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FGF receptor genes and breast cancer susceptibility: results from the Breast Cancer Association Consortium

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Background: Breast cancer is one of the most common malignancies in women. Genome-wide association studies have identified *FGFR2* as a breast cancer susceptibility gene. Common variation in other fibroblast growth factor (FGF) receptors might also modify risk. We tested this hypothesis by studying genotyped single-nucleotide polymorphisms (SNPs) and imputed SNPs in *FGFR1, FGFR3, FGFR4* and *FGFRL1* in the Breast Cancer Association Consortium.

Methods: Data were combined from 49 studies, including 53 835 cases and 50 156 controls, of which 89 050 (46 450 cases and 42 600 controls) were of European ancestry, 12 893 (6269 cases and 6624 controls) of Asian and 2048 (1116 cases and 932 controls) of African ancestry. Associations with risk of breast cancer, overall and by disease sub-type, were assessed using unconditional logistic regression.

Results: Little evidence of association with breast cancer risk was observed for SNPs in the FGF receptor genes. The strongest evidence in European women was for rs743682 in *FGFR3*; the estimated per-allele odds ratio was 1.05 (95% confidence interval = 1.02–1.09, $P = 0.0020$), which is substantially lower than that observed for SNPs in *FGFR2*.

Conclusion: Our results suggest that common variants in the other FGF receptors are not associated with risk of breast cancer to the degree observed for *FGFR2*.

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Breast cancer is a complex disease, with multiple genetic and environmental factors involved in its etiology. Rare mutations in the DNA repair genes *BRCA1* and *BRCA2* confer a high lifetime risk of breast cancer (Antoniou *et al*, 2003) and are routinely screened for in women with a strong family history of the disease. Studies focused on other DNA repair genes have led to the discovery that rare coding variants in *CHEK2, ATM*, *BRIP1* and *PALB2* (Swift *et al*, 1987; Meijers-Heijboer *et al*, 2002; Seal *et al*, 2006; Rahman *et al*, 2007) are associated with moderately increased breast cancer risk. However, few, if any, candidate-gene- or pathway-based association studies have identified convincing associations with breast cancer risk for common genetic variants (The Breast Cancer Association Consortium, 2006). In contrast, empirical genome-wide association studies (GWAS) have proven to be a successful approach to identify common variants associated with small increases in risk, with more than 70 identified in this way to date (Easton *et al*, 2007; Hunter *et al*, 2007; Stacey *et al*, 2007, 2008; Ahmed *et al*, 2009; Thomas *et al*, 2009; Zheng *et al*, 2009; Antoniou *et al*, 2010; Turnbull *et al*, 2010; Cai *et al*, 2011; Fletcher *et al*, 2011; Haiman *et al*, 2011; Ghoussaini *et al*, 2012; Siddiq *et al*, 2012; Bojesen *et al*, 2013; Garcia-Closas *et al*, 2013; Michailidou *et al*, 2013). For the great majority of these associations, the causal variant(s), and even the causal gene, are unknown; thus, the identification of novel candidate genetic susceptibility pathways through this approach is not straightforward.

An intronic variant in the *FGFR2* gene was one of the first single-nucleotide polymorphisms (SNPs) identified by GWAS as tagging a breast cancer susceptibility locus (Easton *et al*, 2007; Hunter *et al*, 2007). It is now well-established that the minor allele of this SNP is associated with increased risk of breast cancer, particularly estrogen receptor (ER)-positive disease (Garcia-Closas *et al*, 2008). Fine-mapping of the region has suggested that at least one causal variant is located in intron 2 of *FGFR2* (Easton *et al*, 2007; Udler *et al*, 2009), and functional studies have proposed that rs2981578 affects *FGFR2* expression (Meyer *et al*, 2008; Udler *et al*, 2009; Huijts *et al*, 2011). These findings strongly suggest that *FGFR2* is a breast cancer susceptibility gene.

FGFR2 is a fibroblast growth factor (FGF) receptor gene; the amino-acid sequence of the protein it encodes is highly conserved across all FGF receptors. The other FGF receptor genes and other genes acting downstream of them in the FGF pathway may also be implicated in the development of breast cancer, although associations with disease risk have not been assessed comprehensively by a study with adequate sample size to detect odds ratios (ORs) of the magnitude observed for SNPs in *FGFR2*.

We hypothesised that common variants in other genes in the FGF pathway, and in the other FGF receptor genes in particular, might also confer increased breast cancer risk. The primary aim of our investigation was to comprehensively assess associations between breast cancer risk and common variation in the FGF receptor genes *FGFR1, FGFR3, FGFR4* and *FGFRL1* by genotyping selected tag-SNPs in the Breast Cancer Association Consortium (BCAC). A secondary objective was to assess common variants in other genes in the FGF pathway based on a two-stage design.

MATERIALS AND METHODS

Participants. Study participants were women from 49 studies participating in BCAC: 38 from populations of predominantly European ancestry, 9 of Asian women and 2 of African–American women (Table 1 and Supplementary Table 1). The majority were population-based or hospital-based case–control studies, but some studies selected subjects based on age or oversampled for cases with a family history or bilateral disease. Cases and controls from the CNIO-BCS were also studied in a previous assessment of selected genes in the FGF pathway. All study participants gave informed consent and each study was approved by the corresponding local ethics committee.

Gene and SNP selection. Ingenuity Pathways Analysis and selected publications (Eswarakumar *et al*, 2005; Presta *et al*, 2005; Chen & Forough, 2006; Schwertfeger, 2009) were used to identify genes reported to be involved downstream of the *FGF* genes in the FGF pathway, particularly those related to angiogenesis. A total of 39 genes, including the FGF receptors *FGFR1* (located at 8p11.22), *FGFR2* (10q26.13), *FGFR3* (4p16.3), *FGFR4* (5q35.2) and *FGFRL1* (4p16.3), was selected for tagging. Single-nucleotide polymorphisms with minor allele frequency (MAF) $>5\%$ in the coding and non-coding regions, and within 5 kb upstream and 5 kb downstream of each gene, were identified using HapMap CEU genotype data and dbSNP 128 as reference. The minimum number of tag-SNPs were then selected among all identified SNP using Haploview (Barrett *et al*, 2005) based on the following criteria: $r^2>0.8$ and Illumina assay score >0.60. A total of 384 SNPs tagging 39 genes was genotyped in the CNIO-BCS, 324 of which were successfully genotyped (Supplementary Table 2). The 31 SNPs tagging genes *FGFR1, FGFR3, FGFR4* and *FGFRL1* were all genotyped in BCAC, along with a further 26 of the 324 tag-SNPs. The latter group comprised SNPs selected based on evidence of association with breast cancer under a log-additive model in the Stage 1 CNIO-BCS. Single-nucleotide polymorphisms in *FGFR2* were not considered, as all were included as part of a separate fine-mapping study (Meyer *et al*, submitted). Results from Stage 1 are summarised in Supplementary Table 2.

Genotyping. Genotyping of the 57 SNPs in the BCAC samples was conducted using a custom Illumina Infinium array (iCOGS) in four centers, as part of a multi-consortia collaboration (the Collaborative Oncological Gene–Environment Study, COGS) as described previously (Michailidou *et al*, 2013). Genotypes were called using Illumina's proprietary GenCall algorithm.

For the genotyping of the 384 SNPs in the Stage 1 CNIO-BCS, genomic DNA was isolated from peripheral blood lymphocytes using automatic DNA extraction (MagNA Pure, Roche Diagnostics, Indianapolis, IN, USA) according to the manufacturer's recommended protocols. This DNA was quantified using Picogreen (Invitrogen, Life Technologies, Grand Island, NY, USA) and for each sample a final quantity of 250 ng was extracted and used for GoldenGate genotyping with VeraCode Technology (Illumina Inc., San Diego, CA, USA). Samples were arranged on 25 96-well plates containing one negative control and at least one study sample in duplicate. Three Centre d'Etude du Polymorphisme Humain (CEPH) trios were used as internal intra- and inter-plate duplicates and to check for Mendelian segregation errors. DNA was extracted, quantified, plated and genotyped at the Spanish National Genotyping Centre (CeGen), Madrid, Spain. All genotypes were determined for each SNP and each plate using manual clustering. Single-nucleotide polymorphisms with call rate $<90\%$ were excluded, as were samples with no-calls for more than 20% of included SNPs.

Statistical methods. For each SNP, we estimated ORs and 95% confidence intervals (CIs) using unconditional logistic regression. For the analysis of BCAC data, we considered per-allele and co-dominant models using common-allele homozygotes as reference and including study and ethnicity-specific principal components as covariates, as previously described (Michailidou *et al*, 2013). Departure from the Hardy–Weinberg equilibrium (HWE) was tested for in controls from individual studies using the *genhwi* module in STATA 11.2 (College Station, TX, USA). A study-stratified χ^2 test (1df) was applied across studies (Haldane, 1954; Robertson & Hill, 1984). Between-study heterogeneity in ORs was

assessed for each of the three broad racial groups using the *metan* command in STATA to meta-analyse study-specific per-allele log-OR estimates and generate I^2 statistics; values greater than 50% were considered notable (Higgins & Thompson, 2002). Odds ratios specific to disease subtypes defined by ER, PR and HER2 status (positive and negative) were estimated separately for each ethnic subgroup using polytomous logistic regression with control status as the reference outcome. Differences in ORs by disease subtypes were assessed using a likelihood ratio test (LRT). All statistical tests were two-sided.

The effective number of independent SNPs (V_{effLi}) was estimated using the method described by Li & Ji (2005). This method was applied via the web-interface matSpDlite (http://gump.qimr.edu.au/general/daleN/matSpDlite/), based on the observed correlations between SNPs (Nyholt, 2004). V_{effLi} was then used to calculate a Bonferroni-corrected significance threshold (α^*). Power calculations were carried out using Quanto v1.2.4 (http://hydra.usc.edu/gxe/).

Single-nucleotide polymorphism imputation. The genotypes of untyped SNPs were imputed based on data from the March 2012 release of the 1000 genomes project using IMPUTE v2.2. These were converted to allele doses using the *impute2mach* function in the *GenABEL* library in R (Aulchenko *et al*, 2007) and analysed under a per-allele model. Imputed SNPs with an estimated MAF $<5\%$ were excluded, as were SNPs with an imputation $r^2<80\%$.

RESULTS

All SNPs in the present analysis had overall call rates $>95\%$. Very strong evidence of departure from HWE was observed for rs34869253 for one study (pKarma, $P=3.3\times10^{-21}$), which was excluded from the subsequent analyses of that SNP. After quality control, there were data available for 53 835 cases and 50 156 controls from BCAC, including 89 050 European women (46 450 cases and 42 600 controls), 12 893 Asian (6269 cases and 6624 controls) and 2048 African–American women (1116 cases and 932 controls) (Table 1).

Results from the analysis of the 31 tag-SNPs in *FGFR* genes for white Europeans are summarised in Table 2. No strong evidence of association was observed, although one SNP (rs743682) in *FGFR3* (MAF = 9%) was marginally significant after correction for multiple testing based on a V_{effLi} of 23 (per-allele OR = 1.05, 95%CI = 1.02–1.09, $P=0.0020$, $\alpha^*=0.0022$). All SNPs with an associated *P*-value <0.05 were intronic, with the exception of rs1966265, which is a missense variant in *FGFR4*. However, PolyPhen (http://genetics.bwh.harvard.edu/pph2/) predicts this amino acid change to be benign, with a score of 0.000. On the basis of ENCODE data, no SNP with an associated *P*-value <0.05 was located in a region involved or predicted to be involved in epigenetic regulation, nor at, or within 2 kb of, a CpG island. For European women, we did not observe any evidence of between-study heterogeneity for any SNPs ($I^2\leqslant19\%$; $P\geqslant0.15$) and little evidence of differential associations by disease subtypes defined by ER ($P\geqslant0.036$), PR ($P\geqslant0.084$) or HER2 status ($P\geqslant0.019$).

We similarly observed little evidence of association with overall breast cancer risk in Asian and African–American women (Supplementary Tables 3 and 4, respectively). Nevertheless, a consistent result was observed for Europeans and Asians for rs1966265 in *FGFR4*. The estimated OR per risk (G) allele was 1.03 (95%CI = 1.01–1.05; $P=0.0060$) for European women and 1.08 (95%CI = 1.03–1.14; $P=0.0036$) for Asian women. There was no evidence of heterogeneity by race for any of the 31 SNPs in FGF receptors ($I^2=18\%$; $P=0.14$).

The SNPs genotyped were estimated to capture a variable proportion of the common variation in the four genes considered, as described in the 1000 genomes project; at $r^2\geqslant0.80$, this coverage was 75% for *FGFR1*, 77% for *FGFR3*, 66% for *FGFR4* and 17% for *FGFRL1*. This coverage was dramatically improved with the inclusion of imputed common SNPs (with imputation $r^2>0.80$) to 95%, 93%, 97% and 84% for *FGFR1, FGFR3, FGFR4* and *FGFRL1,* respectively. No stronger evidence of association was observed for any imputed SNPs (Supplementary Tables 5–8).

Finally, we observed little evidence of association for any of the 26 SNPs in other genes in the FGF pathway, selected based on results from Stage 1 (Supplementary Table 9). The results were consistent across the three ethnic groups considered and for disease subtypes defined by ER, PR and HER2 expression.

It is noteworthy that strong association signals were observed in the Stage 1 Spanish study for selected tag-SNPs rs10736303 (MAF = 0.49; per-allele OR = 1.37, 95% CI = 1.21–1.55, $P=2.8\times10^{-7}$), and rs2981582 (MAF = 0.40; per-allele OR = 1.35, 95% CI = 1.19–1.53, $P=8.3\times10^{-7}$), both in *FGFR2*.

DISCUSSION

In this multicentre case–control study, we comprehensively assessed common variation in the FGF receptor genes *FGFR1, FGFR3, FGFR4* and *FGFRL1* in 53 835 cases and 50 156 controls and found little evidence of association with risk of breast cancer. This is the largest study we know of assessing a family of genes via a candidate approach based on the findings from GWAS.

A non-trivial issue in analyses of this kind is the establishment of a statistical significance threshold that adequately controls the proportion of false-positive findings. As permutation-testing was not feasible due to the sample size and number of dummy variables required to adjust for study, we dealt with the issue of non-independence of multiple tests by estimating that the 31 tag-SNPs represented an effective number of 23 independent variables, and applying a Bonferroni correction accordingly. The association of one SNP (rs743682) in *FGFR3* for European women was found to be statistically significant on this basis. However, the *P*-value threshold applied is somewhat questionable in the context of the total of more than 70 000 SNPs nominated for genotyping by BCAC and the total 210 000 genotyped on the iCOGS array. Thus, the current result is far from genome-wide statistical significance and certainly requires independent replication. In any case, the per-allele ORs for *FGFR3*_rs743682 (1.05, 95% CI = 1.02–1.09) and *FGFR4*_rs1966265 (1.03, 95% CI = 1.01–1.05) appear to be substantially lower than that for rs2981582 in *FGFR2* (1.26, 95% CI = 1.23–1.30) (Easton *et al*, 2007).

We estimated that for common SNPs (MAF >0.05) associated with overall breast cancer risk in European women, we had greater than 99% power to detect at genome-wide statistical significance ($P<5\times10^{-8}$) a per-allele OR as low as 1.23 (the lower 95% confidence limit for the OR for *FGFR2*_rs2981582). For a per-allele OR as low as 1.05 and for SNPs with MAF of 0.10, 0.20 and 0.30, the estimated power was 1%, 10% and 24%, respectively. That is, our study provides strong evidence that common variation in *FGFR1, FGFR3, FGFR4* and *FGFRL1* are not associated with breast cancer risk to the degree observed for SNPs in *FGFR2*, although associations of smaller magnitude may exist.

The hypothesis underlying our study was based on the identification of a functional SNP in intron 2 of *FGFR2* associated with breast cancer susceptibility (Easton *et al*, 2007; Meyer *et al*, 2008; Udler *et al*, 2009; Huijts *et al*, 2011). A recent study has subsequently identified three independent risk signals within *FGFR2*, and uncovered likely causal variants and functional mechanisms behind them (Meyer *et al*, 2013). Although an association between these SNPs and expression of FGFR2 has not been established, these results provide strong

Table 1. Number of cases and controls included, by study

Study	Country	Controls	Cases	ER+	ER−
White European women					
Australian Breast Cancer Family Study[a] (ABCFS)	Australia	551	790	456	261
Amsterdam Breast Cancer Study (ABCS)	Netherlands	1429	1325	420	153
Bavarian Breast Cancer Cases and Controls (BBCC)	Germany	458	564	460	83
British Breast Cancer Study (BBCS)	UK	1397	1554	507	114
Breast Cancer In Galway Genetic Study (BIGGS)	Ireland	719	836	495	154
Breast Cancer Study of the University Clinic Heidelberg (BSUCH)	Germany	954	852	499	154
CECILE Breast Cancer Study (CECILE)	France	999	1019	797	144
Copenhagen General Population Study (CGPS)	Denmark	4086	2901	1919	357
Spanish National Cancer Centre Breast Cancer Study (CNIO-BCS)	Spain	876	902	242	88
California Teachers Study (CTS)	USA	71	68	0	17
ESTHER Breast Cancer Study (ESTHER)	Germany	502	478	304	98
Gene–Environment Interaction and Breast Cancer in Germany (GENICA)	Germany	427	465	328	119
Helsinki Breast Cancer Study (HEBCS)	Finland	1234	1664	1295	237
Hannover-Minsk Breast Cancer Study (HMBCS)	Belarus	130	690	37	0
Karolinska Breast Cancer Study (KARBAC)	Sweden	662	722	338	63
Kuopio Breast Cancer Project (KBCP)	Finland	251	445	304	97
kConFab/Australian Ovarian Cancer Study (kConFab/AOCS)	Australia	897	613	162	59
Leuven Multidisciplinary Breast Centre (LMBC)	Belgium	1388	2671	2071	379
Mammary Carcinoma Risk Factor Investigation (MARIE)	Germany	1778	1818	1349	399
Milan Breast Cancer Study Group (MBCSG)	Italy	400	488	149	42
Mayo Clinic Breast Cancer Study (MCBCS)	USA	1931	1862	1486	295
Melbourne Collaborative Cohort Study (MCCS)	Australia	511	614	352	119
Multi-ethnic Cohort (MEC)	USA	741	731	415	87
Montreal Gene–Environment Breast Cancer Study (MTLGEBCS)	Canada	436	489	421	64
Norwegian Breast Cancer Study (NBCS)	Norway	70	22	0	22
Oulu Breast Cancer Study (OBCS)	Finland	414	507	407	100
Ontario Familial Breast Cancer Registry[b] (OFBCR)	Canada	511	1175	630	268
Leiden University Medical Centre Breast Cancer Study (ORIGO)	Netherlands	327	357	211	70
NCI Polish Breast Cancer Study (PBCS)	Poland	424	519	519	0
Karolinska Mammography Project for Risk Prediction of Breast Cancer (pKARMA)	Sweden	5537	5434	3672	702
Rotterdam Breast Cancer Study (RBCS)	Netherlands	699	664	368	131
Singapore and Sweden Breast Cancer Study (SASBAC)	Sweden	1378	1163	663	144
Sheffield Breast Cancer Study (SBCS)	UK	848	843	377	105
Studies of Epidemiology and Risk factors in Cancer Heredity (SEARCH)	UK	8069	9347	5160	1181
Städtisches Klinikum Karlsruhe Deutsches Krebsforschungszentrum Study (SKKDKFZS)	Germany	29	136	0	136
IHCC-Szczecin Breast Cancer Study (SZBCS)	Poland	315	365	165	60
Triple Negative Breast Cancer Consortium Study (TNBCC)	Various	542	881	0	881
UK Breakthrough Generations Study (UKBGS)	UK	470	476	96	22
Asian women					
Asian Cancer Project (ACP)	Thailand	636	423	92	53
Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC)	Japan	1376	694	395	139
Los Angeles County Asian-American Breast Cancer Case–Control (LAABC)	USA	990	812	528	138
Malaysian Breast Cancer Genetic Study (MYBRCA)	Malaysia	610	770	422	291
Shanghai Breast Cancer Genetic Study (SBCGS)	China	892	848	510	276
Seoul Breast Cancer Study (SEBCS)	South Korea	1129	1162	657	375
Singapore Breast Cancer Cohort (SGBCC)	Singapore	502	533	272	108
IARC-Thai Breast Cancer (TBCS)	Thailand	253	138	26	26
Taiwanese Breast Cancer Study (TWBCS)	Taiwan	236	889	460	204
African					
Southern Community Cohort Study (SCCS)	USA	680	679	0	0
Nashville Breast Health Study (NBHS)	USA	252	437	199	222
Total		50156	53835	30635	9120

Abbreviations: ER− = estrogen receptor-negative cases; ER+ = estrogen receptor-positive cases.
[a]Australian site of the Breast Cancer Family Registry.
[b]Ontario site of the Breast Cancer Family Registry.

evidence that *FGFR2* is the target gene, and it therefore seems plausible that other FGF receptors or genes acting in the FGF pathway might also be implicated in breast cancer risk. However, we find little evidence that this is the case for the receptors, at least not to the extent observed for common variants in *FGFR2*. Admittedly, the degree to which common variation in the FGF

Table 2. Summary results for SNPs in FGF receptor genes for white European women

			OR (95%CI)				OR (95%CI)		
SNP	Alleles	MAF	Aa	aa	per-a-allele	*P*	ER−	ER+	*P-het*
FGFR1									
rs10958704	A**G**	0.40	0.98 (0.95–1.01)	0.98 (0.94–1.02)	0.99 (0.97–1.01)	0.18	0.99 (0.96–1.03)	0.99 (0.97–1.02)	0.91
rs17182141	A**G**	0.06	1.05 (1.00–1.09)	0.95 (0.75–1.22)	1.04 (1.00–1.08)	0.057	1.08 (1.00–1.17)	1.04 (0.99–1.09)	0.30
rs2288696	G**A**	0.21	1.02 (0.99–1.05)	1.07 (1.00–1.14)	1.03 (1.00–1.05)	0.023	1.05 (1.01–1.10)	1.03 (1.00–1.06)	0.35
rs2411256	G**A**	0.24	1.02 (0.99–1.05)	1.01 (0.95–1.07)	1.01 (0.99–1.03)	0.36	1.00 (0.95–1.04)	1.01 (0.99–1.04)	0.44
rs2978076	G**A**	0.08	0.99 (0.96–1.03)	1.22 (1.04–1.44)	1.01 (0.98–1.05)	0.53	0.99 (0.92–1.06)	1.02 (0.98–1.06)	0.37
rs2978083	G**A**	0.05	0.99 (0.96–1.03)	1.22 (1.04–1.44)	1.01 (0.98–1.05)	0.53	0.97 (0.89–1.06)	1.03 (0.97–1.08)	0.27
rs3758102	G**A**	0.26	1.01 (0.98–1.04)	1.02 (0.96–1.07)	1.01 (0.99–1.03)	0.35	1.01 (0.97–1.05)	1.01 (0.98–1.04)	0.95
rs3925	G**A**	0.23	1.01 (0.98–1.04)	1.00 (0.95–1.07)	1.01 (0.99–1.03)	0.51	0.99 (0.95–1.04)	1.01 (0.99–1.04)	0.39
rs4733930	G**A**	0.42	1.00 (0.97–1.03)	1.04 (1.00–1.08)	1.02 (1.00–1.04)	0.11	1.03 (0.99–1.07)	1.02 (1.00–1.04)	0.67
rs4733946	C**A**	0.08	1.00 (0.97–1.03)	1.04 (1.00–1.08)	1.02 (1.00–1.04)	0.11	1.01 (0.95–1.08)	1.04 (1.00–1.09)	0.39
rs6474354	G**A**	0.21	0.98 (0.95–1.01)	0.99 (0.92–1.05)	0.98 (0.96–1.01)	0.18	0.96 (0.92–1.01)	0.98 (0.96–1.01)	0.37
rs6996321	G**A**	0.39	1.01 (0.98–1.04)	1.00 (0.96–1.04)	1.00 (0.98–1.02)	0.95	1.00 (0.97–1.04)	0.99 (0.97–1.02)	0.54
rs6983315	G**A**	0.44	1.01 (0.97–1.04)	0.98 (0.94–1.02)	0.99 (0.97–1.01)	0.39	0.97 (0.93–1.00)	0.99 (0.97–1.02)	0.13
rs7012413	G**A**	0.30	1.00 (0.97–1.02)	0.99 (0.95–1.04)	1.00 (0.98–1.02)	0.69	1.00 (0.97–1.04)	1.00 (0.98–1.02)	0.82
FGFR3									
rs12502543	G**A**	0.10	1.04 (1.01–1.08)	1.10 (0.96–1.25)	1.04 (1.01–1.08)	0.0076	0.99 (0.93–1.05)	1.06 (1.02–1.10)	0.036
rs2234909	A**G**	0.14	0.99 (0.95–1.02)	0.97 (0.88–1.07)	0.99 (0.96–1.01)	0.29	0.99 (0.94–1.04)	0.98 (0.95–1.02)	0.77
rs3135848	A**G**	0.28	1.02 (0.99–1.04)	1.02 (0.96–1.07)	1.01 (0.99–1.03)	0.31	1.00 (0.96–1.04)	1.01 (0.99–1.04)	0.55
rs743682	G**A**	0.09	1.05 (1.01–1.09)	1.16 (1.00–1.34)	1.05 (1.02–1.09)	0.0020	1.01 (0.95–1.08)	1.06 (1.02–1.10)	0.24
rs746779	G**A**	0.18	0.99 (0.96–1.02)	0.98 (0.90–1.06)	0.99 (0.96–1.01)	0.29	1.00 (0.95–1.05)	0.98 (0.95–1.01)	0.48
FGFR4									
rs1076891	G**A**	0.06	1.03 (0.99–1.08)	0.99 (0.81–1.22)	1.03 (0.99–1.07)	0.14	1.06 (0.98–1.14)	1.01 (0.97–1.06)	0.25
rs1966265	G**A**	0.23	0.97 (0.94–1.00)	0.93 (0.88–0.99)	0.97 (0.95–0.99)	0.0060	0.98 (0.94–1.03)	0.97 (0.95–1.00)	0.54
rs2456173	G**A**	0.21	1.00 (0.97–1.03)	0.99 (0.92–1.05)	0.99 (0.97–1.02)	0.66	0.98 (0.94–1.02)	1.00 (0.98–1.03)	0.34
rs376618	A**G**	0.24	1.00 (0.97–1.03)	0.96 (0.91–1.02)	0.99 (0.97–1.01)	0.33	0.97 (0.93–1.01)	0.99 (0.97–1.02)	0.29
rs641101	G**A**	0.31	1.01 (0.98–1.04)	0.99 (0.94–1.03)	1.00 (0.98–1.02)	0.98	0.99 (0.95–1.03)	1.00 (0.98–1.02)	0.56
rs6556301	C**A**	0.36	0.99 (0.97–1.02)	0.96 (0.92–1.00)	0.98 (0.97–1.00)	0.13	0.99 (0.95–1.02)	0.98 (0.96–1.01)	0.84
FGFRL1									
rs34869253	A**G**	0.43	1.00 (0.97–1.04)	1.00 (0.96–1.04)	1.00 (0.98–1.02)	0.96	0.98 (0.94–1.01)	0.99 (0.97–1.01)	0.52
rs3755955	G**A**	0.16	1.00 (0.97–1.03)	1.02 (0.94–1.11)	1.00 (0.98–1.03)	0.82	1.00 (0.95–1.05)	1.00 (0.97–1.03)	0.83
rs4505759	G**A**	0.30	0.99 (0.96–1.02)	0.98 (0.93–1.03)	0.99 (0.97–1.00)	0.38	1.00 (0.96–1.04)	0.99 (0.97–1.02)	0.78
rs4647932	G**A**	0.06	1.04 (0.99–1.08)	0.98 (0.80–1.20)	1.03 (0.99–1.07)	0.14	1.06 (0.98–1.14)	1.02 (0.97–1.06)	0.31
rs6855233	A**G**	0.29	0.99 (0.97–1.02)	1.03 (0.98–1.08)	1.01 (0.98–1.03)	0.62	0.98 (0.94–1.02)	1.00 (0.98–1.03)	0.31
rs748651	A**G**	0.48	1.00 (0.97–1.03)	1.02 (0.98–1.06)	1.01 (0.99–1.03)	0.31	1.03 (0.99–1.07)	1.01 (0.98–1.03)	0.22

Abbreviations: SNP = single-nucleotide polymorphism; FGF = fibroblast growth factor; OR = odds ratio where A is the common allele, a is the rare allele and both Aa and aa are compared with AA genotypes; CI = confidence interval; MAF = minor allele frequency; *P* = *P*-value for the per-a-allele model; ER− = results (per a-allele) for risk of estrogen receptor-negative disease; ER+ = results (per a-allele) for risk of estrogen receptor-positive disease; *P-het* = *P*-value for heterogeneity by disease sub-type defined by estrogen receptor status.

receptor genes was tagged by the genotyped SNPs was good for *FGFR1, FGFR3* and *FGFR4* and poor for *FGFRL1*, but substantial improvement was afforded by imputation. Nevertheless, it is possible that common variation not captured by the genotyped or imputed SNPs may be associated with breast cancer risk. It is also possible that these genes may be implicated in disease susceptibility via regulatory mechanisms involving variants outside the chromosomal boundaries defined for each gene considered. That said, few studies have assessed common variation in candidate genes to this extent, in terms of both gene coverage and sample size.

The power of our study was much lower for Asian and African–American women; however, our primary focus on European women is consistent with our hypothesis, based on the previous finding in *FGFR2* in this population. Our study was also limited by the power and gene coverage of the stage 1 component which assessed tag-SNPs in the selected genes of the FGF pathway. Therefore, no conclusions can be drawn about the potential implication of common variation in these genes in breast cancer susceptibility. Nevertheless, we checked the chromosomal locations of the 76 established risk-associated loci (http://www.nature.com/icogs/primer/shared-susceptibility-loci-for-breast-prostate-and-ovarian-cancers/) and found that none were located within 10 kb of any of the 39 genes considered, with the exception of the *FGFR2* locus.

In conclusion, in this, possibly the largest candidate-gene association study carried out to date, we have observed little evidence of association between common variation in the *FGFR1, FGFR3, FGFR4* and *FGFRL1* genes and risk of breast cancer. Our results suggest that common variants in these FGF receptors are not associated with risk of breast cancer to the degree observed for *FGFR2*.

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CONFLICT OF INTEREST

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