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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

Mammographic breast density is a major risk factor for breast cancer that has a significant genetic component. Through linkage analysis of sibling-pairs, we proposed to identify chromosomal regions that may harbor the underlying genes. We collected blood, risk factors, and mammograms from women in a subset of 23 families (from a total of 426) that have been participating in an ongoing cohort study. We collected 384 blood samples (79% participation). We adopted a computer-assisted approach to refine the phenotype. The laboratory genotyped panels of 75 microsatellite markers distributed across on 8 chromosomes (5, 6, 9, 17, 18, 19, 20 and 21). Variance components linkage analyses were performed to estimate LOD scores for the unadjusted and adjusted (for weight and age) breast density trait. All analyses were two-point (only one marker and putative trait-associated locus examined at one time). The maximum LOD score for the genome screen (LOD=1.4) lies on chromosome 5, but this result is not statistically significant. At present, these findings are not strong enough to merit publication. However, with subsequent funding from the NCI we have expanded the size of the study and the breadth of the genome screen and are optimistic about our chances of success.

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Vachon et al.,1999

Introduction

The interindividual variability in breast tissue on mammographic images, as defined by several measures of mammographic breast density, has been shown to be a major risk factor for breast cancer with three to five-fold increases in risk associated with densities greater than 50% (Boyd, 1998). Two studies have previously suggested that parenchymal patterns were more similar among related than unrelated individuals (Kaprio, 1987; Wolfe, 1980). Recently, a twin study reported heritability of the breast density trait on the order of 60-67% (Boyd, 2002). We have previously demonstrated a genetic component to the mammographic breast density trait, using familial correlation and segregation analysis techniques (Pankow, 1997). Our hypothesis is that there is at least one major gene involved in the genetic variation of breast density, but there are no obvious candidate genes or chromosomal regions known with certainty. Our proposal was to identify the chromosomal location for this gene(s) by linkage analysis, as the first step in identifying the gene(s) that is responsible for the differences in breast density. In the body of this report, we will describe the progress to date on the search for the breast density gene(s) as a result of this funding mechanism. The discovery of breast density genes could help in the identification of susceptible individuals to target prevention strategies as well as provide insight into the development of breast cancer.

Body

As stated in previous reports, our first two years involved blood collection on 23 informative families for linkage. We collected 384 blood samples on eligible women in these families who had mammogram and risk factor information. Our participation rate for this component of the study was 79%. The distribution of samples collected per family ranged from 8-39 (table included in year 2 report).

Previously, in year 2 of the grant, we also worked on the phenotype for our linkage analyses. We had previously proposed a subjective visual estimate of percent breast density for the phenotype in our linkage analyses, but examined the computer-assisted estimate, finding that it was more precise than the visual estimate. We showed high reliability using this measure. Since this time, we have used this computer-assisted estimate in several other studies, continuing to illustrate excellent reliability (greater than 90%).

The focus of the final year shifted to genotyping panels of microsatellite markers for these 384 individuals. These consist of a screening set of microsatellite markers that are distributed across all autosomes and separated at an average distance of 10 centimorgans. To date, we have genotyped 75 markers on 8 chromosomes. These results are presented in the following tables 1-7. Specifically, we were interested in chromosomes 6, 17 and 20 [Tables 2,3 and 6], where we previously saw a signal of linkage in our small sib-pair analysis (Vachon, 1999).

The following tables illustrate the LOD scores for the unadjusted and adjusted (for weight and age) breast density trait at several locations spanning chromosomes 5, 6, 9, 17, 18, 19, 20 and 21. Variance components linkage analyses were performed using the SOLAR software package. All analyses were two-point (only one marker and putative trait-associated locus examined at one time) and we assumed no dominance variance. The results of these analyses presented in the tables read as follows: the location or marker on each chromosome, distance between markers, cumulative distance from p-terminus, the unadjusted and adjusted LOD score. There are various interpretations of what constitutes a significant LOD score. In general, a significant LOD would be at least 3.0. As shown in the following tables, none of the LOD scores on any of the chromosomes reaches this level of significance. The maximum LOD score for the genome screen (LOD=1.4) lies on chromosome 5. At present, these findings are not strong enough to merit publication in a scientific, peer-reviewed journal.

However, the fact that no marker was statistically significant was not entirely unexpected, and our efforts in this regard continue full steam ahead. After we were funded from the DoD and the project was moved to Mayo, the expertise became available to do more powerful and appropriate simulation studies to determine the necessary sample size and the most informative families to recruit for this effort. Results suggest that we needed nearly three times as many participants (at least 1000 individuals) to detect significant evidence for genetic linkage for this complex trait. Thus, we immediately began to pursue (and successfully obtained) additional funding from the NCI to continue the collection of family members up to the required 1000 (now in 91 families) and perform linkage analyses on the entire sample. In fact, the sample set has been collected, samples obtained, mammograms retrieved, digitized, and analyzed for percent density. We are currently in the process of genotyping these original 75 markers on the remaining 600 family members and will continue with the genome screen (400 markers in total) on all 1000 family members. We anticipate that it will take approximately two more years to complete the entire screen (just the laboratory component) on all family members, with data analysis to take roughly another year. Thus, using the combined resource of family members from both the DOD and NIH projects, we will have adequate power for linkage of the breast density trait.

For all tables below, the LOD score reflects the unadjusted LOD while the Adjusted LOD scores are adjusted for age at mammogram and weight at time of mammogram.

Table 1 LOD Scores for Percent Density. Markers on Chromosome 5

Marker	Incremental Distance	Cumulative Distance	LOD Score	Adjusted LOD Score
D5S1981	0.0	0.0	0.0000	0.0000
D5S406	11.0	11.0	0.2750	0.2397
D5S630	7.6	18.6	0.0000	0.0033
D5S416	9.0	27.6	0.4907	1.3930
D5S419	12.7	40.3	0.4673	0.4501
D5S426	12.9	53.2	0.1707	0.3343
D5S418	7.2	60.4	0.0350	0.1823
D5S407	5.9	66.3	0.0022	0.0482
D5S647	10.2	76.5	0.0217	0.0217
D5S424	6.2	82.7	0.0000	0.0000
D5S641	10.0	92.7	0.3254	0.0000
D5S428	3.0	95.7	0.0000	0.0000
D5S644	10.4	106.1	0.0064	0.0000
D5S433	8.8	114.9	0.0000	0.0000
D5S2027	8.0	122.9	0.0000	0.0000
D5S471	10.0	132.9	0.1603	0.0000
D5S2115	12.0	144.9	0.2206	0.0000
D5S436	11.0	155.9	0.3532	0.0000
D5S410	6.7	162.6	0.6446	0.0357
D5S422	8.0	170.6	0.1296	0.0150
D5S400	13.1	183.7	0.0073	0.1283
D5S408	19.0	202.7	0.0000	0.0000
Maximum LOD score			0.6446	1.3930

Table 2 LOD Scores of Percent Density for Markers on Chromosome 6				
Marker	**Incremental Distance**	**Cumulative Distance**	**LOD Score**	**Adjusted LOD Score**
D6S1574	0.0	0.0	0.0000	0.0000
D6S309	5.0	5.0	0.0000	0.0000
D6S470	5.0	10.0	0.0000	0.1391
D6S289	12.5	22.5	0.0000	0.0000
D6S422	6.2	28.7	0.0000	0.0000
D6S276	7.9	36.6	0.0000	0.0000
D6S1610	7.0	43.6	0.0000	0.0000
D6S257	23.8	67.4	0.0000	0.0000
D6S460	11.0	78.4	0.0000	0.0000
D6S462	10.0	88.4	0.0000	0.1530
D6S287	13.4	111.7	0.0934	0.0000
D6S262	9.7	121.4	0.0000	0.0000
D6S292	5.2	126.6	0.0000	0.0000
D6S308	9.1	135.7	0.0000	0.0000
D6S441	8.6	144.3	0.0521	0.0789
D6S1581	12.3	156.6	0.0025	0.0000
D6S264	10.0	166.6	0.5093	0.1058
D6S446	10.0	176.6	0.0000	0.0000
D6S281	13.0	189.6	0.2718	0.0000
Maximum LOD score			0.2718	0.1530

Table 3 LOD Scores of Percent Density for Markers on Chromosome 17				
Marker	**Incremental Distance**	**Cumulative Distance**	**LOD Score**	**Adjusted LOD Score**
D17S849	0.0	0.0	0.0000	0.0000
D17S831	6.0	6.0	0.6219	0.0111
D17S1852	17.0	23.0	0.4152	0.0761
D17S799	10.0	33.0	0.0255	0.0000
D17S1857	12.0	45.0	0.9048	0.0259
D17S798	12.0	57.0	0.0034	0.0000
D17S1868	15.0	72.0	0.0000	0.0000
D17S787	10.0	82.0	0.0000	0.0000
D17S949	11.0	101.0	0.0000	0.0000
Maximum LOD score			0.9048	0.0761

Table 4 LOD Scores of Percent Density for Markers on Chromosome 18				
Marker	**Incremental Distance**	**Cumulative Distance**	**LOD Score**	**Adjusted LOD Score**
D18S478	53.0	53.0	.0000	.0000
D18S1102	10.0	63.0	.0000	.0000
D18S61	46.8	109.8	.0000	.0000
D18S462	18.0	127.8	.0000	.0025
D18S70	6.0	133.8	.0000	.0000
Maximum LOD score			.0000	.0025

Table 5 LOD Scores of Percent Density for Markers on Chromosome 19				
Marker	**Incremental Distance**	**Cumulative Distance**	**LOD Score**	**Adjusted LOD Score**
D19S216	5.9	5.9	0.0000	0.0000
D19S884	6.0	11.9	0.0033	0.0000
D19S221	10.0	21.9	0.0000	0.0049
D19S414	19.9	41.8	0.0292	0.0420
D19S220	7.9	49.7	0.0000	0.0078
D19S420	5.5	55.2	0.0000	0.0000
D19S902	7.0	62.2	0.0005	0.2380
D19S210	30.8	93.0	0.3141	0.3148
Maximum LOD score			0.3141	0.3148

Table 6 LOD Scores of Percent Density for Markers on Chromosome 20				
Marker	**Incremental Distance**	**Cumulative Distance**	**LOD Score**	**Adjusted LOD Score**
D20S117	0.0	0.0	0.0000	0.0000
D20S889	8.0	8.0	0.0000	0.0000
D20S115	12.0	20.0	0.5530	0.4150
D20S186	12.0	32.0	0.0000	0.0000
D20S112	7.1	39.1	0.0000	0.0000
D20S107	18.5	57.6	0.4462	0.2971
D20S119	5.6	63.2	0.0042	0.0140
D20S196	13.1	76.3	0.0000	0.0000
D20S100	8.7	85.0	0.0000	0.0389
D20S171	16.3	101.3	0.0000	0.0000
Maximum LOD score			0.5530	0.4150

Table 7 LOD Scores of Percent Density for Markers on Chromosome 21				
Marker	**Incremental Distance**	**Cumulative Distance**	**LOD Score**	**Adjusted LOD Score**
D21S1252	28.7	28.7	0	0
D21S266	12.6	41.3	0	0
Maximum LOD score			0	0

Key Research Accomplishments

The major accomplishment performed in this project includes the recruitment of study participants, collections of blood samples and mammograms, preparation of samples and genotyping of DNA in regions of suggestive linkage for the breast density trait. Specifically, our lab personnel

- Pulled all samples from the molecular genetics laboratory
- Confirmed informed consent status
- Designed grids in Microsoft excel to be used for the entire genome screen
- Aliquoted DNA from stored samples to 96-well plates for PCR and sequencing
- Performed PCR on all 75 markers
- Scored marker data
- Evaluated possible Mendelian errors
- Reran markers that did not amplify and any Mendelian errors
- Sent marker data to statisticians for review
- Performed variance components linkage analysis on 7 chromosomes

Our statistical personnel wrote programs to automate the transfer of DNA marker data to the biostatistician. This includes 6 programs in total, of which the first two perform Mendelian error checks.

Additionally, our programmer, Fang-Fang Wu has estimated the percent breast density on all women to be included in the linkage analysis. These phenotype data are ready for inclusion in the non-parametric and parametric linkage analyses.

As summary from the past two years, we also:

- Performed simulation analyses under parametric and non-parametric linkage analysis models to determine the most informative families for linkage analyses.
- Ascertained blood samples on members of the family we did not have (n=197).
- Implemented a computer-assisted algorithm for estimation of percent mammographic breast density.
- Performed comparisons of the computer-assisted estimate to subjective estimates of density.
- Performed intra and inter reliability studies to evaluate the performance of the computer-assisted method.

Reportable Outcomes

Vachon CM, Thibodeau SN, Kulby VJ, Sellers TA. Genetic linkage analysis of mammographic breast Density. Department of Defense Breast Cancer Research Program Meeting, June 2000.

Conclusion

The interindividual variability in breast tissue on mammographic images, as defined by several measures of mammographic breast density, has been shown to be a major risk factor for breast cancer. The magnitude of risk (three to five-fold increases with densities greater than 50%) are second only to inherited mutations in BRCA1 or BRCA2. This risk factor appears to be genetically influenced (Pankow, 1997; Kaprio, 1987; Wolfe, 1980). In this study, we proposed to identify the chromosomal location for this gene(s) by linkage analysis, as the first step in identifying the gene(s) that is responsible for the differences in breast density. We performed simulation analyses to identify the most informative families for linkage. The first two years of this study involved blood collection and DNA extraction on approximately 197 women in 23 families. Combined with the samples that were previously collected, we had 384 processed DNA samples in total. During the second year, we updated the subjective estimate of breast density to a computer-assisted estimate of percent breast density and performed reliability studies of our ability to estimate breast density. The final year involved a genome screen for loci linked to the breast density trait. We performed linkage analysis on these 23 families using a screening set of microsatellite markers that are distributed across all autosomes and separated at an average distance of 10 centimorgans (ABI marker set). To date, we have completed genotyping 75 markers. We updated our analysis programs to incorporate a quantitative phenotype (breast density trait) and ran linkage analyses on 7 chromosomes to date. We found no evidence of linkage to any of these seven chromosomes. We have received additional funding to perform a larger genome screen of breast density from the NIH, which will incorporate information from a much larger sample of families (approximately 1000 individuals). Thus, the data from the DOD grant (384 samples) will be supplemented by this independent sample. The discovery of breast density genes could help in the identification of susceptible individuals to target prevention strategies as well as provide insight into the development of breast cancer.

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Preliminary Sibpair Linkage Analysis of Percent Mammographic Density

Interindividual variability in mammographic breast density has been shown to be a major independent risk factor for breast cancer *(1)*. There is evidence for a genetic influence on breast density *(2,3)*. In the Journal *(4)*, we recently reported a segregation analysis of breast density performed on 1370 women from 258 families in the Minnesota Breast Cancer Family Cohort *(5)*. After adjustment for eight epidemiologic risk factors, percent breast density was consistent with mendelian models of inheritance *(4)*. To provide additional evidence for a major gene influence on breast density, we report results from a preliminary sibpair linkage analysis on a sample of women from the same large breast cancer family cohort.

The sibpairs used in the linkage analysis were selected from a convenience sample of women from the family study who participated in the venipuncture, mammogram, and telephone interview components of the Breast Cancer Family Cohort *(5)*. Women with prior breast cancer were not eligible for this analysis to reduce potential genetic heterogeneity. Written informed consent was obtained from the subjects in this study.

The fraction of the mammogram occupied by fibroglandular elements was estimated visually by a radiologist experienced in mammography (C. C. Kuni). Density estimation was made in 5% increments from a video display of the left mediolateral oblique view; the right mediolateral oblique view was used if the left was unavailable.

Because there are no obvious candidate genes for breast density, we performed a genome screen using a set of highly polymorphic short-tandem repeat polymorphism markers spaced approximately 30 cM apart. Evidence for linkage was determined with both two-point [SIBPAL in SAGE *(6)*] and multipoint [MAPMAKER/SIBS *(7)*] linkage analyses on both the unadjusted breast density trait and the trait adjusted for the influence of nongenetic covariates. The SIBPAL test for linkage is a test of negative slope (i.e., H_o: $\beta_1 \geq 0$ versus H_a: $\beta_1 < 0$), so one-sided P values are presented for these tests.

Table 1. Chromosomal regions of suggestive linkage in sibpair linkage analysis of mammographic percent breast density

Marker name	cM*	Two-point analysis†		Multipoint analysis	
		Unadjusted *P*	Adjusted *P*	Unadjusted LOD score	Adjusted LOD score
Chromosome 6					
F13A1	0	.002	.002	1.58	1.67
D6S1959‡	29	.215	.361	0.43	0.37
GATA163B10	40	.085	.253	0.46	0.34
Chromosome 17					
D17S1303	31	.084	.067	0.20	0.35
GATA185H04‡	51	.236	.283	0.41	0.48
D17S1293	61	.039	.043	0.55	0.65
D17S1299‡	69	.014	.013	0.42	0.43
D17S2180‡	73	.089	.062	0.37	0.31
D17S1290	90	.014	.011	0.36	0.34
ATA43A10‡	100	.047	.114	0.44	0.26
Chromosome 20					
D20S478‡	52	.236	.171	0.88	0.80
D20S481	61	.034	.055	1.07	0.91
SHGC-8524‡	63	.537	.485	1.42	1.09
D20S480	75	.002	.007	1.52	1.22

*Distance from P-terminus. cM = centimorgans.
†*P* value from one-sided *t* test: H_o: $\beta_1 \geq 0$ versus H_a: $\beta_1 < 0$.
‡Markers performed in addition to markers from initial genome screen.

A total of 68 individuals in 71 sibpairs and 10 mother-daughter pairs in 22 families were eligible for the linkage analysis. Mean percent breast density was 36.2% (95% confidence interval [CI] = 31.5–40.9); the mean age was 58 years (95% CI = 55.4–60.4), and 16.4% of the women were premenopausal.

We initially analyzed 147 markers across the genome; six additional markers in suggestive regions were subsequently typed. The two-point sibpair analyses on the unadjusted and adjusted breast density trait revealed three regions of suggestive linkage, including F13A1 on chromosome 6 (*P* value from one-sided *t* test of regression coefficient; $P = .002$), D17S1290 on chromosome 17 ($P = .01$), and D20S480 on chromosome 20 ($P \leq .007$) (*see* Table 1). Of the six additional markers analyzed in the regions on chromosomes 6, 17, and 20, only one marker on chromosome 17 (D17S1299) was statistically significant at $P = .01$ (*see* Table 1).

The multipoint analyses confirmed the suggestion of linkage to the regions on chromosome 6 (logarithm of odds [LOD] score = 1.58) and chromosome 20 (LOD score = 1.52) for the unadjusted percent breast density trait. When adjusted for covariates, only the region on chromosome 6 remained suggestive (LOD score = 1.67).

These preliminary results provide suggestive evidence for a genetic component to percent breast density. Given that increased measures of breast density are common in the population, a gene for breast density could account for a large percentage of breast cancers in the population.

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