Visualizing and identifying the DNA methylation markers in breast cancer tumor subtypes

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Abstract. DNA methylation is an epigenetic mechanism that cells use to control gene expression. DNA methylation has become one of the hottest topics in cancer research, especially for abnormally hypermethylated tumor suppressor genes or hypomethylaed oncogenes research. The analysis of DNA methylation data determines the differential hypermethlated or hypomethylated genes that are candidate to be cancer biomarkers. Visualization the DNA methylation status may lead to discover new relationships between hypomethylated and hypermethylated genes, therefore this paper applied a mathematical modelling theory called formal concept analysis for visualizing DNA methylation status.

Keywords: DNA methylation, Epigenetic, hypomethylated genes, hypermethlated genes, Formal concept analysis

1 Introduction

Epigenetics is the study of heritable changes in gene activity and expression that occur without alteration in the underlying DNA sequence (e.g. DNA methylation). DNA sequence consists of only four different nucleotides : adenine (A), cytosine (C), guanine (G) and thymine (T). Genomic DNA is the complete set of DNA for an organism that holds the genetic instructions (genes). Every cell in the human body has 25,000 genes that are located on 46 chromosomes [1]. Gene is the blueprint to encode proteins. The Central dogma of molecular biology explains how gene can be used to synthesize a protein. Central dogma contains two phases : transcription and translation. In the transcription process, the gene is copied to produce mRNA. In the translation process the mRNA translates to protein. The cell type and the biological state can effect on The gene expression process. There are some genes play a role in regulating cell growth. Oncogenes and tumor suppressors are two broad classes of genes controlling cell growth and proliferation, therefore identifying cancer related genes has become very interesting area of research [2]. Methylation play a role in the regulation of gene expression. Methylation occurs in a region located beside the transcription start site of a gene (promoter). Promoter is a region located upstream of a gene where the polymerase binds to start transcription of a gene. Methylation does not alter DNA sequences but it occurs at CpG islands (CpGs) in the promoter region as shown in Figure 1, the 'C'

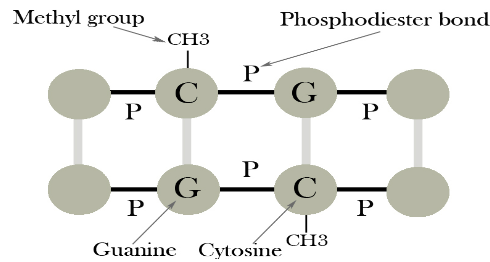

Fig. 1. Methylated CPG sites..

in CpG refers to cytosine, 'G' refers to guanine and 'P' refers to phosphodiester bond between the guanine(G) and the cytosine(c). Methylation of CpG in the promoter can inhibit the expression of genes. Recently microarrays (e.g. Illumina) used to measure many thousands methylation level of CpGs simultaneously in one experiment [3]. Hypomethylated means that the regions are less methylated that can affect the expression of the gene to be more expressed but hypermethylated means that regions have become more methylated that can inhibit the transcription of the gene.

DNA methylation is an important biochemical process for normal development in the higher organisms. DNA methylation occurs by adding a methyl group to the 5 position of cytosine pyrimidine ring, cytosine is one of DNA four nucleotides. Promoters contain a series of a short DNA sequences that provide the binding site for the RNA polymerase enzyme [4,5,6].

Formal concept analysis (FCA) was introduced as a mathematical modelling theory by WILLE (1982) [7]. FCA is very useful for data analysis, also it has been applied in many applications. The concept lattice provides data visualizing which is one of the useful objective of FCA. This lattice is very important for knowledge representation and knowledge discovery therefore becoming more interesting for biologists [8].

The remainder of this paper is organized as follows. Section 2 gives a brief introduction to the biological characteristics of breast cancer subtypes. Section 3 shows the proposed model. Section 4 shows experimental results. Applying FCA for breast cancer subtypes in section 5. Finally, Section 6 offers conclusions and suggestions for future work.

2 The Biological Characteristics Of Breast Cancer Subtypes

Breast cancer can be classified according to receptor status. Receptors are proteins founded on the surface of a cell, in the cytoplasm and nucleus. These receptors have a vital role in receiving chemical signals to keep it from outside into the inside of the cell. Breast cancer receptors such as estrogen receptor (ER), progesterone receptor (PR), and HER2. Breast cancer called estrogen-receptor-positive (ER+) only if it has estrogen receptors. Breast cancer can be called estrogen-receptor-negative (ER-) only if it has not estrogen receptors. It is vital to have a test of hormone receptors to determine the most

Table 1. Hormone receptor status breast cancer tumor subtype.

Subtypes	Hormone receptor status
luminal A	ER+ and/or PR+, HER2-, low Ki67
luminal B	ER+ and/or PR+, HER2+ (or HER2- with high Ki67)
Basal-like	ER-, PR-, HER2-, cytokeratin 5/6 + and/or HER1+
HER2 type	ER-, PR-, HER2+

effective and efficient treatment for this cancer. There are four major breast cancer subtypes called basal-like, ERBB2+, luminal B, and luminal A [9,10]. The relationship of breast cancer subtypes and receptors in Table 1.

2.1 Luminal A and luminal B types

The luminal types are estrogen receptor (ER) positive, usually low grade, grow slowly, and are not aggressive. The growth of Luminal A is slower and the prognosis is better than that of Luminal B tumor.

2.2 HER2 type

This tumor type has HER2 gene over-expression and several other genes disorders. It tends to grow more quickly and has a worse prognosis. Hormone therapy and anti-HER2 therapies can be effective against these types of cancers.

2.3 Basal type

These cancer types are of the so-called triple-negative, they show negative estrogen or progesterone receptors and have normal amounts of HER2. It tends to grow quickly and have a poor prognosis. Hormone therapy and anti-HER2 therapies are not effective against these cancers, however, chemotherapy can be helpful [11,12,13].

3 Proposed Model

Illumina methylation microarray can measure the DNA methylation level in 1505 CPG loci sites from the regulatory regions of 806 cancer related genes (one to five CPG sites per gene). In this paper, we analyze the the DNA methylation data from 28 breast cancer subtypes paired samples, The normal tissue is located at least 2 Centimeters away from site of the tumor. The methylation data reported in this paper have been previously deposited in NCBIs Gene Expression Omnibus (GEO) [14] and are accessible through GEO Series accession number [GEO: GSE22135]. The methylation level measured as a continuous values start from zero (completely unmethylated) to one (completely methylated) [15]. The proposed method implies two phases to identify the most significant hypermethylated genes : non-specific filter and specific filter as shown in Figure 2.

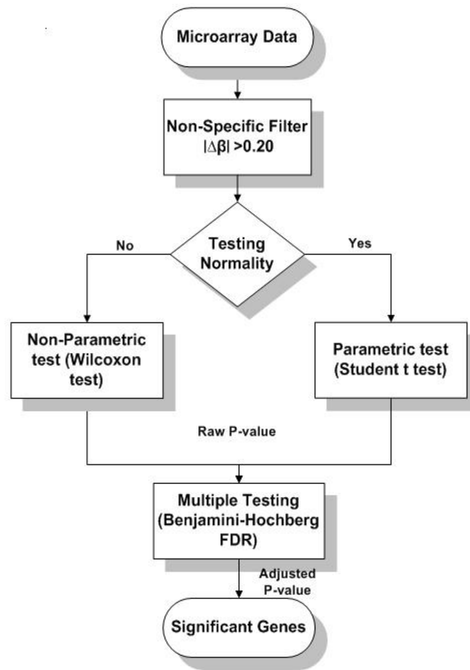

Fig. 2. The proposed model to identify the DNA methylation markers.

3.1 Non-Specific Filtering

It is logical to suppose that genes with $|\Delta\beta|$ greater than 0.2 are candidate to be DNA methylation markers [16], thus the non-specific filter will run to get ride of all genes have $|\Delta\beta|$ less than 0.2 which are not candidate to be DNA methylation markers.

3.2 Specific Filtering

The output of the non-specific filtering phase is used to be the input to the specific filtering phase. In [16, 17] assumed distribution normality for as is generally true for microarray data. In this paper, the one-sample Kolmogorov-Smirnov test is used for testing normality to determine the most appropriate statistical test will be applied [18]. The Wilcoxon singed rank will be used instead of the paired t-test for a paired samples if the data does not follow a normal distribution. It is logical to suppose that CPGs with a methylation value great than 0.2 are candidate to be significant CPGs, therefore the additional filter is applied to reduce the false positives after performing multiple testing.

4 Experimental Results

The non-specific phase has been applied by using the GeneFilter package in R [19]. The output of the first phase reducing CPGs to be 124, 430, 187, 289 for basal-like,

Table 2. The result of identifying significant DNA methylation markers

Subtypes	$\lvert\Delta\beta\rvert > \mathbf{0.2}$	**Wilcoxon singed rank**	**Genes**
Basal-like	124 CpGs	65 CpGs (FDR $<$ 0.001)	54
ERBB2+	430 CpGs	69 CpGs (FDR $<$ 0.001)	60
luminal A	187 CpGs	94 CpGs (FDR $<$ 0.001)	79
luminal B	289 CpGs	85 CpGs FDR $<$ 0.001)	64

ERBB2+, luminal A and luminal B respectively. By using SPSS statistical package, The normality was tested with One-sample Kolmogorov Smirnov test but data did not follow a normal distribution, therefore the most appropriate non-parametric test for the paired samples is Wilcoxon singed rank. The specific filter (Wilcoxon signed rank with FDR $\leq$ 0.001) was performed by using the GeneSelector package in R [20]. The output of this phase filter out CPGs to be 65, 69, 94 and 64 for basal-like, ERBB2+, luminal A and luminal B respectively as shown in Table 2.

5 Applying FCA for breast cancer subtypes

The formal context is first extracted, then we can construct the concept lattice based on a formal context. A formal context represents the relationship between objects (cancer subtypes) and attributes (significant hypermethylated or hypomethylated genes) which can be easily represented by a cross-table as shown in Table 3. In this paper, to distinguish between hypomethylated and hypermethylated, we refer to hypomethylated genes by adding plus (+) in their names (e.g. HOXA9(+)), also we refer to hypermethylated genes by adding minus (-) in their names (e.g. HOXA9(-)). Based on a formal context, the concept lattice will constructed every relationship between breast cancer subtypes and DNA methylated markers. According to the lattice in Figure 3, we can identify 11 concepts. The concept lattice make these subtypes hierarchically grouped together according to the their common markers. In addition to identify the common distinct DNA methylation markers in breast cancer subtypes that can be derived from lattice as shown in table 4, the lattice give us an important information that Mos is hypomethylated in Luminal A and ERBB2+ but in the same time Mos is hypermethylated in Luminal B and Basal-like, also, it is noticed that HOXA9 is hypomethylated in Luminal A and hypermethylated in Luminal B as shown in table 5.

Table 3: The formal context

Genes	**Basal-like**	**ERBB2+**	**luminal A**	**luminal B**	**Genes**	**Basal-like**	**ERBB2+**	**luminal A**	**luminal B**
ABCB1(-)	×				ACVR1(-)				×
ADAMTS12(-)				×	ADCYAP1(-)				×
AIM2(+)	×		×		ALOX12(-)				×
APC(-)			×		APOC1(+)		×	×	
ARHGDIB(+)			×		ASCL2(-)			×	
ATP10A(+)		×			B3GALT5(+)		×	×	
BCAP31(+)	×	×	×		BGN(+)		×		
BLK(+)	×				BRCA1(+)		×		

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Table 3 – *Continued from previous page*

Genes	Basal-like	ERBB2+	luminal A	luminal B	Genes	Basal-like	ERBB2+	luminal A	luminal B
C4B(+)		×			CARD15(+)	×		×	
CASP8(+)	×				CCKAR(+)		×		
CCL3(+)	×	×	×		CCNA1(-)				×
CCR5(+)	×				CD1A(+)			×	
CD2(+)	×				CD40(-)				×
CD9(-)				×	CDH13(-)				×
CEACAM1(+)	×		×		CFTR(-)	×		×	×
CHGA(-)			×		CLDN4(+)	×	×	×	
COL18A1(-)				×	COL1A1(-)				×
COL1A2(-)			×	×	CSF3R(+)	×			
CXCL9(+)			×		CYP2E1(+)		×		
DAB2IP(-)				×	DAPK1(-)			×	
DBC1(-)				×	DLC1(+)		×	×	
DLK1(-)				×	DNASE1L1(+)		×		
DSG1(+)		×			EGF(+)		×	×	
EMR3(+)	×	×	×		EPHA5(-)				×
EPHX1(+)		×			ETS1(-)			×	
ETS2(+)	×				EVI2A(+)	×			
EYA4(-)				×	F2R(+)	×			
FES(-)				×	FGF2(-)				×
FLJ20712(+)	×	×	×		FZD9(-)				×
GABRA5(+)		×	×		GABRG3(+)	×			
GALR1(-)				×	GRB7(+)		×	×	
GSTM1(-)				×	H19(+)		×		
HBII-52(+)	×	×	×		HDAC1(+)	×			
HDAC6(+)		×			HDAC9(-)				×
HIC1(+)			×		HLA-DOA(-)				×
HLA-DOB(+)	×				HLA-DPA1(+)			×	
HOXA5(-)				×	HOXA9(-)				×
HOXA9(+)			×		HS3ST2(-)			×	×
HTR1B(-)	×		×	×	IFNG(+)	×	×	×	
IGF2AS(-)				×	IGFBP3(-)				×
IGFBP7(-)				×	IL12B(+)		×	×	
IL1RN(+)		×			IL2(+)			×	
IL8(+)	×		×		IPF1(-)	×			×
IRAK1(+)		×			ISL1(-)			×	×
ITK(+)	×		×		JAK3(-)			×	×
KLK11(+)			×		KRAS(+)			×	
L1CAM(-)				×	LEFTY2(-)				×
LIF(+)	×				MAGEA1(+)			×	
MAGEC3(+)		×	×		MAPK10(+)		×		
MAPK4(+)		×	×		MBD(+)		×		
MCF2(+)		×	×		MECP2(+)			×	
MEST(+)			×		MME(-)			×	
MMP10(+)	×	×			MMP14(-)				×
MOS(-)	×			×	MOS(+)		×	×	
MPL(+)	×		×		MT1A(+)	×			
MUC1(+)	×	×	×		MYCL2(-)				×
MYOD1(-)				×	NBL1(+)		×		
NEFL(-)				×	NID1(+)		×	×	
NOS3(+)		×	×		NPY(-)				×
OSM(+)	×				PADI4(+)		×	×	
PARP1(+)		×			PDGFB(+)		×	×	
PDGFRB(-)	×			×	PECAM1(+)		×	×	
PENK(-)	×			×	PGR(+)	×			
PITX2(-)			×	×	PLA2G2A(+)		×	×	
PLAT(-)	×				POMC(-)				×
PRKCDBP(-)				×	PROM1(+)		×		
PRSS1(+)			×		PSCA(+)		×	×	
PTGS2(-)				×	PTHR1(+)	×	×	×	
PTK6(+)	×		×		PTPN6(+)	×		×	
PTPRH(+)	×	×	×		RARA(+)		×	×	
RASSF1(-)				×	RHOH(+)	×			
RIPK3(+)			×		RUNX3(+)	×			
S100A2(+)		×			SCGB3A1(-)			×	
SLC14A1(+)	×				SLC22A3(-)				×

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Table 3 – *Continued from previous page*

Genes	Basal-like	ERBB2+	luminal A	luminal B	Genes	Basal-like	ERBB2+	luminal A	luminal B
SLIT2(-)			×	×	SNRPN(+)		×		
SNURF(+)		×	×		SOX1(-)	×		×	×
SOX17(-)	×			×	SPARC(-)				×
SPDEF(+)		×			SPI1(+)	×	×	×	
SPP1(+)	×		×		SRC(+)	×			
SRPK3(+)			×		ST6GAL1(-)				×
STAT5A(-)				×	TAL1(-)				×
TBX1(-)			×	×	TDG(+)		×	×	
TDGF1(+)		×			TERT(-)				×
TFF1(+)		×	×		THBS2(+)			×	
TIMP1(+)	×	×			TMEFF2(-)				×
TNFRSF10D(-)			×	×	TNFSF8(+)	×		×	
TRIP6(+)		×			VAMP8(+)	×		×	
VBP1(+)		×			WNT10B(+)	×			
WNT2(-)				×	WNT8B(+)			×	
XIST(+)		×			ZNF215(-)			×	×
ZNF264(-)				×					

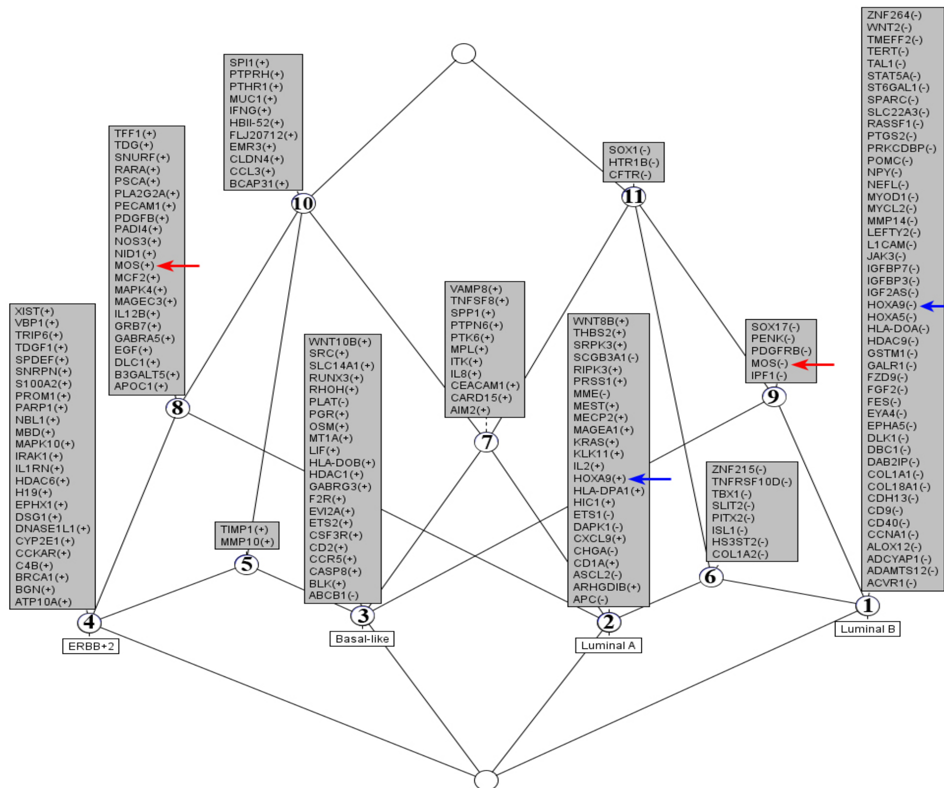

Fig. 3. The concept lattice of hypomethylated genes in breast cancer subtypes.

Table 4: The distinct DNA methylation markers in breast cancer subtypes.

Concept	Subtypes	DNA methylation markers
C(11)	Luminal A, Luminal B, Basal-like	SOX1(-), HTR1B(-), CFTR(-)
C(10)	Luminal A, ERBB+2, Basal-like	SPI1(+), PTPRH(+), PTHR1(+), MUC1(+), IFNG(+), HBII-52(+), FLJ20712(+), EMR3(+), CLDN4(+), CCL3(+), BCAP31(+)
C(9)	Luminal B, Basal-like	SOX17(-), PENK(-), PDGFRB(-), MOS(-), IPF1(-)
C(8)	Luminal A, ERBB+2	APOC1(+),B3GALT5(+), DLC1(+), EGF(+), GABRA5(+), GRB7(+), IL12B(+), MAGEC3(+), MAPK4(+), MCF2(+), MOS(+), NID1(+), NOS3(+), PADI4(+), PDGFB(+), PECAM1(+), PLA2G2A(+), PSCA(+), RARA(+), SNURF(+), TDG(+), TFF1(+)
C(7)	Luminal A, Basal-like	AIM2(+),CARD15(+),CEACAM1(+), IL8(+), ITK(+), MPL(+), PTK6(+), PTPN6(+), SPP1(+), TNFSF8(+), VAMP8(+)
C(6)	Luminal A, Luminal B	COL1A2(-), HS3ST2(-), ISL1(-), PITX2(-), SLIT2(-), TBX1(-), TNFRSF10D(-), ZNF215(-)
C(5)	ERBB+2, Basal-like	MMP10(+), TIMP1(+)
C(4)	ERBB+2	ATP10A(+), BGN(+), BRCA1(+), C4B(+), CCKAR(+), CYP2E1(+), DNASE1L1(+), DSG1(+), EPHX1(+), H19(+), HDAC6(+), IFNG(+), IL1RN(+), IRAK1(+), MAPK10(+), MBD(+), NBL1(+), PARP1(+), PROM1(+), S100A2(+), SNRPN(+), SPDEF(+), TDGF1(+), TRIP6(+), VBP1(+), XIST(+)
C(3)	Basal-like	ABCB1(-), BLK(+), CASP8(+), CCR5(+), CD2(+), CSF3R(+), ETS2(+), EVI2A(+), F2R(+), GABRG3(+), HDAC1(+), HLA-DOB(+), LIF(+), MT1A(+), OSM(+), PGR(+), PLAT(-), RHOH(+), RUNX3(+), SLC14A1(+),SRC(+), WNT10B(+)
C(2)	Luminal A	APC(-), ASCL2(-), CD1A(+), CHGA(-), COL1A2(-), CXCL9(+), DAPK1(-), ETS1(-), HIC1(+), HLADPA1(+), HOXA9(+), HS3ST2(-), IL2(+), ISL1(-), KRAS(+), MAGEA1(+), MECP2(+), MEST(+), MME(-), PITX2(-), PRSS1(+), RIPK3(+), SCGB3A1(-), SLIT2(-), SRPK3(+), TBX1(-), THBS2(+), TNFRSF10D(-), WNT8B(+), ZNF215(-),ARHGDIB(+), KLK11(+)
C(1)	Luminal B	ACVR1(-), ALOX12(-), CD9(-), CDH13(-), COL18A1(-), COL1A1(-), DAB2IP(-), DBC1(-), DLK1(-), EPHA5(-), EYA4(-), FES(-), FGF2(-), FZD9(-), GALR1(-), GSTM1(-), HDAC9(-), HLADOA(-), HOXA5(-), HOXA9(-), IGF2AS(-), IGFBP3(-), IGFBP7(-), JAK3(-), L1CAM(-), LEFTY2(-), MMP14(-), MYCL2(-), MYOD1(-), NEFL(-), NPY(-), POMC(-), PRKCDBP(-), PTGS2(-), RASSF1(-), SLC22A3(-), SPARC(-), ST6GAL1(-), STAT5A(-), TAL1(-), TERT(-), TMEFF2(-), WNT2(-), ZNF264(-), CCNA1(-), ADAMTS12(-), ADCYAP1(-), CD40(-)

Table 5. DNA methylation markers

Gene	Basal-like	ERBB2+	luminal A	luminal B
Mos(+) Hypomethylated		√	√	
Mos(-) Hypermethylated	√			√
HOXA9(+) Hypomethylated			√	
HOXA9(-) Hypermethylated				√

6 Conclusion and Future work

DNA methylation have been associated with cancer in several investigations. Hypermethylated or hypomethylated of CPG islands can affect the expression of genes, therefore there is a need of mining and visualizing the DNA methylation status among breast cancer molecular subtypes. The results of mining DNA methylation data using FCA are encouraging. The visualization of DNA methylation status leads to discover very important relationships between hypermethylated and hypomethylated genes. In this paper, formal concept analysis which is a very powerful for identify the relationship between objects, proposed as data-mining approach to handle this problem, by constructing a concept lattice based on a formal context. In future work we will use FCA for mining DNA methylation status by using data obtained from Illumina Infinium HumanMethylation27 BeadChip, this BeadChip allows researchers to interrogate 27,578 targeted CpGs sites in total, spread across promoter regions of 14,495 genes, therefore we can identify a new relationship among cancer tumor subtypes.

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