Metagenomic Analysis of Molecular Profile of Breast Cancer Using Genie a Literature Based Gene Prioritizing Tool: A Novel Approach

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Abstract

**Background:** The biological complexity and heterogeneity of breast cancer can be explained by molecular profile. Microarray technique is the method of choice to study it. But there are certain limitations. Computational techniques are a novel method to study gene expression profile.

**Materials and method:** Genie, a freely available web based software was used to analyze literature, gene and homology information from MEDLINE, NCBI Gene and HomoloGene databases. Inputs given were target species (Homo sapiens) and biomedical topic (breast cancer). According to input provided genes of target species are prioritized.

**Results:** The ranking given to 1906 reported genes was not along expected lines. Therefore, they were manually re-ranked according to number of hits. These were narrowed to 70. The proteins encoded by these genes and their functions were obtained from NCBI database. On the basis of their function and role in carcinogenesis these genes were then grouped together into distinct categories.

**Conclusion:** A novel computational approach to study molecular profile of breast cancer has been demonstrated. A panel of 70 genes to study gene expression profile of breast cancer has been suggested. These genes comprehensively evaluate all aspects of molecular pathogenesis of breast cancer and recommended for future clinical studies.

Keywords: Breast cancer; Molecular profile; Genie; Gene prioritization; Metagenomic analysis

Introduction

Breast cancer is a very complex and heterogeneous disease. The vast majority of cases are morphologically infiltrating ductal carcinoma NOS. However, in these morphologically similar looking cases the biological behaviour is different. This leads to difference in response to therapy and outcome. Clinical parameters like age, tumour stage, grade and routinely used biomarkers like estrogen receptor (ER), progesterone receptor (PR) and HER2-neu cannot fully explain this heterogeneity [1,2]. This is due to the difference in molecular profile of each case.

Traditional classification of breast cancer is based on morphology. The study of gene expression profile has led to a new system of classification. In 2000, Perou and co-workers [3] in a seminal paper classified breast cancer into intrinsic subtypes based on gene expression profile. Subsequent work of numerous authors has fundamentally changed the way breast cancer is understood and classified [4-6].

Microarray technique which allows simultaneous analysis of expression of thousands of genes has been the method of choice to study gene expression profile of breast cancer [7]. The disadvantage of this technique is the limited sample and variability [8,9]. Also a comprehensive summarization of the genes is not possible due to the large number of genes and abstracts involved.

A novel approach to study molecular profile is using computational techniques to study gene function by analyzing the vast literature which is now available. Fontaine and co-workers [10] developed the Genie algorithm and web server. The input for the software is a biological topic.

It evaluates the entire MEDLINE database for relevance to that subject, and then evaluates all the genes of a user’s requested organism according to the relevance of their associated MEDLINE records. The advantage of this approach is that large amount of published data regarding genes in a particular disease can be analyzed. This kind of analysis at a multi genomic scale is not possible without computational approach. To the best of our knowledge this approach has not been used to date for studying molecular profile of breast cancer.

**Materials and Method**

Genie is freely available to all researchers at http://cbdm.mdc-berlin.de/tools/genie/. The algorithm and web server takes advantage of literature, gene and homology information from the MEDLINE, NCBI Gene and HomoloGene databases [8].

The system requires two basic inputs: a target species (e.g., Homo sapiens) and a biomedical topic ideally related to a gene function (breast cancer in the present study). According to the input provided the genes of the target species are prioritized. The target species is defined by its scientific name or its taxonomic ID (e.g., Homo sapiens - 9606).

The biomedical topic is ultimately defined by a set of biomedical references represented by MEDLINE records. After giving the inputs the software initialised in 9 seconds and the analysis was complete in 73 seconds. It went through 796 abstracts on PubMed. All the relevant protein coding genes as per the input provided were analyzed. In order to ensure that only significant genes were reported the cut offs were...
taken as p<0.01 for abstracts and false discovery rate<0.01 for genes. A one-sided Fisher's exact test was carried out by the algorithm to define the significance of gene-to-topic relationship. It compared the number of selected abstracts to what is observed in a simulation using a set of ten thousand randomly selected abstracts.

Literature extension by orthology was not done as it was not needed. This is done when genes from poorly studied organisms are studied. The genes are ranked using, in addition to the abstracts directly associated to them, the abstracts associated to their orthologs in other species.

The genes are then presented in a list sorted by false discovery rate (FDR) with hyperlinks to the most significant abstracts. Entrez Gene and HomoloGene databases. A list of the words found to be relevant to the topic is provided to facilitate the interpretation of the results.

Results

A total number of 1906 genes were reported by the software to be associated with breast cancer. These genes were prioritized and ranked according to the abstracts directly associated with them. It was observed that the ranking given by the software was not along expected lines as it did not correlate with the data available from previous work [11-14]. For example, ZNF703 (zinc finger protein 703) was given first rank while ERBB2 (erb-b2 receptor tyrosine kinase) and ESR1 (estrogen receptor 1) were ranked third and seventh respectively.

In order to remove this discrepancy an alternative method of ranking was devised. The genes were ranked manually according to the number of hits that is the gene with the maximum number of hits was ranked first and one with minimum number of hits was ranked last. In order to find out the most important genes different cut offs for the number of hits were used – 50 and 100 (Table 1). The number of cut offs was arrived at by trial method.

When cut off was used as 50 a total of 70 genes were selected, whereas a cut off of 100 yielded 33 genes. The first 5 ranks are now occupied by EGFR (epidermal growth factor receptor), TP53 (tumor protein p53) and HomoloGene databases. A list of the words found to be relevant to the topic is provided to facilitate the interpretation of the results.

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Table 1: Genes reported by genie software with their rank, gene ID, symbol, PMID and number of hits.

and BRCA1 (breast cancer 1, early onset) genes. Previously these were taken by ZNF703 (zinc finger protein 703), GREB1 (Growth regulation by estrogen in breast cancer 1), ERBB2 (erb-b2 receptor tyrosine kinase 2), CST6 (cystatin E/M) and WISP2 (WNT1 inducible signalling pathway protein 2).

The proteins encoded by these genes and their functions were obtained from NCBI database. These are summarized in Table 2. On
 Gene Cyclin-dependent kinase inhibitor 2a Stimulates transcription of androgen responsive genes. 

AR Progestrone receptor MAPK3 Chemokine (c-x-c motif) receptor 4 Prostaglandin-endoperoxide synthase 2 Acts on endothelial cells and leads to increased vascular permeability, inducing angiogenesis, 

CYP19A1 Cytochrome p450, family 19, subfamily a, Member of a family of proteins involved in mediating growth and development. 

CTNNB1 Catenin (cadherin-associated protein), beta 1, Breast cancer 1, early onset 

ERBB2 erb-b2 receptor tyrosine kinase 2 Member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. It forms a heterodimer, stabilizing ligand binding and enhancing kinase-mediated activation of downstream signaling pathways, 

MAPK1 Cyclin-dependent kinase inhibitor 1a (p21, cip1) Controls the cell cycle progression at G1. 

SRC V-akt murine thymoma viral oncogene homolog 1 Role in cell survival and inhibition of apoptosis. 

EZH2 Estrogen receptor 2 Binds to estrogen hormone and interact with specific DNA sequences to activate transcription. 

HIF1A Hypoxia inducible factor 1, alpha subunit Master regulator of cellular and systemic homeostatic response to hypoxia by activating transcription of many genes. 

MAPK1A Mitogen-activated protein kinase 1 

MAPK1B Cyclin-dependent kinase inhibitor 1b 

MET Met proto-oncogene, receptor tyrosine kinase Encodes tyrosine-kinase activity. 

UBC Ubiquitin c Protein degradation, DNA repairs, cell cycle regulation, kinase modification, endocytosis, and regulation of other cell signalling pathways. 

CD44 Cdc44 molecule (Indian blood group) Participates in a wide variety of cellular functions including lymphocyte activation, recirculation and homing, hematopoiesis, and tumor metastasis. 

SRC Src proto-oncogene, non-receptor tyrosine kinase Regulation of embryonic development and cell growth. 

CDKN1B Cyclin-dependent kinase inhibitor 1b 

Kras Kirsten rat sarcoma viral oncogene homolog Member of the small GTPase superfamily. 

MAPK1 Mitogen-activated protein kinase 1 Integration point for multiple biochemical signals, and involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation and development. 

MYC V-myc avian myelocytomatosis viral oncogene homolog Role in cell cycle progression, apoptosis and cellular transformation. 

NCOA3 Nuclear receptor coactivator 3 Nuclear receptor coactivator that interacts with nuclear hormone receptors to enhance their transcriptional activator functions. 

IGF1 Insulin-like growth factor 1 Member of a family of proteins involved in mediating growth and development. 

CDK2 Cyclin-dependent kinase inhibitor 2a Involved in cell cycle G1 control and is an important tumor suppressor gene. 

MAPK3 Mitogen-activated protein kinase 3 Act in a signaling cascade that regulates various cellular processes such as proliferation, differentiation, and cell cycle progression in response to a variety of extracellular signals. 

MMP2 Matrix metalloproteinase 2 Zinc-dependent enzymes capable of cleaving components of the extracellular matrix and molecules involved in signal transduction. 

ESR1 Estrogen receptor 1 Localizes to nucleus and binds estrogen hormone. 

PTGS2 Prostaglandin-endoperoxide synthase 2 Prostaglandin biosynthesis 

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MMP2 Matrix metalloproteinase 2 Zinc-dependent enzymes capable of cleaving components of the extracellular matrix and molecules involved in signal transduction.
43 MUC1  Mucin 1, cell surface associated  Membrane-bound protein playing an essential role in forming protective mucous barriers on epithelial surfaces and intracellular signaling.

44 ABCG2  ATP-binding cassette, sub-family g (white), member 2 (junior blood group)  Transport various molecules across extra- and intra-cellular membranes. Also referred to as a breast cancer resistance protein, this protein functions as a xenobiotic transporter which may play a major role in multi-drug resistance.

45 IL6  Interleukin 6  Cytokine that functions in inflammation and the maturation of B cells.

46 VEGFC  Vascular endothelial growth factor c  Promotes angiogenesis and endothelial cell growth, and can also affect the permeability of blood vessels.

47 EZH2  Enhancer of zeste 2 polycomb repressive complex 2 subunit  Involved in maintaining the transcriptional repressive state of genes over successive cell generations.

48 ABCB1  ATP-binding cassette, sub-family b (mdr/tap), member 1  Transport various molecules across extra- and intra-cellular membranes. Involved in multidrug resistance by acting as an ATP-dependent drug efflux pump. It often mediates the development of resistance to anticancer drugs.

49 MKI67  Marker of proliferation ki-67  Associated with and may be necessary for cellular proliferation.

50 CXCL12  Chemokine (c-x-c motif) ligand 12  Functions as the ligand for the G-protein coupled receptor, chemokine (C-X-C motif) receptor 4, and plays a role in many diverse cellular functions, including embryogenesis, immune surveillance, inflammation response, tissue homeostasis, and tumor growth and metastasis.

51 PPARG  Peroxisome proliferator-activated receptor gamma  Regulator of adipocyte differentiation.

52 ERBB3  Erb-b2 receptor tyrosine kinase 3  Forms heterodimers with other EGF receptor family members having kinase activity. This leads to the activation of pathways which lead to cell proliferation or differentiation.

53 TNFSF10  Tumor necrosis factor (ligand) superfamily, member 10  Preferentially induces apoptosis in transformed and tumor cells, but does not appear to kill normal cells although it is expressed at a significant level in most normal tissues.

54 SPP1  Secreted phosphoprotein 1  Cytokine that upregulates expression of interferon-gamma and interleukin-12.

55 NOTCH1  Notch 1  Play a role in a variety of developmental processes by controlling cell fate decisions.

56 PTK2  Protein tyrosine kinase 2  Cell growth and intracellular signal transduction pathways triggered in response to certain neural peptides or to cell interactions with the extracellular matrix.

57 SP1  Sp1 transcription factor  Zinc finger transcription factor involved in many cellular processes, including cell differentiation, cell growth, apoptosis, immune responses, response to DNA damage, and chromatin remodeling.

58 TNF  Tumor necrosis factor  Regulation of a wide spectrum of biological processes including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation.

59 HDAC1  Histone deacetylase 1  Component of the histone deacetylase complex. It also interacts with retinoblastoma tumor-suppressor protein and this complex is a key element in the control of cell proliferation and differentiation.

60 CAV1  Caveolin 1, caveole protein, 22kda  Promote cell cycle progression and tumor suppressor gene

61 RELA  V-rel avian reticuloendotheliosis viral oncogene homolog a  Inhibitor of NF-kappa-B (NFKB1).

62 SERPINB5  Serpin peptidase inhibitor, clade b (ovalbumin), member 5  Tumor suppressor. It blocks the growth, invasion, and metastatic properties of mammary tumors.

63 CD24  CD24 molecule  Modulates growth and differentiation signals to granulocytes and B cells.

64 SNAI1  Snail family zinc finger 1  Zinc finger transcriptional repressor which downregulates the expression of ectodermal genes within the mesoderm.

65 PLA2  Phospholipase a, urokinase  Serine protease involved in degradation of the extracellular matrix and possibly tumor cell migration and proliferation.

66 RASSF1  Ras association (gldgs/af-6) domain family member 1  Tumour suppressor function.

67 MDM2  Mdm2 proto-oncogene, e3 ubiquitin protein ligase  Promote tumor formation by targeting tumor suppressor proteins, such as p53, for proapoptotic degradation.

68 RB1  Retinoblastoma 1  Negative regulator of the cell cycle and a tumor suppressor gene.

69 IGFBP3  Insulin-like growth factor binding protein 3  Protein forms a ternary complex with insulin-like growth factor acid-labile subunit (IGFALS) and either insulin-like growth factor (IGF) I or II. It circulates in the plasma, prolonging the half-life of IGFs and altering their interaction with cell surface receptors.

70 GSTP1  Glutathione s-transferase pi 1  Function in xenobiotic metabolism and play a role in susceptibility to cancer, and other diseases.

Table 2: Proteins encoded by the genes and their function.

- a) Proliferation.
- b) Evading apoptosis.
- c) Invasion and metastasis.
- d) Sustained angiogenesis.
- e) Tumour suppressor genes.
- f) Estrogen.
- g) Her-2 neu.
- h) Miscellaneous.

Discussion

Breast cancer is a leading cause of cancer related mortality in women. As per WHO statistics [15] nearly 1.7 million new cases were diagnosed in 2012 (second most common cancer overall). This represents about 12% of all new cancer cases and 25% of all cancers in women. Traditionally clinical parameters like age, tumour stage, grade and routinely used biomarkers like oestrogen receptor(ER), progesterone receptor (PR) and HER2-neu have been used to evaluate the prognosis and guide therapy [16,17].
Vast amount of molecular information in breast cancer is now available from gene expression profiling studies. These have become an extremely important tool to assess the prognosis and guide appropriate management [18]. The technique of choice for this is microarray. The data that has become available from gene expression profile studies has impacted not only the management of breast cancer but also tumours like lung [19,20] and colon cancer [21]. However, microarray technique suffers from many disadvantages as mentioned previously [8,9]. Thus there is a need to explore alternative methods to study gene expression profile of breast cancer.

The authors have used one such technique Genie algorithm and web server in the present study to evaluate molecular profile of breast cancer. The utility of computational approach to find human genes associated with a disease has been shown previously [22-24]. However, Genie goes one step ahead and besides highlighting well known genes it brings out new candidate genes [10]. This helps in better characterization of a disease.

There are alternative gene prioritizing tools that perform automatic gene name extraction and normalization [25,26]. The basic concept behind such an analysis is that when two words repeatedly occur together in an abstract they are likely to be functionally related. However, these methods suffer from a disadvantage that they wrongly identify genes in text which leads to ambiguous results [27,28]. Genie overcomes this limitation by using NCBI curated gene associations and unambiguous gene identifiers [10].

A total number of 1906 genes were found to be associated with breast cancer. These genes were manually ranked using the number of hits as a parameter. Then the number of genes was further narrowed down by using two cut offs, i.e., 50 and 100 hits. These yielded 70 and 33 genes respectively. The authors feel that 33 genes are not sufficient for a comprehensive analysis of gene expression profile. Thus it is recommended that at least 70 genes should be studied for a proper examination. On categorization of these genes on the basis of function it was observed that amongst all the categories maximum number of genes belonged to the proliferation related group (24 genes). This was followed by tumour suppressor genes (12 genes). Overall the genes reported by the software comprehensively cover all aspects of the biology of breast cancer.

The availability of new data from microarray studies led to the development of many multigene prognostic tests to improve assessment of prognosis and therapeutic response in breast cancer [29]. The most widely used amongst these are Oncotype DX [14] and MammaPrint [13].

Oncotype DX (Genomic Health, Redwood City, CA, USA) is based on high-throughput real time, reverse transcriptase polymerase chain reaction (RT-PCR) analysis of formalin fixed paraffin-embedded (FFPE) tumor tissue [30,31]. Thus, it can also be used on archival blocks. The test utilizes 16 genes which have been shown to have highest correlation with distant recurrence after 10 years along with five housekeeping genes. The test algorithm is designed to calculate recurrence score (RS) from 0 to 100. A higher RS is associated with greater probability of recurrence at 10 years and vice versa.

MammaPrint (Agilent, Amsterdam, Netherlands) is a microarray-based test. It measures the expression of 70 genes. The test is recommended as an adjunctive prognostic test for breast cancer patients who are less than 61 years of age with stage I/II disease, lymph node-negative or one to three lymph node-positive [12]. MammaPrint stratifies patients into low-risk or high-risk prognostic groups [13]. The prognostic risk discrimination is good among. In patients who are ER-positive the assay has a good prognostic risk assessment. However, almost all ER-negative cases are stratified as high risk. This makes the prognostic score of limited clinical value in this group [32].

A large multicenter retrospective study suggested that adjuvant chemotherapy was beneficial only in the high-risk ER positive patients [33]. MammaPrint as described originally needed fresh-frozen tissue. This was a major drawback and reason for its limited clinical utilization. However, recently described version of the test can be performed on FFPE tissue [34].

Using a novel computational technique to carry out molecular
profiling at a multi-genomic scale the authors suggest an alternative panel of genes (Table 1) to study gene expression profile of breast cancer. It is believed that this panel includes some of the important genes which were not present in the initial panels.

A comparison was done between the panel suggested in the present study and those included in Oncotype DX [14] and MammaPrint [13]. In case of Oncotype DX out of the total 16 genes related to breast cancer 6 (38%) are also present in the new panel. While in the case of MammaPrint out of the total 70 only a single gene i.e. MMP9 is shared with our panel. Thus there was greater correlation with Oncotype DX as compared to MammaPrint.

In a recent review of clinical utility of gene-expression profiling in women with early breast cancer Marrone and his co-workers [35] have said that five systematic reviews found no direct evidence of clinical utility for either Oncotype DX or MammaPrint. Indirect evidence showed Oncotype DX was able to predict treatment effects of adjuvant chemotherapy, whereas no evidence of predictive value was found for MammaPrint. No studies provided any direct evidence that using gene-expression profiling tests to direct treatment decisions improved outcomes in women with breast cancer. The authors believe that one of the main reasons for this apparent failure of the two techniques to influence treatment outcome is probably inappropriate gene selection. On going through the list of genes in both the tests it was felt that possibly some important genes have not been included. Thus there is a need for an alternative panel.

Conclusion

The present study has demonstrated a novel computational approach to study molecular profile of breast cancer using gene, a gene prioritizing software. A novel panel of 70 genes to study gene expression profile of breast cancer has been suggested in which the majority of genes are different from currently used panels. These genes we believe comprehensively evaluate all aspects of the molecular pathogenesis of breast cancer. However, the clinical utility of the present study can only be found out by carrying out well designed clinical studies in the future.

References


