Journal of Medical Genetics and Genomics Vol. 4(1), pp. 6 - 12, January 2012
Available online at http://www.academicjournals.org/JMGG
DOI: 10.5897/JMGG11.021
ISSN 2141-2278 ©2012 Academic Journals

Full Length Research Paper

A comparative study of cDNA microarray analysis of familial and sporadic breast cancer in India

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Accepted 5 January, 2012

Many genes and signalling pathways controlling cell proliferation, death and differentiation, as well as genomic integrity, are involved in cancer development. Techniques, such as cDNA microarrays, have enabled measurement of the expression of thousands of genes in a single experiment, revealing many new, potentially important cancer genes. Human breast cancer is usually caused by genetic alterations of somatic cells of the breast, but occasionally, susceptibility to the disease is inherited. As a step towards understanding the differences between familial and sporadic breast cancer in humans, gene expression patterns were examined in breast tumours. Sporadic (n=7) and familial (n=6) tissue samples, and normal breast tissue (n=3) samples, were collected from women who underwent breast surgery at Karnataka Cancer Therapy and Research Institute (KCTRI), Hubli. Total RNA was isolated and subjected to cDNA microarray for 14,992 genes on Agilent's Human 8x15K Array. Gene expression profiles were analysed using Genespring software. F-Test was carried out to find the variance in terms of gene expression patterns between familial and sporadic breast cancer tissue samples. Our study revealed, that, there is no significant variation between sporadic and familial breast cancer in terms of gene expression profiles. With this, it can be concluded that both familial and sporadic breast cancers are similar in terms of the gene expression profiles. This will guide in development of common biomarkers for both familial and sporadic breast cancer and will also help in diagnosis, prognosis and treatment.

Key words: cDNA microarray, gene expression profiling, familial breast cancer, sporadic breast cancer, F-test, variance, India.

INTRODUCTION

Breast cancer and other malignancies result from stepwise genetic alterations of normal host cells, and, possibly from other nongenetic (or epigenetic) changes in the behaviour of not only malignant cells, but also host cells that interact with the tumour, such as immune, vascular, and stromal cells (Nowell, 1976; Beckmann et al., 1997; Lerebours and Lidereau, 2002; Balmain et al., 2003). A growing understanding of these changes and

the associated pathways through which they operate has led to opportunities for diagnostic and therapeutic applications (Osborne et al., 2004). Gene-expression profiling with the use of cDNA microarrays allows measurement of thousands of messenger RNA (mRNA) transcripts in a single experiment.

Results of such studies have confirmed that breast cancer is not a single disease with variable morphologic features and biomarkers but, rather, a group of molecularly distinct neoplastic disorders. Moreover, such profiling has uncovered molecular signatures that could influence clinical care (Sotiriou and Pusztai, 2009). Familially occurring breast cancer has been an area of interest for a long time because of its potential for providing clues concerning the cause of, and identifying those at high risk for this disease. Studies comparing patients with familial and sporadic breast cancers have been ongoing for at least eight decades. Two findings have been reported as follows:

(a) A family history of breast cancer can increase a woman's risk of getting the disease twofold to threefold; and
(b) Patients with familial breast cancer are younger when the diagnosis is made and have a higher frequency of bilateral disease than those with sporadic breast cancer (Kelsey and Hildreth, 1983; Petrakis et al., 1982).

These differences led to the hypothesis that familial and sporadic breast cancers are the consequences of two biologically distinct mechanisms (Lynch et al., 1984) resulting in different clinicopathologic characteristics or other markers that might aid in the identification of high-risk families and women. Comparisons between patients with familial and sporadic breast cancer were done with respect to the age at menarche (Anderson and Badzioch, 1989; Ruder et al., 1988), age at the birth of their first child (Mosimann et al., 1990; Wobbes et al., 1987) parity (Burki et al., 1990; Wobbes et al., 1987), histopathology findings (Anderson, 1970; Castiglione-Gertsch et al., 1990; Mulcahy Platt, 1981; Mosimann et al., 1990; Burki et al., 1990), site and size of the primary tumor (Castiglione-Gertsch et al., 1990; Wobbes et al., 1987) stage of the disease (Ruder et al., 1988; Burki et al., 1990; Wobbes et al., 1987), survival (Ruder et al., 1988; Castiglione-Gertsch et al., 1990; Wobbes et al., 1987; Anderson et al., 1986; Anderson, 1971; Langlands et al., 1976; Lynch et al., 1981; Lynch, 1981; Albano et al., 1982), receptor status (Castiglione-Gertsch et al., 1990), response to therapy (Castiglione-Gertsch et al., 1990), number of involved nodes (Castiglione-Gertsch et al., 1990) and blood groups and other genetic markers, including oncogene (Anderson et al., 1971; Anderson and Haas, 1984; Costantini et al., 1990; Barkardottir et al., 1989).

However, either no consistent differences were found, or the results were equivocal. In 1971, a two-step mutation model was proposed (Knudson, 1971). According to this model, all cancers are of two types, hereditary and sporadic, and both types involve the same genomic change. The model is based on the premise that most cancers are derived from a single cell and that at least two mutational events are required for the development of cancer. The only difference between the two types is that, in hereditary (or familial) cancers, the first mutational event is inherited. In this case, the first anomaly is present in all cells of an individual at birth and can be transmitted through the germ cells; the second event is somatic. In sporadic cancers, both mutations are somatic.

Thus, hereditary cancers occur early in life and are multiple, whereas sporadic cancers occur late in life and are single because of the rare occurrence of two somatic events happening at the same genomic site. This model has been shown to apply to several childhood and adult cancers, including breast cancer (Cavenee et al., 1986; Fearon et al., 1984; Koufos et al., 1984; Lundberg et al., 1987; Ali et al., 1987; MacKay et al., 1988; MacKay et al., 1988; Devilee et al., 1990; Sato et al., 1990). Based on this model, it is not surprising that consistent differences were not observed between patients with familial and sporadic breast cancer because both types involve the same genomic change and the pathogenesis of both types would be expected to be the same (Moolgavkar et al., 1981; Anderson, 1992).

Considering the aforementioned facts, our research group carried out cDNA based gene expression profiling for sporadic and familial breast cancer tissue samples for 14,992 genes and compared them for variance. Among these, a set of major oncogenes and tumour suppressor genes were also selected and compared for variance in sporadic and familial breast cancer.

MATERIALS AND METHODS

Patient selection

Cytologically diagnosed cases of breast cancer patients admitted to KCTRI were included in this study. Tissue samples were collected with the informed consent of the patient. Familial breast cancer patients were selected based on the condition that each of them had at least one first degree relative affected with breast cancer (Phipps andd Perry, 1988). The criteria for the selection of familial breast cancer patients were based on the earlier studies (Kumar et al., 2002). A total of six familial breast cancer, seven sporadic breast cancer and three normal breast tissue samples were selected for the analysis.

Sample collection

Tumor as well as normal samples from the same breast of enrolled

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patients were collected within 15 min of surgery. The collected samples were stored at -70°C in RNAlater® solution (Ambion®, AM7020) for RNA isolation.

RNA extraction and target labeling

Total RNA was extracted from all the tissue samples using the Qiagen RNA Easy minikit (Cat.No.74104), according to the instructions of the manufacturer. The RNA integrity was assessed using RNA 6000 Nano Lab chip on the 2100 Bioanalyser following manufacturer's protocol. Total RNA purity was assessed by the Eppendorf UV-VIS Biophotometer. Total RNA with OD 260/OD280>1.8 and OD260/OD270>1.3 was used for micro array based gene expression experiments. The RNA was considered to be of good quality when the rRNA 285/185 ratios are greater than or equal to 1.5 with the rRNA contribution being 30% or more and an RNA Integrity Number (RIN) to be >7.0.

Agilent's Quick-Amp labeling Kit (p/n5190-0442) was used for 1Labeling. Briefly, both first and second strand cDNA was synthesized by incubating 500 ng of total RNA with 1.2 µl of oligo dT-T7 promoter primer in nuclease free water at 65°C for 10 min followed by incubation with 4.0 µl of 5x First Strand buffer, 2 µl of 0.1 M DTT, 1 µl of 10 mM dNTP mix 1 µl of 200 U/µl MMLV-RT and 0.5 µl of 40 U/µl RNase OUT, at 40°C for 2 h. Immediately following cDNA synthesis, the reaction mixture was incubated with 2.4 µl of 10 mM Cyanine 3-CTP (Perkin–Elmer, Boston MA) 20 µl of 4X Transcription buffer, 8 µl of NTP mixture, 6 µl of 0.1 M DTT, 0.5 µl of RNase OUT, 0.6 µl of Inorganic pyrophosphatase, 0.8 µl of TT RNA polymerase and 15.3 µl of nuclease free water at 40°C for 2 h. Qiagens RNeasy mini spin columns were used for hybridization. 825 ng of Cyanine 3 labeled cDNA in a volume of 41.8 µl was combined with 1.1 µl of 10X Blocking reagent and 2.2 µl of 25X fragmentation buffer and incubated at 60°C for 30 min in the dark.

The fragmented cDNA was mixed with 5.5 µl of 2X hybridization buffer. About 110 µl of the resulting mixture was applied to Human 8x15K Array covering 14,992 genes, (AMADID: 035928) Gene expressions Micro Array (Agilent Technologies, USA) and hybridized at 65°C for 17 h in an Agilent Microarray Hybridization Chamber with hybridization oven. After hybridization, the slides were washed with Agilent gene expression wash buffer I for 1 min at room temperature followed by 1 min wash with Agilent gene expression wash buffer II at 37°C. Slides were finally rinsed with acetonitrite for cleaning up and drying.

Hybridization, scanning, and feature extraction

Hybridized arrays were scanned at 2 µm resolution on an Agilent DNA Microarray scanner.

Data extraction from images was carried out using Agilent feature extraction software

cDNA microarray data analysis

Feature extracted data were analyzed using GeneSpring GX Version 11.5 software from Agilent. Normalization of the data were done using per spot per chip intensity dependent lowest normalization. Further quality control of normalized data was done using correlation based condition tree to eliminate bad experiments. One fold and above differentially regulated genes were filtered from the data. Differentially regulated genes were clustered using gene tree to identify significant gene expression patterns (Figure 1).

Analysis of variance

Comparing the normal tissue gene expression profiles with that of sporadic and familial breast cancer tissue gene expression, the data were grouped. The data from both familial and sporadic cancer tissue samples were subjected to F-Test in Microsoft Excel 2007. Similar test was also carried out on results of gene expression profiles of major oncogenes and tumour suppressor genes (Osborne et al., 2004) in both familial and sporadic breast cancer tissue samples.

RESULTS

The results of the analysis of gene expression profiling using Human 8x15K Array covering 14,992 genes for 6 familial breast cancer tissue samples, 7 sporadic breast cancer tissue samples and 3 normal breast tissue samples are presented in Figure 1 and Tables 1 to 4. The cluster analysis of differentially regulated genes using gene tree to identify significant gene expression patterns (Figure 1), shows two major clusters. The first major cluster consists of normal breast tissue. But the second major cluster consists of sub-clusters of both sporadic and familial breast cancer tissues in mixed patterns. Fold variation of all the genes were obtained in terms of log in base 2. To filter upregulated genes, we followed the methodology that a gene which is detected and expressed in the cancer sample should be detected and expressed in the normal sample≥0.6 fold and ≥0.8 in the geomeanfold (average). Similarly, to select downregulated genes, we considered a gene which is detected and expressed in the cancer sample should be detected and expressed in the normal sample -≤0.6 fold and -≤0.8 in the geomeanfold (average).

The fold variations in terms of gene expression of all the genes were subjected to F-Test two samples for variance in two groups namely sporadic and familial breast cancer tissue samples. The analysis of variance was carried out with 95% confidence and 5% α error (Table 1). It was observed that the critical F value 1.2072 is greater than the calculated F value 1.1408. The F-Test result revealed that there is no significant variation between sporadic and familial breast cancer tissue samples interms of gene expression profiles when all the detected genes were compared. Similarly, the fold variations of major oncogenes (Table 2) were subjected to F-Test two samples for variance (Table 3) and it was found that critical F value 1.8820, is greater than calculated F value 1.0323. Hence, the F test results for oncogenes suggest that there is no significant variance between familial and sporadic breast cancer in terms of oncogene expressions. But in case of tumor suppressor genes (Table 4), when F-Test of two samples for variance was calculated, it was found that critical F value is smaller than the calculated F value, showing the slight variance in terms of tumor suppressor gene expression.

DISCUSSION

Breast cancer is a disease caused by a complex

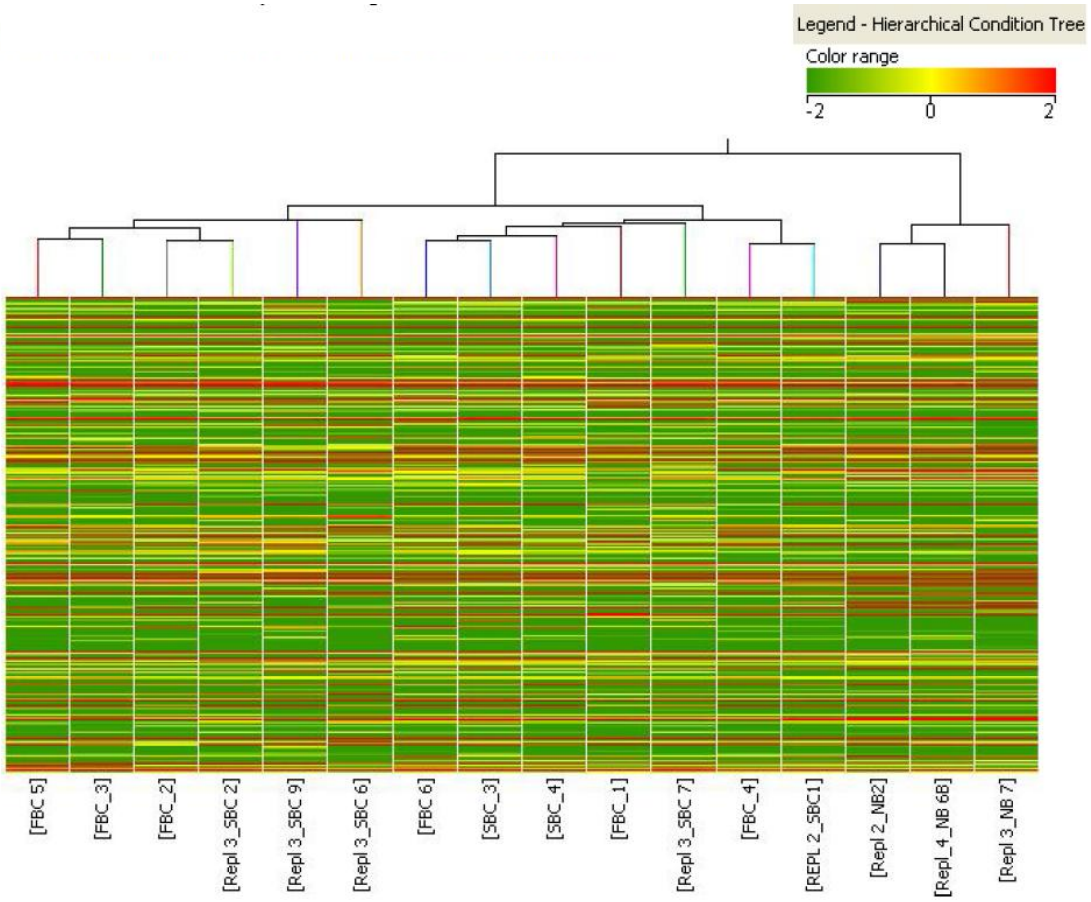

Figure 1. Clusters for Intra array QC. The normalization has been done using GeneSpring GX 11.5 Software. [Normalization Used for QC: 75th Percentile shift Normalization. Percentile shift normalization is a global normalization, where the locations of all the spot intensities in an array are adjusted. This normalization takes each column in an experiment independently, and computes the percentile of the expression values for this array, across all spots (where n has a range from 0-100 and n=50 is the median). It subtracts this value from the expression value of each entity]. FBC: Familial breast cancer; SBC: sporadic breast cancer; NB: normal breast.

Table 1. F-Test results for all the detected genes.

Observation	Familial breast cancer	Sporadic breast cancer
Mean	-0.28816924838	-0.224580363
Variance	2.0115	1.7632
Observations	14992	14992
Degree of freedom	14991	14991
F	1.1408	
P(F<=f) one-tail	3.6596	
F Critical one-tail	1.2072	

F-Test was carried out with 95% confidence and 5% α error.

interaction of genetic and environmental factors. Well-established risk factors have been described for breast cancer, such as early menarche, late menopause, age of first child's birth, nulliparity and family history (FH) (Dumitrescu and Cotarla, 2005). FH of breast cancer is a particularly important high-risk factor for this disease. Two genes were identified as the major susceptibility genes in high-risk families, namely BRCA1 and BRCA2. However, these genes account for only a minority of the overall family risk of breast cancer (Dapic et al., 2005).

Table 2. Showing the list of fold variation in terms of gene expression profiling in major oncogenes. Negative value (-) indicates down regulation of the gene.

S/N	Gene name	Mean fold variation familial breast cancer	Mean fold variation sporadic breast cancer
1	AKT1	0.27	0.36
2	AKT2	-0.77	-1.03
3	AKT3	-1.42	-1.22
4	CDK10	0.56	0.83
5	CDK2	-0.37	-0.59
6	CDK3	-0.04	-0.08
7	CDK4	0.38	0.70
8	CDK5	0.88	0.85
9	CDK6	-0.29	1.02
10	CDK7	0.57	0.14
11	CDK8	1.02	1.47
12	CDK9	-0.26	-0.66
13	EIF4E	-0.08	0.44
14	FOS	-2.06	-1.88
15	HERC1	-0.74	-0.94
16	HERC2	0.91	0.95
17	HERC3	-2.75	-2.21
18	HERC5	0.62	0.10
19	HRAS	0.12	0.07
20	KRAS	0.88	1.25
21	MRAS	-2.61	-2.26
22	MYC	-1.02	-0.73
23	PI3	-0.44	-0.93
24	RASA1	-0.36	-0.40
25	RASA2	0.71	0.82
26	RASA3	-0.95	-0.81
27	RASA4	-0.10	0.09
28	RASD1	-3.11	-2.82
29	RASD2	0.29	0.01

Table 3. F-Test results for major oncogenes genes.

Observation	Familial breast cancer	Sporadic breast cancer
Mean	-0.35034482	-0.2572
Variance	1.2757	1.2357
Observations	29	29
Degree of freedom	28	28
F	1.0323	
P(F<=f) one-tail	0.4667	
F Critical one-tail	1.8820	

F-Test was carried out with 95% confidence and 5% α error.

Furthermore, approximately 10% of all breast cancer cases exhibit a familial pattern of incidence (Ford et al., 1998). In this way, the identification of genetic susceptibility factors that account for low to moderate breast cancer risk is an important step in the definition of individual risk to this malignancy.

Some studies have demonstrated a strong association of higher levels of DNA damage and lower DNA repair capacity in breast cancer patients and in healthy women with a positive FH of breast cancer (Jyothish et al., 1998;

Table 4. Showing the list of fold variation in terms of gene expression profiling in major tumour suppressor genes. Negative value (-) indicates down regulation of the gene.

S/ No.	Gene name	Mean fold variation familial breast cancer	Mean fold variation sporadic breast cancer
1	TP53	0.78	-0.14
2	MMP27	-1.32	-1.52
3	BRCA1	0.62	0.46
4	BRCA2	2.17	2.53
5	CHKA	-0.10	0.68
6	CHKB	0.04	0.10
7	ATM	0.76	0.49
8	RB1	-0.42	-0.66

Helzlsouer et al., 1996). Genetic polymorphisms in DNA repair genes are very common events (Kuschel et al., 2002; Shen et al., 1998; Mohrenweiser et al., 2002), and some studies have shown a significant effect of some of these polymorphisms in DNA repair capacity (Pachkowski et al., 2006; Clarkson and Wood, 2005; Matullo et al., 2001; Costa et al., 2007).

In our study, we analyzed for variance between sporadic and familial breast cancer tissue samples in terms of gene expression. This study is first of its kind in this population. Our results suggest that there is no significant variation between sporadic and familial breast cancer tissue samples in terms of gene expression. Similarly, major oncogenes and tumor suppressor genes were also analyzed for variance. We found that there is no significant variation between sporadic and familial breast cancer tissue samples, when only major oncogenes were compared. But slight variance was observed in tumor suppressor genes. This might be because of a very small number of tumor suppressor genes considered. Our results are in agreement with the hypothesis proposed in 1971; a two step mutation model (Knudson, 1971). This study suggests that the genetic signature in both familial and sporadic breast cancer is similar.

ACKNOWLEDGMENTS

The authors are thankful to the Department of Medical and Higher Education Government of Karnataka for providing financial assistance to undertake this work. The authors are also grateful to the doctors and the staff of KCTRI, Hubli; for their cooperation in the collection of breast cancer tissue samples.

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