Variation In Genes Required For Normal Mitosis And Risk Of Breast Cancer

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Abstract

The down-regulation of genes involved in normal cell division can cause aberrant mitoses and increased cell death. Surviving cells exhibit aneuploidy and/or polyploidy. Since mitotic disruption has been linked with tumor development and progression, alterations in the expression or activity of these mitotic regulators may contribute to breast tumor formation. We evaluated associations between common inherited variation in these genes and breast cancer risk. Two hundred-five tagging and candidate functional single nucleotide polymorphisms in 30 genes required for normal cell division were genotyped in 798 breast cancer cases and 843 controls from the Mayo Clinic breast cancer study. Two variants in *EIF3A* (rs10787899 and rs3824830; p<0.001) and four variants in *SART1* (rs660118, rs679581, rs754532 and rs735942; $p_{trend} \leq 0.004$) were significantly associated with an altered risk of breast cancer along with single variants in *RRM2, PSCD3, C11orf51, CDC16, SNW1, MFAP1,* and *CDC2* (p<0.05). Variation in both *SART1* (p=0.009) and *EIF3A* (p=0.02) was also significant at the gene level. Analyses suggested that SART1 SNPs rs660118 and rs679581 accounted for the majority of the association of that gene with breast cancer. The observed associations between breast cancer risk and genetic variation in the *SART1* and *EIF3A* genes that are required for maintenance of normal mitosis suggests a direct role for these genes in the development of breast cancer.

INTRODUCTION

Breast cancer is the most common cancer in women in the U.S., with over 184,000 new cases expected in 2008 [1]. One of the strongest and most consistent risk factors identified to date is family history of the disease [2]. While some of this familial risk can be attributed to known genetic factors, syndromes account for less than 25% of the familial clustering of breast cancer [3]. Therefore, other genes and environmental factors remain to be elucidated.

A hallmark of most cancers, and the great majority of breast cancers (>80%), is chromosomal instability, which often presents as aneuploidy or polyploidy [4]. Aneuploidy results from aberrant chromosome segregation during metaphase and is associated with disruption of the spindle assembly checkpoint and with centrosome amplification. Polyploidy results from failure of cell division and is associated with disruption of karyokinesis or cytokinesis. The changes in copy number and expression levels of genes in response to aneuploidy and polyploidy have been linked to tumor development and progression. Indeed, strong *in vitro* and *in vivo* evidence has shown that chromosomal instability and disrupted cell division in the

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absence of other cell cycle and DNA repair defects can transform cells and predispose to cancer [5]. Chromosomal instability has also been shown to be one of the earliest steps in breast tumor formation, with the detection of centrosome amplification and aneuploidy in a large proportion of atypical ductal hyperplasia and ductal carcinoma *in situ* of the breast [6,7].

Several genes have been implicated in regulation of cell division through functional studies. In particular, a functional screen using 2500 short interfering RNA (siRNA) showed that depletion of 37 genes resulted in severe disruption of cell division [8]. Down regulation of these genes led to disruption of all phases of mitosis leading to delayed mitotic entry, failure of chromosome congregation, monopolar and multipolar spindles, lagging chromosomes during anaphase, premature chromosome decondensation, failure of the mitotic checkpoint and failure of cytokinesis. As the great majority of breast tumors exhibit similar chromosomal instability, we hypothesized that inherited genetic variation that alters the expression or function of these 37 genes that are involved in regulating cell division may contribute to the development of breast cancer. We selected 30 of these 37 genes, eliminating those that were very large (i.e., had very many tag-SNPs) and those that had no known functional SNPs. The remainder were examined for association between genetic variation and risk of breast cancer in a clinic-based series of breast cancer cases and controls.

METHODS

Mayo Study Subjects

The Mayo Clinic Breast Cancer Study is an on-going clinic-based case-control study. This analysis is based on participants enrolled from February 1, 2001 through June 30, 2005. Briefly, cases were 798 Caucasian women aged 18 and older diagnosed with invasive cancer of the breast within the previous six months. Controls were 843 Caucasian women visiting the Mayo Clinic for a pre-scheduled general medical exam in the Department of Internal Medicine and were frequency matched to cases on region of residence, race, and five-year age group. Case participation was 69%, and control participation was 71%. Eligible women were asked to provide informed consent, risk factor information via a self-administered questionnaire, and a sample of blood as a source of DNA. Postmenopausal status was defined as having no menstrual period for 12 months or having the uterus and/or ovaries removed. .

SNP Selection and Genotyping

For each candidate gene, tagSNPs (pairwise $r^2 > 0.80$) with a minor allele frequency (MAF) in European-Americans greater than 0.05 located within 5 kb upstream and downstream of the largest cDNA isoform (genome build 35) were selected from publicly-available genotype data from HapMap release 21 and Perlegen Sciences ldSelect [9]. All putative functional SNPs in the coding region, promoter and 5′ and 3′ UTRs with MAF>0.05 were also selected. In total 182 tagSNPs and 33 functional SNPs were selected from 30 genes. Ten of the 33 functional SNPs were also selected as tagSNPs, yielding a total of 205 SNPs for genotyping. Gene coverage (the proportion of the SNP variability accounted for by our binning and genotyping) was greater than 82% for all genes.

A total of 1,748 samples (805 cases, 843 controls, 100 duplicates) were assayed on custom OPAs at Illumina Corporation (San Diego, California) using the Illumina BeadLab and GoldenGate genotyping. Full details of quality control statistics of the genes included in these analyses are summarized in Supplementary Table 1.

SEARCH Replication Study Population

The Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH), an ongoing population-based study of breast cancer cases ascertained through the East Anglian Cancer

Registry in the UK [10][11] was used as a second, replication population to examine *EIF3A* rs10787899, the SNP with the smallest *P* in the Mayo Clinic Study. All women diagnosed after 1990 in East Anglia with invasive breast cancer under the age of 70 years were eligible for inclusion in the study. Unaffected controls, ages 45–74 years, from the same geographic region were randomly selected from the Norfolk component of the European Prospective Investigation of Cancer (EPIC). Over 98% of cases and controls were white Europeans. Genotyping of 4,470 cases and 4,560 controls was performed by a 5′ nuclease assay (Taqman®) using the ABI PRISM 7900HT Sequence detection system. Successful genotyping was achieved for 96.7% of DNA samples.

Statistical Analysis

Genotypes obtained from the study subjects were used to estimate allele frequencies in cases and controls. Departures from Hardy-Weinberg equilibrium amongst the controls were assessed using standard goodness-of-fit tests or, when minor allele frequency was less than 5%, exact tests [12]. Associations of SNPs with case-control status were assessed using unconditional logistic regression analyses. Odds ratios and corresponding 95% confidence intervals were calculated separately for heterozygote and rare homozygote subjects, with subjects homozygous for the major allele serving as the reference group. Primary tests for associations with breast cancer risk were carried out assuming an ordinal (log-additive) genotypic relationship (using simple one-degree-of-freedom tests for trend within the logistic regression models).

All logistic regression models for the Mayo Breast Cancer Study were adjusted for age, region of residence and variables associated with case-control status, including: age at menarche (≤11, 12, 13, ≥14), oral contraceptive use (never, ≤4 years, >4 years), age at first child birth, pack-years of cigarettes smoked, HRT use (never, ≤5 years, >5 years), and menopause status (post vs. pre-menopausal). Family history of breast cancer was also significantly related to disease in our population but was not included in the final models. Since our main variables of interest (genes) can cause familial clustering, to include adjustment for family history would be akin to adjusting for our main variables of interest.

Estimates of pair-wise linkage disequilibrium, both D-prime and r-squared, were also obtained using the genotype data from the control subjects. We determined haplotype blocks within and across genes using the method of Gabriel *et al* [13] using the parameters described therein and implemented in Haploview [14].

Overall differences in breast cancer risk across gene-specific haplotypes (with estimated frequencies greater than 0.01) were estimated using the global score statistic of Schaid *et al* [15]. After these global tests were performed we examined individual haplotype effects and individual SNPs associations with breast cancer.

All analyses described above were specified *a priori*. However, we also explored the possibility of gene-gene interactions through the use of multifactor dimensionality reduction (MDR) [16] and logistic regression. All statistical tests were two-sided, and all analyses were carried out using the SAS (SAS Institute, Inc., Cary, NC) and S-Plus (Insightful, Seattle, WA) software systems.

RESULTS

The goal of this analysis was to look for evidence for an association of SNPs in 30 genes, identified by Kittler and colleagues [8] as essential for normal mitosis, with risk of breast cancer. A list of all genes and the number and type of SNPs examined, categorized by function as described by Kittler *et al* [8], is provided in Supplementary Table 2.

Eleven of the 205 SNPs examined from these 30 candidate genes were associated individually with breast cancer risk in our population under a log-additive model ($p \leq 0.05$) (Table 1). These SNPs were located in *EIF3A, SART1, RRM2, PSCD3, C11orf51* and *CDC2*. We also evaluated all associations under a co-dominant model in order to gain more information about the relationships between the 205 SNPs and breast cancer. In this setting eight of the 11 SNPs identified under the log-additive model and three additional SNPs in *CDC16, SNM1, MFAP1* displayed significant association ($p \leq 0.05$) (Table 1). Supplementary Table 3 presents the breast cancer risk associated with all SNPs evaluated.

Two SNPs in *EIF3A* (Eukaryotic translation initiation factor 3, subunit A), rs10787899 (OR = 1.26; $P_{trend} = 0.001$) and rs3824830 (OR = 1.21; $P_{trend} = 0.009$) were associated with an increased risk of breast cancer. These two SNPs were highly correlated ($r^2 = 0.87$)(Figure 1). Haplotype analysis in Haploview showed that these SNPs in EIF3A make up a single haplotype block. The global haplotype test for *EIF3A* showed a significant association with breast cancer ($P_{Global-stat} = 0.019$) (Table 2). In addition, an individual haplotype containing the minor alleles of rs10787899 and rs3824830 (10001) was significantly associated with an increased risk of breast cancer (score statistic = 2.061; p=0.039). In contrast, relative to all other common haplotypes, a haplotype of the major alleles of all five SNPs was associated with decreased breast cancer risk (score statistic = −2.257; P=0.024).

We attempted to replicate the association between the SNP rs10787899 in *EIF3A* and risk of breast cancer using 4470 cases from the SEARCH Study in the U.K. and 4560 controls from the EPIC study (Norfolk, UK)[17]. Carriers of one copy had an OR=1.03 (95% CI 0.93–1.13), and those with two copies had an OR=1.00 (0.89–1.13) suggesting no association with risk in that population. No other SNPs were genotyped in the SEARCH/EPIC populations.

Four SNPs in *SART1* (Squamous cell carcinoma antigen recognized by T cells), depletion of which caused mitotic arrest, were associated with breast cancer risk (Table 2). The rs660118 and rs679581 SNPs associated with an increased risk of breast cancer were highly correlated ($r^2 = 0.89$). Similarly, the rs754532 and rs735942 SNPs associated with reduced breast cancer risk were highly correlated ($r^2 = 0.81$). All four statistically significant SNPs in *SART1* were located in a single haplotype block defined by the Gabriel method. The global haplotype test and two common individual haplotypes, including the most common haplotype (11000, rare alleles at rs660118 and rs679581), were associated with risk of breast cancer. Adjustment for rs754532 and rs735942 in the haplotype analyses established that the common haplotype containing rs660118 and rs679581 (p=0.006) likely accounted for the influence on risk of breast cancer.

Eight additional SNPs from seven other genes were also associated with breast cancer risk and are presented in Table 1. Two SNPs, rs17136052 in *PSCD3* and rs3793938 in *C11orf51*, are located in regions that suggest these SNPs may play a role in gene function and/or influence expression levels. The odds ratio associated with each copy of the minor allele for *PSCD3* (Pleckstrin homology, Sec7 and coiled-coil domains 3) SNP rs17136052, which is located in the 3′-untranslated region (UTR) of the gene, was 0.82 ($P_{trend} = 0.05$). *C11orf51*, depletion of which caused mitotic arrest [8], had one SNP (rs3793938) located in the 5′ upstream region of the putative gene which was associated with increased risk of breast cancer (OR=1.46, $P_{trend} = 0.02$). All other SNPs that were individually associated with risk of breast cancer were tagSNPs located in an intron or adjacent to the following genes: ribonucleotide reductase M2 polypeptide (*RRM2*), cell division cycle 16 homolog (*CDC16*), SNW domain containing 1 (*SNW1*) microfibrillar-associated protein 1 (*MFAP1*), and cell division cycle 27 homolog (*CDC27*). Summary haplotype data on the remaining genes are presented in Supplementary table 3.

In an exploratory analysis, we used MDR to test for evidence of multi-locus genetic interactions with risk of breast cancer. The most predictive combination of SNPs in these 30 genes was a model that included rs3821116 in AD024 (SPC25, NDC80 kinetochore complex component, homolog (*S. cerevisiae*)), rs10787899 in *EIF3A*, and rs7214914 in *DHX8* (DEAH (Asp-Glu-Ala-His) box polypeptide 8). The combination of these SNPs provided the best model with a high cross-validation consistency (90%) suggesting that these three SNPs may work together to influence risk of breast cancer. However, the test for interaction of these three SNPs was not statistically significant when all were included in a multivariate logistic regression model ($P_{\text{likelihood ratio test}} = 0.19$), possibly due to low statistical power to detect an interaction.

DISCUSSION

This analysis was based upon the hypothesis that inherited genetic variation in genes involved in regulating cell division may be important in the development of breast cancer. Our data provide evidence that genetic variation in *SART1* and *EIF3A* may be associated with the development of breast cancer. Our data furthermore suggest that genetic variation in eight other genes (*RRM2, PSCD3, PSCD3, C11orf51, CDC16, SNW1, MFAP1, CDC27*) may also be associated with risk of breast cancer.

SART1 is located on chromosome 11q13.1 and encodes two protein forms that make up important components of the splicing machinery. *SART1* is expressed in both normal breast cells and malignant breast cells [18]. Flow cytometry and Western blot analysis have shown that expression of *SART1* protein induces cell cycle arrest followed by apoptosis [19]. All five variants examined were associated with altered risk of breast cancer. The variant rs660118 in this gene codes for a change in amino acid from glycine to alanine at codon 485 and was associated with increased risk of breast cancer in our population. We theorize that genetic variation at this locus may affect the induction of cell cycle arrest in cancer cells.

Another gene that plays an important role in mitosis is *EIF3A*, a eukaryotic translation initiation factor (EIF) that is involved in initiation of protein synthesis [20]. Kittler *et al* [8] showed that knockdown of this gene resulted in mitotic spindle defects. Homozygote variants of two SNPs in this gene (rs3824830 5′ upstream, and rs10787899 located in an intron) were associated with a 50% increased risk of breast cancer compared to those with no copies of the variant SNP. However, our finding in rs10787899 was not replicated when examined within the SEARCH cohort (OR=1.001, 95% CI 0.94–1.08) in 4300 cases and 4500 controls. The minor allele frequency (MAF) was 0.44 in both cases and controls in the SEARCH cohort. In comparison, the MAF among Mayo breast cancer cases was 0.47 but 0.41 in the Mayo controls. These differences might be caused by chance or slight differences in ethnicity between these two groups. Although both groups are primarily of Northern European descent, the Mayo subjects are mainly from descendants of settlers from Germany and Scandinavia. In contrast, subjects in the SEARCH cohort are from the East Anglica region of England. Neither *SART1* nor *EIF3A* SNPs were significant in the population of patients included in the CGEMS breast cancer data (http://cgems.cancer.gov/data/) [21].

Two other SNPs of interest had a higher probability of function than other SNPs examined. SNP rs17136052 is located in 5′ upstream region of *PSCD3* (pleckstrin homology, Sec7 and coiled-coil domains 3). PSCD3 is involved in the regulation of protein sorting and membrane trafficking [22,23]. Kittler *et al* reported that inhibition of the *PSCD3* protein caused the cells to arrest during mitosis [8]. The other SNP with a higher likelihood of function is the SNP rs3793938 in *C11orf51* (chromosome 11 open reading frame 51). Carriers of the minor allele of this SNP were at 40% increased risk of breast cancer compared to non-carriers (OR=1.4, 95% CI 1.01–1.95). Although only one tagSNP was selected in this small gene it was significantly associated with breast cancer in our population (p=0.02). This tagSNP was located

in the 5′ upstream region. Knockdown of this gene by Kittler *et al.* resulted in mitotic arrest and severe spindle defects in the cells [8]. No other function has been attributed to this gene.

The other SNPS associated with breast cancer risk were located in the following genes: *RRM2*, *CDC16*, *SNW1, MFAP1*, and *CDC27*. *RRM2* encodes an enzyme that catalyzes the formation of deoxyribonucleotides from ribonucleotides [24]. Inhibition of *RRM2* was shown to lead to cellular death upon entry into mitosis [8]. *CDC16* encodes a subunit of the anaphase-promoting complex/cyclosome (APC/C), which is a ubiquitin-protein ligase required for degradation of cell cycle regulators [25]. Knockdown of expression of this gene with siRNA led to cellular arrest in mitosis [8]. *SNW1* is a important nuclear protein involved in the regulation of transcription and mRNA splicing [26]. Kittler *et al.* found that knockdown of this gene's expression resulted in mitotic arrest and cytokinesis defects which led to the creation of cells fragments without chromatin [8]. MFAP1 is component of the elastin-associated microfibrils that is located in the extracellular matrix; mass spectrometry also showed MFAP1 to be a component of the spliceosome 27 [8]. CDC27 is a subunit of the anaphase promoting complex subunit CDC27 whose knockdown led to cellular arrest in mitosis [8]. All of these genes are interesting candidates for further analysis of their potential involvement in breast cancer development.

This is the first epidemiological study to focus on these genes known to be involved in mitotic arrest, cell death and cytokinesis defects. All these genes were selected based upon *a priori* knowledge of their involvement in these functions from basic science benchwork with short interfering RNAs [8]. Data from our study suggest that several of these genes are associated with risk of breast cancer. This opens up a new area for investigation that is worthy of follow-up in other populations and in other cancer types.

Several limitations should be considered when interpreting our results. Thirty genes were included in this analysis, each with numerous SNPs. When the estimates of statistical probability were adjusted for the 30 gene tests, none of these associations remained statistically significant. However, the strong functional data upon which these genes were selected strengthen the evidence in support of a real biological connection between these genes and development of breast cancer. Another limitation is the ethnic makeup of our population, which was 100% Caucasian from the upper Midwest portion of the United States. Although this may reduce generalizability, the homogeneous nature of our population limits the effects of population stratification on the association with risk.

In summary, we have examined associations between genetic variation in genes known to regulate spindle mechanics, mitotic checkpoints, cytokinesis, and/or cell death during mitosis and breast cancer in a breast cancer case control study at the Mayo Clinic. Of the 30 genes examined, two of the genes, *SART1* and *EIF3A*, had the strongest associations with risk of breast cancer in our population. This association was not seen in either the SEARCH study [10][11] or CGEMS [21]. Our data furthermore suggest that genetic variation in eight other genes (*RRM2, PSCD3, PSCD3, C11orf51, CDC16, SNW1, MFAP1, CDC27*) may also be associated with risk of breast cancer. We recommend further investigation of these genes in other populations to confirm the associations noted here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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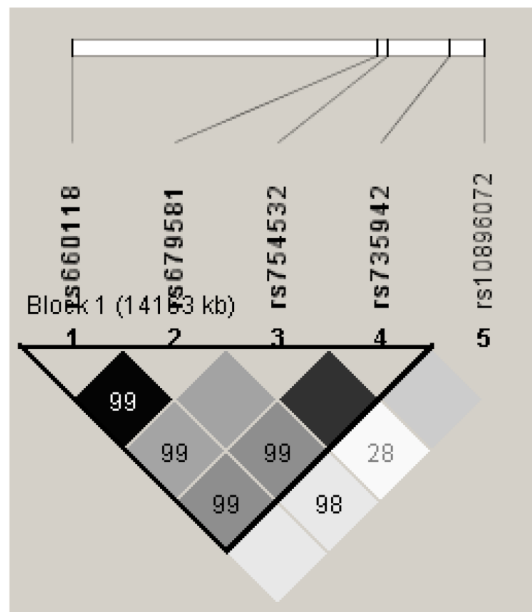
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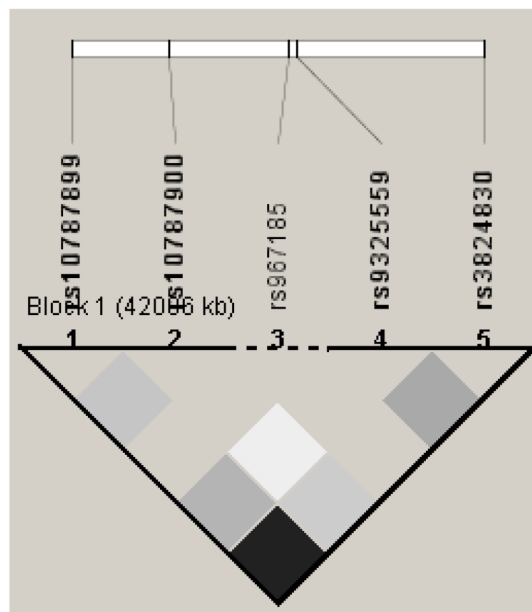
EIF3A

Figure 1.
Haploview diagram of haplotype structure of *SART1* and *EIF3A*. Numbers in boxes represent |D′| and missing values imply |D′|=1. Shading represents r^2 value, with darker colors corresponding to higher r^2 value.

Table 1

Multivariate adjusted odds ratios and 95% confidence intervals on all variants with p< 0.05 in the 2 degree of freedom test or ordinal (1 df). Mayo Clinic Breast Cancer Case-Control Study, Rochester, MN

SNP ID	Chr.	Chromosome Position (bp)*	Gene Name	Entrez Gene ID	Description	Minor Allele Frequency		Multivariate-adjusted Odds Ratio (95% Confidence Interval)			P ordinal model	P 2 degree-of-freedom model
						Cases	Controls	1 copy of variant allele	2 copies of variant allele			
rs10787899	10	120788645	*EIF3A* **	8661	Tag-intron 19	0.468	0.407	1.18 (0.94 – 1.49)	1.63 (1.22 – 2.18)	0.001	0.004
rs3824830	10	120830651	*EIF3A* **	8661	5'-upstream	0.427	0.380	1.15 (0.92 – 1.44)	1.50 (1.11 – 2.02)	0.009	0.028
rs660118	11	65491750	*SART1* **	9092	G485A, exon 12	0.472	0.425	1.19 (0.94 – 1.51)	1.50 (1.12 – 2.03)	0.007	0.027
rs679581	11	65503229	*SART1* **	9092	3'utr, exon 20	0.476	0.425	1.19 (0.94 – 1.51)	1.55 (1.15 – 2.08)	0.004	0.015
rs754532	11	65503633	*SART1* **	9092	3'utr, exon 20	0.286	0.325	0.88 (0.71 – 1.08)	0.65 (0.45 – 0.93)	0.020	0.053
rs735942	11	65505913	*SART1* **	9092	Tag-downstream	0.328	0.377	0.78 (0.63 – 0.97)	0.69 (0.50 – 0.96)	0.008	0.027
rs6759180	2	10217161	*RRM2*	6241	Tag-intron 5	0.279	0.316	0.74 (0.60 – 0.91)	0.75 (0.52 – 1.09)	0.010	0.014
rs17136052	7	5975975	*PSCD3*	9265	3'utr, exon 13	0.142	0.165	0.87 (0.69 – 1.10)	0.46 (0.22 – 0.96)	0.045	0.073
rs10240988	7	5996520	*PSCD3*	9265	Tag-intron 4	0.179	0.210	0.90 (0.72 – 1.13)	0.53 (0.31 – 0.88)	0.032	0.043
rs3793938	11	71500781	*C11orf51*	25906	5' upstream	0.064	0.046	1.32 (0.94 – 1.84)	-	0.018	0.268
rs7998576	13	114059290	*CDC16*	8881	Tag-gene region	0.211	0.232	1.00 (0.81 – 1.25)	0.52 (0.32 – 0.83)	0.081	0.020
rs1477261	14	77290731	*SNW1*	22938	Tag-intron 2	0.192	0.201	0.83 (0.67 – 1.03)	1.81 (1.03 – 3.17)	0.938	0.017
rs678084	15	41907851	*MFAP1*	4236	Tag-gene region	0.171	0.179	0.78 (0.62 – 0.98)	1.69 (0.95 – 3.01)	0.571	0.012

SNP ID	Chr.	Chromosome Position (bp)[*]	Gene Name	Entrez Gene ID	Description	Minor Allele Frequency		Multivariate-adjusted Odds Ratio (95% Confidence Interval)		P ordinal model	P 2 degree-of-freedom model
						Cases	Controls	1 copy of variant allele	2 copies of variant allele		
rs16941635	17	42616954	CDC27	996	Tag-intron 1	0.080	0.104	0.81 (0.62 – 1.06)	0.36 (0.11 – 1.17)	0.035	0.081

*
NCBI Build 35 coordinates

**
These genes were also associated with risk of breast cancer at the gene level (P haplotype < 0.05)

Multivariate adjusted models were adjusted for age, residence, menopause, menarche, oral contraceptives, age at first birth, hormone therapy use, pack-years of smoking.

Table 2

Breast Cancer Risk Associated with Specific Haplotypes in Cell Division Related Genes

Haplotype	Est. Freq	Score	*P*
EIF3A			
00000	0.337	−2.257	0.024
01000	0.226	−1.330	0.184
10001	0.218	2.061	0.039
10011	0.185	1.074	0.283
10000	0.034	1.767	0.077
SART1			
00110	0.254	−1.990	0.047
00011	0.047	−1.022	0.307
00111	0.051	−0.693	0.489
00000	0.198	−0.449	0.654
01000	0.002	2.113	0.035
11000	0.446	2.528	0.011

0=common allele, 1=rare allele for individual SNPs in each haplotype, listed for each gene in the following order:
EIF3A: rs10787899, rs10787900, rs967185, rs9325559, rs3824830.
SART1: rs660118, rs679581, rs754532, rs735942, rs10896072

Multivariate adjusted (age, area, menopause, menarche, oral contraceptive use, age at first birth, hormone therapy, pack-years of smoking)

Haplotype-specific p-values compare each haplotype of interest to all others combined

Table 3

Gene-level results of haplotype analysis with risk of breast cancer within the Mayo Clinic Breast Cancer Case Control Study

Function	Gene	Chr #	#SNPs	# Haplotypes	Haplotype *P*
Mitotic Arrest					
	FLJ30851	2	9	8	0.250
	CENPE	4	6	6	0.886
	LSM6	4	11	11	0.669
	FLJ20311	7	8	8	0.167
	PSCD3	7	17	16	0.108
	VCP	9	4	4	0.941
	KIF11	10	12	12	0.857
	SART1	11	5	5	**0.009**
	ZDHHC5	11	6	6	0.328
	CDC16	13	8	8	0.245
	MGC3248	16	9	9	0.734
	CDC27	17	10	9	0.351
	DDX48	17	8	8	0.772
	DDX5	17	4	4	0.724
Cytokinesis					
	CKLFSF4	16	5	5	0.321
Mitotic Arrest and Cytokinesis					
	AD024	2	7	7	0.689
	RBM22 (FLJ10290)	5	5	5	0.085
	KIAA0056	11	16	15	0.792
	SNW1	14	11	11	0.486
	MFAP1	15	3	3	0.785
	SNRPA1	15	4	4	0.777
	DHX8	17	4	3	0.942
	KPNB1	17	4	3	0.629
	SNRPB	20	5	5	0.067
Cell Death Upon Entry Into Mitosis					

Function	Gene	Chr #	#SNPs	# Haplotypes	Haplotype *P*
	MGC2603	1	2	2	0.167
	RRM2	2	5	5	0.245
	EIF3S3 (not PTK2)	8	16	15	0.470
	EIF3A	10	5	5	**0.019**
	FLJ38663	12	2	2	0.298

Multivariate adjusted (age, area, menopause, menarche, OC, age first birth, HRT, packyears)