Admixture mapping of uterine fibroid size and number in African American women

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Objective: To evaluate the relationship between genetic ancestry and uterine fibroid characteristics.
Design: Cross-sectional study.
Setting: Not applicable.
Patient(s): A total of 609 African American participants with image- or surgery-confirmed fibroids in a biorepository at Vanderbilt University electronic health record biorepository and the Coronary Artery Risk Development in Young Adults studies were included.
Intervention(s): None.
Main Outcome Measure(s): Outcome measures include fibroid number (single vs. multiple), volume of largest fibroid, and largest fibroid dimension of all fibroid measurements.
Result(s): Global ancestry meta-analyses revealed a significant inverse association between percentage of European ancestry and risk of multiple fibroids (odds ratio: 0.78; 95% confidence interval 0.66, 0.93; $P=6.05 \times 10^{-3}$). Local ancestry meta-analyses revealed five suggestive ($P<4.80 \times 10^{-3}$) admixture mapping peaks in 2q14.3-2q21.1, 3p14.2-3p14.1, 7q32.2-7q33, 10q21.1, 14q24.2-14q24.3, for number of fibroids and one suggestive admixture mapping peak ($P<1.97 \times 10^{-3}$) in 10q24.1-10q24.32 for volume of largest fibroid. Single variant association meta-analyses of the strongest associated region from admixture mapping of fibroid number (10q21.1) revealed a strong association at single nucleotide polymorphism variant rs12219990 (odds ratio: 0.41; 95% confidence interval 0.28, 0.60; $P=3.82 \times 10^{-6}$) that was significant after correction for multiple testing.
Conclusion(s): Increasing African ancestry is associated with multiple fibroids but not with fibroid size. Local ancestry analyses identified several novel genomic regions not previously associated with fibroid number and increasing volume. Future studies are needed to explore the genetic impact that ancestry plays into the development of fibroid characteristics. (Fertil Steril® 2017;108:1034–42. ©2017 by American Society for Reproductive Medicine.)
Key Words: Fibroids, leiomyomata, admixture mapping, local ancestry, global ancestry

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Uterine leiomyomata, or fibroids, are the most common female pelvic tumor (1) affecting most US women by menopause (2). Fibroids cost the United States 5.9–34.4 billion dollars annually for treatment, healthcare, and work loss costs (3). The incidence and progression of fibroids are highly heterogeneous, with some women developing a single small fibroid, whereas other women develop multiple and/or large fibroids. For example, African American (AA) women have a two- to threefold higher risk of fibroids when compared with European American (EA) women (4). The AA women also have more numerous and larger fibroids (2). In addition, AAs are two times

more likely than EAs to receive surgical treatments for fibroids such as hysterectomies (5).

Although the heritability of specific fibroid characteristics, such as fibroid size and number, is unknown, heritability estimates of fibroid risk from twin studies have ranged between 26% and 69% (6, 7). Additional support for genetic etiology for fibroids comes from racial differences in fibroid risk (2, 4, 8), as well as the racial differences in fibroid size and number between AA and EA women. A few studies have shown a direct relationship between increasing fibroid size and gene variants (9, 10). Edwards et al. (9) 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 genome-wide association study of fibroid risk (11). Aissani et al. (10) showed associations between fibroid risk and largest fibroid dimension when evaluating a set of candidate gene variants.

Admixture mapping is an analytic approach in genetics to evaluate the relationship between genetic ancestry and disease risk. Admixture mapping analyses are performed using admixed populations, such as AAs, where there are known prevalence differences in disease risk across racial groups. The AA women have on average approximately 80% African ancestry and 20% European ancestry (12). Admixture mapping has been successfully applied in studies examining multiple sclerosis (13), keloids (14), and prostate cancer (15) in AA populations. A few previous studies have performed admixture mapping analyses on fibroid risk using AA individuals (16, 17). In the first study by Wise et al. (16), the investigators performed an admixture mapping study using ultrasound- or image-confirmed 2,453 cases and 2,102 controls with no fibroid diagnosis from the prospective cohort, the Black Women's Health Study, with women throughout the United States. Using ANCESTRYMAP (18–20) and ADMIXMAP (21), they found that the mean percentage of African ancestry was significantly higher in fibroid cases when compared with controls but did not find a region in the genome that was significantly associated with fibroid risk (16). They did, however, find suggestive associations in chromosomal regions 2q33, 4p16, and 10q26 (16). In the second admixture mapping study on fibroid risk by Zhang et al. (17), the investigators performed a cross-sectional study using 393 ultrasound-confirmed cases and 132 ultrasound-confirmed controls from the National Institute of Environmental and Health Sciences-Uterine Fibroid Study. Using ADMIXMAP (21), they did not find a significant association between global ancestry and fibroid risk. Zhang et al. (17) did find a region within chromosome 1q42.2 with suggestive to significant associations where each African allele increased risk after stratifying by body mass index (BMI). In the most recent admixture mapping study by Giri et al. (22), the investigators performed a cross-sectional study using AA women from the biorepository at Vanderbilt University (BioVU) and the Coronary Artery Risk Development in Young Adults (CARDIA) cohorts. They found that BMI interacts with local European ancestry and fibroid risk in AA women in two genomic regions, 6p24 and 2q31-31 (22).

Fibroids are a heterogeneous disease. Each fibroid characteristic difference, such as single versus multiple fibroids or a small versus large fibroid, could be affected by a set of genetic loci. A study examining fibroid characteristics might have better power to detect genetic determinants of fibroid subphenotypes that might be more closely related to a potential targeted treatment than a genetic study on fibroid risk. To our knowledge, no study has performed an admixture mapping analysis on fibroid characteristics in AA individuals. The objective of this study is to examine the relationship between African ancestry and fibroid characteristics, namely size and number.

MATERIALS AND METHODS

Study Population

Coronary Artery Risk Development in Young Adults. The Coronary Artery Risk Development in Young Adults (CARDIA) study was initiated in 1985-1986 with the goal of measuring risk factors for coronary heart disease in a cohort of black and white Americans (23). The cohort consists of 5,115 AA and EA participants between the ages of 18 and 30 years who were selected based on approximately equal proportions of 18 to 24 and 25 to 30 year olds, sex, race (black and white), and education status with respect to high school graduation. Cohort recruitment took place at four locations in the United States: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California (23).

The CARDIA Women's Study is an ancillary study of CARDIA that conducted pelvic ultrasounds 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 (PCOS) and cardiovascular disease. Largest fibroid dimensions, fibroid number, and other relevant data to our project were collected and recorded by trained CARDIA Women's Study research staff (24). A transvaginal ultrasound 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- to 7.5-MHz transvaginal probe. The dimensions of the largest fibroid were measured and number of fibroids was noted (24).

Our analyses used lifestyle and sociodemographic information that was collected by self- and interviewer-administered questionnaires (24). Measurements for height and weight were collected using a standardized protocol described previously (25).

The biorepository at Vanderbilt University. The BioVU DNA Repository (2007–present) is a deidentified database of electronic health records that is linked to DNA. The BioVU consists of stored deidentified demographic and clinical information for each patient who visits the Vanderbilt University Medical Center (26). A detailed description of BioVU has been previously given (26, 27). The Office of Human Research Protections and the Institutional Review Boards deemed the BioVU DNA repository as non-human subjects research (27).

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