Original Article
Genetic variants in anti-Mullerian hormone and anti-Mullerian hormone receptor genes and breast cancer risk in Caucasians and African Americans

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Abstract: Anti-Mullerian hormone (AMH) regulates ovarian folliculogenesis by signaling via its receptors, and elevated serum AMH levels are associated with an increased risk of breast cancer. No previous studies have examined the effects of genetic variants in AMH-related genes on breast cancer risk. We evaluated the associations of 62 single nucleotide polymorphisms (SNPs) in *AMH* and its receptor genes, including AMH type 1 receptor (*ACVR1*) and AMH type 2 receptor (*AMHR2*), with the risk of breast cancer in the Women's Insights and Shared Experiences (WISE) Study of Caucasians (346 cases and 442 controls), as well as African Americans (149 cases and 246 controls). Of the 62 SNPs evaluated, two showed a nominal significant association (*P* for trend < 0.05) with breast cancer risk among Caucasians, and another two among African Americans. The age-adjusted additive odds ratios (ORs) (95% confidence interval (95% CI)) of those two SNPs (*ACVR1* rs12694937[C] and *ACVR1* rs2883605[T]) for the risk of breast cancer among Caucasian women were 2.33 (1.20-4.52) and 0.68 (0.47-0.98), respectively. The age-adjusted additive ORs (95% CI) of those two SNPs (*ACVR1* rs1146031[G] and *AMHR2* functional SNP rs2002555[G]) for the risk of breast cancer among African American women were 0.63 (0.44-0.92) and 1.67 (1.10-2.53), respectively. However, these SNPs did not show significant associations after correction for multiple testing. Our findings do not provide strong supportive evidence for the contribution of genetic variants in AMH-related genes to the risk of developing breast cancer in either Caucasians or African Americans.

Keywords: Single nucleotide polymorphism, anti-Mullerian hormone, anti-Mullerian hormone receptors, breast cancer

Introduction

Anti-Mullerian hormone (AMH) is a member of the transforming growth factor-β (TGFβ) family of growth and differentiation factors known primarily for its role in regulating the in-utero sexual differentiation of males [1]. In women, AMH is secreted by the premenopausal ovary [2-4] and regulates ovarian folliculogenesis by signaling via its receptors, including non-specific activin receptor-like kinase 2 receptor (ALK2) encoded by AMH type 1 receptor (*ACVR1*) gene and specific AMH type II receptor (AMHR2) encoded by *AMHR2* gene. Upon binding to

AMHR2, AMH promotes heterodimerization with ALK2, resulting in downstream signaling via Smads [5]. Moreover, binding of AMH to AMHR2 suppresses follicle maturation by inhibiting recruitment of primordial follicles into the pool of growing follicles and by decreasing responsiveness of growing follicles to follicle stimulating hormone (FSH) [6]. Our previous study showed that women with elevated serum levels of AMH are at a 10-fold excess risk of developing breast cancer [7].

Given that ovarian follicle development is intimately related to steroidogenesis and breast

cancer risk has clearly been shown to be related to the ovarian steroid hormones, genetic variants in folliculogenesis-related genes, such as *AMH* and its receptors, could be related to breast cancer risk via effects on hormone production or other as yet unidentified mechanisms. However, only a few previous studies have focused on genes involved in regulation of folliculogenesis [8-11] and none have evaluated associations of genetic variants in *AMH* and its receptors with breast cancer risk.

In this study, we evaluated the associations of 62 single nucleotide polymorphisms (SNPs) in *AMH* and its receptor genes (*ACVR1* and *AMHR2*) with the risk of breast cancer in the Women's Insights and Shared Experiences (WISE) study of Caucasians (346 cases and 442 controls), as well as African Americans (149 cases and 246 controls).

Materials and methods

Study population and data collection

The WISE study is a population-based retrospective case-control study. Incident primary breast cancer cases were identified through hospitals and the Pennsylvania State Cancer Registry, and frequency-matched controls were identified from the community using random digit dialing. The source population for this study was from the three counties of Philadelphia (Pennsylvania), Delaware (Pennsylvania), and Camden (New Jersey). Details of the study have been reported previously [12-14].

Potentially eligible cases were women residing in these counties at the time of diagnosis who were aged 50-79 years and newly diagnosed with breast cancer between July 1, 1999 and June 30, 2002. The cases were identified through active surveillance at hospitals in these counties. Pennsylvania Cancer Registry lists were reviewed quarterly to validate completeness of case ascertainment. Breast cancer diagnoses were validated by review of pathology reports and medical records. Breast cancer was confirmed if a pathology report was compatible with a first primary, invasive breast cancer. Controls were selected from the same geographic region as the cases and were frequency matched to the cases on race, age (in 5-year age groups) and calendar date of inter-

view (within 3 months). Eligible controls had no history of breast cancer. Both cases and controls were required to live in a non-institutional setting, to have a household telephone, to have the ability to speak English, and to have no severe cognitive, language, or speech impairment.

Telephone interviews were used to collect data on demographic characteristics, anthropometry, family history of breast cancer, menstrual and menopausal history, reproductive history, medical history, oral contraceptive (OC) and hormone replacement therapy (HRT) use, smoking and alcohol ingestion. Participants collected buccal swabs according to standard directions and mailed them to the University of Pennsylvania. A total of 346 cases and 442 controls for Caucasians, as well as 149 cases and 246 controls for African Americans were included in this study.

Participants provided verbal informed consent for the interview and written informed consent for the buccal samples. The University of Pennsylvania Committee on Studies Involving Human Beings, the institutional review boards at University of Maryland School of Medicine, and the institutional review boards of all the participating hospitals approved this study.

Laboratory assays

Using the International HapMap project, we identified single nucleotide polymorphisms (SNPs) that effectively cover 3 candidate genes of interest. Some of these SNPs are in linkage disequilibrium; therefore, a more efficient set of tagging SNPs can be used to capture the same genetic variation [15]. Using Haploview program and a minimum r^2 threshold of 0.8, we identified a set of 62 parsimonious tagging SNPs with minor allele frequency greater than 5% to capture genetic variation in each locus (introns and exons, as well as 20 kb upstream of the start of transcription and 10 kb downstream of the end of transcription) of three genes including *AMH* (13), *ACVR1* (42), and *AMHR2* (7), in a race specific manner for Caucasians and African Americans separately. Information on these 62 SNPs is presented in Supplementary Table 1.

We genotyped these SNPs using the Sequenom platform with 10ng of all DNA samples in 384-

Table 1. Basic characteristics of breast cancer cases and controls in WISE case-control study

Characteristic	Caucasians		African Americans	
	Cases (n = 346)	Controls (n = 442)	Cases (n = 149)	Controls (n = 246)
Age (yrs, mean)	63.4	62.5	62.2	61.0
Body-mass index (kg/m^2, mean)	24.0	24.0	25.7	26.0
Age at menarche (yrs, mean)	12.5	12.7	12.8	12.7
Age at menopause (yrs, mean)	48.2	48.4	48.2	47.5
Age at first full term pregnancy among parous women (yrs, mean)	24.3	24.6	21.2	20.9
Number of full term pregnancies (%)				
0	19.9	11.5	16.8	6.9
1~2	32.7	39.6	43.0	41.5
≥3	47.4	48.9	40.3	51.6
Duration of breast feeding (%)				
Never	69.1	56.1	66.9	67.1
< 12 months	22.3	28.1	19.6	19.8
≥ 12 months	8.7	15.8	13.5	13.2
Menopausal status (%)				
Premenopausal	7.2	7.7	7.4	8.1
Postmenopausal	76.0	80.1	80.5	72.8
Induced (e.g., surgical)/unknown	16.8	12.2	12.1	19.1
Family history of breast cancer in 1st degree relative (%)				
Yes	18.8	19.0	18.1	11.4
No	81.2	81.0	81.9	88.6
Duration of combined estrogen and progestin (CHRT) use (%)				
Never/other HRT use	75.1	70.6	92.6	87.8
< 3 years	8.4	13.6	1.3	6.9
≥ 3 years	16.5	15.8	6.0	5.3
Duration of oral contraceptive (OC) use (%)				
Never	53.8	47.7	55.7	46.8
< 3 years	22.0	26.6	19.5	22.4
≥ 3 years	24.3	25.7	24.8	30.9

well format. Laboratory personnel were blinded to case-control status, and 3% blinded quality control samples were inserted to validate genotyping procedures; concordance for the blinded quality control samples was 100%.

Statistical methods

We used the X^2 test to assess whether the genotypes for all 62 SNPs were in Hardy-Weinberg equilibrium (HWE) among the controls. We evaluated the association between each SNP and breast cancer risk using unconditional logistic regression. An additive model was used to calculate the *p*-value for trend on breast cancer risk according to an ordinal coding for genotype (0, 1 or 2 copies of SNP minor allele). All statisti-

cal analyses were two-sided and carried out using SAS V9.2 (SAS Institute, Cary, NC).

Results and discussion

Descriptive characteristics of cases and controls in this study are summarized in **Table 1**. The mean age at diagnosis of breast cancer cases was 63.4 years for Caucasians and 62.2 years for African Americans. Compared with controls, breast cancer cases in both Caucasians and African Americans had lower number of full term pregnancies. Among Caucasians, cases were less likely to breastfeed, more likely to have used long-term (≥ 3 years) combined estrogen and progestin hormone replacement therapy (CHRT). Among

African Americans, cases were more likely to have a family history of breast cancer in a first degree relative and less likely to have used long-term (≥ 3 years) oral contraceptives (OCs).

The distributions of genotypes for the four SNPs (rs1220135, rs13395576, rs16842009, and rs16842143 in ACVR1) among Caucasians and two SNPs (rs10933441 in ACVR1 and rs17695156 in AMHR2) among African Americans were not in Hardy-Weinberg equilibrium among controls (P for HWE = 0.000); thus were excluded from the analyses (Supplementary **Table 1**). We evaluated the association of each SNP with breast cancer risk among Caucasians and African Americans separately. Of the 62 SNPs evaluated, two showed a nominal significant association with breast cancer risk among Caucasians (P for rs12694937, 0.01; P for rs2883605, 0.04), and another two among African Americans (P for rs1146031, 0.01; P for rs2002555, 0.02). The age-adjusted additive odds ratios (ORs) (95% confidence interval (95% CI)) of those two SNPs (ACVR1 rs12694937[C] and ACVR1 rs2883605[T]) for the risk of breast cancer among Caucasian women were 2.33 (1.20-4.52) and 0.68 (0.47-0.98), respectively. The age-adjusted additive ORs (95% CI) of those two SNPs (ACVR1 rs1146031[G] and AMHR2 functional SNP rs2002555[G]) for the risk of breast cancer among African American women were 0.63 (0.44-0.92) and 1.67 (1.10-2.53), respectively (**Table 2**). These findings remained consistent after adjusting for breast cancer-related factors (**Table 2**). After correction for multiple testing (Bonferroni correction), these SNPs did not show significant associations with breast cancer risk (all p-values > 0.05/62 = 0.001).

Considering that the relationship of genetic variants in folliculogenesis-related genes with breast cancer risk could be affected by HRT or OC use, for those four SNPs that showed nominal associations in the main effect analyses, we conducted additional analyses in which users of HRT or OC were excluded. The results did not materially change for each of the four SNPs (data not shown).

A few previous studies have examined genetic variants in genes involved in regulation of folliculogenesis. A previous study of Dutch and German cohorts reported that women who carry the variant allele of the common polymor-

phism Ile49Ser (rs10407022) in the AMH gene have significantly higher serum estradiol levels in the follicular phase of the menstrual cycle compared to those who are homozygous wild-type [11]. This variant was also associated with altered hormonal profiles in polycystic ovary syndrome (PCOS) patients [16], and its interaction with AMHR2 variant may modify age at natural menopause [17]. Similar to women who carry the Ile49Ser variant allele in AMH, women who carry the variant allele of the common A-482G promoter polymorphism in AMHR2 gene (rs2002555) have significantly higher follicular phase serum estradiol levels compared to women who are homozygous wild-type in the cohorts of Dutch and German [11]. Furthermore, women who carry variant alleles for both Ile49Ser in AMH and A-482G in AMHR2 have the highest follicular phase estradiol levels. It has been shown that the A-482G polymorphisms in AMHR2 is associated with infertility in Italy [18] and Japanese women [19], and interacts with parity in relation to age at menopause [10]. In this study, -482G allele in AMHR2 (rs2002555) was associated with an increased risk of breast cancer among African American women. Considering the effect of A-482G polymorphisms on serum estradiol level and well-known relationship between ovarian steroid hormone and breast cancer risk, it is plausible that this SNP is related to breast cancer risk partially through alteration of hormone production. For ACVR1, several tagging SNPs (rs1220134, rs10497189, and rs2033962/ rs13021202) and their corresponding haplotypes were associated with AMH levels and follicle number in PCOS patients [20]. However, little is known about variants in ACVR1 in relationship to AMH and follicle number in healthy women. In this study, we did not find an association of these SNPs with breast cancer risk.

One limitation of this study is potential recall bias from the retrospective case-control study design. However, deviations due to the major factors related to AMH, such as use of HRT and OC, could be minimized, because OC use is only modestly related to breast cancer risk and risk is limited in duration after discontinuation [21], and WISE was completed before the Women's Health Initiative heightened public awareness of the association of HRT use with breast cancer risk.

In summary, we evaluated the associations between 62 SNPs in three AMH-related genes

Table 2. SNPs significantly associated with breast cancer risk in WISE case-control study

SNP (gene)	Caucasians				African Americans			
rs12694937 (*ACVR1*)	Cases (%)	Controls (%)	Age-adjusted OR	Multivariate-adjusted OR[a]	Cases (%)	Controls (%)	Age-adjusted OR	Multivariate-adjusted OR[a]
TT	292 (92.4)	417 (96.5)	1.00	1.00	102 (71.8)	163 (71.5)	1.00	1.00
TC	24 (7.6)	15 (3.5)	2.33 (1.20-4.52)	2.35 (1.20-4.63)	38 (26.8)	59 (25.9)	1.02 (0.64-1.65)	0.89 (0.53-1.48)
CC	0 (0.0)	0 (0.0)	-	-	2 (1.4)	6 (2.6)	0.51 (0.10-2.61)	0.47 (0.09-2.49)
Additive OR			2.33 (1.20-4.52)	2.35 (1.20-4.63)			0.93 (0.61-1.42)	0.83 (0.53-1.29)
p for trend			0.01	0.01			0.74	0.40
rs2883605 (*ACVR1*)	Cases (%)	Controls (%)	Age-adjusted OR	Multivariate-adjusted OR[a]	Cases (%)	Controls (%)	Age-adjusted OR	Multivariate-adjusted OR[a]
GG	286 (86.1)	347 (80.5)	1.00	1.00	138 (97.9)	232 (97.9)	1.00	1.00
GT	44 (13.3)	80 (18.6)	0.66 (0.44-0.99)	0.67 (0.44-1.01)	3 (2.1)	5 (2.1)	1.09 (0.26-4.67)	1.34 (0.30-5.94)
TT	2 (0.6)	4 (0.9)	0.60 (0.11-3.31)	0.67 (0.12-3.74)	0 (0.0)	0 (0.0)	-	
Additive OR			0.68 (0.47-0.98)	0.69 (0.47-1.01)			1.09 (0.26-4.67)	1.34 (0.30-5.94)
p for trend			0.04	0.06			0.91	0.70
rs1146031 (*ACVR1*)	Cases (%)	Controls (%)	Age-adjusted OR	Multivariate-adjusted OR[a]	Cases (%)	Controls (%)	Age-adjusted OR	Multivariate-adjusted OR[a]
AA	323 (97.6)	430 (99.1)	1.00	1.00	95 (66.0)	133 (55.6)	1.00	1.00
AG	7 (2.1)	4 (0.9)	2.30 (0.67-7.92)	2.55 (0.71-9.10)	46 (31.9)	89 (37.2)	0.73 (0.47-1.14)	0.70 (0.43-1.12)
GG	1 (0.3)	0 (0.0)	-	-	3 (2.1)	17 (7.1)	0.24 (0.07-0.84)	0.28 (0.08-1.03)
Additive OR			2.60 (0.83-8.17)	2.82 (0.86-9.27)			0.63 (0.44-0.92)	0.63 (0.43-0.93)
p for trend			0.10	0.09			0.01	0.02
rs2002555 (*AMHR2*)	Cases (%)	Controls (%)	Age-adjusted OR	Multivariate-adjusted OR[a]	Cases (%)	Controls (%)	Age-adjusted OR	Multivariate-adjusted OR[a]
AA	216 (69.9)	304 (71.2)	1.00	1.00	98 (68.5)	176 (76.5)	1.00	1.00
AG	77 (24.9)	109 (25.5)	0.99 (0.71-1.40)	0.99 (0.70-1.41)	38 (26.6)	53 (23.0)	1.32 (0.81-2.15)	1.23 (0.73-2.08)
GG	16 (5.2)	14 (3.3)	1.67 (0.79-3.50)	1.84 (0.86-3.94)	7 (4.9)	1 (0.4)	12.4 (1.51-103)	13.3 (1.53-115)
Additive OR			1.12 (0.86-1.46)	1.14 (0.87-1.50)			1.67 (1.10-2.53)	1.62 (1.04-2.52)
p for trend			0.41	0.34			0.02	0.03

[a]Multivariate-adjusted ORs are adjusted for age, age at menarche (< 12 yr, 12 yr, or > 12 yr), number of full term pregnancies (0, 1 to 2, or ≥ 3), menopausal status (premenopausal, postmenopausal, or induced/unknown), family history of breast cancer in 1st degree relative (yes or no), body-mass index (< 25, 25 to 30, or ≥ 30), duration of CHRT use (never/other HRT use, < 3 yrs, or ≥ 3 yrs), and duration of OC use (never, < 3 yrs, or ≥ 3 yrs).

and breast cancer risk in both Caucasians and African Americans. We did not find strong supportive evidence for the contribution of genetic variants in AMH-related genes to the risk of developing breast cancer, although four SNPs showed suggestive association. The sample size of this study was modest, and additional larger studies are warranted to confirm the suggestive associations observed in the present study.

Disclosure of conflict of interest

None.

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Supplementary Table 1. 62 SNPs in *AMH*, *ACVR1*, and *AMHR2* genes

Gene	rs#	Caucasians			African Americans		
		Major/minor allele	MAF (%)[a]	P for HWE	Major/minor allele	MAF (%)[a]	P for HWE
Anti-mullerian hormone (AMH)	rs733846	T/G	16	0.340	G/T	43	0.016
	rs2074860	A/G	18	0.379	G/A	42	0.224
	rs3746158	A/G	23	0.528	A/G	42	0.203
	rs3761021	T/C	2	0.654	T/C	15	0.537
	rs4806834	C/T	3	0.456	C/T	29	0.281
	rs6510652	G/T	9	0.098	G/T	26	0.976
	rs6510653	A/G	10	0.427	G/A	45	0.068
	rs7249235	C/A	9	0.052	C/A	29	0.170
	rs7250822	G/C	16	0.228	G/C	18	0.366
	rs7253181	T/G	22	0.398	G/T	48	0.859
	rs8112524	A/G	38	0.229	G/A	37	0.038
	rs10407022	T/G	13	0.012	T/G	39	0.723
	rs10415913	G/A	9	0.816	A/G	49	0.073
AMH type 1 receptor (ACVR1)	rs12936	G/T	0	0.961	G/T	5	0.605
	rs1146031	A/G	0	0.923	A/G	26	0.691
	rs1146033	A/G	1	0.904	A/G	26	0.024
	rs1146037	T/C	22	0.569	T/C	19	0.042
	rs1220110	T/A	27	0.739	A/T	36	0.090
	rs1220133	G/A	28	0.477	A/G	33	0.583
	rs1220134	T/A	28	0.761	A/T	35	0.234
	rs1220135	T/C	0	0.000	T/C	8	0.778
	rs2883605	G/T	10	0.796	G/T	1	0.870
	rs3738927	T/C	0	0.981	T/C	5	0.581
	rs4233672	G/A	19	0.023	A/G	32	0.363
	rs4380178	G/A	16	0.124	G/A	20	0.369
	rs4664898	A/G	19	0.661	A/G	26	0.522
	rs4664901	T/C	23	0.140	C/T	23	0.560
	rs7561419	C/T	0	0.962	C/T	23	0.415
	rs7563276	G/A	6	0.886	G/A	9	0.932
	rs7565550	C/A	20	0.329	C/A	29	0.688
	rs7603425	T/C	0	0.981	T/C	9	0.151
	rs9288697	G/T	5	0.924	G/T	29	0.312
	rs10168000	C/T	18	0.137	T/C	23	0.068
	rs10497189	T/C	12	0.542	T/C	1	0.842
	rs10497190	C/T	19	0.215	C/T	27	0.776
	rs10497191	C/T	13	0.312	T/C	21	0.006
	rs10497192	T/C	27	0.494	C/T	16	0.002
	rs10497193	A/G	18	0.728	A/G	42	0.413
	rs10933441	C/T	7	0.913	C/T	5	0.000
	rs10933443	T/C	25	0.885	C/T	38	0.581
	rs12694937	T/C	2	0.713	T/C	16	0.812
	rs12987698	T/G	17	0.071	G/T	30	0.020
	rs13021202	C/T	19	0.060	C/T	27	0.474
	rs13395576	T/C	0	0.000	T/C	6	0.884
	rs13398650	G/A	8	0.340	A/G	44	0.026
	rs13426299	C/G	0	0.981	C/G	20	0.435
	rs16842009	C/T	0	0.000	C/T	5	0.703
	rs16842018	G/T	1	0.902	G/T	32	0.106
	rs16842023	C/T	1	0.904	C/T	15	0.710
	rs16842091	C/T	0	0.962	C/T	5	0.407
	rs16842126	A/T	1	0.828	A/T	11	0.445
	rs16842128	G/T	0	0.981	G/T	6	0.888
	rs16842130	C/T	0	0.961	C/T	12	0.033

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	rs16842143	G/A	0	0.000	G/A	6	0.351
	rs17182166	G/T	18	0.232	G/T	17	0.394
AMH type 2 receptor (AMHR2)	rs784888	C/G	0	0.922	C/G	33	0.623
	rs784892	C/T	0	0.962	C/T	27	0.715
	rs784893	T/C	1	0.904	T/C	47	0.825
	rs2002555	T/C	16	0.279	T/C	12	0.152
	rs11170550	G/T	16	0.396	G/T	16	0.625
	rs17695156	C/T	7	0.169	C/T	1	0.000
	rs36120387	C/T	10	0.254	C/T	2	0.768

[a]Minor allele frequency (MAF) was calculated among controls in this study.

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