

BRIEF REPORT

Applicability of ancestral genotyping in pharmacogenomic research with hormonal contraception

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Abstract

To compare etonogestrel pharmacokinetic and pharmacodynamic outcomes by both self-reported race/ethnicity and genetically determined ancestry among contraceptive implant users. We conducted a secondary analysis of our parent pharmacogenomic study of 350 implant users. We genotyped these reproductive-aged (18–45 years) women for 88 ancestry-informative single nucleotide polymorphisms. We then assigned each participant a proportion value for African (AFR), European (EUR), and Indigenous American (AMR) ancestry based on reference population data. We correlated genetic ancestry with self-reported race/ethnicity and utilized genetic ancestry proportion values as variables for previously performed association analyses with serum etonogestrel concentrations and progestin-related side effects (e.g., bothersome bleeding and subjective weight gain). We successfully estimated genetically determined ancestry for 332 participants. EUR, AFR, and AMR ancestry were each highly correlated with self-reported White/non-Hispanic race ($r = 0.64$, $p = 4.14 \times 10^{-40}$), Black/African American race ($r = 0.88$, $p = 1.36 \times 10^{-107}$), and Hispanic/Latina ethnicity ($r = 0.68$, $p = 4.03 \times 10^{-47}$), respectively. Neither genetically determined ancestry nor self-reported race/ethnicity were significantly associated with serum etonogestrel concentrations. AFR ancestry and self-reported Black race had similar associations with reporting monthly periods (odds ratio [OR] 2.18, $p = 0.09$ vs. OR 2.22, $p = 0.02$) and having received treatment for bothersome bleeding (OR 5.19, $p = 0.005$ vs. OR 4.73, $p = 2.0 \times 10^{-4}$). In multivariable logistic regression for subjective weight gain, AMR ancestry dropped out of the model in preference for self-reported Hispanic/Latina ethnicity. We found no new associations between genetically determined ancestry and contraceptive implant pharmacodynamics/pharmacokinetics. Self-reported race/ethnicity were strong surrogates for genetically determined ancestry among this population of contraceptive implant users. Our data suggest that self-reported race/ethnicity, capturing societal and cultural aspects, remain important to the investigation of progestin-related side effects.

Clinical Trial Registration: Clinicaltrials.gov, NCT03092037.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Individual women using the exact same contraceptive method demonstrate widely variable pharmacokinetics and side effect profiles. Self-reported race/ethnicity has associations with progestin-related side effects among etonogestrel contraceptive implant users. Self-reported race/ethnicity and genetically determined ancestry may provide complementary information, but contraceptive research does not routinely evaluate for genetically determined ancestry.

WHAT QUESTION DID THIS STUDY ADDRESS?

Is genetically determined ancestry associated with pharmacokinetic or pharmacodynamic (side effect) outcomes among contraceptive implant users?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Genetically determined ancestry was highly correlated with self-reported race/ethnicity among this population of young contraceptive implant users. Genetically determined ancestry was not associated with etonogestrel pharmacokinetics and had very similar associations as self-reported race/ethnicity with progestin-related side effects. However, the associations with genetically determined ancestry were at higher risk of stemming from type 1 errors (i.e., higher *p* values) compared with the associations with self-reported race/ethnicity.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

In hormonal contraceptive research, self-reported race/ethnicity remains an important variable as it may capture sociodemographic differences in the contraceptive experience unrelated to genetic differences.

INTRODUCTION

Wide variability exists in the pharmacokinetics and pharmacodynamics of hormonal contraceptive methods, with much research focused on understanding the contribution of individual patient characteristics to this variability.¹⁻³ The demographics of patients, reported in the form of race and ethnicity, have demonstrated associations with progestin-related side effects, such as abnormal bleeding, amenorrhea (i.e., absence of menses), and weight gain.^{4,5} These progestin-related side effects are the most commonly reported reasons for early contraceptive method discontinuation, which places patients at increased risk of unintended pregnancies and related adverse health and social outcomes.¹ From our own work, we found that participants who self-reported their race as Black or African American were more likely to report a monthly period during contraceptive implant use (adjusted odds ratio [aOR] 2.22, 95% confidence interval [CI] 1.14–4.32) and that women of self-reported Asian or Pacific Islander race were more likely to report amenorrhea (aOR 3.25, 95% CI 1.15–9.22) as compared with all other participants.⁴ These associations are not solely found with bleeding side effects, as we also found that self-reported Hispanic or Latina participants had almost three times the odds of reporting subjective weight gain during contraceptive implant use.⁶

However, self-reported race and ethnicity are social, cultural, and geopolitical constructs that are not always representative of genetic ancestry.⁷ As much of the variability in these contraceptive side effects remain unaccounted for, and given the increasingly admixed population in countries like the United States, genetic ancestry measured along the continuous spectrum of human diversity may help further explain individual differences in contraceptive pharmacodynamics not captured by self-reported race and ethnicity alone.^{4,7,8}

Additionally, in our previous work, we found that differences in contraceptive pharmacokinetics (i.e., increased serum etonogestrel concentrations) were associated with key pharmacodynamic outcomes among contraceptive implant users, such as increased odds of abnormal bleeding and increased odds of having received medical treatment for bothersome bleeding.⁴ Etonogestrel shares a common metabolic pathway to all steroid hormones that is primarily mediated by cytochrome P-450 (CYP) 3A enzymes, specifically CYP3A4 and CYP3A5.¹ The gene encoding CYP3A5 is known to have functional variants with differing prevalence by genetic ancestry.⁹ *CYP3A5*3* is the most common allele among individuals with European ancestry and results in a nonfunctional enzyme, whereas *CYP3A5*1* is the most common allele among individuals with African ancestry and results in a fully functional enzyme.⁹ Theoretically, given the metabolic

pathway of steroid hormones, contraceptive implant users that self-report as Black or African American should have increased metabolism of etonogestrel given higher prevalence of functional CYP3A5 enzymes, but we previously found a trend toward decreased metabolism of etonogestrel among these participants.⁴ As with pharmacodynamic aspects of contraception, much of the variability in contraceptive pharmacokinetics remains unaccounted for, and genetic ancestry may help explain some of these individual differences and counterintuitive trends in contraceptive pharmacokinetics.

Pharmacogenomics is the study of how genetic variation can affect medication response and toxicity.¹⁰ Portions of this genetic variation have remained consistent across generations and can be used to determine the ancestral heritage of individuals.⁷ Precision medicine research has found that genetic ancestry and self-reported race/ethnicity may provide complementary information in relation to pharmacogenomic outcomes.^{8,11,12} For example, there is a recognized need for ethnicity-specific pharmacogenetic algorithms for warfarin dosing due to differential variant allele frequencies in the *CYP2C9* gene among certain ethnic populations (e.g., African Americans and Chinese) compared with the European population studied to develop the original algorithm.¹² Thus, by focusing solely on self-reported race and ethnicity, contraceptive research may be missing key genetic components or other components captured by continuous ancestry patterns that are contributing to persistent differences in health outcomes and other health disparities in women.^{11,12} To evaluate for potential associations between genetic ancestry and the variable pharmacokinetic and pharmacodynamic profiles found with hormonal contraception, we conducted ancestral genotyping on our cohort of etonogestrel contraceptive implant users. We hypothesized that genetically determined ancestry would be a more informative predictor of these outcomes than self-reported ancestry.

METHODS

This was a secondary analysis of a parent pharmacogenomic association study.¹³ The methodology for study enrollment has been previously published, including all inclusion and exclusion criteria, assessment of bleeding side effect profiles and subjective weight gain, and measurement of etonogestrel concentrations.^{4,6,13} All participants in the parent study were users of the etonogestrel contraceptive implant and had used their implant between 12 and 36 months at the time of enrollment.¹³ The contraceptive implant reaches steady-state drug release after the first 12 months of use, and therefore single-time measurements of serum etonogestrel concentration were used to determine etonogestrel pharmacokinetic profiles.^{4,13} The protocol was approved by the Colorado Multiple Institutional Review Board and all participants gave written

consent for utilization of stored DNA samples for this analysis. The prepared DNA samples ($n = 350$) were de-identified and shipped to the University of Minnesota Genomics Center for iPLEX genotyping. During shipment, two samples were irreparably damaged. The remaining 348 samples underwent 2 quality checks and 94% ($n = 326$) passed both checks. An additional 10 samples with marginal quality were included in the genotyping. The samples ($n = 336$) were then genotyped for 88 ancestry-informative single nucleotide polymorphisms using Agena Bioscience iPLEX genotyping (Table S1).¹⁴

The iPLEX genotypes were converted to .ped/.map format using a custom python script and alleles were harmonized to match an ancestry reference panel consisting of three continental super-populations from the phase III 1000 Genomes Project: African (ESN, MSL, GWD, YRI, LWK, ASW, and ACB), American (CLM, MXL, PEL, and PUR), and European (CEU, FIN, GBR, IBS, and TSI).¹⁵ Because individuals in the American population of 1000 Genomes are admixed, we also included 109 unadmixed individuals from three additional populations (Fej_Eur, Fej_Afr, and Fej_Nat) from Dr. Laura Fejerman (University of California San Francisco), including 30 indigenous American individuals in the reference panel.¹⁶ Data were made available to us by Avena et al. and are available upon request to the authors.¹⁶ Strand-ambiguous alleles that were flipped during allele harmonization were manually identified by comparing the frequencies of alleles between 1000 Genomes Europeans and self-identified White non-Hispanic individuals from our data set.

Following allele harmonization, we removed loci and individuals ($n = 4$) with excessive missingness using two consecutive filter steps: (1) loci missing more than 5% genotypes were removed, and (2) individuals missing more than 10% of genotypes were removed. These missingness thresholds were chosen to maximize the number of samples passing filter criteria while maintaining a sufficient number of loci for confident admixture analysis. We merged our study data with the reference panel, and ran ADMIXTURE (version 1.3.0) using unadmixed populations from the reference panel (EUR-CEU, FIN, GBR, IBS, TSI, Fej_Eur; AFR-ESN, GWD, MSL, LWK, YRI, Fej_Afr; and AMR-Fej_Nat) to train population allele frequencies and estimate individual admixture proportions for each participant in our study.

The output of admixture yields a proportion of ancestry (0–1, summing to 1 total per participant) for each of three super-populations: African (AFR), European (EUR), and Indigenous American (AMR). We used IBM SPSS version 25 statistical software for our analyses. We determined Pearson correlation coefficients between genetic ancestry and self-reported race and ethnicity. Self-reported race and ethnicity were categorized according to National Institutes of Health racial and ethnic categories.¹⁷ We also used these proportion values as variables for our previously performed

statistical analyses.^{4,6,13} Specifically, we again performed generalized linear modeling to determine associations with serum etonogestrel concentrations and multivariable logistic regression for associations with the pharmacodynamic outcomes of experiencing abnormal bleeding, amenorrhea, monthly periods, receiving treatment for abnormal bleeding, and subjective weight gain.

TABLE 1 Participant characteristics and demographics ($N = 332$)

	Median (range)
Age, years	22.5 (18.0–39.1)
Months of implant use	26.0 (12.0–36.0)
BMI, kg/m ²	25.5 (18.5–52.0)
Serum etonogestrel concentration, pg/ml	138.2 (55.8–695.1)
	<i>n</i> (%)
Race	
White	153 (46.1)
Black or African American	39 (11.7)
Asian or Pacific Islander	17 (5.1)
Native American or Alaskan	7 (2.1)
More than one	43 (13.0)
No response or unknown	73 (22.0)
Ethnicity	
Hispanic or Latina	169 (50.9)
Non-Hispanic	163 (49.1)
	Median (range)
Genetic ancestry^a	
African	0.05 (0.00–0.98)
European	0.55 (0.00–0.99)
Indigenous American	0.23 (0.00–0.96)

Abbreviation: BMI, body mass index.

^aBased on proportion of ancestry (0–1, summing to 1 total per participant) for each of three super populations.

RESULTS

We successfully assigned genetic ancestry for 332 participants. The most frequent self-reported race was White (46.1% [153/332]) and the majority (50.9% [169/332]) reported Hispanic or Latina ethnicity. Table 1 contains the full breakdown of self-reported race and ethnicity. When evaluating all 332 participants, the cohort had a median AFR ancestry of 0.05 (range 0.00–0.98), median EUR ancestry of 0.55 (range 0.00–0.99), and median AMR ancestry of 0.23 (range 0.00–0.96). Ancestry proportions by self-reported race and ethnicity are presented in Table 2.

AFR ancestry was significantly correlated with self-reported Black (African American) race ($r = 0.88$, $p = 1.36 \times 10^{-107}$). EUR ancestry was significantly correlated with self-reported White race ($r = 0.64$, $p = 4.14 \times 10^{-40}$). This correlation was stronger when EUR ancestry was compared to self-report of White race and non-Hispanic ethnicity ($r = 0.79$, $p = 1.45 \times 10^{-70}$). AMR ancestry was significantly correlated with self-reported Hispanic or Latina ethnicity ($r = 0.68$, $p = 4.03 \times 10^{-47}$).

No genetic ancestry was significantly associated with serum etonogestrel concentrations with generalized linear modeling. EUR and AMR ancestry both trended toward decreases in serum etonogestrel concentrations ($\beta = -15.36$, $p = 0.26$ and $\beta = -3.41$, $p = 0.84$, respectively), whereas AFR ancestry trended toward increases in serum etonogestrel concentrations ($\beta = 23.14$, $p = 0.13$). When patient characteristics known to have significant associations with serum etonogestrel concentrations (i.e., body mass index and duration of implant use) were added to the generalized linear models,² the associations found with genetic ancestry became more likely to be type 1 errors (EUR $p = 0.34$, AMR $p = 0.88$, and AFR $p = 0.21$).

Genetic ancestry was also not associated with reports of experiencing abnormal bleeding or amenorrhea during

TABLE 2 Genetic ancestry proportions by self-reported race and ethnicity

Self-reported race/ethnicity ^a	AFR	EUR	AMR
White/non-Hispanic ($n = 96$)	<0.001 (0.00–0.14)	0.96 (0.63–1.00)	0.002 (0.00–0.30)
White/Hispanic ($n = 57$)	0.04 (0.00–0.40)	0.54 (0.21–0.87)	0.41 (0.08–0.79)
Black/non-Hispanic ($n = 33$)	0.79 (0.46–0.98)	0.19 (0.00–0.53)	0.03 (0.00–0.17)
Black/Hispanic ($n = 6$)	0.47 (0.00–0.67)	0.27 (0.11–0.49)	0.26 (0.00–0.51)
Asian/non-Hispanic ($n = 16$)	0.13 (0.01–0.23)	0.42 (0.26–0.74)	0.45 (0.18–0.61)
All Hispanic ^b ($n = 169$)	0.05 (0.00–0.67)	0.50 (0.00–0.90)	0.44 (0.00–0.96)
Native American or Alaskan ($n = 7$)	0.05 (0.00–0.16)	0.29 (0.20–0.67)	0.63 (0.25–0.79)
More than one race ($n = 43$)	0.08 (0.00–0.77)	0.54 (0.16–0.90)	0.23 (0.00–0.71)

Note: All values are median (range) for genetic ancestry proportion values.

Abbreviations: AFR; African ancestry; EUR; European ancestry; AMR; Indigenous American ancestry.

^aNumbers in this column will not add up to $n = 332$ due to overlap between categories.

^bAll participants who self-reported their race as “No response or unknown” ($n = 73$) reported their ethnicity as “Hispanic” and so are included in this row.

contraceptive implant use. AFR ancestry was suggestively associated with higher odds of having a monthly period with the implant (odds ratio [OR] 2.18, 95% CI 0.89–5.33). This association was similar to that of self-reported Black race and having a monthly period (OR 2.22, 95% CI 1.13–4.35) among the same 332 participants, but the association with self-reported race ($p = 0.02$) was less likely to be a type 1 error as compared with that found with AFR ancestry ($p = 0.09$). We found similar associations between having received an oral contraceptive pill prescription for treatment of bothersome bleeding with the implant and both self-reported Black race and AFR ancestry: OR 4.73, 95% CI 2.08–10.75 and OR 5.19, 95% CI 1.65–16.32, respectively. This association was again less likely to be a type 1 error for self-reported Black race ($p = 2.0 \times 10^{-4}$ vs. $p = 0.005$). When using a backward-stepwise approach for these multivariable logistic regression analyses, AFR ancestry was consistently removed from the models in favor of self-reported Black race.

Both self-reported Hispanic/Latina ethnicity and AMR ancestry were associated with increased odds of subjective weight gain (OR 2.97, 95% CI 1.88–4.68 [$p = 3.0 \times 10^{-6}$] vs. OR 7.07, 95% CI 2.72–18.35 [$p = 5.9 \times 10^{-5}$]). However, when performing multivariable logistic regression analysis of subjective weight gain using a backward stepwise approach and including body mass index as a covariate, AMR ancestry was removed from the model in preference for self-reported Hispanic/Latina ethnicity.

DISCUSSION

In this large group of etonogestrel implant users, we found that genetically determined ancestry was highly correlated with self-reported race and ethnicity, similar to correlations previously found in larger populations.⁷ However, genetic ancestry was not associated with our pharmacokinetic outcome (serum etonogestrel concentrations) and was not more informative than self-reported race and ethnicity in regard to bleeding and weight gain-related side effects with the contraceptive implant. We found that AFR ancestry had very similar associations as to those we previously found with self-reported Black (African American) race, but Black race was the better predictor for these bleeding-related outcomes of interest. Similarly, AMR ancestry had a strong association with subjective weight gain, but this association was not significant after taking into account self-reported Hispanic/Latina ethnicity. Ultimately, genetic ancestry was no better than self-reported race and ethnicity in explaining variability in bleeding patterns and perceived weight gain with the contraceptive implant, lending support that there are likely environmental, social, and cultural aspects to these outcomes not explained solely by genetic

heritage. Self-reported race and ethnicity have also been associated with health disparities in sexual and reproductive health services, including contraception, despite improvements in contraceptive access and reductions in cost barriers.¹⁸ These findings further support the importance of this sociodemographic variable in contraceptive research that may capture differences in the contraceptive experience unrelated to genetic differences.^{11,12} However, genetically determined ancestry may still play an essential role in research on progestin-related side effects when self-reported race and ethnicity data are not available. Future research pertaining to side effects with hormonal contraception should continue to explore the influence of self-reported race and ethnicity, given the societal and cultural differences captured by this measure.

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CONFLICT OF INTEREST

Dr. Teal serves on a Data Monitoring Board for a study funded by Merck and Co. and has served as a consultant for Bayer Healthcare. The University of Colorado Department of Obstetrics and Gynecology has received research funding from Bayer, Agile Therapeutics, Merck and Co., and Medicines360. All other authors declared no competing interest for this work.

AUTHOR CONTRIBUTIONS

A.L., C.A., J.S., J.S., S.T., and C.G. wrote the manuscript. A.L., C.A., J.S., J.S., S.T., and C.G. designed the research. A.L., J.S., and C.G. performed the research. A.L., J.S., J.S., and C.G. analyzed the data. A.L., J.S., and C.G. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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