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Genetic Variation in Bone Morphogenetic Proteins and Breast Cancer Risk in Hispanic and non-Hispanic white women: the Breast Cancer Health Disparities Study

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Abstract

Bone morphogenetic proteins (BMP) are thoughtx to be important in breast cancer promotion and progression. We evaluated genetic variation in BMP-related genes and breast cancer risk among Hispanic (2111 cases, 2597 controls) and non-Hispanic white (NHW) (1481 cases, 1586 controls) women who participated in the 4-Corner's Breast Cancer Study, the Mexico Breast Cancer Study, and the San Francisco Bay Area Breast Cancer Study. BMP genes and their receptors evaluated include *ACVR1*, *AVCR2A*, *ACVR2B*, *ACVRL1*, *BMP1*, *BMP2*, *BMP4*, *BMP6*, *BMP7*, *BMPR1A*, *BMPR1B, BMPR2*, *MSTN* and *GDF10*. Additionally, 104 ancestral informative markers were assessed to discriminate between European and Native American ancestry. The importance of estrogen on BMP-related associations was suggested through unique associations by menopausal status and estrogen (ER) and progesterone (PR) receptor status of tumors. After adjustment for multiple comparisons *ACVR1* (8 SNPs) was modestly associated with ER+PR+ tumors [odds ratios (ORs between 1.18 and 1.39 $p_{adj} < 0.05$]. *ACVR1* (3 SNPs) and *BMP4* (3 SNPs) were associated with ER+PR− tumors (ORs 0.59 to 2.07 $p_{adj} < 0.05$). *BMPR2* was associated with ER−PR+ tumors (OR 4.20, 95% CI 1.62, 10.91 $p_{adj} < 0.05$) as was *GDF10* (2 SNPs ORs 3.62 and 3.85 $p_{adj} < 0.05$). After adjustment for multiple comparisons several SNPs remained associated with ER−PR− tumors ($p_{adj} < 0.05$) including *ACVR1 BMP4*, and *GDF10* (ORs between 0.53 and 2.12). Differences in association also were observed by percentage of Native ancestry and menopausal status. Results support the hypothesis that genetic variation in BMPs is associated with breast cancer in this admixed population.

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Keywords

BMP; ACVR1; BMPRIB; breast cancer; Hispanic; genetic admixture; survival; ER status

Introduction

Bone morphogenetic proteins (BMP) are thought to be involved in the initiation and progression of cancer [1, 2]. As members of the *TGFβ*-signaling pathway they play a critical role in carcinogenesis through regulation of cell growth, differentiation, proliferation, and apoptosis [3]. Members of the human BMP family include BMP1-7, growth differentiation factors (GDF) including GDF10 and GDF8 (also known as myostatin) [4] and their receptors. BMP ligands bind to type 1 and type 2 receptors. Type 1 receptors include BMPR1A, BMPR1B, activin A receptor type 1 (ACVR1), and activin receptor-like kinase 1 (ACVRL1) ; type II receptors include BMPR2, activin A receptor type IIA (ACVR2A) and type IIB (ACVR2B) [4]. Both types of receptors are needed for BMP signaling, although type I receptors bind with a higher affinity than the type II receptors. BMPs have been shown to trigger a SMAD-signaling cascade that is linked to reduced cell proliferation and cellular growth kinetics of glioblastomas [5, 6] and may play a key role in regulating tumor initiation.

Little is known about the genetic variation in BMP genes and their associations with breast cancer risk, although these genes have been shown to be important in colorectal cancer[7]. Some studies suggest a link of BMPs to breast cancer disease progression and metastasis. Because of BMPs role in bone formation, they have been examined for their involvement in metastasis to the bone after diagnosis with breast cancer [8]. Additionally BMPs have been associated with estrogen-induced proliferation of breast cancer cells [9]. One study has shown that BMP-SMAD activation is involved in the progression of estrogen receptor positive (ER +) breast cancers specifically [10].

In this study, we examined genetic variation in *BMP1*, *BMP2*, *BMP4, BMP6, BMP7,* Growth Differentiation Factor 10 (*GDF10*) also known as *BMP3B, myostatin (MSTN),* and their relevant receptor genes *BMPR1A*, *BMPR1B*, *BMPR2*, and *ACVR1*, *ACVR2A*, *ACVR2B*, and *ACVRL1*. We assessed overall associations as well as associations by ER and progesterone receptor (PR) status of the tumors and by menopausal status. Given our ethnically diverse population we also evaluated associations by genetic admixture to determine whether differences in these genes may contribute to observed ethnic differences in breast cancer incidence rates.

Methods

The Breast Cancer Health Disparities Study includes participants from three population-based case-control studies, the 4-Corner's Breast Cancer Study, the Mexico Breast Cancer Study, and the San Francisco Bay Area Breast Cancer Study[11]. All participants signed informed written consent prior to participation and each study was approved by the Institutional Review Board for Human Subjects at each institution.

Participants from the 4 Corner's Breast Cancer Study were NHW, Hispanic, or Native American women living in non-reservation areas in the states of Arizona, Colorado, New Mexico, or Utah at the time of diagnosis or selection [12] and included female breast cancer cases between 25 and 79 years of age with a histological confirmed diagnosis of *in situ* (n=341) or invasive (n=1492) cancer between October 1999 and May 2004 and who provided a blood sample and completed the interview. Controls were selected from the target populations and were frequency matched to cases on ethnicity and 5-year age

distribution. Of the 852 Hispanic, 22 American Indian, and 1683 NHW cases and 913 Hispanic, 23 American Indian, and 1669 NHW controls who participated in the interview, a blood sample for DNA extraction was provided for 76% of participants in Arizona, 71% of participants in Colorado, 75% of participants in New Mexico, and 94% of participants in Utah.

Participants from the Mexico Breast Cancer Study were between 28 and 74 years of age, living in one of three states, Monterrey, Veracruz and Mexico City, for the past five years as previously described[13]. Eligible cases were women diagnosed with either a new histologically confirmed *in situ* or invasive breast cancer between January 2004 and December 2007 at 12 participating hospitals from three main health care systems in Mexico. Controls were randomly selected from the catchment area of the 12 participating hospitals using a probabilistic multi-stage design. A total of 1000 cases and 1074 controls completed the in-person interview, and blood was collected and DNA extracted for 85% and 96% of women, respectively.

The San Francisco Bay Area Breast Cancer Study included women aged 35 to 79 years from the San Francisco Bay Area diagnosed with a first primary histologically confirmed invasive breast cancer between 1995 and 2002; controls were identified by random-digit dialing (RDD) and frequency-matched to cases based on the expected race/ethnicity and 5-year age distribution.[14, 15] This analysis included subjects with bio-specimen collection, including Hispanic cases diagnosed between April 1997 and April 2002 and a 10% random sample of NHW cases diagnosed between April 1997 and April 1999 and their matched controls. A total of 1105 cases (793 Hispanic, 312 NHW) and 1318 controls (998 Hispanic, 320 NHW) completed the in-person interview, and blood or mouthwash samples were collected and DNA extracted for 93% of cases and 92% of controls.

Data Harmonization

Data were harmonized across all study centers and questionnaires. Variables used in the analyses included body mass index (BMI) calculated as weight (kg) divided by height squared [meters squared (m^2)], based on measured height (or self-reported height if the measurement was declined) and self-reported weight during the referent year or more distantly recalled weight if referent year weight was not available or measured weight if neither were available. The referent year was defined as the year prior to diagnosis for cases or selection for controls. Parity was defined as the number of full-term pregnancies, age at first birth was defined as age at first live birth or still birth, and race/ethnicity in the U.S. studies was based on self-report (all women in Mexico were classified as Hispanic since information on race/ethnicity was not collected). Women were classified as either pre - menopausal or post-menopausal based on responses to questions on menstrual history. Women who reported still having periods during the referent year were classified as pre-menopausal. Center-specific definitions were used to define post-menopausal women. Women were classified as post-menopausal if they reported a natural menopause. If they reported taking hormone therapy (HT) and were still having periods and were at or above the 95th percentile of age for race/ethnicity of those who reported having a natural menopause (i.e., ≥ 12 months since their last period) within their study center they were classified as post-menopausal. This age was 58 for NHW and 56 for Hispanics from the 4-Corner's Breast Cancer Study, 54 for the Mexico Breast Cancer Study, and 55 for NHW and 56 for Hispanics from the San Francisco Bay Area Breast Cancer Study. Mean daily grams of alcohol intake consumed over the lifetime were available for all but about 600 cases and controls from California. For those women we used alcohol consumption during the referent year as an adjustment variable. Physical activity was harmonized as hours of vigorous

activity performed at leisure and chores during the referent year and analyzed using center-specific cut-points to accommodate the level of inquiry of each study questionnaire

Genetic Data

DNA was extracted from either whole blood or mouthwash samples; 7287 blood-derived and 634 mouthwash-derived samples were available. Whole Genome Amplification (WGA) was applied to the mouthwash-derived DNA samples prior to genotyping. A tagSNP approach was used to characterize variation across candidate genes. TagSNPs were selected using the following parameters: linkage disequilibrium (LD) blocks were defined using a Caucasian LD map and an r^2=0.8; minor allele frequency (MAF) >0.1; range= −1500 bps from the initiation codon to +1500 bps from the termination codon; and 1 SNP/LD bin. Additionally, 104 Ancestral Informative Markers (AIMs) were used to distinguish European and Native American ancestry in the study population[11]. All markers were genotyped using a multiplexed bead array assay format based on GoldenGate chemistry (Illumina, San Diego, California). A genotyping call rate of 99.93% was attained (99.65% for WGA samples). We included 132 blinded internal replicates representing 1.6% of the sample set. The duplicate concordance rate was 99.996% as determined by 193,297 matching genotypes among sample pairs.

In the current analysis, we evaluated 138 SNPs in 14 genes: *ACVR1* (16 SNPs), *AVCR2A* (6 SNPs), *ACVR2B* (3 SNPs), *ACVRL1* (4 SNPs), *BMP1* (10 SNPs), *BMP2* (6 SNPs), *BMP4* (4 SNPs), *BMP6* (23 SNPs), *BMP7* (24 SNPs), *BMPR1A* (9 SNPs), *BMPR1B* (18 SNPs), *BMPR2* (8 SNPs), *MSTN (1 SNPs,)* and *GDF10* (6 SNPs). Online Supplement 1 describes the SNPs in detail, including the minor allele frequency (MAF) and Hardy-Weinberg equilibrium (HWE) p value.

Tumor Characteristics

Cancer registries in Utah, Colorado, Arizona, New Mexico, and California provided information on stage at diagnosis and ER and PR status. Information on ER and PR status was available for 1019 (69%) NHW cases and 977 (75%) Hispanic cases.

Statistical Methods

The program STRUCTURE was used to compute individual ancestry for each study participant assuming two founding populations[16, 17]. A three-founding population model was assessed but did not fit the population structure with the same level of repeatability and correlation among runs as the two-founding population model. Participants were classified by level of percent Native American ancestry. Assessment across categories of ancestry was done using cut-points based on the distribution of genetic ancestry in the control population with the goal of creating distinct ancestry groups that had sufficient power to assess associations. Three strata, 0-28%, 29 to 70%, and 71 to 100%, were used to evaluate associations by level of Native ancestry. Genetic ancestry was used as a continuous variable when used to adjust for possible confounding. Genes were assessed for their association with breast cancer risk by strata of genetic ancestry, ER/PR status, and menopausal status. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). Logistic regression models were used to estimate the age, genetic ancestry, and study center-adjusted odds ratios (OR) and 95% confidence intervals (CI) for breast cancer risk associated with SNPs. Except for the California study, both invasive and *in situ* cases were included given associations that the Mexico Study did not distinguish between these categories. Additionally, we adjusted for potential confounding variables of BMI, parity, age at first birth, hours per week of vigorous physical activity, alcohol consumption, and genetic admixture. SNPs were assessed assuming a co-dominant model. Based on the initial

assessment, SNPs which appeared to have a dominant or recessive mode of inheritance were evaluated with those inheritance models in subsequent analyses. Interactions between genetic variants and genetic ancestry and menopausal status were assessed using p values from a Wald chi-square test.

Haplotypes were developed to help define risk associated with genes. SNPs were selected based on their individual significance overall or within a genetic admixture group as well as for those considered in higher linkage disequilibrium (LD) or an R-squared linkage disequilibrium measure greater than or equal to 0.5. Haplotypes were estimated using the EM algorithm. Per-copy haplotype risk estimates were obtained using logistic regression and adjusted for age, study, genetic admixture, BMI in referent year, age at first birth, parity, alcohol consumption and vigorous physical activity.

The p values were based on one degree of freedom (1-df) Wald test statistics and were adjusted for multiple comparisons taking into account tagSNPs within the gene using the step-down Bonferroni correction (i.e., Holm method). This method isbased on the effective number of independent SNPs as determined using the SNP spectral decomposition method proposed by Nyholt [18] and modified by Li and Ji [19]. We provide an online Supplement 2 that shows the number of SNPs analyzed and the number of SNPs considered for adjustment based on correlation between SNPs within a gene. The interaction p values, based on 1-df Wald chi-square tests, were adjusted using the step-down Bonferroni correction or the Holm's test [20]. This method of correction for multiple comparisons is very conservative, especially for correlated variables such as SNPs within a gene. Given that we are assessing hypothesized associations within a candidate pathway and candidate genes, we considered an adjusted p value of 0.15 or less as potentially important. However, we include in the text only those SNPs with adjusted p values of <0.05 and highlight those associations using bold font in the tables.

Results

The majority of participants were Hispanic (59% of cases and 62% of controls) (Table 1). More Hispanic women than NHW were diagnosed prior to 40 years of age (9% vs. 6%). Hispanic cases were more likely to be pre-menopausal at diagnosis than NHW cases (41% vs. 34%). Hispanic cases were more likely to have ER−PR− tumors than NHW women (23% vs. 18%).

There were few associations with breast cancer risk overall. However, when we examined cases defined by ER/PR status, several genes appeared to be associated with specific breast cancer subtypes (Table 2 shows those that remained significant at the 0.05 level after multiple comparison adjustment, whereas Supplement 3 shows those that were initially significant at the 0.05 level but after multiple adjustment testing had adjusted p values of >0.05). Variants in *ACVR1* (8 SNPs) and *BMP4* (1 SNP) were associated with ER+PR+ tumors, although the level of association was modest with ORs between 1.19 and 1.33. *ACVR1* (4 SNPs), *BMP4* (3 SNPs), and *GDF10* (1 SNP) were associated with ER+PR− tumors, with OR estimates ranging from 0.59 to 2.07. *BMPR2* (1 SNP) and *GDF10* (2 SNPs) were associated with ER−PR+ tumors (ORs between 3.62 and 4.20). *ACVR1* (1 SNP), *ACVRL1* (1 SNP), *BMP4 (1 SNP),* and *GDF10 (1 SNP)* were associated with ER −PR− tumors.

Several genes were associated with breast cancer risk within genetic admixture groups (Table 3). *BMP4* rs17563 was associated with breast cancer among women with greater European ancestry at the 0.05 level or less after adjustment for multiple comparisons. However, among Hispanic women with low Native American ancestry (0-28%) *BMP4*

rs17563 was associated with increased risk (OR 2.42 95% CI 1.40,4.16 for CC vs. TT genotypes) and *BMP6* rs270417 was associated with reduced risk (OR 0.55 95% CI 0.38,0.79 dominant model) (data in Supplement 4 that shows associations for NHW women and for Hispanic women by admixture category).

ACVR2A rs1014064, rs2161983, rs10497025, and rs3768687, and *ACVR2B* rs928813 and rs2276541 were associated with breast cancer among those with the greatest Native American ancestry; the *ACVR2B* associations were statistically different from those observed for women with more European ancestry. *ACVR2A* rs10497025, *BMP4* rs762642, and rs2761887, *BMP7* rs7273197, and *BMPR2* rs17199235 were associated with breast cancer in the intermediate ancestry group.

Haplotype analysis showed rare haplotypes to carry some risk beyond SNPs themselves (Table 4). For the *ACVR1* the rare A-T haplotype of rs4380178 and rs17182166 (0.028% of the population) was associated with an OR of 1.51 (95% CI 1.14,2.00). The rare C-T-A-G haplotype of *BMP6* rs10498671, rs1225929, rs1107495, and rs911749 which occurred in 0.012% of the population was associated with reduced breast cancer risk (OR 0.34, 95% CI 0.19,0.62). Among the highest Native ancestry group, two haplotypes of *BMP7* were associated with increased breast cancer risk: *BMP7* rs174080735, rs6025446, and rs6025468 A- A-A (0.014% of the population) OR 2.25 (95% CI 1.11,4.58) and *BMP7* rs6127983 and rs6025468 T-G (0.008% of the population) (OR 4.55 95% CI 1.09,19.00). Additional haplotypes based on SNPs in higher LD also were identified as being statistically significant. These haplotypes were observed in less than 5% of the population and were primarily in *BMP6* and *BMP7*.

We observed differences in association by menopausal status for several genes; Figure 1 shows those associations that remained significant at the 0.05 level after adjustment for multiple comparisons. Supplement 5 shows all associations that were significant prior to adjustment along with the associated unadjusted and adjusted p values. For women with low Native American ancestry, *ACVR1* rs1220134 and *ACVR2A* rs10497025 were associated with reduced breast cancer risk and *BMRP1B* rs1863652 was associated with increased risk among pre-menopausal women, whereas *BMP4* rs17563 was associated with increased breast cancer risk among post-menopausal women. Breast cancer risk was different for pre-menopausal and post-menopausal women for several genes among women with the highest level of Native American ancestry. Among pre-menopausal women, *ACVR2B* rs2276541 was associated with reduced risk whereas *rs928813* was associated with increased risk. Among post-menopausal women *ACVR2B* rs503327 and *GDF10* rs1902725 were associated with increased risk. *ACVR2A* rs1097025, *BMP4* rs762642 and rs2761887, *BMP7* rs7273197, and *BMPR2* rs17199235 showed differences in risk by menopausal status among women in the intermediate ancestry category.

Discussion

BMPs are extracellular signaling molecules and are the largest group of the TGFβ superfamily. Because of their role in cell regulation, proliferation, apoptosis, and migration, they have been implicated as potentially important in cancer etiology. Our data suggest that genetic variation in BMPs and their receptors are involved in breast cancer etiology and prognosis. Few SNPs were associated overall with breast cancer risk after adjustment for multiple comparisons and associations were very modest. However, several BMPs and their receptors were associated with specific ER and PR tumor phenotype and the associations were generally stronger for specific subtypes than for breast cancer risk. Additionally we observed unique associations by genetic ancestry as well as by menopausal status.

BMPs have been associated with estrogen in several studies, some of which have linked BMPs to expression of estrogen receptors and estrogen signaling [21]. BMP6 and BMP7 have been shown to inhibit estrogenic enzyme expression [9]. Helms and colleagues [10] have reported that BMPR1B is involved in the progression and differentiation of ER-positive breast cancer. BMP6 and BMP7 preferentially bind to BMPR1B and ACVR1. Estrogen also has been shown to reduce expression of BMPR1A, BMPR1B, ACVR2A, and ACVR2B [9]. BMP7 has been shown to be associated with expression of both the estrogen and progesterone receptor [22]. In another study, hypermethylation of *BMP6* was observed in all ER-negative breast cancers, but in only 18% of ER-positive breast cancers, suggesting a correlation between *BMP6* expression and ER status of breast cancers[23]. BMP6 also has been shown to inhibit ER –induced mitosis [9]; BMP2 has been associated with ER-negative tumors [24]. Our results add to the knowledge about the association between BMPs and their receptors and risk of breast cancer defined by hormone receptors. Overall we observed few associations with *BMP6* and *BMP7* that remained significant after adjustment for multiple comparisons given the size of the genes and number of SNPs assessed. However, rare haplotypes of these genes were associated with breast cancer risk, primarily among women with intermediate and high Native American ancestry. Given associations observed between menopausal status and ER/PR tumor status, we believe that our data support the findings by Takahashi and Wang that showed the importance of BMP receptors and estradiol[9, 25]. Many of our associations by ER and PR status were observed for type 1 receptors (*ACVR1* and *ACVRL1*). Most SNPs in these genes appeared to be more strongly associated with ER+ tumors than ER− tumors. However, for some SNPs associations were stronger for ER− tumors, and for some the associations were similar for ER− PR− tumors (e.g. *ACVR1* rs17182166, *ACVRL1* rs11169953, *BMP4* rs17563, *GDF10* rs762454). Several SNPs were associated with ER− PR+ tumors (*BMPR2* rs12621870, and *GDF10* rs7093975 and rs2853838).

In our assessment of genetic associations by menopausal status, we observed differences in risk by genetic admixture within menopausal groups. While no associations were observed for *BMP7* and ER/PR tumor status, three SNPs were associated with decreased risk of pre-menopausal breast cancer risk among women in the intermediate admixture group and one SNP was associated with post-menopausal breast cancer risk among women with more Native American ancestry. *BMP6* rs1225929 was associated with post-menopausal breast cancer among women in the middle admixture group, and *BMP6* rs270417 was associated with pre-menopausal breast cancer for those with the most Native ancestry. Most associations found were with type 1 and type 2 *BMP* receptors, again stressing the importance of receptors in the estrogen-related associations with BMPs [9].

We and others have previously reported that women with higher Native ancestry were at reduced risk of breast cancer[11, 26-28]. Given this difference in risk, it is of interest to determine whether unique genetic factors are associated differently with breast cancer based on genetic admixture. For the most part we found that associations with *BMP*-related genes did not differ by genetic admixture. Among those that did, we observed generally stronger risk estimates and more associations with increasing Native American ancestry, with the exception of *BMP4* rs17563 which was associated among women with more European ancestry. Others have not examined these genes in similar admixed populations.

The study is the largest to date reporting associations with breast cancer in a genetically admixed population of European and Native American ancestry. We were able to evaluate associations by genetic admixture as well as by ER/PR status of tumors. However, the study has some limitations. Data on tumor characteristics were not available for the entire study population, which restricted our ability to evaluate these characteristics across the same genetic admixture spectrum as we did for the analysis of SNP and breast cancer risk

associations. Additionally, we were limited in power to evaluate some tumor phenotypes, for instance there were only 43 cases of ER−PR+ tumors. We evaluated SNPs in several candidate genes. While we hypothesized associations with specific genes, we were limited in our ability to make similar hypotheses regarding specific SNPs. Although we adjusted for multiple comparisons, it is possible that associations are spurious, and thus replication in other studies is needed. Additionally, we have limited information on functionality of these SNPs and our interpretation of findings is greatly guided by the literature on BMPs and their association with cancer in general.

Our findings support the role of genetic variation in BMPs in the etiology of breast cancer. Associations of *BMP*-related SNPs were in some instances influenced by menopausal status and resulted in associations that were specific to ER and PR status of tumors. Overall, *BMP* genes were more commonly associated with breast cancer in women with more Native American ancestry, suggesting the importance of genetic ancestry to understanding risk associated with breast cancer. Studies to confirm these findings are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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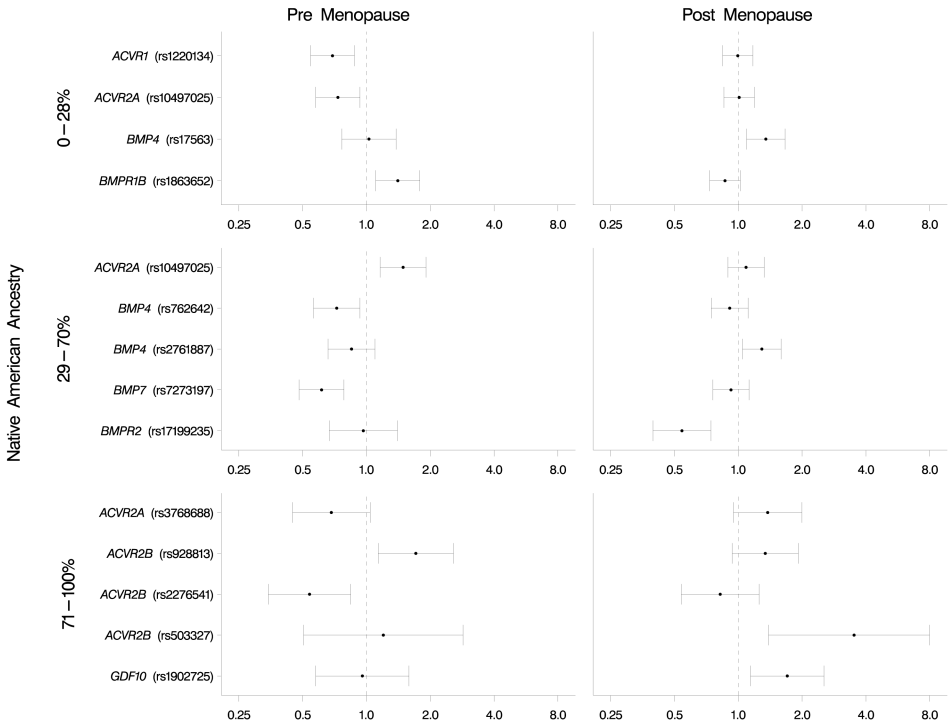

Figure 1.

Associations between *BMP*-related genes and breast cancer risk by menopausal status and Native American Ancestry

Table 1

Description of Study Population by Self-reported Race/Ethnicity

	NHW				Hispanic			
	Controls		Cases		Controls		Cases	
	N	%	N	%	N	%	N	%
Total	1586	37.9	1481	41.2	2597	62.1	2111	58.8
Study Site								
4 Corner's States	1322	83.4	1227	82.8	723	27.8	597	28.3
Mexico	0	0.0	0	0.0	994	38.3	816	38.7
California	264	16.6	254	17.2	880	33.9	698	33.1
Age (years)								
<40	116	7.3	89	6.0	311	12.0	200	9.5
40-49	408	25.7	409	27.6	831	32.0	713	33.8
50-59	409	25.8	413	27.9	756	29.1	617	29.2
60-69	350	22.1	361	24.4	526	20.3	430	20.4
70+	303	19.1	209	14.1	173	6.7	151	7.2
Mean	56.6		56.0		52.3		52.7	
Menopausal Status								
Pre-menopausal	494	31.5	489	33.5	1027	40.7	836	40.9
Post-menopausal	1076	68.5	970	66.5	1499	59.3	1210	59.1
Estimated Native American Ancestry								
Low (0 - 28%)	1578	99.5	1472	99.4	278	10.7	275	13.0
Intermediate (29 - 70%)	7	0.4	7	0.5	1686	64.9	1393	66.0
High (71 - 100%)	1	0.1	2	0.1	633	24.4	443	21.0
ER/PR Status *								
ER+PR+	NA		695	68.2	NA		605	61.9
ER+PR−	NA		121	11.9	NA		115	11.8
ER−PR+	NA		15	1.5	NA		28	2.9
ER−PR−	NA		188	18.4	NA		229	23.4

* Tumor information was unavailable for the Mexico study sites.

Table 2

Associations between *BMP*-related genes and risk of breast cancer overall and by ER/PR status

	Controls	Overall Cases			ER + PR +[1] (N=1292 cases)		ER + PR − (N=235 cases)		ER − PR + (N=41 cases)		ER − PR − (N=411 cases)	
	N	N	OR[2]	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
ACVR1 (rs2033962)												
GG	2940	2452	1.00		1.00		1.00		1.00		1.00	
GT/TT	1159	1081	1.09	(0.99, 1.20)	**1.27**	**(1.11, 1.46)**	0.96	(0.71, 1.29)	0.94	(0.46, 1.90)	1.13	(0.91, 1.42)
ACVR1 (rs4380178)												
GG	3046	2538	1.00		1.00		1.00		1.00		1.00	
GA/AA	1053	997	1.12	*(1.01*, 1.24)	**1.25**	**(1.08, 1.44)**	0.96	(0.71, 1.30)	1.01	(0.50, 2.04)	1.25	(1.00, 1.57)
ACVR1 (rs920522)												
TT	3501	2970	1.00		1.00		1.00		1.00		1.00	
TC/CC	601	565	1.13	(1.00, 1.28)	**1.33**	**(1.12, 1.59)**	**1.43**	**(1.01, 2.03)**	0.79	(0.31, 2.04)	0.94	(0.70, 1.27)
ACVR1 (rs17182166)												
GG/GT	4051	3466	1.00		1.00		1.00		1.00		1.00	
TT	51	68	1.40	(0.97, 2.03)	1.47	(0.93, 2.33)	1.27	(0.49, 3.24)	1.66	(0.22, 12.62)	**2.12**	**(1.13, 3.97)**
ACVR1 (rs1146035)												
GG	2958	2467	1.00		1.00		1.00		1.00		1.00	
GT/TT	1144	1066	1.08	(0.98, 1.20)	**1.26**	**(1.10, 1.45)**	0.97	(0.72, 1.30)	1.02	(0.52, 2.03)	1.10	(0.88, 1.38)
ACVR1 (rs10497191)												
CC	3050	2578	1.00		1.00		1.00		1.00		1.00	
CT/TT	1050	957	1.09	(0.98, 1.21)	**1.20**	**(1.04, 1.39)**	1.23	(0.92, 1.66)	0.92	(0.45, 1.89)	1.06	(0.84, 1.33)
ACVR1 (rs10497192)												
TT	2206	1852	1.00		1.00		1.00		1.00		1.00	
TC	1606	1409	1.04	(0.95, 1.15)	1.20	(1.05, 1.38)	1.01	(0.76, 1.34)	0.86	(0.45, 1.66)	1.08	(0.87, 1.34)
CC	290	274	1.13	(0.94, 1.35)	**1.39**	**(1.09, 1.77)**	1.13	(0.68, 1.87)	0.84	(0.25, 2.85)	1.02	(0.68, 1.53)
ACVR1 (rs4233672)												
GG	2764	2303	1.00		1.00		1.00		1.00		1.00	
GA/AA	1337	1231	1.10	(1.00, 1.21)	**1.22**	**(1.07, 1.40)**	0.99	(0.75, 1.32)	0.95	(0.48, 1.85)	1.14	(0.92, 1.41)
ACVR1 (rs10933443)												

	Controls	Overall Cases			ER + PR +[1] (N=1292 cases)		ER + PR − (N=235 cases)		ER − PR + (N=41 cases)		ER − PR − (N=411 cases)	
	N	N	OR[2]	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
TT	2341	1994	1.00		1.00		1.00		1.00		1.00	
TC/CC	1756	1538	1.02	(0.93, 1.12)	**1.19**	**(1.04, 1.35)**	1.00	(0.76, 1.31)	1.21	(0.65, 2.26)	1.07	(0.87, 1.32)
ACVR1 (rs2883605)												
GG	3568	3047	1.00		1.00		1.00		1.00		1.00	
GT/TT	483	438	1.00	(0.87, 1.15)	1.06	(0.87, 1.28)	**0.59**	**(0.37, 0.95)**	0.95	(0.37, 2.48)	1.11	(0.82, 1.49)
ACVR1 (rs10497193)												
AA/AG	4002	3447	1.00		1.00		1.00		1.00		1.00	
GG	99	87	1.04	(0.77, 1.39)	1.01	(0.66, 1.53)	**2.07**	**(1.08, 3.98)**	1.76	(0.41, 7.51)	0.80	(0.40, 1.61)
ACVR1 (rs4664901)												
TT/TC	3891	3338	1.00		1.00		1.00		1.00		1.00	
CC	207	195	1.10	(0.90, 1.35)	1.11	(0.84, 1.48)	**1.94**	**(1.21, 3.11)**	1.31	(0.40, 4.32)	1.01	(0.64, 1.58)
ACVRL1 (rs11169953)												
CC	2003	1787	1.00		1.00		1.00		1.00		1.00	
CT/TT	2098	1747	0.91	(0.83, 1.00)	0.93	(0.81, 1.06)	1.05	(0.80, 1.37)	1.31	(0.70, 2.46)	**0.73**	**(0.60, 0.90)**
BMP4 (rs17563)												
TT	1449	1056	1.00		1.00		1.00		1.00		1.00	
TC/CC	2376	2159	**1.16**	**(1.05, 1.29)**	**1.29**	**(1.10, 1.51)**	1.26	(0.90, 1.77)	1.39	(0.64, 3.02)	**1.38**	**(1.06, 1.80)**
BMP4 (rs762642)												
TT/TG	3391	2957	1.00		1.00		1.00		1.00		1.00	
GG	710	578	0.93	(0.82, 1.05)	0.96	(0.80, 1.14)	**0.62**	**(0.40, 0.94)**	1.26	(0.58, 2.77)	0.90	(0.68, 1.20)
BMP4 (rs2761887)												
AA	1295	1067	1.00		1.00		1.00		1.00		1.00	
AC/CC	2805	2466	1.07	(0.97, 1.18)	1.10	(0.95, 1.27)	**1.54**	**(1.13, 2.11)**	1.10	(0.55, 2.16)	1.19	(0.95, 1.50)
BMP4 (rs4898820)												
TT/TG	3147	2743	1.00		1.00		1.00		1.00		1.00	
GG	955	790	0.95	(0.85, 1.06)	0.95	(0.81, 1.11)	**0.62**	**(0.43, 0.90)**	1.00	(0.47, 2.11)	0.95	(0.74, 1.22)
BMPR2 (rs12621870)												
TT	2525	2171	1.00		1.00		1.00		1.00		1.00	
TC	1354	1178	1.00	(0.91, 1.10)	1.04	(0.91, 1.20)	0.94	(0.70, 1.25)	1.93	(0.98, 3.77)	0.90	(0.72, 1.13)

	Controls	Overall Cases			ER + PR +[1] (N=1292 cases)		ER + PR − (N=235 cases)		ER − PR + (N=41 cases)		ER − PR − (N=411 cases)	
	N	N	OR[2]	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
CC	212	174	0.94	(0.76, 1.17)	1.06	(0.79, 1.42)	1.24	(0.71, 2.16)	**4.20**	**(1.62, 10.91)**	0.76	(0.45, 1.28)
GDF10 (rs7093975)												
CC	2346	2001	1.00		1.00		1.00		1.00		1.00	
CT	1526	1285	0.97	(0.88, 1.06)	0.93	(0.81, 1.06)	0.90	(0.67, 1.20)	1.61	(0.82, 3.15)	0.96	(0.77, 1.20)
TT	229	244	1.22	(1.01, 1.48)	1.19	(0.91, 1.56)	1.42	(0.86, 2.33)	**3.62**	**(1.40, 9.41)**	1.24	(0.82, 1.89)
GDF10 (rs762454)												
AA	2228	1802	1.00		1.00		1.00		1.00		1.00	
AG	1553	1432	1.12	(1.02, 1.23)	1.13	(0.99, 1.30)	1.26	(0.95, 1.68)	0.65	(0.32, 1.31)	1.02	(0.82, 1.26)
GG	312	293	1.09	(0.92, 1.30)	1.07	(0.84, 1.36)	**1.77**	**(1.15, 2.71)**	1.31	(0.49, 3.50)	**0.53**	**(0.33, 0.87)**
GDF10 (rs2853838)												
CC	2554	2197	1.00		1.00		1.00		1.00		1.00	
CA	1379	1182	1.00	(0.90, 1.10)	0.97	(0.84, 1.12)	0.94	(0.71, 1.26)	2.04	(1.06, 3.91)	1.03	(0.82, 1.28)
AA	169	155	1.09	(0.87, 1.36)	1.07	(0.77, 1.48)	1.24	(0.67, 2.30)	3.85	(1.27, 11.71)	1.33	(0.82, 2.15)

[1]Estrogen Receptor (ER) and Progesterone Receptor (PR) data were compared to 3125 controls from sites where cases have ER/PR data

[2]Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, study, BMI in referent year, vigorous activity in referent year, parity, age at first birth, alcohol consumption and genetic admixture; bold text designates significant associations at the 0.05 level after adjustment for multiple comparisons

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Table 3

Associations between candidate genes and breast cancer by genetic admixture

	0 - 28% Native American Ancestry				29 - 70% Native American Ancestry				71 -100% Native American Ancestry				Interaction	
	Controls	Cases			Controls	Cases			Controls	Cases			Raw	Holms
	N	N	OR[1,2]	(95% CI)	N	N	OR	(95% CI)	N	N	OR	(95% CI)	P-value	P-value
ACVR2A (rs1014064)														
AA	848	837	1.00		552	435	1.00		141	129	1.00		0.20	0.39
AG/GG	971	897	0.93	(0.82, 1.06)	1109	935	1.08	(0.92, 1.26)	481	302	**0.69**	**(0.51, 0.92)**		
ACVR2A (rs2161983)														
CC	835	822	1.00		545	432	1.00		138	129	1.00		0.13	0.39
CT/TT	983	911	0.94	(0.82, 1.07)	1116	938	1.07	(0.92, 1.25)	484	302	**0.67**	**(0.50, 0.90)**		
ACVR2A (rs3768687)														
GG	847	834	1.00		550	435	1.00		140	129	1.00		0.16	0.39
GA/AA	968	896	0.94	(0.82, 1.07)	1109	931	1.07	(0.91, 1.25)	480	302	**0.68**	**(0.51, 0.92)**		
ACVR2A (rs10497025)														
CC	1024	1013	1.00		1097	837	1.00		400	300	1.00		0.60	0.60
CG/GG	795	720	0.92	(0.80, 1.05)	564	533	**1.23**	**(1.05, 1.43)**	222	131	**0.75**	**(0.57, 0.99)**		
ACVR2B (rs928813)														
GG	359	353	1.00		685	531	1.00		360	217	1.00		0.005	0.01
GT/TT	1454	1369	0.97	(0.82, 1.15)	973	834	1.11	(0.95, 1.29)	262	210	**1.35**	**(1.04, 1.76)**		
ACVR2B (rs2276541)														
AA	672	600	1.00		452	371	1.00		139	119	1.00		0.02	0.03
AG/GG	1147	1132	1.10	(0.95, 1.26)	1209	999	1.01	(0.86, 1.20)	483	312	**0.69**	**(0.51, 0.93)**		
BMP4 (rs17563)														
TT	396	316	1.00		692	500	1.00		361	240	1.00		0.82	1.00
TC/CC	1365	1330	**1.24**	**(1.05, 1.47)**	785	660	1.16	(0.99, 1.36)	226	169	1.13	(0.86, 1.49)		
BMP4 (rs762642)														
TT	635	587	1.00		550	495	1.00		226	147	1.00		0.659	1.00
TG	878	857	1.05	(0.91, 1.22)	814	665	0.89	(0.76, 1.05)	288	206	1.09	(0.81, 1.45)		
GG	305	290	1.01	(0.83, 1.24)	297	210	**0.77**	**(0.62, 0.96)**	108	78	1.08	(0.74, 1.57)		

	0 - 28% Native American Ancestry				29 - 70% Native American Ancestry				71 -100% Native American Ancestry				Interaction	
	Controls	Cases			Controls	Cases			Controls	Cases			Raw	Holms
	N	N	OR[1,2]	(95% CI)	N	N	OR	(95% CI)	N	N	OR	(95% CI)	P-value	P-value
BMP4 (rs2761887)														
AA/AC	1468	1399	1.00		1373	1088	1.00		480	345	1.00		0.91	1.00
CC	350	334	1.01	(0.86, 1.20)	287	281	**1.27**	**(1.05, 1.53)**	142	86	0.85	(0.62, 1.16)		
BMP7 (rs7273197)														
CC	839	792	1.00		949	854	1.00		381	269	1.00		0.26	0.84
CT/TT	980	942	1.02	(0.90, 1.17)	712	516	**0.79**	**(0.68, 0.92)**	241	162	0.88	(0.67, 1.15)		
BMPR2 (rs17199235)														
AA	1426	1348	1.00		1441	1236	1.00		598	413	1.00		0.12	0.73
AG/GG	393	386	1.03	(0.88, 1.21)	220	134	**0.67**	**(0.53, 0.84)**	24	18	0.93	(0.48, 1.81)		

[1] Bold indicates adjusted odds ratio (OR) estimates remained significant at ≤0.05 after adjustment for multiple comparisons.

[2] Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, study, genetic admixture, BMI in referent year, vigorous activity in referent year, parity, age at first birth and alcohol consumption.

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Table 4

Associations between haplotypes and breast cancer risk by Native American ancestry

Haplotype	Frequency	OR[2]	(95% CI)	Haplotype	Frequency	OR[2]	(95% CI)	Haplotype	Frequency	OR[2]	(95% CI)
0 to 28% Native American Ancestry				**29 - 70% Native American Ancestry**				**71 - 100% Native American Ancestry**			
BMP7 (rs1475000 A>G; rs4811822 T>C)[1]				*ACVR1* (rs2165436 C>T; rs6437117 A>T)[1]				*BMP7* (rs17480735 G>A; rs6025446 A>G; rs6025468 A>G)			
A-T	0.480	0.98	(0.89, 1.08)	C-A	0.837	0.98	(0.85, 1.12)	G-A-A	0.427	1.12	(0.93, 1.35)
G-C	0.367	0.96	(0.87, 1.06)	T-T	0.115	1.07	(0.91, 1.26)	G-G-A	0.342	0.94	(0.78, 1.14)
A-C	0.117	1.05	(0.91, 1.22)	**T-A**	**0.035**	**0.73**	**(0.55, 0.98)**	G-G-G	0.188	0.82	(0.65, 1.03)
G-T	**0.036**	**1.32**	**(1.01, 1.73)**	**C-T**	**0.014**	**1.69**	**(1.07, 2.68)**	G-A-G	0.021	1.63	(0.73, 3.64)
BMP7 (rs4811822 T>C; rs2180780 C>G)[1]				*ACVR1* (rs4380178 G>A; rs17182166 G>T)				**A-A-A**	**0.014**	**2.25**	**(1.11, 4.58)**
T-C	0.474	0.97	(0.88, 1.07)	G-G	0.801	0.98	(0.85, 1.12)	A-G-A	0.005	2.83	(0.45, 17.68)
C-G	0.397	0.95	(0.86, 1.04)	A-G	0.115	0.89	(0.75, 1.05)	A-A-G	0.002	0.35	(0.03, 3.64)
C-C	0.087	1.12	(0.95, 1.33)	G-T	0.056	1.01	(0.80, 1.27)	A-G-G	0.002	<0.001	<0.001 >999
T-G	**0.042**	**1.34**	**(1.05, 1.72)**	**A-T**	**0.028**	**1.51**	**(1.14, 2.00)**	*BMP7* (rs6127983 T>C; rs6025468 A>G)			
BMP7 (rs12481628 A>G; rs2180780 C>G)[1]				*BMP6* (rs10498671 T>C; rs1225929 A>T; rs1107495 A>G; rs911749 G>A)				T-A	0.474	1.17	(0.97, 1.40)
A-C	0.523	0.97	(0.88, 1.07)	T-T-A-G	0.229	1.28	(1.13, 1.45)	C-A	0.314	0.96	(0.79, 1.17)
G-G	0.390	0.96	(0.87, 1.06)	T-A-A-G	0.217	0.95	(0.84, 1.08)	C-G	0.204	0.81	(0.64, 1.01)
A-G	0.048	1.17	(0.93, 1.46)	T-A-G-G	0.155	0.95	(0.82, 1.09)	**T-G**	**0.008**	**4.55**	**(1.09, 19.00)**
G-C	**0.039**	**1.35**	**(1.05, 1.73)**	T-A-G-A	0.094	0.96	(0.81, 1.14)	*BMP2* (rs1979855 T>C; rs3178250 T>C)[1]			
				C-A-G-A	0.067	0.95	(0.78, 1.15)	T-T	0.920	1.04	(0.73, 1.46)
				T-T-G-G	0.060	0.89	(0.69, 1.14)	C-C	0.046	0.65	(0.41, 1.02)
				T-A-A-A	0.048	0.91	(0.69, 1.21)	**T-C**	**0.029**	**1.83**	**(1.04, 3.22)**
				C-A-A-A	0.036	0.91	(0.70, 1.19)	C-T	0.005	1.03	(0.25, 4.16)
				C-T-A-A	0.028	0.78	(0.54, 1.12)	*BMP6* (rs267190 T>G; rs267806 C>T)[1]			
				C-A-A-G	0.017	1.06	(0.71, 1.58)	T-T	0.723	0.86	(0.70, 1.07)
				T-T-A-A	0.016	1.09	(0.61, 1.97)	G-C	0.189	1.05	(0.83, 1.34)
				T-T-G-A	0.014	1.71	(0.99, 2.97)	**T-C**	**0.066**	**1.49**	**(1.04, 2.14)**
				C-T-A-G	**0.012**	**0.34**	**(0.19, 0.62)**	G-T	0.021	0.75	(0.38, 1.46)
				BMP7 (rs1475000 A>G; rs4811822 T>C)[1]				*BMP7* (rs1475000 A>G; rs162317 G>A)[1]			
				A-T	0.502	0.97	(0.87, 1.07)	A-G	0.576	0.90	(0.75, 1.09)

Haplotype	Frequency	OR[2]	(95% CI)	Haplotype	Frequency	OR[2]	(95% CI)	Haplotype	Frequency	OR[2]	(95% CI)
				G-C	0.366	1.02	(0.92, 1.14)	G-A	0.396	1.09	(0.91, 1.31)
				A-C	0.095	0.91	(0.76, 1.09)	A-A	0.015	0.55	(0.24, 1.25)
				G-T	**0.037**	**1.41**	**(1.06, 1.88)**	**G-G**	**0.012**	**2.71**	**(1.14, 6.47)**
				BMP7 (rs1475000 A>G; rs6025446 A>G)[1]				*BMP7* (rs1475000 A>G; rs2180780 C>G)[1]			
				A-G	0.465	0.90	(0.82, 1.00)	A-C	0.568	0.91	(0.76, 1.09)
				G-A	0.371	1.03	(0.92, 1.14)	G-G	0.399	1.09	(0.91, 1.32)
				A-A	0.132	1.09	(0.93, 1.27)	A-G	0.023	0.64	(0.33, 1.22)
				G-G	**0.032**	**1.47**	**(1.07, 2.02)**	**G-C**	**0.010**	**3.11**	**(1.16, 8.33)**
				BMP7 (rs4811822 T>C; rs2180780 C>G)[1]				*BMP7* (rs12438 A>G; rs3787380 T>C)[1]			
				T-C	0.491	0.97	(0.87, 1.07)	A-C	0.551	0.84	(0.70, 1.01)
				C-G	0.373	1.02	(0.92, 1.14)	G-T	0.392	1.05	(0.87, 1.27)
				C-C	0.088	0.90	(0.75, 1.09)	**A-T**	**0.052**	**1.78**	**(1.19, 2.67)**
				T-G	**0.048**	**1.30**	**(1.01, 1.67)**	G-C	0.005	1.16	(0.31, 4.30)
				BMP7 (rs162315 G>A; rs172983 G>A)[1]				*BMP7* (rs6127983 T>C; rs162317 G>A)[1]			
				G-G	0.656	0.93	(0.84, 1.04)	C-G	0.518	0.84	(0.70, 1.00)
				A-A	0.244	1.02	(0.91, 1.16)	T-A	0.412	1.05	(0.88, 1.27)
				A-G	0.097	1.10	(0.93, 1.31)	**T-G**	**0.070**	**1.62**	**(1.14, 2.32)**
				G-A	**0.002**	**6.17**	**(1.31, 29.05)**	*BMP7* (rs6127983 T>C; rs2180780 C>G)[1]			
				BMP7 (rs172983 G>A; rs6014967 G>A)[1]				C-C	0.506	0.85	(0.71, 1.02)
				G-G	0.679	0.95	(0.85, 1.06)	T-G	0.410	1.07	(0.89, 1.29)
				A-A	0.238	1.01	(0.89, 1.14)	**T-C**	**0.072**	**1.50**	**(1.06, 2.14)**
				G-A	0.074	1.06	(0.87, 1.29)	C-G	0.013	0.63	(0.25, 1.56)
				A-G	**0.008**	**2.14**	**(1.17, 3.91)**	*BMP7* (rs3787380 T>C; rs6014949 G>A)[1]			
								C-G	0.552	0.85	(0.71, 1.02)
								T-A	0.399	1.07	(0.89, 1.29)
								T-G	**0.045**	**1.76**	**(1.15, 2.69)**
								C-A	0.004	0.73	(0.17, 3.06)
								BMP7 (rs12481628 A>G; rs2180780 C>G)[1]			
								A-C	0.530	0.88	(0.74, 1.06)

Haplotype	Frequency	OR[2]	(95% CI)	Haplotype	Frequency	OR[2]	(95% CI)	Haplotype	Frequency	OR[2]	(95% CI)
								G-G	0.383	1.09	(0.91, 1.32)
								G-C	**0.047**	**1.57**	**(1.03, 2.40)**
								A-G	0.040	0.75	(0.45, 1.24)
								BMPR1A (rs7088641 T>C; rs2168730 A>G)[1]			
								T-A	0.582	1.01	(0.84, 1.22)
								C-G	0.398	0.94	(0.78, 1.14)
								C-A	**0.017**	**2.36**	**(1.15, 4.86)**
								T-G	0.004	0.42	(0.08, 2.22)

[1]Indicates haplotypes were generated from SNPs where R^2 values was greater than 0.50

[2]Adjusted for age, study, genetic admixture, BMI in referent year, vigorous activity in referent year, parity, age at first birth and alcohol consumption; no important haplotypes were identified for lowest Native American ancestry group.