(1-P_N))$. The lower bound is $1-(1-P_i)^N$, where $P_i$ is the power for the lowest-powered SNP. We have excellent power to detect genetic effects for POP (Figure): $\geq 80\%$ to detect variants with MAF $\geq 5\%$ for ORs of 1.15 and higher. As expected, power improves if $K=3$ or 5. For low frequency variants (i.e. MAF $=1\%$), we have 80% power to detect ORs of 1.45 and higher; at 80% power we can detect ORs of 1.25 and 1.20 if $K=3$ and 5, respectively.

**Figure 1.** Statistical power a genome-wide study of pelvic organ prolapse. Power curves are presented for $K=1$, 3, and 5 variants and MAFs of 1% (black), 5% (blue) and 20% (red). Shading shows 80% power.

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**6.E. Potential limitations and or challenges:**

One potential limitation is that the phenotype of pelvic organ prolapse will be defined by two methods: 1) ICD-9 and CPT codes and 2) pelvic examination. While some of our cases have pelvic examinations which provide details regarding severity of prolapse, defining prolapse using ICD-9 and CPT codes is a well-accepted and commonly performed strategy. The ICD-9 codes listed above are specific for pelvic organ prolapse, and ICD-9 codes 618.X encompass all of the
prolapse diagnoses. The surgeries listed above based on CPT codes are also specifically utilized to treat prolapse and are not used for any other indication.

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 ICTDER 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)?

I searched pelvic organ prolapse as well as other pelvic floor disorders including the search terms “urinary incontinence”, “fecal incontinence”, “incontinence,” “pelvic floor”, and “pelvic floor disorders” and was not able to identify any manuscript proposals.

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/
12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.csc.c.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.
References:


