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Genomics of Reproductive Traits and Cardiometabolic Disease Risk in African American Women

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Abstract

Background: Age at menarche and age at natural menopause occur significantly earlier in African-American women than in other ethnic groups. African-American women also have twice the prevalence of cardiometabolic disorders related to the timing of these reproductive traits.

Objectives: The objectives of this integrative review were to (a) summarize the genome-wide association studies (GWAS) of reproductive traits in African-American women; (b) identify genes that overlap with reproductive traits and cardiometabolic risk factors in African-American women; and (c) propose biological mechanisms explaining the link between reproductive traits and cardiometabolic risk factors.

Methods: PubMed was searched for GWAS of genes associated with reproductive traits in African-American women. After extracting and summarizing the primary genes, we examined whether any of the associations with reproductive traits had also been identified with cardiometabolic risk factors in African-American women.

Results: Seven studies met the inclusion criteria. Associations with both reproductive and cardiometabolic traits were reported in or near the following genes: *FTO*, *SEC16B*, *TMEM18*, *APOE*, *PHACTR1*, *KCNQ1*, *LDLR*, *PIK3R1* and *RORA*. Biological pathways implicated include bodyweight regulation, vascular homeostasis, and lipid metabolism.

Discussion: A better understanding of the genetic basis of reproductive traits in African-American women may provide insight into the biological mechanisms linking variation in these traits with increased risk for cardiometabolic disorders in this population.

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Ethical Conduct of Research: As an integrative review of the literature, this study was exempt from IRB approval.

Keywords

African American; genomics; reproductive

The female reproductive lifespan is the result of a complex interplay of genetic and environmental factors. There is significant variability in the timing of reproductive traits, such as age at menarche and age at natural menopause, events that mark the beginning and end of the female reproductive lifespan, respectively. In addition to problems with fertility, variation in the timing of reproductive traits is associated with increased cardiovascular disease risk (Lakshman et al., 2009). Researchers have found an inverse association between age at menarche and cardiometabolic risk factors including BMI, body fat, insulin resistance and triglyceride levels (Dreyfus et al., 2015; Lakshman et al., 2009; Luijken, van der Schouw, Mensink, & Onland-Moret, 2017), and an inverse association between age at menopause and lipid levels, blood pressure, and mortality due to cardiovascular disease (de Kat et al., 2017).

Heritability estimates of age at menarche and age at natural menopause are high, with genetic inheritance explaining 53–74% and 44–65% of variation, respectively (Coignet et al., 2017). Genome-wide association studies (GWAS) have identified numerous loci associated with these reproductive traits in European-American (EA) populations (Elks et al., 2010; Stolk et al., 2009). However, there are significant racial differences in the timing of reproductive traits. Compared to EA women, African-American (AA) women are more likely to undergo earlier menarche and natural menopause (Biro et al., 2018; Nowakowski & Graves, 2017). AA women also have twice the prevalence of chronic diseases related to the timing of reproductive traits including childhood obesity, metabolic syndrome, diabetes, and hypertension (Long et al., 2012).

Researchers have explored genes associated with both reproductive traits and cardiovascular disease risk in order to elucidate potential biological mechanisms explaining the relationship between these physiological processes (Luijken, van der Schouw, Mensink, & Onland-Moret, 2017; van der Kemp, van der Schouw, Asselbergs, & Onland-Moret, 2018). In these studies, the authors utilized genetic loci from GWAS in EA women, limiting generalization across diverse populations (Carlson et al., 2013). The purpose of this systematic review was to (a) summarize the GWAS of reproductive traits in AA women; (b) identify overlap in genes associated with both reproductive traits and cardiometabolic risk factors in AA women; and (c) propose biological mechanisms underlying the relationship between reproductive traits and cardiometabolic risk factors.

Methods

We conducted an integrative review to summarize the GWAS of reproductive traits in African-American women using criteria by Whittemore and Knafl (2005). We used PubMed to conduct our search, as it is the most highly utilized literature search engine that includes GWAS data. We searched for publications from 2008 to 2018 using the keywords *GWAS* and *reproductive*. The following inclusion criteria were used:

1. GWAS examining reproductive traits (e.g., age at menarche, age at menopause) or biomarkers of a reproductive trait (e.g., follicle stimulating hormone).
2. The population studied was African-American women or included African-American women. African American/Black is inclusive of Black populations in the U.S.

We identified 206 publications in our search on November 14, 2018, and retrieved four additional studies through references of retrieved articles. After removing duplicates and excluding studies that did not meet the review criteria, seven studies were included in the final review (Figure 1). After extracting and summarizing the primary genes associated with reproductive traits in AA women, we searched PubMed to examine overlapping genetic associations with cardiometabolic risk factors (e.g., BMI, hypertension) in AA. We conducted independent searches for each of the reproductive genes by searching for the <gene symbol> and *African American*. For each of the genes where overlap was identified, potential biological mechanisms were explored.

Results

Seven studies met the inclusion criteria. The study purpose, sample size, and methods are summarized in Table 1. All studies included AA women, and three studies examined populations comprised AA women only (Chen et al., 2014; Demerath et al., 2013; Spencer et al., 2013). All studies used ancestry informative markers to adjust for population stratification. Sample sizes ranged from 200 to 18,089 subjects. All studies aimed to replicate single nucleotide polymorphisms (SNP) associated with reproductive traits previously identified in EA populations, and five of these had the additional aim of discovering novel variants of reproductive traits in AA women (Chen et al., 2014; Demerath et al., 2013; Schuh-Huerta, Johnson, Rosen, Sternfeld, Cedars, & Pera, 2012; Schuh-Huerta et al., 2012b; Spencer et al., 2013).

Three (43%) of the studies examined genetic associations with both age at menopause and age at menarche (Carty et al., 2013; Coignet et al., 2017; Spencer et al., 2013). One (13%) examined only age at menopause (Chen et al., 2014), and one (13%) examined only age at menarche (Demerath et al., 2013). Two (29%) studies examined genetic associations with biomarkers of the ovarian reserve, or the remaining ovarian follicle pool (Schuh-Huerta et al., 2012a; Schuh-Huerta, 2012b). Biomarkers of the ovarian reserve, such as anti-Müllerian hormone and antral follicle count, predict with reasonable accuracy the onset of natural menopause, and thus are useful measures of reproductive age in women (Depmann et al., 2016).

Overall, SNPs previously identified in studies of EA women did not generalize to AA women. The top SNPs that replicated in AA women (nominally significant) are summarized in Table 2. The SNPs that replicated for age at menarche were *CENPW* and *TMEM18* and for age at natural menopause were *BRSK1*, *APOE*, *UIMC1*, *AMHR2*, *RHBLD2*, *PRIM1*, *HK3/UMC1*, *BRSK1/TMEM150B* and *MCM8*. Demerath et al. (2013) conducted fine-mapping of index signals in EA populations, and the authors identified SNPs that more closely associated with the trait in AA women (Table 2). These SNPs were in high linkage

disequilibrium with index signals in EA populations but not with the index signal in AA populations (Demerath et al., 2013). Several novel variants were identified through meta-analysis and these are listed in Table 3.

In the two studies that examined genetic associations with biomarkers of the ovarian reserve, the authors observed associations between *DIAPH3*, *TAF4B*, *CCDC53*, *MCM8* and antral follicle count (Schuh-Huerta et al., 2012a); *MYADML* and *ITIH2* and follicle stimulating hormone; and *TPRXL* and *TMEM86A* and anti-Müllerian hormone (Schuh-Huerta et al., 2012b).

Discussion

An in-depth discussion of the role of each gene identified is outside the scope of this review; however, the main pathways will be discussed. The genes associated with age at menarche that replicated in AA women are primarily involved in bodyweight regulation and energy homeostasis. Many of the genes associated with age at menopause that replicated in AA women are involved in DNA replication and repair. For example, *UIMC1* (ubiquitin interaction motif containing 1) is a transcriptional repressor involved in DNA damage resistance. It is also involved in DNA repair through binding with the *BRCA1* (breast cancer 1 early onset) gene complex (Moron, Ruiz, & Galan, 2009). *BRSK1* (BR serine/threonine kinase 1) is involved in cell division and may function as a cell cycle checkpoint in response to DNA damage (Wood & Rajkovic, 2013). The role of DNA repair in the process of ovarian aging has been discussed extensively in other reviews (Titus, Stobezki, & Oktay, 2015), and the findings from our review further extend this understanding to AA women. Several genes associated with age at menopause and biomarkers of the ovarian reserve are involved in ovarian follicle growth and regulation. *AMH/AMHR2* functions to prevent premature activation of primordial follicles. *MCM8* is involved in follicle development and is expressed within primordial, primary, and secondary ovarian follicles (Wood & Rajkovic, 2013). Many of the remaining genes are novel and further research is needed to elucidate how they may contribute to variation in reproductive traits across diverse populations.

The secondary purpose of this review was to identify genes associated with both reproductive traits and cardiometabolic risk factors in AA women. Several of the genes associated with age at menarche and age at natural menopause were also associated with cardiometabolic traits in AA populations (Table 4). Genetic overlap was identified in or near the following genes: *FTO*, *SEC16B*, *TMEM18*, *APOE*, *PHACTR1*, *KCNQ1*, and *LDLR*. Biological pathways implicated include bodyweight regulation, vascular homeostasis and lipid metabolism.

Bodyweight Regulation

Several genes associated with age at menarche in AA women also play a role in bodyweight regulation. The relationship between adiposity and menarcheal timing is complex. Retrospective studies have demonstrated that women who experience menarche at earlier age are at increased risk for obesity in adulthood (Racho & Teede, 2010). Several studies have identified genes linking puberty and childhood obesity (Cousminer et al., 2013); however, most genetic associations were observed in EA and did not replicate well in AA

(Tu et al., 2015). This is likely due to underrepresentation of AA in GWAS and the failure to take into account underlying differences in genomic architecture.

Studies attempting to replicate BMI-associated SNPs identified in GWAS of EA in AA have shown limited success (Gardner, Sapienza, & Fisher, 2015; Hester et al., 2012). In a study by Graff et al. (2017), several SNPs in/or near *FTO*, *SEC16B*, and *TMEM18* were significantly associated with BMI slope in the ancestry-wide meta-analysis, but were no longer significant when limiting the analysis to AA alone. The authors suggest this may be due to low linkage disequilibrium between the index SNPs in EA and the relevant signals in AA (Graff et al., 2017). Studies that selected BMI-associated loci that had been identified in GWAS of AA had greater success (Ruiz-Narváez, Haddad, Rosenberg, & Palmer, 2016). Additionally, studies that conducted fine-mapping of regions near the index SNPs in EA identified novel variants in AA, demonstrating the need for a more thorough examination of candidate genes in order to better identify causal variants (Tan et al., 2014).

TMEM18 and *FTO* regulate bodyweight through their actions in the central nervous system (CNS) and adipose tissue (Bernhard et al., 2013; Hester et al., 2012; Ruiz-Narváez et al., 2016). A growing body of evidence suggests that *FTO* affects bodyweight in part through regulation of food intake (Frayling et al., 2007). *FTO* may be involved in regulating bodyweight and menarcheal timing through leptin (Do et al., 2008). Leptin is an adipocyte hormone that controls appetite and satiety in humans. The role of leptin in puberty is not well understood, but it is proposed to have a permissive role, with direct action on hypothalamic luteinizing hormone releasing hormone (LHRH)-secreting neurons (Grumbach, 2002). During puberty, the CNS-suppressed LHRH pulse generator is reactivated or disinhibited, and leptin may act indirectly to reactivate the LHRH pulse generator (Grumbach, 2002).

The protein coded by *FTO* effects demethylation of RNA (Jia et al., 2011). As DNA methylation contributes to epigenetic changes, the regulatory role of *FTO* expression on bodyweight and menarcheal timing may be mediated by environmental exposures (Ruiz-Narváez et al., 2016). *SEC16B* also plays a role in appetite-regulation and is expressed in subcutaneous adipose tissue—unlike *FTO* and *TMEM18*, which are expressed primarily in the brain. Thus, the association of *SEC16B* with menarcheal timing may be more indirect, signaling the initiation of puberty when the amount of peripheral adiposity necessary for reproductive function has been met.

Obesity is more prevalent among AA than among non-Hispanic Whites, and obesity rates are higher among AA women than AA men. Because obesity and menarche are both highly heritable traits, further examination of how these complex traits interact is warranted (Racho & Teede, 2010).

Vascular Homeostasis

Spencer et al. (2013) identified a novel SNP variant in *KCNQ1* (rs79972789) associated with age at menopause in AA women that also plays a role in vascular homeostasis (Spencer et al., 2013). *KCNQ1* encodes voltage-gated potassium channels required for cardiac repolarization. Fox et al. (2011) identified SNPs in genes across Chromosome 11, including

KCNQ1, associated with elevated BP in AA (Fox et al., 2011). Several SNP variants in *KCNQ1* have also been found to be associated with increased risk of Type 2 Diabetes (Long et al., 2012; Ng et al., 2013) and QT-interval prolongation (Avery et al., 2017) in AA. Type 2 Diabetes is a well-known risk factor for cardiovascular disease, and QT interval prolongation is associated with ventricular arrhythmias, which predisposes individuals to sudden cardiac death (Avery et al., 2017). Coignet et al. (2017) found a suggestive association between *PHACTR1* and both age at menarche and age at menopause in AA women. *PHACTR1* is associated with increased risk for coronary artery calcification among African Americans (Wojczynski et al., 2013).

The link between menopause and increased cardiovascular disease risk in women is well established, but the mechanism underlying the relationship between these physiological processes is not well understood (de Kat et al., 2017). Estrogens are cardio-protective, regulating vascular function through the renin-angiotensin system and endothelin (Maric-Bilkan, Gilbert, & Ryan, 2014). The declining estrogen levels that accompany menopause may increase risk for hypertension and metabolic disorders in women. Additionally, as ovarian function relies on vascular support, atherosclerotic-induced ischemia may compromise ovarian vascular supply and contribute to premature menopause (Tempfer et al., 2005).

Lipid Metabolism

Several SNP variants in *APOE* and *LDLR* associated with age at menopause in AA women are involved in lipid metabolism (Spencer et al., 2013). Low-density lipoprotein receptor (*LDLR*) is involved in cholesterol regulation and *LDLR* variants are associated with atherosclerosis and early-onset cardiovascular disease in AA (Deo et al., 2009; Feng, Wei, Levinson, Mosley, & Stein, 2017; Lettre et al., 2011). Apolipoprotein E (*APOE*) plays an important role in lipid transport and metabolism and genetic variability of *APOE* is a major determinant of serum lipoprotein levels (Li et al., 2015). SNP variants in *APOE* are associated with total cholesterol and low-density lipoprotein (LDL) cholesterol in AA (Feng et al., 2017) as well as increased risk of overall and cardiovascular mortality in both AA and EA (Rajan et al., 2017). The association between *APOE* variants and age at menopause may be due to variations in lipid metabolism. Lipid metabolism is involved in ovarian steroidogenesis. Several studies have demonstrated decreases in total and LDL cholesterol during the luteal phase of the menstrual cycle, as well as increases in high-density lipoprotein (HDL) cholesterol with rising estradiol levels during the follicular phase (Jensen, Addis, Hennebold, & Bogan, 2017). Thus, the atherosclerotic changes associated with hypercholesterolemia may alter the ovarian endocrine milieu, modifying ovarian steroidogenesis and contributing to a less favorable lipid profile.

Other Potential Pathways

Several additional biological pathways may be involved in the genetic link between reproductive traits and cardiometabolic risk factors; however, more studies are needed to elucidate these pathways in AA women. Demerath et al. (2013) found suggestive associations between a variant near *PIK3R1* and age at menarche in AA women. *PIK3R1* is involved in regulating the metabolic actions of insulin, and variants in this gene have been

associated with insulin resistance and type 2 diabetes in EA women (Cheng et al., 2016). Insulin resistance is one of the cardinal features of ovulatory disorders, such as polycystic ovary syndrome. It is hypothesized that normal insulin levels stimulate ovarian androgen production, which regulates follicle development; insulin resistance may lead to increased ovarian androgen production and unregulated follicle growth subsequently resulting in anovulation (Leeners, Geary, Tobler, & Asarian, 2017).

And finally, the biological pathway involved in the stress response may link reproductive traits with cardiometabolic risk factors. Demerath et al. (2013) identified an association between two independent SNPs near *RORA* and age at menarche in AA. The protein encoded by *RORA* is involved in a variety of processes including brain development, neuroprotection, and the regulation of circadian rhythms and steroid hormones. Logue et al. (2013) found evidence for a significant association between a SNP in *RORA* and PTSD in AA. Traumatic stress increases steroid hormone levels and inflammation. The genes involved in responding to traumatic or environmental stressors may indirectly affect menarcheal timing and cardiometabolic disease risk through alterations in endocrine function provoked by oxidative stress (Logue et al., 2013). These biological pathways are suggestive and warrant further analysis.

Limitations

The current review was limited by the lack of GWAS on reproductive traits in AA women. The findings from this review suggest that overall SNPs identified in GWAS of reproductive traits in EA women do not generalize to AA women. This highlights the importance of conducting GWAS in diverse populations before generalization across populations (Coignet et al., 2017). We are aware that in many studies a limitation is self-report or assignment to the social construct of a race category. However, in future studies we will take into account both self-report and ancestry informative markers for statistical purposes when reporting results based on ancestry. In addition, several of the studies combined data from multiple cohorts with varied data collection procedures, which may have limited the ability to replicate prior genetic signals and identify novel associations. This is especially true with measures of self-report such as age at menarche and age at natural menopause, which are susceptible to recall bias (Cooper et al., 2006). Additionally, cardiometabolic risk factors vary by sex, and many of the GWAS examining these traits did not include sex-stratified analyses. This may have limited the ability to detect genes where reproductive and cardiometabolic trait-associations overlap (Ng et al., 2017). Another limitation of this review is that the SNPs associated with reproductive traits were not close proxies of SNPs associated with cardiometabolic risk factors. More research is needed to narrow genomic regions that may be involved in the coregulation of reproductive and cardiometabolic traits in AA women.

Future Research

Replication of GWAS in non-EA populations have had limited success due to differences in genomic architecture and diverse environmental factors across populations (Peprah, Xu, Tekola-Ayele, & Royal, 2015). The lack of generalizability of previously identified SNPs in EA women and the identification of novel genetic signals in AA women demonstrate the

need for additional GWAS in diverse populations. Several reviews have provided strong evidence for the inclusion of diverse populations in GWAS to account for differences in allele frequency and linkage disequilibrium (Carlson et al., 2013; Peprah et al., 2015). GWAS in diverse populations will help to clarify the causal variants of reproductive traits, broaden the generalizability of findings and provide insight into the reasons for health disparities.

Reproductive and cardiometabolic traits are complex and multifactorial, and single SNP variants are unlikely to have a large effect on phenotype. Studies that incorporate gene-gene interactions as well as gene-environment interactions are likely to offer greater explanatory value (Demerath et al., 2011; Liu et al., 2016). There is significant environmental heterogeneity that influences reproductive phenotypes, including nutritional status, economic disadvantage and exposure to endocrine-disrupting chemicals (Demerath et al., 2013). In order to unravel the effect of genetic and environmental factors on complex traits, it is vital to include diverse racial groups to account for these underlying differences. Ongoing genomic and epigenomic studies in AA and other minority populations may help to address these gaps in our understanding (Taylor, Wright, Crusto, & Sun, 2016).

Additionally, epigenetic changes have been proposed as the link between biology, environment, and genetics contributing to premature reproductive aging (Crujeiras & Casanueva, 2015; Nilsson et al., 2012). More research is needed to examine the effect of epigenetic changes on reproductive lifespan, as well as how these changes may mediate the relationship between reproductive traits and cardiometabolic risk factors in AA women.

Conclusion

In this review, we identified genes associated with reproductive traits in AA women that are also implicated in cardiovascular and metabolic risk factors. This overlap provides insight into the biological mechanisms that may link these phenotypes in AA women. As the timing of reproductive traits is linked to cardiovascular and metabolic disease risk, a better understanding of the genetic architecture underlying reproductive lifespan in AA women may improve our understanding of a wide range of diseases.

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Figure 1.
PRISMA diagram: study selection

Table 1

Included Studies

Study	Purpose	Sample	Methods
Spencer et al. (2013)	<ul style="list-style-type: none"> To replicate previously reported AM and ANM findings in AA women To identify novel AM and ANM variants in AA women 	<p>$n = 4,159$ $n = 1,860$</p>	Genotyping performed using MetaboChip, a custom Illumina iSelect associated with metabolic traits and cardiovascular disease
Carty et al. (2013)	<ul style="list-style-type: none"> To replicate genetic associations identified in GWAS of AM and ANM in women of diverse ancestry 	<p>$n = 42,251$ including European American, African American, Hispanic, American Indian, and Native Hawaiian women</p>	Utilized genetic data from PAGE study, consisting of four study sites
Chen et al. (2014)	<ul style="list-style-type: none"> To identify novel genetic loci influencing ANM in AA women To replicate loci identified in European ancestry populations in AA women 	<p>$n = 6,510$ (11 studies)</p>	Performed meta-analysis across 11 studies using association results from each cohort
(Demerath et al., 2013)	<ul style="list-style-type: none"> To test the genome wide association of self-reported AM with common SNPs To replicate SNPs in 42 previously identified AM loci in EA women in AA women 	<p>$n = 18,089$ (15 studies)</p>	Performed meta-analysis across 15 studies, performed replication analysis of meta-analysis findings in a separate cohort and replication analysis of SNP association in EA women
Coignet et al. (2017)	<ul style="list-style-type: none"> To replicate 53 GWAS variants from AM and ANM in AA and EA groups 	<p>$n = 1,307$ EA women $n = 1,365$ AA women</p>	Utilized genetic data from WCHS
Schuh-Huerta et al. (2012)	<ul style="list-style-type: none"> To identify genetic variants associated with ovarian reserve (oocyte number as measured by antral follicle count) 	<p>$n = 450$ (203 AA women)</p>	Genotyping performed using Genome-Wide Human SNP Array 6.0
Schuh-Huerta et al. (2012)	<ul style="list-style-type: none"> To identify genetic variants associated with two hormonal markers of ovarian reserve (follicle stimulating hormone and anti-Müllerian hormone) 	<p>$n = 432$ (200 AA women)</p>	Genotyping performed using Genome-Wide Human SNP Array 6.0

Note. GWAS = genome wide association study, AA = African American, EA = European American, AM = Age at menarche, ANM = Age at natural menopause

Table 2

Replication

Age at menarche						
Study (date)	Sample size	SNP EA (index)	SNP AA	MAF ^a	LD ^b (r ²)	p-value
Significance threshold						
Closest gene						
Spencer (2013)	4,159/1,860	rs1361108	rs9385399	0.70	1.00	0.01
Demerath (2013)	18,089/2,850	rs3743266	rs339978	0.84		10×10^{-7}
		rs3743266	rs980000	0.70		4.9×10^{-6}
		rs10980926	rs10441737	0.52	0.98	6.6×10^{-6}
		rs9939609	rs12149832	0.91	0.88	2.0×10^{-4}
		rs633715	rs543874	0.33	0.91	4.9×10^{-4}
		rs4929923	rs12575252	0.47	0.92	9.9×10^{-4}
		rs6589964	rs1461499	0.39	0.41	3.8×10^{-4}
		rs7759938	rs314266	0.66	0.65	2.9×10^{-4}
		rs17268785	rs17047854	0.65	0.99	5.8×10^{-4}
		rs2687729	rs2075402	0.29	0.56	2.2×10^{-3}
		rs10899489	rs1006411	0.82		3.8×10^{-3}
Coignet (2017)	1,365		rs2947411	0.86		0.03
			rs757647	0.60		0.002

Age at menopause

Study (date)	Sample size	SNP EA (index)	SNP AA	MAF ^a	LD ^b (r ²)	p-value
Significance threshold						
Closest gene						
Spencer (2013)	4,159/1,860	rs897798	rs8113016	0.87	0.72	0.03
		rs769450	rs769450	0.67	NA	0.03
Chen (2014)	6,510		rs402511	0.79		0.042
			rs11668344	0.61		6.54×10^{-4}
		rs16991615	rs6139882	0.96	0.01	1.35×10^{-3}
			rs4246511	0.35		0.031
			rs2277339	0.84		0.022
			rs2002555	0.82		0.0062
Curry (2013)	8,541		rs365132	0.79		0.001

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Note. AA = African American, EA = European American, SNP = single nucleotide polymorphism, LD = linkage disequilibrium
Minor allele frequency for Americans of African Ancestry in SW USA
Linkage disequilibrium with index SNP in European American

Table 3

Novel Variants

Age at menarche						
Study (date)	Sample size	SNP	MAF	p-value	Significance threshold	Closest gene
Demerath (2013)	18,089/2,850	rs4557202	0.43	3.51×10^{-7}	$p \ 1 \times 10^{-5}$	<i>B3GALNT3</i>
		rs11216435	0.32	6.33×10^{-7}	$p \ 1 \times 10^{-5}$	<i>DSCAML1</i>
		rs8014131	0.42	0.021	$p < 0.05$	<i>FLR2</i>
		rs10940138	0.19	0.018	$p < 0.05$	<i>PIK3R1</i>
Age at menopause						
Study (date)	Sample size	SNP AA	MAF	p-value	Significance Threshold	Closest gene
Spencer (2013)	4,159 1,860	rs189596789		4.98×10^{-8}	$p < 3.1 \times 10^{-7}$	<i>LDLR</i>
		rs79972789	1.0	1.90×10^{-7}	$p < 3.1 \times 10^{-7}$	<i>KCNQ1</i>
Coignet (2017)	1,365	rs181686584	1.0	2.85×10^{-7}	$p < 3.1 \times 10^{-7}$	<i>COL4A3BP</i>
		rs1859345	0.89	0.004	$p < 0.10$	<i>SPOCK</i>

Note. AA = African American, EA = European American, SNP = single nucleotide polymorphism, LD = linkage disequilibrium

^aMinor allele frequency for Americans of African Ancestry in SW USA

^bLinkage disequilibrium with index SNP in European American

Table 4

Overlap of Cardiovascular and Reproductive Genes

Gene	Cardio SNP	Race	Cardio	Repro	References
<i>SEC16B</i>	rs543874	EA	BMI slope	AM	(Graff et al., 2017; Ng et al., 2017)
<i>SEC16B</i>	rs6664268	EA	Fat mass, % fat mass	AM	(Sahibdeen et al., 2018)
<i>FTO</i>	rs9939609	EA	BMI slope	AM	(Graff et al., 2017)
<i>FTO</i>	rs17817964	AA	BMI, BW × BMI	AM	(Monda et al., 2013; Ng et al., 2017; Ruiz-Narváez et al., 2016)
<i>FTO</i>	rs708262, rs11076017, rs16952725, rs9932411, rs7191513, rs2689269, rs16952987	AA	BMI	AM	(Tan et al., 2014)
<i>FTO</i>	rs8057044	AA	BMI	AM	(Bollepalli, Dolan, Deka, & Martin, 2010)
<i>FTO</i>	rs8050136	AA	BMI (children)	AM	(Grant et al., 2008)
	rs3751812				
<i>FTO</i>	rs10521303	AA	Obesity	AM	(Liu et al., 2016)
<i>FTO</i>	rs1861554	EA	Waist-hip ratio	AM	(Sahibdeen et al., 2018)
<i>TMEM18</i>	rs6548238	EA	BMI slope	AM	(Graff et al., 2017)
<i>TMEM18</i>	rs1320330	AA	BW × BMI	AM	(Ruiz-Narváez et al., 2016)
<i>TMEM18</i>	rs2867125	EA	BMI	AM	(Hester et al., 2012)
<i>TMEM18</i>	rs62105306	EA	BMI	AM	(Ng et al., 2017)
<i>KCNQ1</i>	rs2237892	AA	T2D	ANM	(Long et al., 2012; Ng et al., 2013)
<i>KCNQ1</i>	rs231362, rs2237897	AA	T2D	ANM	(Long et al., 2012)
<i>KCNQ1</i>			Hypertension	ANM	(Fox et al., 2011)
<i>KCNQ1</i>			QT interval prolongation	ANM	(Avery et al., 2017)
<i>PHACTR1</i>	rs9349379	EA	Coronary artery calcification	AM, ANM	(Wojczynski et al., 2013)
<i>LDLR</i>	rs6511720	EA	Total cholesterol, LDL	ANM	(Deo et al., 2009; Feng et al., 2017; Lettre et al., 2011)
<i>APOE</i>	rs7412	AA	Total cholesterol, LDL	ANM	(Feng et al., 2017; Li et al., 2015)
<i>APOE</i>	rs4420638	EA	HDL	ANM	(Adeyemo et al., 2012)

Note. AA = African American, EA = European American, SNP = single nucleotide polymorphism, BMI = body mass index, BW = birth weight, T2D = Type II Diabetes, LDL = low density lipoprotein, HDL = high density lipoprotein, ANM = age at natural menopause, AM = age at menarche