Transethnic and race-stratified genome-wide association study of fibroid characteristics in African American and European American women

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Objective: To identify, through genome-wide association studies, genetic loci that associate with differences in fibroid size and number in a population of African American and European American women.
Design: Cross-sectional study.
Setting: Not applicable.
Patient(s): Using BioVU, a clinical population from the Vanderbilt University Medical Center, and the Coronary Artery Risk Development in Young Adults cohort, a prospective cohort, we identified 1520 women (609 African American and 911 European American) with documented fibroid characteristics.
Intervention(s): None.
Main Outcome Measure(s): Outcome measurements include volume of largest fibroid, largest fibroid dimension, and number of fibroids (single vs. multiple).
Result(s): In race-stratified analyses we achieved genome-wide significance at a variant located between *MAT2B* and *TENM2* (rs57542984, $\beta = 0.13$; 95% confidence interval 0.09, 0.17) for analyses of largest fibroid dimension in African Americans. The strongest signal for transethnic analyses was at a variant on 1q31.1 located between *PLA2G4A* and *BRINP3* (rs6605005, $\beta = 0.24$; 95% confidence interval 0.15, 0.33) for fibroid volume. Results from MetaXcan identified an association between predicted expression of the gene ER degradation enhancing alpha-mannosidase like protein 2 (*EDEM2*) in the thyroid and number of fibroids (Z score $= -4.51$).
Conclusion(s): This study identified many novel associations between genetic loci and fibroid size and number in both race-stratified and transethnic analyses. Future studies are necessary to further validate our study findings and to better understand the mechanisms underlying these associations. (Fertil Steril® 2018;110:737-45. ©2018 by American Society for Reproductive Medicine.)

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Key Words: Fibroids, genome-wide association study, leiomyomata, transethnic meta-analysis

The majority of US women develop at least one leiomyoma, or uterine fibroid, by the age of menopause (1), which results in approximately $5.9–$34.4 billion annually from treatments and costs associated with loss of work and healthcare (2). Fibroids are heterogeneous and vary in size and number between women, likely leading to a range of symptoms, including pressure of the abdomen, chronic pelvic pain, and heavy or painful periods (3).

Heritability estimates for fibroid number and size remain unknown, although twin studies estimate that between 26% and 69% of fibroid risk is heritable (4, 5). Additional support for a genetic etiology for fibroids comes from racial differences in fibroid risk (1, 6, 7), as well as the racial differences in fibroid size and number between African American (AA) and European American (EA) women (1, 8). For example, the incidence rate for fibroids is two to three times larger for AA women than for EA women (7), and AA women are more likely to have a hysterectomy because of fibroids than EA women (9). Additionally, AA women have larger and more numerous fibroids than EA women (1, 8). In an admixture mapping study on fibroid number and size, our laboratory group observed that AA women with more African ancestry were more likely to have multiple fibroids using genetic data from BioVU and Coronary Artery Risk Development in Young Adults (CARDIA) (10).

There have been no prior genome-wide association studies (GWASs) of fibroid characteristics; however, a few studies have shown a direct relationship between increasing fibroid size and gene variants (11, 12). Edwards et al. (11) observed associations between increasing fibroid size in EAs with gene variants in trinucleotide repeat containing 6B (*TNRC6B*) and Bet1 Golgi vesicular membrane trafficking protein like (*BET1L*) that were originally found in a GWAS of fibroid risk (13). Aissani et al. (12) showed associations between fibroid risk and largest fibroid dimension when evaluating a set of candidate gene variants. There have been two previous GWASs on fibroid risk (13,14). In the first GWAS examining fibroid risk using a population of Japanese women, Cha et al. (13) found three chromosomal regions that were associated with increased fibroid risk: 10q24.33, 22q13.1, and 11p15.5. The second GWAS on fibroid risk was performed in AA populations (14). In the study the authors observed a genome-wide significant association between rs739187 in cytohesin 4 (*CYTH4*) in 22q13.1 and fibroid risk (14).

Fibroids are heterogeneous, and it is possible that there are distinct genetic variants that associate with fibroid size and number. Additionally, there may be genetic loci affecting fibroid size and number that are race-specific, as well as others that are common across racial/ancestral groups. The objective of this study was to identify genetic loci that associate with differences in fibroid size and number in a population of AA and EA individuals.

MATERIALS AND METHODS

Study Population

Coronary Artery Risk Development in Young Adults. The CARDIA cohort was initiated between 1985 and 1986 with the goal of measuring risk factors for coronary heart disease in a cohort of AA and EA individuals (15). The cohort consists of 5115 AA and EA participants between 18 and 30 years of age who were selected on the basis of approximately equal proportions of 18–24- and 25–30-year-olds, sex, race (black and white), and education status with respect to high school graduation. Cohort recruitment took place at four places in the United States: Birmingham, AL, Chicago, IL, Minneapolis, MN, and Oakland, CA (15).

The CARDIA Women's Study is an ancillary study of CARDIA that conducted pelvic ultrasound examinations among women in the CARDIA cohort at 16 years after enrollment. The goal of the CARDIA Women's Study was to evaluate the association between risk factors of polycystic ovary syndrome and cardiovascular disease. Largest fibroid dimensions, fibroid number, and relevant demographic data to our project were collected and recorded by trained CARDIA Women's Study research staff (16). A transvaginal ultrasound scan was performed by sonographers who were certified by the American Registry of Diagnostic Medical Sonographers and who had performed at least 50 prior transvaginal ultrasound examinations. The sonographers used a 5–7.5-MHz transvaginal probe. The dimensions of the largest fibroid were measured, and number of fibroids was noted (16).

Our analyses used lifestyle and sociodemographic information that was collected via self- and interviewer-administered questionnaires (16). Measurements for height and weight were collected using a standardized protocol described previously (17).

The BioVU DNA Repository. The BioVU DNA Repository (2007–present) is a deidentified database of electronic health records that is linked to DNA. BioVU consists of stored deidentified demographic and clinical information for each patient who visits the Vanderbilt University Medical Center (18). A detailed description of BioVU has been previously published (18, 19). The Office of Human Research Protections and the institutional review boards (20) deemed the BioVU DNA repository as nonhuman subjects research (19).

A validated phenotyping algorithm with a positive predictive value of 96% was used to identify fibroid cases