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Gene-based analysis of the fibroblast growth factor receptor signaling pathway in relation to breast cancer in African American women: the AMBER consortium

Edward A. Ruiz-Narváez[1], **Stephen A. Haddad**[1], **Kathryn L. Lunetta**[2], **Song Yao**[3], **Jeannette T. Bensen**[4], **Lara E. Sucheston-Campbell**[3], **Chi-Chen Hong**[3], **Christopher A. Haiman**[5], **Andrew F. Olshan**[4], **Christine B. Ambrosone**[2], and **Julie R. Palmer**[1]

[1]Slone Epidemiology Center at Boston University, Boston, MA.

[2]Department of Biostatistics, Boston University School of Public Health, Boston, MA.

[3]Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY.

[4]Department of Epidemiology, Gillings School of Global Health, University of North Carolina at Chapel Hill, Chapel Hill, NC.

[5]Department of Preventive Medicine, Keck School of Medicine, University of Southern California/ Norris Comprehensive Cancer Center, Los Angeles, CA.

Abstract

Purpose—We conducted gene-based analysis in 26 genes in the FGFR signaling pathway to identify genes carrying genetic variation affecting risk of breast cancer and the specific estrogen receptor (ER) subtypes.

Methods—Tagging single nucleotide polymorphisms (SNPs) for each gene were selected and genotyped on a customized Illumina Exome Array. Imputation was carried out using 1000 Genomes haplotypes. The analysis included 3,237 SNPs in 3,663 breast cancer cases (including 1,983 ER positive, and 1,098 ER-negative and 4,687 controls from the African American Breast Cancer Epidemiology and Risk consortium, a collaborative project of four large studies of breast cancer in African American women (Carolina Breast Cancer Study, Black Women's Health Study, Women's Circle of Health Study, and Multiethnic Cohort). We used a multi-locus adaptive joint (AdaJoint) test to determine the association of each gene in the FGFR signaling pathway with overall breast cancer and ER subtypes.

Results—The *FGF1* gene was significantly associated with risk of ER negative breast cancer (P = 0.001). The *FGFR2* gene was associated with risk of overall breast cancer (P = 0.002) and ER positive breast cancer (P = 0.002).

Conclusions—The *FGF1* gene affects risk of ER negative breast cancer in African American women. We confirmed the association of the *FGFR2* gene with risk of overall and ER positive

Corresponding author: Edward A. Ruiz-Narváez, Slone Epidemiology Center at Boston University, 1010 Commonwealth Avenue, Boston, MA 02215. Phone: 617-206-6173; Fax: 617-738-5119; ; Email: eruiznar@bu.edu

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breast cancer. These results highlight the importance of the FGFR signaling pathway in the pathogenesis of breast cancer, and suggest that different genes in the same pathway may be associated with different ER breast cancer subtypes.

INTRODUCTION

Signaling by fibroblast growth factors (FGFs) and their receptors (FGFRs) regulates multiple cellular processes such as tissue repair, differentiation, survival, proliferation, and migration, among others (see reviews [1,2]). Deregulation of the FGF/FGFR signaling pathway through somatic alterations has been widely implicated in breast cancer [1-3]. Less is known about germline variation in the FGF/FGFR signaling pathway and risk of breast cancer. Only genetic variants in the *FGFR2* gene have been consistently associated with risk of breast cancer, and they appear to be more strongly associated with estrogen-receptor (ER) positive tumors [4-8]. To date, no systematic evaluation of germline variation in the FGF/FGFR signaling pathway in relation to breast cancer has been carried out. The Breast Cancer Association Consortium (BCAC) which includes predominantly European-ancestry subjects, evaluated genetic variation in four FGF gene receptors (*FGFR1*, *FGFR3*, *FGFR4*, and *FGFRL1*) and found little evidence of association with risk of breast cancer [9]. The Breast Cancer Health Disparities Study, which includes Hispanic and non-Hispanic white women, conducted gene-based analysis of seven growth factor genes including three genes in the FGF/FGFR signaling pathway (*FGFR2*, *FGF1*, and *FGF2*). *FGFR2* was significantly associated with breast cancer risk only among those with ER+ tumors, and *FGF1* showed borderline association with ER−/PR− breast cancer [10]. It is unclear whether other genes in the pathway may also carry breast cancer risk variants, and whether they may differentially affect risk of specific breast cancer subtypes. In addition, no systematic study of the FGF/FGFR pathway in African American women has been conducted to date.

Because multiple independent single nucleotide polymorphisms (SNPs) with small to modest effect may be present in the same gene (e.g. at least three independent signals have been identified in the *FGFR2* gene [11]), the standard single SNP analysis may fail to fully capture the joint effect of multiple SNPs in a given gene [12,13]. Gene-based tests provide a powerful alternative to the single SNP approach to combine the evidence of association from several genetic variants within a gene in relation to disease [14,15]. Gene-based tests have been successfully used to identify new loci in relation to height and body mass index [12], Crohn's disease [16], and glucose and lipid levels [17] among others.

We postulate that common SNPs may act jointly in genes in the FGF/FGFR signaling pathway to affect risk of breast cancer. We evaluated this hypothesis through a comprehensive assessment of common genetic variation in FGFs, FGFRs, and downstream genes in the FGF/FGFR pathway in relation to breast cancer risk. We conducted this work in the African American Breast Cancer Epidemiology and Risk (AMBER) consortium, a collaborative project from four of the largest studies of breast cancer in African American women (Carolina Breast Cancer Study (CBCS), Black Women's Health Study (BWHS), Women's Circle of Health Study (WCHS), and Multiethnic Cohort (MEC)).

MATERIALS AND METHODS

Study subjects

The CBCS [18], WCHS [19,20], BWHS [21], and MEC [22] – have been described previously. Each study was granted Institutional Review Board approval and all study subjects provided informed consent. Briefly, the CBCS is a population-based case-control study of women aged 20 to 74 years that began in North Carolina in 1993. Cases were identified through the North Carolina Central Cancer Registry's rapid case ascertainment system, and controls were enrolled through 2001 using Division of Motor Vehicles lists (age < 65 years) and Health Care Financing Administration lists (age ≥ 65). Questionnaire data and samples for DNA analysis were obtained by interviewers in home visits. The WCHS is a case-control study that began in 2002 with ascertainment of cases aged 20 to 75 years from New York City hospitals, later expanding to several counties in New Jersey, with case identification using the New Jersey State Cancer Registry's rapid case ascertainment system. Controls have been recruited through random digit dialing as well as community-based efforts. In-person interviewers collect risk factor data and obtain samples for DNA analysis.

The BWHS is a prospective cohort study that began in 1995 when 59,000 African American women 21-69 years of age from across the United States completed a postal health questionnaire. Breast cancer cases are identified by self-report in biennial follow-up questionnaires, and cases are confirmed by medical records or from state cancer registry data and the National Death Index. Approximately 27,000 BWHS participants have given saliva samples for DNA analysis. The MEC is a prospective cohort study in Hawaii and Southern California that began in 1993 with the enrollment of men and women aged 45-75 years. Data is collected through questionnaires mailed at 5-year intervals, and breast cancer cases are confirmed by linkage with the California and Hawaii state cancer registries and the National Death Index. Controls for BWHS and MEC were selected from among all non-cases in those studies.

Eligible cases for analysis were women with a first diagnosis of incident invasive breast cancer or ductal carcinoma in situ, with available DNA samples for genotyping. Determination of ER status for cases was based on pathology data from hospital records or cancer registry records.

Replication testing of the most significant SNPs was conducted in a subset of samples of the African American Breast Cancer (AABC) consortium, which included participants from 9 epidemiological studies [23,24], after excluding MEC, WCHS, and CBCS subjects who were already included in AMBER. Genotype data from 1426 breast cancer cases (709 ER+, 415 ER−, and 302 unknown ER status) and 927 controls were available from this reduced AABC subset.

Gene and SNP selection

Table 1 shows the list of the 26 genes included in the present analysis. In addition to the four FGFR paralog genes (*FGFR1*, *FGFR2*, *FGR3*, and *FGFR4*), and eight FGF genes (*FGF1*, *FGF2*, *FGF3*, *FGF4*, *FGF6*, *FGF7*, *FGF9*, *FGF10*) whose products bind to more than one FGFR [25], additional selected genes code for proteins that participate in the initial steps of

FGF/FGFR signaling or are downstream effectors of the pathway. Tag SNPs were then selected for all 26 genes in order to capture (at r^2 ≥0.8) as many SNPs as possible with minor allele frequency ≥10%, based on the haplotype structure of the Yoruban population (YRI) in 1000 Genomes (http://www.1000genomes.org/).

Genotyping and quality control

Genotyping using the Illumina Human Exome Beadchip v1.1 with custom content was performed by the Center for Inherited Disease Research (CIDR) (http://genome.sph.umich.edu/wiki/Exome_Chip_Design). The variants selected were included as part of the more than 159,000 custom content SNPs added to the Exome Beadchip to support the scientific goals of the AMBER consortium.

Of the 405,555 SNPs attempted for genotyping, 381,212 were released by CIDR and 299,873 of these remained after removing SNPs that were monomorphic, were positional duplicates, were on the Y chromosome, had Hardy-Weinberg Equilibrium (HWE) $P<1\times10^{-4}$, had call rate < 0.98, had > 1 Mendelian errors in trios from HapMap (http://hapmap.ncbi.nlm.nih.gov), or had > 2 discordant calls in duplicate samples. Of these remaining variants, 1691 SNPs were in the genes of interest for the present analyses. Genotypes were attempted for 6936 study subjects from the BWHS, CBCS, and WCHS, and were completed with call rate > 98% for 6828 participants (3130 cases, 3698 controls). The University of Washington (UW) performed imputation using the IMPUTE2 software [26] and the 1000 Genomes Phase I reference panel (5/21/2011 1000 Genomes data, December 2013 haplotype release on the IMPUTE2 website: https://mathgen.stats.ox.ac.uk/impute/impute_v2.html#reference.

Genetic data from 533 cases and 989 controls in the MEC study had been genotyped on the Illumina Human 1M-Duo array and SNPs were imputed from 1000 Genomes. MEC's imputed genotypes were combined with the imputed data for the BWHS, CBCS, and WCHS into a final data set after additional quality control. Variants with mismatching alleles or allele frequencies that were different by more than 0.15 in MEC vs. the other three studies were omitted. Also, SNPs with minor allele frequencies < 0.5% or imputation score INFO < 0.5 in either study were removed. After these exclusions, there were 9264 genotyped and imputed SNPs in the 26 genes of interest.

Genotype principal components were computed using the smartpca program in the EIGENSOFT package [27]. Relationship checking using PLINK version 1.07 [28] (http://pngu.mgh.harvard.edu/~purcell/plink/) identified several relatives among and within the individual studies. Related individuals and those with more extreme principal components were flagged so that relationships could be taken into account and sensitivity analyses could be performed. The principal components of genotype were tested for association with case status after accounting for the study covariates: study, age (10 year groupings, matching variable), geographic region (matching variable), and DNA source (Oragene-saliva, blood, mouthwash-saliva). No principal components were strongly associated with case status after controlling for the study covariates. For case status and subtype association analyses, we included principal components that were associated in the full covariate model with P < 0.1.

Statistical Analysis

We conducted gene-based tests for the 26 selected genes in the FGFR signaling pathway. We use a multi-locus adaptive joint test [15] as implemented in the R package AdaJoint [29]. The test identifies the best subset of SNPs that jointly show the strongest evidence for association with disease in a given gene through a variable selection procedure that takes into account the LD structure. The significance level of the gene-based test is evaluated through a direct simulation approach that generates the null distribution of the statistic. Because the score test implemented in AdaJoint is not optimal for rare variants, we excluded SNPs with minor allele frequency (MAF) less than 2%. For highly correlated SNPs (r^2>0.9), we excluded the SNP with the smaller MAF. These exclusions resulted in a final analytic list of 3237 SNPs in 26 genes. Our primary analysis searched up to the best pair of SNPs within each gene. In secondary analysis we searched up to the best five SNPs within each gene. Statistical significance at the gene-based analysis was declared at the 0.002 level (=0.05/26 genes).

Odds ratios (ORs) and 95% confidence intervals (CIs) for the most significant SNPs on the identified genes were estimated using the glm function in R version 3.1.1 (http://www.r-project.org/). Models were adjusted for the covariates noted above and for genotype principal components 5, 6, and 8.

RESULTS

Table 2 shows the distribution of subtypes and age at diagnosis of cases by study site. A total of 3663 breast cancer cases (1983 ER+ cases, 1098 ER− cases, and 582 unknown ER status) and 4687 controls were included in the present analysis.

Table 3 shows the results of gene-based association analyses based on the top pair of SNPs in each gene. Results were similar when we used a gene-based test that examined up to the top five SNPs (data not shown). The *FGF1* gene was found to be associated with risk of ER− breast cancer (P = 0.001). As expected, *FGFR2* was associated with risk of overall breast cancer (P = 0.002) and ER+ breast cancer (P = 0.002). There was suggestive evidence of an association of the *MAPK3* gene with ER− breast cancer (P = 0.008).

The most significant risk model for *FGF1* was a one-SNP model (rs143172501), which was associated with risk of ER− breast cancer at pathway-wide significance (Table 4). The minor T-allele (3.6% frequency in AMBER controls) was associated with 88% higher risk of ER− breast cancer ($P = 1.4\times10^{-6}$) and 31% higher risk of overall breast cancer (P = 0.005). No association was observed for ER+ breast cancer (P = 0.77). In the AABC replication subset, there was no association of rs143172501 with ER− breast cancer (P = 0.61). The combined odds ratio from the two studies was 1.65 (95% CI 1.30-2.08) ($P = 2.7\times10^{-5}$) for ER− breast cancer (Supplementary Table 1).

A 2-SNP model (rs10736303 and rs3135774, r^2 = 0.001 between both SNPs) was the most significant model for *FGFR2* for both overall breast cancer and ER+ breast cancer (Table 4). Rs10736303 is a perfect proxy (r^2 = 0.99) of rs2981578, which is the previously reported *FGFR2* risk variant in African Americans [24]. The rs10736303 major G-allele (84.2%

frequency) was associated with 25% higher risk of overall breast cancer ($P = 3.3\times10^{-6}$), 30% higher risk of ER+ breast cancer ($P = 8.4\times10^{-6}$), and 21% higher risk was observed for ER− breast cancer (P = 0.01). The rs3135774 minor C-allele (2.2% frequency) was associated with 47% higher risk of overall breast cancer ($P = 4.9\times10^{-4}$), and 62% higher risk of ER+ breast cancer (2.1×10^{-4}). Rs3135774 was not associated with either overall breast cancer (P = 0.81) or ER+ breast cancer (P = 0.69) in the AABC subset. Meta-analysis of rs3135774 in AMBER and AABC resulted in OR (95% CI) = 1.37 (1.12-1.67) ($P = 2.0\times10^{-3}$) for overall breast cancer, and 1.48 (1.17-1.87) ($P = 1.1\times10^{-3}$) for ER+ breast cancer (Supplementary Table 1).

The suggestive association of *MAPK3* with ER− breast cancer was explained by a one-SNP model (rs78564187) (Table 4). The minor A-allele (18.0% frequency) was exclusively associated with ER− breast cancer, with a 26% higher risk per allele ($P = 3.7\times10^{-4}$). No association was observed for either overall breast cancer or ER+ breast cancer. The odds ratio for ER− breast cancer in the AABC subset was in the same direction as in AMBER data but not statistically significant (P = 0.46). The combined OR (95% CI) from a meta-analysis of the two consortia was 1.22 (1.09-1.36) ($P = 4.9\times10^{-4}$) (Supplementary Table 1).

DISCUSSION

In this large gene-based analysis of the FGFR signaling pathway, we found that the *FGF1* gene was associated with risk of ER− breast cancer. *FGF1* is a member of the FGF superfamily in humans and codes for the fibroblast growth factor 1 (FGF1). FGF1 is able to bind to the four FGF receptors, and mediates a wide variety of biologic processes such as cell migration, proliferation, differentiation, and survival among other functions (see review in [30]). Amplification of the *FGF1* gene is observed in ovarian cancer and is a predictor of poor survival [31].

The gene association was explained by a single SNP (rs143172501) located 9 kb upstream of *FGF1*. The risk allele (T) of rs143172501 is present only in African-ancestry populations from 1000 genomes (4% in the combined African populations), and in some Hispanic admixed populations (Colombian in Medellin, 1%; and Puerto Rican in Puerto Rico, 1%), which may be due to recent admixture with African-ancestry subjects. In AMBER controls, the frequency of the risk T-allele was 3.6%. This finding was not replicated in a smaller number of ER− cases and controls from a subset of the AABC consortium. Although we had excellent power (>80%) to replicate an OR equal to 1.88 (i.e. the point estimate found in AMBER), we had only 45% power if the true OR was 1.45 (i.e. the lower bound of the 95% CI in the present study). Heterogeneity of effects due to interaction with unmeasured genetic and non-genetic factors may also explain in part the lack of replication. Results from recent reports support our finding that genetic variation in *FGF1* are associated with risk of ER− breast cancer. The Breast Cancer Health Disparities Study found a borderline association (P = 0.07) of *FGF1* with ER−/PR− breast cancer in gene-based analysis, with three common SNPs (rs34001, rs152524, and rs34021) showing significant associations with ER−/PR− tumors in Hispanic and non-Hispanic white women [10]. In addition, the Guangzhou Breast Cancer Study found a significant association of rs250108, located in a transcription factor binding site of the first intron of *FGF1*, with ER− breast cancer in Chinese women [32].

None of these four *FGF1* SNPs was associated with risk of ER− tumor in the present study (data not shown). Nevertheless, our results as well as those from the Breast Cancer Health Disparities Study and the Guangzhou Breast Cancer Study do suggest the presence of genetic variation in *FGF1* associated with risk of ER− breast cancer although the identity of the particular polymorphisms remains elusive. If there are indeed true risk *FGF1* variants they may differ by ethnic groups as suggested by the different SNPs found by us, and the Breast Cancer Health Disparities Study and the Guangzhou Breast Cancer Study.

FGFR2 rs10736303 is perfectly correlated ($r^2 = 0.99$) with rs2981578, which was previously identified as the SNP with the strongest association with overall and ER+ breast cancer in *FGFR2* in African Americans [24]. A recent fine-mapping of *FGFR2* identified three independent signals in Europeans and East Asians: the first signal represented by rs35054928, the second signal by rs45631563, and the third one by rs2981578 [11]. However, rs35054928 (signal 1) and rs2981578 (signal 3) show high correlation in Europeans ($r^2 = 0.79$) and they most likely represent a single signal. We found in AMBER that rs10736303 (proxy of rs2981578, signal 3) is in moderate correlation with rs35054928 (signal 1) ($r^2 = 0.27$). After adjustment for rs10736303, rs35054928 was no longer associated with either overall or ER+ breast cancer (data not shown), suggesting that signal 1 and signal 3 could be the same signal in African Americans, and is best tagged by rs10736303 (or rs2981578). Rs45631563 (signal 2) is a rare variant in African Americans (MAF = 0.9% in AMBER controls) suggesting that this signal may be rare in African-ancestry groups. It is unclear whether there is a second *FGFR2* independent signal in African Americans. Although we found suggestive evidence of such signal in AMBER tagged by rs3135774 ($r^2 = 0.001$ with rs10736303), this result must be interpreted with caution given that the association did not replicate in AABC. Because of the low frequency of the rs3135774 risk allele insufficient power cannot be ruled out as an explanation of the lack of replication.

MAPK3 codes a protein that is member of the mitogen-activated protein (MAP) kinase family, which participates in the MAPK/extracellular regulated-signal kinase (ERK) pathways. MAPK/ERK pathways integrate a variety of external and internal signals to regulate diverse cellular processes such as proliferation, survival, and differentiation among others (see review [33]). Although expression and activation of *MAPK3* are de-regulated in a variety of human cancers including breast [34–37], no GWAS has reported germline variants in *MAPK3* associated with any type of cancer. It is possible that as one of the final effectors of several signaling pathways, MAPK3 activity may be de-regulated by events/mutations upstream in diverse signaling pathways including the FGF/FGFR pathway. Our results suggest that genetic variation in *MAPK3* may be associated with risk of ER− breast cancer.

In summary, our findings confirm the role of *FGFR2* in breast cancer etiology and ER+ tumor in particular, and suggest that variants in *FGF1* and *MAPK3* may affect risk of ER− breast cancer. Although the *FGF1* SNP association with risk of ER− breast cancer that we found in AMBER was not replicated in AABC, recent studies have also reported associations of *FGF1* variants with ER− tumors in Hispanic, non-Hispanic white, and Chinese women [32,10]. Taken together, ours and previous reports suggest the presence of

FGF1 gene variants associated with risk of ER− breast cancer although the identity of these variants and whether they are the same across different populations are still uncertain. The present findings stress the need of further evaluation of the FGFR pathway in relation to breast cancer and ER subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

List of selected genes in the FGFR signaling pathway

Gene	Chromosome	Protein function
SHC1	1q21	Adaptor protein that binds to the FGFRs
IL17RD	3p14	Transmembrane protein. Antagonist of FGF signaling
FGFR3	4p16	Fibroblast growth receptor 3. Tyrosine kinase
KLB	4p14	Klotho beta protein. Helps in the FGF-FGFR binding
FGF2	4q26	Fibroblast growth factor 2
SPRY1	4q28	Antagonist of FGFs signaling
FGF10	5p13	Fibroblast growth factor 10
SPRY4	5q31	Antagonist of FGFs signaling
FGF1	5q31	Fibroblast growth factor 1
FGFR4	5q35	Fibroblast growth factor receptor 4. Tyrosine kinase
FRS3	6p21	FGFR substrate 3. Links FGFRs to downstream activators
FGFR1	8p11	Fibroblast growth factor receptor 1. Tyrosine kinase
FGFR2	10q26	Fibroblast growth factor receptor 2. Tyrosine kinase
FGF4	11q13	Fibroblast growth factor 4
FGF3	11q13	Fibroblast growth factor 3
CBL	11q23	E3 ubiquitin protein ligase. Negative regulator of signaling pathways
FGF6	12p13	Fibroblast growth factor 6
FRS2	12q15	FGFR substrate 2. Links FGFRs to downstream activators
FGF9	13q11	Fibroblast growth factor 9
KL	13q12	Klotho protein. Helps in the FGF-FGFR binding
SPRY2	13q31	Antagonist of FGFs signaling
FGF7	15q21	Fibroblast growth factor 7
MAPK3	16p11	MAP kinase 3. Downstream effector
GRB2	17q24	Downstream effector. Recruits negative regulators
PLCG1	20q12	Phospholipase C gamma 1. Substrate of activated FGFRs
MAPK1	22q11	MAP kinase 1. Downstream effector

Table 2

Characteristics of participants by study in the AMBER consortium

	BWHS	CBCS	WCHS	MEC	AMBER
Controls	2249	615	834	989	4687
Cases	901	1408	821	533	3663
ER+ cases	498	741	435	309	1983
ER− cases	233	565	165	135	1098
Unknown ER	170	102	221	89	582
Age at diagnosis					
<40	47	204	85	0	336
40-49	262	459	215	9	945
50-59	302	381	292	112	1087
60-69	204	267	173	175	819
≥70	86	97	56	237	476

ER estrogen receptor; *BWHS* Black Women's Health Study, *CBCS* Carolina Breast Cancer Study, *WCHS* Women's Circle of Health Study, *MEC* Multi-Ethnic Cohort, *AMBER* African American Breast Cancer Epidemiology and Risk

Table 3

P values for gene-based association tests[a]

Gene	Number of SNPs	Number of SNPs pruned in	P value[b]		
			All cases	ER+	ER−
SHC1	31	15	0.10	0.11	0.38
IL17RD	581	183	0.81	0.97	0.11
FGFR3	186	117	0.98	0.93	0.61
KLB	343	142	0.50	0.04	0.71
FGF2	620	206	0.83	0.20	0.89
SPRY1	135	66	0.70	0.67	0.86
FGF10	469	118	0.15	0.12	0.07
SPRY4	185	92	0.87	0.83	0.77
FGF1	861	399	0.64	0.90	0.001
FGFR4	181	80	0.48	0.14	0.46
FRS3	126	52	0.33	0.88	0.08
FGFR1	264	95	0.17	0.64	0.37
FGFR2	821	395	0.002	0.002	0.08
FGF4	195	91	0.21	0.39	0.93
FGF3	229	85	0.98	0.96	0.86
CBL	435	99	0.68	0.89	0.58
FGF6	227	116	0.99	0.93	0.68
FRS2	668	155	0.94	0.62	0.99
FGF9	257	129	0.15	0.11	0.18
KL	525	184	0.74	0.95	0.16
SPRY2	128	60	0.32	0.15	0.89
FGF7	356	77	0.38	0.59	0.22
MAPK3	24	11	0.46	0.84	0.008
GRB2	607	110	0.47	0.05	0.13
PLCG1	118	36	0.57	0.36	0.62
MAPK1	692	124	0.91	0.42	0.62

[a]Adjusted for study site, age (10 year groupings), geographic region, DNA source (saliva, blood, mouthwash), and genotype principal components 5, 6, and 8

[b]An alpha level of 0.002 (=0.05/26 genes) was used to determine statistical significance

Table 4

Single SNPs associations in genes with P ≤ 0.01

Gene, SNP	Type[a]	INFO[b]	Alleles[c]	RAF[d] (%)	OR (95% CI)[e], P value		
					All cases (3663)	ER+ (1983)	ER− (1098)
FGF1[f]							
rs143172501	I	0.87	T/C	3.6	1.31 (1.09-1.58), 0.005	1.04 (0.82-1.31), 0.77	1.88 (1.45-2.42), 1.4×10^{-6}
FGFR2[g]							
rs10736303	G		G/A	84.2	1.25 (1.14-1.38), 3.3×10^{-6}	1.30 (1.16-1.47), 8.4×10^{-6}	1.21 (1.05-1.40), 0.01
rs3135774	I	0.99	G/C	2.2	1.47 (1.18-1.83), 4.9×10^{-4}	1.62 (1.25-2.08), 2.1×10^{-4}	1.34 (0.96-1.88), 0.09
MAPK3[h]							
rs78564187	G		A/G	18.0	1.07 (0.98-1.16), 0.13	1.03 (0.93-1.14), 0.58	1.26 (1.17-1.35), 3.7×10^{-4}

[a] SNP type; imputed (I) or genotyped (G)

[b] INFO score for imputed SNPs

[c] Risk allele/reference allele

[d] Risk allele frequency in AMBER

[e] Adjusted for study site, age (10 year groupings), geographic region, DNA source (saliva, blood, mouthwash), and genotype principal components 5, 6, 8

[f] SNP in the best 1-SNP model for ER− breast cancer

[g] SNPs in the best 2-SNP model for all breast cancer and ER+ breast cancer

[h] SNP in the best 1-SNP model for ER− breast cancer