**Research Paper** 

# Identification of a gene signature for different stages of breast cancer development that could be used for early diagnosis and specific therapy

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## ABSTRACT

Breast cancer (BC) is a heterogeneous disease where the survival rate of patients decreases with progression of the disease. BC usually has a linear progression, classified into normal/benign, atypical ductal hyperplasia (ADH), ductal carcinoma *in situ* (DCIS), and invasive ductal carcinoma (IDC). This study aimed to identify gene signature for each of these subgroups.

We performed human transcriptome array analysis on 5 patient samples from each Normal, ADH, IDC and DCIS and 2 replicates of MCF10A cell line representative of each subgroup.

We identified *SFRP1* and snoRNAs (especially *SNORD115* and *SNORD114*) as the initial regulators of cancer progression, accompanied by significant changes in extracellular matrix organization. Tumor progression to the IDC stage showed upregulation of tumor promoting genes responsible for increased invasion, inflammation, survival in stress environment and metastasis.

The gene signatures identified in this study could represent potential biomarkers for each subgroup of breast cancer progression, which could assist in early diagnosis of breast cancer progression as well as treatment interventions. Moreover, these gene signatures could serve in discovery of specific targeted therapies for each subgroup.

#### **INTRODUCTION**

Breast cancer (BC) is the most common cancer in women and the leading cause of cancer-associated death among women worldwide [1]. According to 2017 data of BC Organization, one out of 8 U.S. women (around 12%) will be diagnosed with invasive BC in their life time, thus constituting 25% of all new cases of cancer reported and 13% of cancer-associated death [2]. BC is a complex disease, represented by a collection of tumors with different behavior and clinical outcome, reflecting the biological heterogeneity and difference of genetic changes.

BC can be divided in two major histological subtypes, namely ductal carcinomas and lobular carcinomas, for which a large proportion (about  $\geq$ 75%) is diagnosed as ductal carcinomas [3]. The initial diagnosis of BC relies on mammography, epidemiological data and morphological observations. Based on these parameters, a simple and linear BC progression is suggested and

attributed to a continuum of epithelial cell transformation starting from atypical ductal hyperplasia (ADH) to ductal carcinoma in situ (DCIS), both conferring an increased risk of developing invasive ductal carcinoma (IDC) [4]. On the other hand, several studies have proposed two separate pathways of progression which are characterized by 16q loss (in low grade tumors) and second by amplification of 11q13 and 17q1 [5]. Additionally, studies have shown that there is predisposed genetic alterations in the low or intermediate grade tumors that could lead them to any of these pathways [6]. Reports suggest that the degree of increased BC risk depends on the specific epithelial abnormality, pointing toward IDC as possibly originating from benign diseases [7]. The major problem is to identify which benign disease will eventually transform into IDC, so that an early preventive measure could be taken in these patients.

Studies on BC evolution from benign lesions to invasive disease have been facilitated by the use of well characterized cell lines, such as the MCF10A series [8, 9]. These cells provide a tool to study the different stages of BC development between benign lesions, ADH, DCIS, and malignant cells able to form tumors with metastatic capabilities.

Many studies have been carried out in an attempt to identify biomarkers of BC [10, 11]. These studies identified gene expression signatures or other kinds of genetic alterations such as epigenetic signatures, loss of heterozygosity and allelic imbalance resulting from the development of malignancy. Studies have also identified alterations in various gene loci (loss and gains) resulting in dysregulated gene expression observed in BC tissues classified according to their molecular subtypes [12]. Still, early markers to identify benign or premalignant diseases likely evolving into breast cancer are missing.

In the present study, we have identified preventive molecular biomarkers in breast lesions of varying severity and MCF10A cell line series, which could likely be involved in the progression and transformation of premalignant breast lesions into IDC. These early biomarkers of IDC predisposition are deeply needed in prevention and would be a huge step further in clinical settings. Although numerous studies investigated the role of specific genes in different stages or transitions of cancer progression, to our knowledge this study represents the first gene expression analysis performed in a whole continuum of breast lesions.

# RESULTS

### Gene expression signatures clustered according to their stage of BC progression

Ductal breast disease represents  $\simeq 75\%$  of all diagnosed breast diseases and it is further divided into ADH, DCIS, and IDC, according to its morphological

and histopathological features. Besides its prevalence, the molecular signature associated with each stage is not well established. To identify the gene signature which could differentiate each subgroup of BC development, we performed HTA analysis on breast lesions of varying aggressiveness (5 samples/group) namely Normal (Benign), ADH, DCIS and IDC. We also incorporated in our study MCF10A cell lines, which is a well-established in vitro model widely used in BC research. As displayed in Figure 1, gene expression data showed hierarchical clustering of each sample according to their subgroup. Samples from a given subgroup clustered distinctively together, demonstrating the reliability of breast tissue selection and molecular characterization. We identified 255 genes differentially expressed in breast lesions (Figure 1A) and 2800 genes differentially expressed in MCF10A cell line series (Figure 1B) (both ANOVA p < 0.05).

# Gene enrichment ontology highlighted extracellular matrix re-organization and response to cellular stress as key factors in BC progression

The distinct clustering of breast tissue samples according to their subgroup led us to further evaluate their gene enrichment ontology. We performed comparison analysis (metascape server) of all differentially expressed genes by comparing the expression profile of each subgroup to that of normal (ANOVA p < 0.05; fold difference  $\pm 1.5$ ). The circos plot depicted in Figure 1C shows that the total number of genes whose expression was altered in the IDC subgroup (Green) was very distinct from ADH and DCIS subgroups when compared to normal (Figure 1C), and this was further confirmed by TAC software analysis. The comparison of expression patterns of these genes showed that a significant number of gene isoforms were over-expressed in IDC when compared to normal subtype in both breast lesions (Supplementary Figure 1A) and MCF10A cell lines (Supplementary Figure 1B), as depicted by scatter plots.

In attempt to further classify the changes in gene ontology, which could suggest characteristic features to each subgroup, we identified in Figure 1D statistically significant enriched ontology for each subgroup according to the changes in the hallmark gene set identified by HTA analysis (ANOVA p < 0.05; fold difference  $\pm 1.5$ ).

The results described in Supplementary Figure 2A showed the network of the gene ontology cluster identified. The network is visualized with Cytoscape (v3.1.2) with "force-directed" layout and edge bundled for clarity. The same enrichment network was displayed as pies in Supplementary Figure 2B. The enrichment cluster (Supplementary Figure 2A and 2B) highlighted significant gene enrichments related to collagen degradation (R-HAS-1442490), extracellular matrix organization (GO:0030198) and focal adhesion

(ko04510) in ADH, whereas genes related to extracellular matrix organization (GO:0030198), epithelial cell proliferation (GO:0050673) and regulation of cell migration (GO:0030334) were enriched in DCIS. Genes related to response to oxidative stress (GO:0006979), mitotic cell cycle process (GO:1903047), extracellular matrix organization (GO:0030198), focal adhesion (ko04510), epithelial cell proliferation (GO:0050673) and

regulation of cell migration (GO:0030334) were enriched in IDC. Similar analysis with Panther classification system software showed enrichment of genes associated with catalytic activity, receptor activity and transporter activity in ADH, whereas DCIS has enrichment of genes involved in catalytic activity and enzyme regulatory activity. As for IDC, it showed enrichment of genes related to structural molecular activity, nucleic acid



**Figure 1: Analysis of BC progression by Human Transcriptome analysis and Metascape.** (http://metascape.org). Hierarchical clustering of breast lesions (A) and representative MCF10A cell lines (B) based on 255 and 2800 differentially expressed gene isoforms, respectively ( $\pm$  1.5-fold and p < 0.05). Clustering analysis was performed using the Transcriptome Analysis Console (TAC) Software (Thermo Fisher Scientific, Canada). The circos plot showing the gene distribution ( $\pm$  1.5-fold and p < 0.05) of differentially expressed genes in the three subgroups (ADH, DCIS and IDC) as compared to Normal breast lesions (C). On the outside, each arc represents the identity of each gene list (ADH= Red, DCIS= Blue and IDC= Green). On the inside, each arc represents a gene list, where each gene has a spot on the arc. Dark orange = genes in multiple lists; Light orange = unique to the list. Purple lines link the same genes that are shared by multiple gene lists. Enrichment Ontology cluster across the study (D) depicting statistically enriched pathways clustered based on Kappa-statistical similarities (Kappa score = 0.3). The colour of the heatmap depicts their p-values, white cells = lack of enrichment. Normal breast lesion: benign breast tissue; ADH: Atypical ductal hyperplasia; DCIS: Ductal carcinoma *in situ*; Invasive: Invasive ductal carcinoma. MCF10A: non-tumorigenic, non-metastatic; MCF10AT (atypical): tumorigenic, non-metastatic; MCF10DCIS (Ductal carcinoma *in situ*): tumorigenic; locally invasive, non-metastatic and MCF10CA1a (invasive): metastatic.

binding transcription factor activity and receptor activity (Supplementary Figure 3). The results obtained from these two analysis tools complement each other, further confirming our analysis.

Further, we verified the fold difference in the expression level of genes enriched for a particular gene ontology identified by metascape server in breast lesion samples. The fold difference indicated an increase in genes involved in epithelial cell proliferation (23.37%), extracellular matrix organization (24.65%), mitotic cell cycle progression (53.52%) and response to oxidative stress (37.14%) in IDC (Figure 2) as compared to other subgroups. Similar results were also found in MCF10A cell line series (data not shown).

# IPA analysis identified major regulatory pathways for each subtype of BC progression

Using IPA, the comparison analysis of gene expression fold changes of each subgroup when compared to normal tissue allowed the identification of potential deregulated pathways. As displayed in Figure 3, the analysis revealed a significant upregulation of genes leading to inhibition of matrix metalloproteases in ADH (5.2-fold; p value=7.01E-06) and PTEN signaling (2.9-fold; p-value=1.43E-03), which is not observed in transition to DCIS and IDC. In addition, regulation of epithelial to mesenchymal pathway (4.9; p-value=1.29E-05), epithelial adherens junction signaling (5.8; p-value=1.57E-06), VEGF signaling (3; p-value=1.1E-03) and actin cytoskeleton signaling (4.25; p-value=5.66E-05) were significantly upregulated in the normal-DCIS transition. Moreover, for the normal-IDC transition, a significant increase in EGF signaling (5.1; p-value=8.4E-06), GADD45 signaling (3.3; p-value=4.9E-04), Th2 pathway (3.03; p-value=9.2E-04), PDGF signaling (4.1; p-value=8.2E-05), eNOS signaling (3; p-value=1.2E-03), dendritic cell maturation (3.3; p-value=4.8-04) and chemokine signaling (2; p-value=1.4E-02) was observed. Further, IPA analysis also highlighted a significant increase in the number of genes affecting cellular growth and proliferation, cellular development and cellular movement in a linear fashion from ADH to IDC (Supplementary Table 1).

In addition, a few pathways showed an increasing trend along BC progression from normal to IDC state. FAK signaling (1.5-4.5, ADH to IDC; p-value=3.03E-05), integrin signaling (0.7-5; p-value=9.7E-0.6), paxillin signaling (0.07-4.7; p-value=1.7E-05), ILK signaling (2-5.6; p-value=2.3E-06), growth hormone signaling (1.7-3; p-value=1.2E-03), NFkB signaling (2-3; p-value=1E-03), NRF2 mediated oxidative stress response (0.4-2.73; p-value=1.9E-03) and IL-17 signaling (0.9-2.13; p-value=7.3E-03) all showed an increasing regulation.

#### Gene signature for each subgroup

In our study we found genes whose expression was changed as the normal cell progresses towards different stages of cancer development. In addition to coding genes, various non-coding RNAs (ncRNA), whose expression was significantly altered, were also identified (Figure 4A). A total of 55, 41 and 48 differentially expressed ncRNAs in ADH, DCIS and IDC subgroup, respectively, were identified (Figure 4A). Particularly, ncRNAs such as SNORD115, SNORD116, SNORD114, SNORD113, SNORD78 and miR205 were highlighted in this study. Corresponding gene signatures were then established for each transition. SNORD115 (SNORD116 for MCF10A cell line) gene cluster was found as a potential specific gene signature through ADH and DCIS subgroups (Figure 4B). In order to understand the role of SNORD115 and SNORD116 in tumor development, we analyzed data obtained from Falaleeva et al. [13], which showed SNORD115/116 as the initial regulator of gene expression, directing the cell towards an invasive phenotype (Supplementary Figure 4). A decrease in expression level of SNORD114, SFPR1 and P115 was observed with tumor development (Figure 4B, 4C). Furthermore, SPP1, FN1, TOP2A, ANLN, POSTN, CENPF, LRRC15, and SNORD78 gene expression and other genes related to invasion, extracellular matrix organization and epithelial cell cycle progression, mitotic cell cycle progression and response to oxidative stress showed a significant upregulation in IDC sub-group (Figure 2, 4B, 4C). It should be noted that a similar expression pattern was also found in MCF10A cell lines for some of these genes (data not shown).

Seven genes namely *SFRP1*, *PI15*, *SNORD114*, *SNORD115*, *POSTN*, *SPP1* and *FN1* identified as significantly deregulated among subgroups were then selected from the top 30 genes (Figure 4B, 4C) for quantitative PCR (qPCR) validation (Figure 5). As depicted in Figure 5, the qPCR validated the accuracy of our findings. A similar expression pattern of these genes in MCF10A cell lines was indicated in Supplementary Table 2.

# DISCUSSION

The identification and characterization of a breast tumor is routinely performed based on morphological and histopathological features. The quantitative analysis of DCIS lesions differentiating them from ADH lesions is based on the presence of a homogenous population in at least two membrane bound spaces with a size of more than 2mm [14], making the identification difficult. It has been shown that 30% of ADH upgrade to DCIS or IDC by the time of surgery [15] and 30% of DCIS upgrade to IDC [16]. Efforts have been undertaken to develop a clinical test [17] that could predict which patient has a predisposition regarding factors that could lead to transformation of benign or low grade tumours to IDC, but so far none has been successful in clinical setting. So far, molecular gene signatures that could identify the early changes in BC progression remain to be elucidated. To identify a subset of gene signatures which could be associated with a specific pathological subgroup of BC progression continuum, we carried out HTA analysis on each subgroup namely Normal, ADH, DCIS and IDC. We observed a total of 255 genes differentially expressed when considering all different types of breast lesions, and 2800 genes in MCF10A cell lines were identified. Results



**Figure 2: Changes in genes responsible for the gene annotation.** Heat map indicating the fold change of the gene expression in each subgroup based on the enriched ontology (Green = Downregulation, Red= Upregulation).



**Figure 3: Changes in pathways responsible for the gene annotation.** Bar chart showing the changes in the canonical pathways in the three subgroups as compared to normal breast lesions. Normal: benign breast tissue; ADH: Atypical ductal hyperplasia; DCIS: Ductal carcinoma *in situ*; IDC: Invasive ductal carcinoma.

suggested tremendous changes in gene expression levels of several genes/pathways, which correlated with the transformation of breast cells from normal to IDC. Indeed, a total of 231 genes (out of 255 differentially expressed genes) were deregulated in IDC when compared to normal cells in breast tissue samples while 1595 genes (out of 2800 differentially expressed genes) were significantly dysregulated in MCF10A cell line series between normal and invasive.

Gene expression data highlighted that during the transformation of breast cells from Normal to ADH and then to DCIS stage, the major biological functions involved were extracellular matrix organization and signaling, which includes the enzymatic activity to



В

		Norr	nal vs ADH					Norm	al vs DCIS					Norn	nal vs IDC		
Gene Symbol	Р	FC	Gene Symbol	Р	FC	Gene Symbol	Р	FC	Gene Symbol	Р	FC	Gene Symbol	Р	FC	Gene Symbol	Р	
ADAM12	2E-04	-2,9	NPY1R	2E-04	6,6	SNORD114-3	0,026	-3,7	CRIP1P4	3E-04	7,7	SFRP1	3E-04	-6	SPP1	0,041	
FIGF	1E-04	-2,8	RP11-53O19.1	2E-05	6	SNORD114-12	0,025	-3,6	CPB1	0,047	5,4	PTN	0,002	-5,9	RNU5D-1	0,013	
OR2A7	0,02	-2,7	SNORD115-4	0,016	6	SNORD114-1	0,017	-3,5	SPP1	0,008	4,6	KRT5	0,001	-5,6	FN1	0,002	4
AC005152.3	0,046	-2,6	SNORD115-34,20,15,21	0.03	5,8	SNORD114-25	0,021	-3.5	RP11-206M11.7	0,022	4,5	EGR1	0,002	-5	TOP2A	0,034	3
SNORD114-20	0,033	-2,6	SNORD115-5,9	0.025	5.7	VTRNA2-1	0,003	-3.3	IF16	5E-04	4	KIT	0,043	-4.8	COL10A1	0,023	3
PCDH18	0,004	-2.3	SNORD115-12.9	0.025	5.7	FIGF	2E-04	-3.2	SNORD115-44	0,001	3.9	KRT14	3E-06	-4.5	HIST2H2AA4.3	3E-05	
SNORD114-23	0,033	-2.3	SNORD115-6	0,033	5.7	SNORD114-20	0,003	-3.1	SNORD115-5.9	8E-04	3,7	CAPN6	1E-05	-4.3	NPNT	0,043	
RELN	0,004	-2,2	SNORD115-32	0,029	5.7	SNORD113-6	0,005	-3.1	SNORD115-12.9	8E-04	3,7	APOD	6E-05	-4.3	KPNA2	0,009	
POSTN	0,004	-2,2	SNORD115-11,43,36,29	0,025	5,6	CAPN6	7E-06	-2.9	SNORD115-10	3E-04	3,7	SNORD114-1	0.025	-4,5	CRIP1P4	0,005	
FREM1	0,005	-2.2	SNORD115-44	0,020	5.6	NOVA1	0,004	-2.9	SNORD115-11.43.36.29	0,001	3,6	AC005152.3	0,025	-3,6	SULF1	0,025	
COL6A3	0,012	-2.2	SNORD115-10	0,027	5,6	SNORD114-14	0,004	-2,9	SNORD115-22	0,001	3,5	FIGF	2E-04	-3,6	LRRC15	0,007	
NID1	6E-04			0,029	5,0	KB-1107E3.1	0,021	-2,8		5E-04			2E-04 6E-06	-3,6	CENPF	0,004	
		-2,1	SNORD115-8						SNORD115-34,20,15,21		3,5	PCDH18					
MEG3	7E-06	-2,1	SNORD115-22	0,029	5,4	SNORD114-21	0,018	-2,7	SNORD115-38	0,005	3,5	ITM2A	9E-04	-3,5	RP11-428L9.2	0,045	
PLAGL1	0,002	-2,1	SNORD115-42	0,036	5,2	RP11-706O15.7	0,012	-2,7	SNORD115-33	0,004	3,3	FOS	0,028	-3,4	MKI67	0,005	
SFRP1	0,016	-2,1	SNORD115-14	0,024	5,2	SNORD114-22	0,043	-2,6	RP11-428L9.2	0,05	3,2	SNORD114-20	0,005	-3,3	ANLN	0,017	
MMP2	5E-04	-2,1	SNORD115-39	0,047	5,1	KIT	0,042	-2,6	SNORD115-15	8E-04	3,1	MYH11	0,027	-3,3	HIST1H3A-J	0,032	
OR2A4	0,014	-2,1	SNORD115-41	0,013	5	SNORD114-28	0,023	-2,5	SNORD115-6	9E-04	3	CXCL12	0,02	-3,2	RP11-379F12.4	0,044	
GPR174	0,005	-2	SNORD115-31	0,015	5	FREM1	0,006	-2,5	SNORD115-25	1E-03	3	MGP	0,011	-3,2	HIST1H2AM,H,G,L,K,I	0,005	
NFIB	0,001	-2	SNORD115-33	0,033	4,8	SRPX	0,006	-2,4	SNORD115-39	5E-04	3	TNXB	3E-04	-3,1	ATAD2	0,015	
FLJ37644	0,018	-2	SNORD115-15	0,024	4,7	ADAMTS5	3E-05	-2,4	SNORD115-42	0,001	2,9	SRPX	2E-04	-3,1	HIST1H2BI	0,019	
VCAN	0,039	-2	SNORD115-17,19,18	0,037	4.3	PCDH18	2E-04	-2.3	SNORD115-31	1E-05	2,9	STAC2	0,001	-3,1	MIR1244-1.2	0,006	
LOC100507577	4E-04	-2	SNORD115-38	0,045	4.2	ITM2A	0,002	-2.3	SNORD115-17,19,18	0,001	2,8	RELN	0,002	-3,1	SNORD78	0,013	
ZNF521	5E-04	-2	SNORD115-25	0,034	3,9	SFRP1	0,004	-2,2	SNORD115-40	6E-04	2,7	FBLN5	2E-04	-3	HIST2H3A,D,C	0,003	
RP11-631F7.2	0,019	-2	SNORD115-40	0,04	3,9	MIR2054	0,01	-2,2	KPNA2	0,036	2,7	FREM1	0,002	-3	IFI6	0,004	
MIR3606	0.029	-2	SNORD115-3	0.024	3,8	MME	3E-04	-2,2	SNORD115-21	0.002	2,7	KB-1107E3.1	0,045	-3	HIST1H2AI	0,004	
ITM2A	0,025	-1.9	SNORD115-16	0,024	3,8	FBLN5	0.005	-2.2	MRPS30	0,002	2,7	FOSB	0.018	-2.9	NDUFAB1	0,011	
CAPN6	9E-04	-1,9	SNORD115-21	0,042	3,8	AC005152.3	0.005	-2,2	SNORD115-41	3E-04	2,7	MME	4E-05	-2,9	SLC44A4	0,018	
	0,005			3E-04		TCF7L2	5E-04	-2,2	SNORD115-32	0,003	2,6		4E-05 0,001	-2,8		0,048	
MIR604		-1,9	MRPS30		3,6							MME-AS1			INHBA		
PIK3C2G	0,036	-1,9	SNORD115-1	0,04	3,6	FZD7	3E-06	-2,1	SNORD115-16	6E-04	2,6	OR5P3	6E-04	-2,8	YWHAZP3	0,031	
CPXM1																0,004	
CI MINI	2E-04	-1,9	GFRA1	0,016	3,5	PIK3C2G	0,015	-2,1	SNORD115-3	5E-04	2,6	PIK3C2G	0,003	-2,8	LMNB1	0,004	
CEADI	2E-04	AD	GFRA1 DH vs DCIS	0,016		PIK3C2G	0,013	AD	H vs IDC	5E-04		PIK3C2G	0,003	DC	LMINB1	0,004	
Gene Symbol	P		DH vs DCIS Gene Symbol	P	3,5 FC	Gene Symbol	Р		H vs IDC Gene Symbol	P	Z,6 FC	Gene Symbol	P		IS vs IDC Gene Symbol	P	
Gene Symbol PI15	P 0,015	AD FC	DH vs DCIS Gene Symbol IFI6	P 0,006	FC 3,3	Gene Symbol SCGB2A2	P 0,024	AD	H vs IDC Gene Symbol FN1	P 9E-04	FC 7,4	Gene Symbol CPB1	P 0,041	DC FC -6,4	IS vs IDC Gene Symbol CENPF	P 0,017	
Gene Symbol PI15 NPY1R	P 0,015 5E-04	AD FC -8,4 -5,5	DH vs DCIS Gene Symbol IFI6 CRIPIP4	P 0,006 0,004	FC 3,3 3,1	Gene Symbol SCGB2A2 PIP	P 0,024 0,02	AD FC -18 -17	H vs IDC Gene Symbol FN1 POSTN	P 9E-04 0,022	FC 7,4 4,6	Gene Symbol CPB1 RP11-206M11.7	P 0,041 0,014	DC FC -6.4 -5.1	IS vs IDC Gene Symbol CENPF RP11-706O15.7	P 0,017 0,04	
Gene Symbol P115 NPY1R NOVA1	P 0,015 5E-04 0,007	AD FC -8.4 -5.5 -3.8	DH vs DCIS Gene Symbol FFI6 CRIP1P4 C15orf54	P 0,006 0,004 0,037	FC 3,3 3,1 2,4	Gene Symbol SCGB2A2 PIP PI15	P 0,024 0,02 0,003	AD FC -18 -17 -15	H vs IDC Gene Symbol FNI POSTN HIST2H2AA4,3	P 9E-04 0,022 0,001	FC 7,4 4,6 3,7	Gene Symbol CPB1 RP11-206M11.7 IGHA1	P 0,041 0,014 0,041	DC. FC -6,4 -5,1 -5	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN	P 0,017 0,04 0,044	
Gene Symbol PI15 NPY1R NOVA1 CLIC6	P 0,015 5E-04 0,007 0,02	AD FC -8.4 -5.5 -3.8 -3.7	DH vs DCIS Gene Symbol IFI6 CRIP1P4 C150r754 CDK12	P 0,006 0,004 0,037 0,034	FC 3.3 3.1 2,4 2,3	Gene Symbol SCGB2A2 PIP	P 0,024 0,02 0,003 0,003	AD FC -18 -17 -15 -7,2	H vs IDC Gene Symbol FNI POSTN HIST2H2AA4,3 TOP2A	P 9E-04 0,022 0,001 0,045	FC 7,4 4,6 3,7 3,6	Gene Symbol CPB1 RP11-206M11.7 IGHA1 ERBB2; MIR4728	P 0,041 0,014 0,041 0,031	DC FC -6.4 -5,1 -5 -3,7	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN MK167	P 0,017 0,04 0,044 0,019	
Gene Symbol PI15 NPY1R NOVA1	P 0,015 5E-04 0,007	AD FC -8.4 -5.5 -3.8 -3.7 -3.6	DH vs DCIS Gene Symbol FFI6 CRIP1P4 C15orf54	P 0,006 0,004 0,037	FC 3,3 3,1 2,4 2,3 2,3	Gene Symbol SCGB2A2 PIP PI15 RP11-53019.1 PTN	P 0,024 0,02 0,003	AD FC -18 -17 -15	H vs IDC Gene Symbol FNI POSTN HIST2H2AA4,3	P 9E-04 0,022 0,001	FC 7,4 4,6 3,7	Gene Symbol CPB1 RP11-206M11.7 IGHA1 ERBB2; MIR4728 KRT14	P 0,041 0,014 0,041	DC FC -6.4 -5.1 -5 -3.7 -3.3	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN	P 0,017 0,04 0,044	
Gene Symbol PI15 NPY1R NOVA1 CLIC6	P 0,015 5E-04 0,007 0,02	AD FC -8.4 -5.5 -3.8 -3.7	DH vs DCIS Gene Symbol IFI6 CRIP1P4 C150r754 CDK12	P 0,006 0,004 0,037 0,034	FC 3.3 3.1 2,4 2,3	Gene Symbol SCGB2A2 PIP P115 RP11-53019.1	P 0,024 0,02 0,003 0,003	AD FC -18 -17 -15 -7,2	H vs IDC Gene Symbol FNI POSTN HIST2H2AA4,3 TOP2A	P 9E-04 0,022 0,001 0,045	FC 7,4 4,6 3,7 3,6	Gene Symbol CPB1 RP11-206M11.7 IGHA1 ERBB2; MIR4728	P 0,041 0,014 0,041 0,031	DC FC -6.4 -5,1 -5 -3,7	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN MK167	P 0,017 0,04 0,044 0,019	
Gene Symbol PI15 NPY1R NOVA1 CLIC6 FGF10	P 0,015 5E-04 0,007 0,02 0,015	AD FC -8.4 -5.5 -3.8 -3.7 -3.6	DH vs DCIS Gene Symbol IFI6 CRIP1P4 C15orf54 CDK12 PLK2	P 0,006 0,004 0,037 0,034 0,02	FC 3,3 3,1 2,4 2,3 2,3	Gene Symbol SCGB2A2 PIP PI15 RP11-53019.1 PTN	P 0,024 0,02 0,003 0,003 5E-05	AD FC -18 -17 -15 -7,2 -4,7	H vs IDC Gene Symbol FN1 POSTN HIST2H2AA4,3 TOP2A COLIAI	P 9E-04 0,022 0,001 0,045 0,004	FC 7,4 4,6 3,7 3,6 3,1	Gene Symbol CPB1 RP11-206M11.7 IGHA1 ERBB2; MIR4728 KRT14	P 0,041 0,014 0,041 0,031 3E-06	DC FC -6.4 -5.1 -5 -3.7 -3.3	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN MK167 ATAD2	P 0,017 0,04 0,044 0,019 0,037	
Gene Symbol P115 NPY1R NOVA1 CLIC6 FGF10 SCARNA8 RP11-53019.1	P 0,015 5E-04 0,007 0,02 0,015 0,037	AD FC -8.4 -5.5 -3.8 -3.7 -3.6 -2.7 -2.5	H vs DCIS Gene Symbol FFI6 CRP1P4 C15orf54 CDK12 PLK2 MIR612; NEAT1 IFT1	P 0,006 0,004 0,037 0,034 0,02 5E-04	FC 3.3 3.1 2.4 2.3 2.3 2.2 2	Gene Symbol SCGB2A2 PIP P115 RPI1-53019.1 PTN ANKRD30A KRT14	P 0,024 0,02 0,003 0,003 5E-05 0,047	AD FC -18 -17 -15 -7,2 -4,7 -4,5 -4,3	H vs IDC Gene Symbol FNT POSTN HIST2H2AA4,3 TOP2A COL1A1 BGN	P 9E-04 0,022 0,001 0,045 0,004 0,012	FC 7,4 4,6 3,7 3,6 3,1 2,9 2,8	Gene Symbol CPB1 RP11-206M11.7 IGHA1 ERBB2; MIR4728 KRT14 KRT5 FOS	P 0,041 0,014 0,031 3E-06 0,011 0,036	DC FC -6,4 -5,1 -3,7 -3,3 -3,1	IS vs IDC Gene Symbol CENPF RPI.706015.7 ANLN MK167 ATAD2 KIF11 ZBTB18.ZNP238	P 0,017 0,04 0,044 0,019 0,037 0,007 0,024	
Gene Symbol PI15 NPY1R NOVA1 CLIC6 FGF10 SCARNA8 RP11-53019.1 SCUBE2	P 0,015 5E-04 0,007 0,02 0,015 0,037 0,037	AD FC -8.4 -5.5 -3.8 -3.7 -3.6 -2.7 -2.5 -2.5	DH vs DCIS Gene Symbol FIG CRIP1P4 CDK12 PLK2 VKR2 VKR2 VKR2 VKR2 VKR2 VKR2 VKR2 VK	P 0,006 0,004 0,037 0,034 0,02 5E-04 5E-04	FC 3.3 3.1 2.4 2.3 2.3 2.2 2 2	Gene Symbol SCGB2A2 PIP P115 RP11-53O19.1 PTN ANKRD30A KRT14 SNORD115-4	P 0,024 0,02 0,003 5E-05 0,047 2E-04 0,025	AD FC -18 -17 -15 -7,2 -4,7 -4,5 -4,3 -3,8	H vs IDC Gene Symbol POSTN HIST2H2AA4,3 TOP2A COL1A1 BGN COL10A1 AF178030.2	P 9E-04 0,022 0,001 0,045 0,004 0,012 0,05 0,022	FC 7.4 4.6 3.7 3.6 3.1 2.9 2.8 2.6	Gene Symbol CPB1 RP11-206M11.7 IGHA1 ERBB2; MIR4728 KRT14 KRT5 FOS STEAP4	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019	DC FC -6.4 -5.1 -5 -3.7 -3.3 -3.1 -3.1 -3.1 -3.1	IS vs IDC CENFF RP11-706015.7 ANLN MKI67 ATAD2 KIF11 ZBTB18, ZNP238 CCT3	P 0,017 0,04 0,044 0,019 0,037 0,007 0,024 0,017	
Gene Symbol PI15 NPY1R NOVA1 CLIC6 FGF10 SCARNA8 RP11-53019.1 SCUBE2 SNORD85	P 0,015 5E-04 0,007 0,015 0,037 0,037 0,038 0,005	AD FC -8.4 -5.5 -3.8 -3.7 -3.6 -2.7 -2.5 -2.5 -2.5 -2.4	DH vs DCIS Gene Symbol Fif6 CRIP1P4 C150754 CDK12 PLK2 MIR612, NEAT1 IFIT1 0AS2 IF127	P 0,006 0,004 0,037 0,034 0,02 5E-04 0,01 5E-04 0,038	FC 3.3 3.1 2,4 2,3 2,2 2 2 2 2 2 2	Gene Symbol SCGB2A2 PIP PI15 RP11-53019.1 PTN ANKRD30A KRT14 SN0RD115-4 RP11-53019.2	P 0,024 0,003 0,003 5E-05 0,047 2E-04 0,025 0,027	AD FC -18 -17 -15 -7,2 -4,7 -4,5 -4,3 -3,8 -3,7	H vs IDC Gene Symbol FNI POSTN HIST212AA4,3 T012A C01.1A1 BGN C01.10A1 AF178030.2 MK167	P 9E-04 0,022 0,001 0,045 0,004 0,005 0,005 0,022 0,007	FC 7.4 4.6 3.7 3.6 3.1 2.9 2.8 2.6 2.6	Gene Symbol CPB1 RP11-206M11.7 IGHA1 ERB32; MIR4728 KRT14 KRT5 FOS STEAP4 EGR1	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019 0,004	DC. FC -6.4 -5.1 -5 -3.7 -3.3 -3.1 -3.1 -3.1 -3,1 -3,1 -2,9	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN MK167 ATAD2 K1F11 ZBTB18.72N228 CCT3 SNRPD1	P 0,017 0,04 0,049 0,037 0,007 0,024 0,017 0,019	
Gene Symbol PI15 NPY1R NOVA1 CLIC6 FGF10 SCARNA8 RP11-53019.1 SCUBE2 SNORD85 SNORD50	P 0,015 5E-04 0,002 0,015 0,037 0,037 0,037 0,037 0,038	AD FC -8.4 -5.5 -3.8 -3.7 -3.6 -2.7 -2.5 -2.5 -2.5 -2.4 -2.4	H vs DCIS Gene Symbol TFIP 14 CUSor54 CDK12 PLK2 MIR612.NEAT1 IFTT OAS2 IF127 CLTC	P 0,006 0,004 0,037 0,034 0,02 5E-04 0,01 5E-04 0,038	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 1.9	Gene Symbol SCGB2A2 PIP P115 RPI1-53019.1 PTN ANKRD30A KKRD30A SNORD115-4 RPI1-53019.2 SCGB2A1	P 0,024 0,003 0,003 5E-05 0,047 2E-04 0,025 0,027 0,013	AD FC -18 -17 -15 -7,2 -4,7 -4,7 -4,3 -3,8 -3,8 -3,7 -3,7	H vs IDC Gene Symbol POSTN HIST2012AA43 TOP2A COL1A1 BGN COL10A1 AF178050.2 MK167 MR1244-1.2	P 9E-04 0,022 0,001 0,045 0,004 0,012 0,05 0,022 0,007 0,006	FC 7,4 4,6 3,7 3,6 3,1 2,9 2,8 2,6 2,6 2,5	Gene Symbol CPB1 RP11-206M11,7 IGHA1 ERBB2; MIR4728 KRT14 KRT5 FOS STEAP4 EGR1 IGJ	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019 0,004 0,046	DC FC -6.4 -5.1 -5 -3.7 -3.3 -3.1 -3.1 -3.1 -3,1 -3,1 -2.9 -2.8	IS vs IDC CENTF CENTF RP1-T96015.7 MK167 ATAD2 KIF11 ZBT188: ZNF238 CCT3 SNRPD1 CADM1	P 0,017 0,04 0,044 0,019 0,037 0,007 0,024 0,017 0,019 0,006	
Gene Symbol P115 NPV1R NOVA1 CLIC6 FGF10 SCARNA8 RP11-53019.1 SCUBE2 SNORD85 SNORD70 SNORA11E	P 0,015 5E-04 0,007 0,02 0,015 0,037 0,038 0,003 0,038 0,001	AD FC -8,4 -5,5 -3,8 -3,7 -3,6 -2,7 -2,5 -2,5 -2,5 -2,4 -2,4 -2,4 -2,3	DH vs DCIS Gene Symbol Fif6 CIS0754 CDK12 PI.K2 MIR612, NEAT1 IFIT1 0AS2 IF127 CLTC CXCL10	P 0,006 0,004 0,034 0,02 5E-04 0,01 5E-04 0,048 0,048 0,003	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 1.9 1.9	Gene Symbol SCGB2A2 PIP PTIS RPI1-53019.1 PTN ANKR030A KRT14 SN0RD115-4 RP11-53019.2 SCGB2A1 APOD	P 0,024 0,003 5E-05 0,047 2E-04 0,025 0,027 0,013 0,001	AD FC -18 -17 -15 -7,2 -4,7 -4,5 -4,3 -3,8 -3,7 -3,7 -3,5	H vs IDC Gene Symbol FNI POSTN HIST212AA4,3 TOP2A COL1A1 BGN COL10A1 AF178030.2 MK167 MIR1244-1,2 PPP1F14BP3	P 9E-04 0,022 0,001 0,045 0,004 0,012 0,005 0,002 0,007 0,006 0,004	FC 7.4 4.6 3.7 3.6 3.1 2.9 2.8 2.6 2.6 2.5 2.5	Gene Symbol CPB1 RY11-206M1.7 IGHA1 ERBB2: MIR4728 KRT14 KRT15 FOS STEAP4 EGR1 IGJ PTN	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019 0,004 0,046 0,004	DC FC -6.4 -5.1 -3.7 -3.7 -3.1 -3,1 -3,1 -3,1 -3,2.9 -2.8 -2.7	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN MK167 ATAD2 KIF11 ZBTB18.2NP238 CCT3 SNRPD1 CADM1 LMNB1	P 0,017 0,04 0,044 0,019 0,037 0,007 0,024 0,017 0,019 0,006 0,035	
Gene Symbol P115 NPY1R NOVA1 CLIC6 FGF10 SCARNA8 RP11-53019.1 SUOB22 SNORD55 SNORD70 SNORA11E SNORD91B	P 0,015 5E-04 0,007 0,037 0,037 0,038 0,005 0,038 0,005 0,038 0,001	AD FC -8.4 -5.5 -3.8 -3.7 -3.6 -2.7 -2.5 -2.5 -2.4 -2.4 -2.4 -2.3 -2.3	H vs DCIS Gene Symbol TFIP 14 CUSor54 CDK12 PLK2 MIR612.NEAT1 IFTT OAS2 IF127 CLTC CXCL10 TSPYL5	P 0,006 0,004 0,037 0,034 0,02 5E-04 0,01 5E-04 0,038 0,048 0,003	FC 3,3 3,1 2,4 2,3 2,2 2 2 2 2 1,9 1,9 1,9	Gene Symbol SCGB2A2 PIP PI15 RP11-53019,1 PTN ANKRD30A KRT14 SNORD115-4 RP11-53019,2 SCGB2A1 APOD MGP	P 0,024 0,003 5E-05 0,047 2E-04 0,025 0,027 0,013 0,001 0,008	AD FC -18 -17 -15 -7,2 -4,7 -4,5 -4,3 -3,8 -3,7 -3,7 -3,5 -3,5 -3,5	H vs IDC Gene Symbol PNTN HST2012AA4,3 TOP2A COL.1A1 BGN COL.10A1 AF178050.2 MK167 MK1244-1,2 PPF1K14B73 AC093850.2	P 9E-04 0,022 0,001 0,045 0,004 0,012 0,005 0,022 0,007 0,006 0,004 0,004	FC 7.4 4.6 3.7 3.6 3.1 2.9 2.8 2.6 2.6 2.6 2.5 2.5 2.5	Gene Symbol CPB1 RP1-206M1.7 IGHA1 ERBB2; MIR4728 KRT14 KRT3 FOS STEAP4 EGR1 IGJ PTN PLK2	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019 0,004 0,044 0,044 0,004	DC FC -6.4 -5.1 -3.7 -3.7 -3.7 -3.1 -3,1 -3,1 -3,1 -3,2.9 -2.8 -2.7 -2.7	IS vs IDC CENTF CENTF RP1196015,7 MK107 MK107 KIF11 ZBT118, ZNE238 CCT3 SIRPD1 CADM1 LMNB1 RNU5F-1	P 0,017 0,04 0,044 0,019 0,037 0,007 0,024 0,017 0,019 0,006 0,035 0,039	
Gene Symbol PI15 NPY1R NOVA1 CLIC6 FGF10 SCARNA8 RP11-53019.1 SCUBE2 SNORD50 SNORD50 SNORD510 SNORD5126	P 0,015 5E-04 0,007 0,015 0,037 0,037 0,038 0,005 0,038 0,005 0,038 0,001 0,022 0,04	AD FC -8.4 -5.5 -3.8 -3.7 -3.6 -2.7 -2.5 -2.5 -2.5 -2.5 -2.4 -2.4 -2.3 -2.3 -2.3	DH vs DCIS Gene Symbol IFI6 CRIP1P4 C15o754 CDK12 PLK2 MIR612, NEAT1 IFIT1 OAS2 IF127 CLIC CXCL10 TSPYL5 CST1	P 0,006 0,004 0,037 0,034 0,02 5E-04 0,01 5E-04 0,038 0,048 0,038 0,032 0,036	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 2 1.9 1.9 1.9 1.8	Gene Symbol SCGB2A2 PIP P115 RP11-53019.1 PTN ANKR030A KRT14 SNORD115-4 RP11-53019.2 SCGB2A1 APOD MGP KRT5	P 0,024 0,02 0,003 5E-05 0,047 2E-04 0,025 0,027 0,013 0,001 0,008 0,008	AD FC -18 -17 -15 -7,2 -4,7 -4,5 -4,3 -3,8 -3,7 -3,5 -3,5 -3,5 -3,4	H vs IDC Gene Symbol FNI POSTN HIST2112AA4,3 TOP2A COLIA1 BGN COLIA1 BGN COLIA1 BGN COLIA1 MIR1244-1,2 MIR1244-1,2 MIR1244-1,2 MIR1244-1,2 MIR1244-1,2 MIR124-1,2 MIR14	P 9E-04 0,022 0,001 0,045 0,004 0,012 0,05 0,022 0,007 0,006 0,004 0,017	FC 7.4 4.6 3.7 3.6 3.1 2.9 2.8 2.6 2.6 2.5 2.5 2.5 2.5 2.5	Gene Symbol CPB1 RP11-206M11.7 IGHA1 ERBB2; MIR4728 KRT14 KRT5 FOS STEAP4 EGR1 IGJ PIN PLK2 SFRP1	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019 0,004 0,004 0,004 0,004 0,010	DC FC -6.4 -5.1 -5 -3.7 -3.3 -3.1 -3.1 -3.1 -3.1 -2.9 -2.8 -2.7 -2.7 -2.7	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN MK167 ATAD2 KIF11 ZBTB18.ZNP238 CCT3 SNRPD1 CADM1 LMNB1 RNU5F-1 HIST2H2AC	P 0,017 0,04 0,044 0,019 0,037 0,0024 0,017 0,019 0,006 0,035 0,039 0,05	
Gene Symbol P115 NPY1R NOVA1 CLIC6 FGF10 SCARNA8 SNORD70 SNORD70 SNORA11E SNORD126 SCARNA4	P 0,015 5E-04 0,007 0,025 0,037 0,037 0,038 0,003 0,038 0,001 0,022 0,04 0,048	AD FC -3,8 -3,7 -3,6 -2,7 -2,5 -2,5 -2,5 -2,4 -2,4 -2,4 -2,3 -2,3 -2,3 -2,3	H vs DCIS Gene Symbol IF161 CRIP1F4 CRIP1F4 CRIP1F4 CRIP1F4 PIK2 PIK2 PIK2 PIK2 PIK2 PIK2 CRIP1 CRIP1F4 C	P 0,006 0,004 0,037 0,034 0,02 5E-04 0,038 0,048 0,003 0,032 0,036 0,005	FC 3.3 3.1 2.4 2.3 2.2 2 2 1.9 1.9 1.9 1.8 1.7	Gene Symbol SCGB2A2 PIP PI15 RPI1-53019.1 PTTS SNORD115-4 RPI1-53019.2 SCGB2A1 APOD MGP KRT5 ANPEP	P 0,024 0,02 0,003 0,003 5E-05 0,047 2E-04 0,025 0,027 0,013 0,001 0,008 0,008 0,006	AD FC -18 -17 -15 -7,2 -4,7 -4,7 -4,5 -4,3 -3,8 -3,7 -3,7 -3,7 -3,5 -3,5 -3,4 -3,3	H vs IDC Gene Symbol FNIN HIST2312AA4,3 TOP2A COL10A1 BGN COL10A1 AT78030.2 MK167 MR1244-1,2 PPP1R14BP3 AC093850.2 KPNA2 COL1A2	P 9E-04 0,022 0,001 0,045 0,004 0,012 0,005 0,002 0,007 0,006 0,004 0,011 0,017	FC 7.4 4.6 3.7 3.6 3.1 2.9 2.8 2.6 2.5 2.5 2.5 2.5 2.5 2.5 2.5	Gene Symbol CPB1 RP1-206M1.7 IGHA1 ERBD2: MIR4728 KRT4 KRT5 FOS STEAP4 EGR1 IGJ PTN PLK2 SFRP1 FOSB	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019 0,004 0,004 0,004 0,004 0,002 0,003	DCC FC -6.4 -5.1 -3.3 -3.3 -3.1 -3.1 -3.1 -2.7 -2.8 -2.7 -2.7 -2.7 -2.4	IS vs IDC Gene Symbol CENPP RP1-7kJ 5.5.7 AUN MK107 MK107 KIF11 ZBT185.ZNE238 CCT3 SNRPD1 CADM1 LMNB1 RNU5F-1 HIST2HAC EPRS	P 0,017 0,04 0,044 0,037 0,007 0,024 0,017 0,019 0,006 0,035 0,039 0,05 0,014	
Gene Symbol PI15 NPY1R NOVA1 CLIC6 FGF10 SCARNA8 RP11-53019.1 SCUBE2 SNORD50 SNORD50 SNORD50 SNORD5126 SNORD5126 SCARNA4 PIEZO2	P 0,015 5E-04 0,002 0,015 0,037 0,038 0,005 0,038 0,005 0,038 0,001 0,022 0,04 0,048 0,041	AD FC -8.4 -5.5 -3.8 -3.7 -3.6 -2.7 -2.5 -2.4 -2.4 -2.4 -2.3 -2.3 -2.3 -2.3 -2.2	DH vs DCIS Gene Symbol Fif6 CRIP1P4 C15o754 CDK12 PLK2 MIR612, NEAT1 IF1T1 OAS2 IF127 CLTC CXCL10 TSPYL5 CST1 DYNL71 IF144	P 0,006 0,004 0,034 0,02 5E-04 0,038 0,038 0,032 0,035 0,032 0,036 0,005	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 2 2 1.9 1.9 1.9 1.9 1.7 1.7	Gene Symbol SCGB2A2 PIP PI1-53019.1 PTN ANKRD30A KRT14 SNORD115-4 RP11-53012-4 RP11-53012-4 RP11-53012-4 RP1-53012-4 RF15 ANPEP GLRA3	P 0,024 0,02 0,003 5E-05 0,047 2E-04 0,025 0,027 0,013 0,001 0,008 0,008 0,008 0,008	AD FC -18 -7.2 -4.7 -4.5 -7.2 -4.7 -4.5 -3.7 -3.7 -3.7 -3.5 -3.5 -3.5 -3.5 -3.5 -3.5 -3.3 -3.2	H vs IDC Gene Symbol FNI POSTN HIST2112AA4,3 TOP2A COL1A1 BGN COL10A1 AF178030.2 MK167 MIR1244-1,2 PPP1R14BP3 AC093850.2 KPNA2 COL1A2 CXCL10	P 9E-04 0,022 0,001 0,045 0,004 0,012 0,005 0,002 0,007 0,006 0,004 0,017 0,027 0,022	FC 7,4 4,6 3,7 3,6 3,1 2,9 2,8 2,6 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5	Gene Symbol CPB1 RP11-206M1.7 IGHA1 ERBB2; MIR4728 KRT14 KRT5 FOS STEAP4 EGR1 IGJ PIN PLK2 SFRP1 FOSB APOD	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019 0,004 0,004 0,004 0,004 0,003 0,002	DCC FC -5.1 -5.3 -3.7 -3.3 -3.1 -3.1 -3.1 -2.7 -2.7 -2.7 -2.7 -2.7 -2.4 -2.4 -2.4	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN MK167 ATAD2 KIF11 ZBTB18.ZNP238 CCT3 SNRPD1 CADM1 LMNB1 RNU5F-1 HIST2H2AC EPRS OLR1	P 0,017 0,04 0,044 0,019 0,007 0,024 0,017 0,019 0,006 0,035 0,039 0,05 0,014 0,001	
Gene Symbol PI15 NPY1R NOVA1 CLIC6 FGF10 SCARNA8 RP11-53019.1 SCUBE2 SNORD30 SNORD30 SNORD30 SNORD3126 SCARNA4 PIEZ02 PGR	P 0,015 5E-04 0,007 0,02 0,015 0,037 0,038 0,005 0,038 0,005 0,038 0,001 0,022 0,04 0,048 0,048 0,048	AEC FC -5.5 -3.8 -3.7 -2.5 -2.5 -2.4 -2.4 -2.4 -2.3 -2.3 -2.3 -2.3 -2.2 -2.2 -2.2	DH vs DCIS Gene Symbol TF161 CRIP1164 C150763 DF172 DF172 DF172 DF172 ORS2 FF17 ORS2 CT17C CXCL10 TSPYU5 CST1 DYNLT1 FF144 DH2	P 0,006 0,004 0,037 0,034 0,02 5E-04 0,038 0,048 0,003 0,036 0,005 0,014 0,049	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 2 1.9 1.9 1.9 1.9 1.9 1.7 1.7 1.7	Gene Symbol SCGB2A2 PIP PTN PTN ANKR030A ANKR030A ANKR030A SNORD115-4 RP11-53019.2 SCGB2A1 ANPOD MGP KR75 ANPEP GLRA3 SCGB1D2	P 0,024 0,003 0,003 5E-05 0,047 2E-04 0,025 0,027 0,013 0,001 0,008 0,008 0,008 0,0025	AD FC -18 -17 -15 -7,2 -4,5 -4,3 -3,8 -3,7 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5 -3,4 -3,2 -3,1	H vs IDC Gene Symbol FNI POSTN POSTN POSTN TSTPDA COLIAL COLIAL AFI78030.2 MEIO MEIO MEIO MEIO POPIELABP3 AC003850.2 KPNA2 COLIAL COLIAL MR3606	P 9E-04 0,022 0,001 0,045 0,005 0,002 0,007 0,006 0,004 0,017 0,027 0,027 0,027	FC 2,4 4,6 3,7 3,6 3,1 2,9 2,8 2,6 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5	Gene Symbol CPB1 R11:206M11.7 IG1A0 ERBBMR4728 KRT14 KRT14 KRT14 KRT14 KRT3 FOS STEAP4 EGR1 IGJ PIN PIX STEAP4 EGR1 IGJ FOSB APOD KRT68	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019 0,004 0,046 0,004 0,004 0,002 0,003 0,002	DC. FC -5.4 -5.1 -3.7 -3.3 -3.1 -3.1 -3.1 -3.9 -2.9 -2.9 -2.7 -2.4 -2.7 -2.4 -2.3	IS vs IDC Gene Symbol CENTP RP1-706015.7 ANLW MADD2 KFP1 ZBTB8: ZNP238 CCT3 SNRPD1 CADM1 LMNB1 RNU5F-1 HIST2H2AC EPRS OLR1 CKAP2	P 0,017 0,04 0,019 0,037 0,007 0,019 0,019 0,005 0,039 0,05 0,014 0,001	
Gene Symbol Pi15 NPY1R NPY1R CLLC6 FGF10 SCARNA8 RPI1-53019.1 SCARNA8 SNORD35 SNORD35 SNORD35 SNORD411E SNORD105 SNORD105 SNORD411E SNORD105 SNORD411E SNORD105 SNORD411E SNORD105 FGR	P 0,015 5E-04 0,007 0,02 0,037 0,038 0,003 0,038 0,003 0,038 0,001 0,022 0,044 0,048 0,041 0,022	ADD FC -5.5 -3.8 -3.7 -2.5 -2.5 -2.4 -2.4 -2.3 -2.3 -2.3 -2.3 -2.2 -2.2 -2.2	DH vs DCIS Gene Symbol Fi6 CRIP1P4 C15o754 CDK12 PLK2 MIR612, NEAT1 IFIT1 OAS2 IF127 CLTC CXCL10 TSPYL5 CST1 DYNLT1 IF144 IDH2 BST2	P 0,006 0,004 0,037 0,034 0,02 5E-04 0,01 5E-04 0,048 0,048 0,003 0,032 0,036 0,005 0,014 0,005 0,014	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 2 2 9 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1	Gene Symbol SCGB2A2 PIP PI1-53015.1 PTN ANKRD30A KRT14 SNORD115-4 RP11-53012-4 RP11-53012-4 RP11-53012-4 RGB2A2 SCGB2A1 APOD MGP KRT5 ANPEP GLRA3 SCGB1D2 EGR1	P 0,024 0,003 0,003 5E-05 0,047 2E-04 0,025 0,025 0,001 0,008 0,008 0,008 0,006 0,025 0,025	AD FC -18 -17 -15 -7,2 -4,7 -4,5 -4,3 -3,7 -3,7 -3,7 -3,5 -3,5 -3,4 -3,3 -3,4 -3,3 -3,1 -3,1	H vs IDC Gene Symbol FNI POSTN HIST2112AA4,3 TOP2A COLIA1 BGN COLIA1 BGN COLIA1 MIR1244-1,2 MIR1744B73 AC093850.2 KPNA2 COLIA2 COLIA2 COLIA2 COLIA2 COLIA2	P 9E-04 0,022 0,001 0,045 0,004 0,012 0,005 0,002 0,006 0,004 0,01 0,017 0,027 0,022 0,032 0,032	FC 7.4 4,6 3,7 3,6 2,9 2,8 2,6 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5	Gene Symbol CPB1 RP11-206M1.7 IGHA1 ERBB2; MIR4728 KRT14 KRT15 FOS STEAP4 EGR1 IG1 P1 K2 STEAP4 FOS STEAP4 FOS STEAP4 FOS STEAP4 MGP	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019 0,004 0,046 0,004 0,004 0,004 0,002 0,002 0,002 0,002	DCC FC -5.4 -5.7 -3.3 -3.1 -3.1 -3.1 -3.1 -3.9 -2.9 -2.8 -2.7 -2.7 -2.7 -2.4 -2.4 -2.3 -2.3	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN MK167 ATAD2 KIF11 ZBTB18.ZNP238 CCT3 SNRPD1 CADM1 LMNB1 RNU5F-1 HIST2HZAC EPRS OLR1 CKAP2 ANP32E	P 0,017 0,04 0,044 0,019 0,037 0,024 0,017 0,019 0,006 0,035 0,019 0,005 0,014 0,001	
Gene Symbol PI15 NPV1R NOV1R NOV1CLIC6 FGF10 SCARNA8 SNORD91 S	P 0,015 5E-04 0,007 0,015 0,037 0,037 0,038 0,005 0,038 0,005 0,038 0,005 0,038 0,005 0,022 0,04 0,041 0,02 0,041 0,029	ADD FC 5.5 -3.8 -3.7 -2.5 -2.5 -2.4 -2.4 -2.3 -2.3 -2.2 -2.2 -2.2 -2.2 -2.2 -2.2	DH vs DCIS Gene Symbol TF161 CRIP1F04 C1507612 OK572 DF172 OK522 HF027 CITC CXCL10 TSPYVL5 CST1 DYNLT1 HF144 IDH2 BST2 EZR	P 0,006 0,004 0,037 0,034 0,035 5E-04 0,013 5E-04 0,038 0,048 0,003 0,032 0,036 0,005 0,0014 0,049 0,041 0,043	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 2 2 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.9	Gene Symbol SCGB2A2 PIP PTN PTN AKRT34 SNORD15-4 RP11-53019.1 SNORD15-4 RP11-53019.2 SCGB2A1 ANPOD MGP KRT5 ANPEP GLRA3 SCGB1D2 EGR1 SLC39A6	P 0,024 0,003 5E-05 0,047 2E-04 0,025 0,027 0,013 0,001 0,008 0,006 0,0025 0,0025 0,001 0,003	ADD FC -18 -17 -4,5 -4,3 -3,6 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5 -3,4 -3,3 -3,2 -3,1 -3,1 -3	H vs IDC Gene Symbol FN1 POSTN POSTN TOP2A TOP2A COLIAA AFI 78030.2 MEIO7 MEIO44-1.2 PPP1 R14BP3 AC003850.2 KPNA2 COLIA2 CXCL10 COLIA2 CXCL10 COLIA2 CXCL10 COLIA2 CXCL10 SULF1	P 9E-04 0,022 0,001 0,045 0,025 0,022 0,005 0,002 0,007 0,006 0,004 0,017 0,020 0,021 0,022 0,032 0,031 0,021	FC 7.4 4.6 3.7 3.6 3.1 2.9 2.8 2.6 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5	Gene Symbol CPB1 R11:206M11.7 IG1IA1 ERBEMM1728 KR14 KR14 KR14 KR14 KR15 STEAP4 EGR1 IGJ PIN PIX STEAP4 EGR1 IGJ PIN PIX STEAP4 EGR1 GJ KR76B MGP TA4SF18	P 0,041 0,041 0,031 3E-06 0,011 0,036 0,019 0,004 0,044 0,04 0,004 0,004 0,003 0,002 0,0002 0,001 0,002	DC FC 	IS vs IDC Gene Symbol CENTP RP1-706015.7 ANLM MEMO AKP21 ZBT188.ZNP238 CCT3 CADM1 LMNB1 RNU5F-1 HIST2H2AC EPRS OLR1 CKAP2 ANP32E CCN2	P 0,017 0,04 0,044 0,019 0,037 0,007 0,024 0,019 0,006 0,035 0,039 0,05 0,014 0,001 0,003 0,003 0,003 0,003	
Gene Symbol PI15 NPV1R NV1R NV1CLIC6 FGF10 SCARNA8 RPI1-530191 SUBE2 SNORD3 SNORD10 SNORD10 SNORD10 SNORD10 SNORD10 RV1-300E4.2 CRISPLD1	P 0,015 5E-04 0,007 0,037 0,038 0,005 0,038 0,001 0,022 0,044 0,048 0,041 0,022 0,041 0,029 0,006	ACC FC 5.5 -5.5 -2.5 -2.4 -2.4 -2.3 -2.2 -2.2 -2.2 -2.2 -2.2 -2.2 -2.2	H vs DCIS Gene Symbol Fife CRIPIPA CISor754 CDK12 PLK2 MIR622, NEATI MIR622, NEATI OAS2 FI71 OAS2 CLTCO CXCL10 CXCL10 CXCL10 CXCL10 CXCL10 TSPG15 CYSL17 DYNLT1 DYNLT1 DYNLT1 DYNLT1 DYNLT1 DYNLT1 DYNLT1 DYNLT1 DYNLT1 DYNLT1 ST2 EZR SNORA29, TCP1	P 0,006 0,004 0,037 0,034 0,01 5E-04 0,038 0,003 0,032 0,036 0,005 0,014 0,049 0,041 0,043 0,043	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 2 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.7 1.7 1.6 1.6 1.6	Gene Symbol SCGB2A2 PIP PIT5 RPI1-53019.1 PTN ANKR730A KRT14 SNORD115-4 RPI1-53019.2 SCGB2A1 APOD MCD15-4 RPI1-53019.2 SCGB2A1 APOD MCD15-4 RPI1-53019.2 SCGB2A1 APOD MCD15-4 SCGB12 CGR1 SLC39A6 SLC39A6 SLC39A6 SLC39A6	P 0,024 0,003 0,003 5E-05 0,047 2E-04 0,025 0,027 0,013 0,001 0,008 0,008 0,008 0,008 0,005 0,025 0,001 0,03 0,038	AD FC -18 -17 -4,5 -3,8 -3,7 -3,7 -3,7 -3,7 -3,5 -3,4 -3,3 -3,4 -3,3 -3,2 -3,1 -3,1 -3,2 -2,9	H vs IDC Gene Symbol FNI POSTN HIST2122AA4,3 TOP2A COL1A1 BGN COL1A1 BGN COL10A1 AF178030.2 MK167 MK1244-1,2 PPF1R14B93 AC09356.2 FOL1A2 COL1A2 COL1A1 MK167 HIST1BA-J SULF1 THBS2	P 9E-04 0,022 0,001 0,045 0,004 0,012 0,005 0,002 0,007 0,006 0,004 0,017 0,002 0,001 0,017 0,027 0,022 0,032 0,031 0,026 0,031	FC 7.4 4.6 3.7 3.6 2.9 2.8 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5	Gene Symbol CPB1 CPB1 FR11-206M1.7 IG1A1 ERBB2; MIR4728 KRT14 KRT15 FOS STEAP4 EGR1 IG3 PTN RTS STEAP4 EGR1 IG3 PTN RTS STEAP4 FOS STEAP4 FOS STEAP4 FOS RAVE APOD KRT6B MGP TM4SF18	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,019 0,004 0,046 0,004 0,004 0,002 0,002 0,002 0,002 0,001 0,002	DC FC -6.4 -5.1 -5.7 -3.3 -3.1 -3.1 -3 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7	IS vs IDC CENF CENF RPI-706015.7 MKI67 ATAD2 KIF11 ZBTB18.ZNP238 CCT3 SNRPD1 CADM1 LMNB1 RNU591 NBV51 HISU52AC BPRS ORR1 CKAP2 ANP32E CCNA2 TPX2	P 0,017 0,044 0,019 0,037 0,007 0,024 0,017 0,009 0,006 0,035 0,035 0,035 0,035 0,035 0,035 0,035	
Gene Symbol P115 NP111R1 NP11R1 NP11R1 NP11R1 SV01P10 SC41NA8 SC01P12 SN0RD70 SN0RD70 SN0RD71S SN0RD70 SN0RD126 SC4RNA4 P11-30064-C SN0RD105 SN0RD105 SC4RNA4	P 0,015 5E-04 0,007 0,037 0,037 0,038 0,005 0,038 0,001 0,022 0,044 0,048 0,041 0,022 0,041 0,029 0,004	ACC FC 	DH vs DCIS Gene Symbol TF16 CRIP16 CD50754 CD50754 CD50754 CD50754 MIR612-NEAT1 FFT1 OAS2 MIR612-NEAT1 FFT1 OAS2 CTCC CXCL10 CST1 DYNLT1 FF14 IDH2 BST2 EZR SNORA29; TCP1 HK2	P 0,006 0,004 0,037 0,034 0,01 5E-04 0,038 0,038 0,032 0,036 0,005 0,005 0,014 0,049 0,041 0,043 0,043	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 1.9 1.9 1.9 1.9 1.9 1.7 1.7 1.6 1.6 1.6 1.6	Gene Symbol SCGB2A2 PIP PTN ART14 SNORD115-4 RP11-53019.1 SNORD115-4 RP11-53019.2 SCGB2A1 ANPOD MGP KRT5 ANPEP GLRA3 SCGB1D2 EGR1 SLC39A6 SERPINA3 PLAT	P 0,024 0,02 0,003 0,003 5E-05 0,047 2E-04 0,025 0,025 0,027 0,013 0,008 0,008 0,008 0,008 0,008 0,008 0,0025 0,025 0,025 0,001 0,03 0,038 0,018	AD FC -18 -7.2 -4.5 -4.3 -3.8 -3.7 -3.5 -3.5 -3.5 -3.5 -3.5 -3.5 -3.4 -3.3 -3.2 -3.3 -3.4 -3.3 -3.4 -3.3 -2.9	H vs IDC Gene Symbol FNI POSTN POSTN TOP2A TOP2A TOP2A TOP2A COLIAA AFI78030.2 WEI67 MR1244-1,2 PPP1R14BP3 AC093850.2 KPNA2 COLIA2 CXCL10 COLIA2 CXCL10 COLIA2 CXCL10 COLIA2 CXCL10 SULF1 THBS2 CENFF	P 9E-04 0,022 0,001 0,045 0,05 0,002 0,005 0,002 0,007 0,006 0,004 0,01 0,017 0,002 0,031 0,023 0,031 0,031	FC 7.4 4,6 3,7 3,6 3,1 2,9 2,8 2,6 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5	Gene Symbol CPB1 R11:206M11.7 IG1A0H1728 KR14 KR15 KR14 KR15 KR16 IG1 FOS STEAP4 EGR1 IG3 FOS STEAP4 EGR1 IG3 FOS STEAP4 EGR1 GJ FOS STEAP4 FOS STEAP4 EGR1 GJ FOS STEAP4 FOS FOS FOS FOS FOS FOS FOS FOS FOS FOS	P 0,041 0,041 0,041 0,031 0,011 0,036 0,011 0,004 0,004 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002	DCC FC -5,1 -5,1 -3,3 -3,3 -2,9 -2,8 -2,7 -2,7 -2,7 -2,7 -2,4 -2,4 -2,3 -2,3 -2,3 -2,2	IS vs IDC Gene Symbol CENTP RP1-706015.7 ANLM MEMO KIP11 ZBTD18: ZNP238 CCT3 CCT3 CCT3 CCT3 CCT3 CCT3 CCT3 CC	P 0,017 0,04 0,049 0,037 0,024 0,019 0,006 0,035 0,019 0,006 0,035 0,014 0,001 0,003 0,005 0,014	
Gene Symbol PI15 NPV1R NOV1R NOV1CLC6 FGF10 SCARNA8 RPI1-530191 SCUBE2 SNORD3 SNORD1E SNORD10 SCARNA4 PIE202 PGR SNORD10 SCARNA4 PIE202 PGR SNORD10 SCARNA4 PIE202 PGR SNORD10 SERINA1 TMEM26	P 0.015 5E-04 0.02 0.015 0.037 0.037 0.038 0.003 0.038 0.001 0.022 0.041 0.02 0.041 0.029 0.006 0.029 0.019	ACC FC -5.5 -3.8 -3.7 -2.5 -2.4 -2.3 -2.3 -2.3 -2.2 -2.2 -2.2 -2.2 -2.1 -2.1 -2.1 -2.1	H vs DCIS Gene Symbol Fife CRIPIPA CISor754 CDK12 PLK2 MIR622, NEATI IFITI OAS2 IFI27 CLTC CXCL10 CXCL10 CXCL10 CXCL10 CSTI DITI DITI DITI DITI BST2 EZR SNORA29, TCP1 HK2 TRAF4	P 0,006 0,004 0,037 0,034 0,01 5E-04 0,018 0,038 0,038 0,038 0,036 0,005 0,014 0,049 0,041 0,043 0,048 0,017 0,048	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 2 2 2 2 2 2 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.9	Gene Symbol SCGB2A2 PIP PIT5 RP11-53019.1 PTN ANKRD30A KKT14 SNORD115-4 RP11-53019.2 SCGB2A1 ANPOD MGP SCGB2A1 ANPOD MGP SCGB154 SCCGB12 CGR1 SLC39A6 SERPINA3 PLAT STEAP4	P 0,024 0,02 0,003 0,003 0,005 0,025 0,025 0,025 0,026 0,008 0,008 0,008 0,008 0,008 0,008 0,002 0,025 0,025 0,025	AD FC -18 -17 -15 -7.2 -4.3 -3.8 -3.7 -3.5 -3.4 -3.3 -3.5 -3.5 -3.5 -3.5 -3.5 -3.5 -3.5	H vs IDC Gene Symbol FNI POSTN HIST2122AA4,3 TOP2A COL1A1 BGN COL1A1 BGN COL1A1 BGN COL1A1 PPP1R14B93 AC093850.2 KPNA2 COL1A2 COL1A2 COL1A1 MR1244-1.2 PPP1R14B93 AC093850.2 KPNA3 COL1A1 MR1244-1.2 PP1R14B93 COL1A2 COL1A1 MR1244-1.2 PP1R14B93 COL1A1 MR1244-1.2 PP1R14B93 COL1A1 MR1244-1.2 PP1R14B93 COL1A1 MR1244-1.2 PP1R14B93 COL1A1 MR1244-1.2 PP1R14B93 COL1A1 MR1244-1.2 PP1R14B93 COL1A1 MR1244-1.2 PP1R14B93 COL1A1 COL1	P 9E-04 0,022 0,001 0,045 0,004 0,004 0,012 0,007 0,006 0,002 0,007 0,002 0,002 0,007 0,002 0,002 0,001 0,017 0,022 0,001 0,012 0,002 0,002 0,001 0,012 0,000 0,002 0,000000	FC 7.4 4.6 3.7 3.6 3.1 2.9 2.8 2.6 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5	Gene Symbol CPB1 CPB1 FR15-206M1.7 IGIA1 ERBB2: MIR4728 KRT14 KRT15 FOS STEAP4 EGR1 IGJ PTN SFRP1 KRT08 KRT08 MGP TMASF18 MGP TMASF18 TKFSF10 TAT CPHLIP	P 0,041 0,014 0,031 0,035 0,011 0,035 0,002 0,002 0,002 0,002 0,002 0,002 0,002	DCC FC -504 -5,1 -3,7 -3,3 -3,1 -3,1 -3,1 -3,1 -3,1 -3,1 -3,1	IS vs IDC CENF CENF RPI-706015.7 MKI67 ATAD2 KIF11 ZBTB18.ZNP238 CCT3 SNRPD1 CADM1 LMNB1 RNU5F-1 HIST21ZaC BTRS CKAP2 ANP32E CCNA2 TPX2 KIF23 SIG20.2	P 0,017 0,04 0,044 0,019 0,037 0,007 0,019 0,005 0,039 0,035 0,039 0,035 0,039 0,035 0,039 0,035 0,039 0,035 0,017 0,047 0,001 0,041 0,017 0,010000000000	
Gene Symbol PI15 NPV1R NOVAR CGF0 CGF0 SCARNA8 RP1-530191 SNORD5 SNORD5 SNORD5 SNORD5 SNORD5 SNORD5 SNORD126 SN	P 0,015 5E-04 0,02 0,015 0,037 0,038 0,005 0,038 0,005 0,038 0,001 0,022 0,04 0,048 0,004 1 0,029 0,004 0,029 0,0029 0,0029	AE FC -5.5 -3.8 -2.7 -2.5 -2.4 -2.3 -2.3 -2.3 -2.3 -2.3 -2.3 -2.2 -2.2	DH vs DCIS Gene Symbol IF16 CRIP1F6 CDSr02 CDSr02 CDSr02 MIR6152 MIR6152 CTC CCCL10 CSCL10	P 0,006 0,004 0,037 0,034 0,02 5E-04 0,038 0,048 0,003 0,032 0,036 0,005 0,014 0,043 0,044 0,044 0,044 0,044 0,044 0,017 0,045 6E-04	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 2 2 2 2 2 2 2 2 2	Gene Symbol SCGB2A2 PIP PISO19,1 TNN ANKR030A, KRT14 RP11-53019,2 SCGB2A1 ANPOD MGP KRT5 ANPEP GLRA3 SCGB102 EGR1 SLC39A6 SERPINA3 PLAT STEAP4 SFRP1	P 0.024 0.02 0.003 5E-05 0.047 0.025 0.025 0.025 0.025 0.025 0.001 0.008 0.008 0.0025 0.001 0.008 0.025 0.001	AD FC -18 -7.2 -4.5 -4.3 -3.7 -3.5 -3.4 -3.3 -3.4 -3.3 -3.4 -3.3 -3.5 -3.4 -3.3 -3.5 -3.4 -3.3 -3.2 -2.9 -2.9 -2.9 -2.9	H vs IDC Gene Symbol FNI POSTN POSTN IIST212AA4.3 TOP2A COLLA COLLA ATT78030.2 MEI07 MEI07 MEI24-11.2 PPP1R14BP3 AC093850.2 COLLA2 COL	P 9E-04 0,022 0,001 0,045 0,045 0,004 0,005 0,022 0,007 0,022 0,007 0,022 0,007 0,022 0,007 0,022 0,001 0,015 0,023 0,011	FC 74 4.6 3.7 3.6 3.1 2.9 2.8 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5	Gene Symbol CPB1 R11:2066411.7 IG1IA1 ERBE2, MI4728 KR14 KR15 KR15 EGR1 IGJ FOSB APOD KRT6B MGP TM45F18 TNFSF10 TA45F18	P 0.041 0.041 0.031 3E-06 0.013 0.036 0.019 0.004 0.004 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.001	DCC FC -5.1 -5.1 -3.3 -3.1 -3.1 -3.1 -3.1 -2.9 -2.8 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.2 -2.2	IS vs IDC Gene Symbol CENTP RP11-706015.7 ANLA MEMO AVEVI 2BTB18: ZNP238 CCT3 CADMI LMNB1 RNU5F-1 HIST2HZAC EPRS OLR1 CKAP2 ANP32E CCNA2 TPX2 KIP23 ISG201.2 PARPI	P 0.017 0.04 0.04 0.037 0.007 0.024 0.024 0.024 0.024 0.024 0.025 0.035 0.035 0.035 0.035 0.044 0.003 0.003 0.003 0.003 0.003 0.003 0.003 0.003 0.004	
Gene Symbol PI15 PP11R NOVAI CLIC6 SCARNA8 SCARNA8 SCARNA8 SCARNA8 SNORD91S SNORD91S SNORD91S SNORD91S SNORD91S SNORD91S PI1-T00E4.2 CRISPLD1 SERINAI TMEM26	P 0.015 5E-04 0.02 0.015 0.037 0.037 0.038 0.003 0.038 0.001 0.022 0.041 0.02 0.041 0.029 0.006 0.029 0.019	ACC FC -5.5 -3.8 -3.7 -2.5 -2.4 -2.3 -2.3 -2.3 -2.2 -2.2 -2.2 -2.2 -2.1 -2.1 -2.1 -2.1	H vs DCIS Gene Symbol Fife CRIPIPA CISor754 CDK12 PLK2 MIR622, NEATI IFITI OAS2 IFI27 CLTC CXCL10 CXCL10 CXCL10 CXCL10 CSTI DITI DITI DITI DITI BST2 EZR SNORA29, TCP1 HK2 TRAF4	P 0.006 0.004 0.034 0.02 5E-04 0.01 5E-04 0.038 0.048 0.003 0.038 0.038 0.038 0.032 0.036 0.005 0.036 0.001 0.041 0.041 0.041 0.041	FC 3.3 2.4 2.3 2.2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Gene Symbol SCGB2A2 PIP PIT5 RP11-53019.1 PTN ANKRD30A KKT14 SNORD115-4 RP11-53019.2 SCGB2A1 ANPOD MGP SCGB2A1 ANPOD MGP SCGB154 SCCGB12 CGR1 SLC39A6 SERPINA3 PLAT STEAP4	P 0,024 0,02 0,003 0,003 0,005 0,025 0,025 0,025 0,026 0,008 0,008 0,008 0,008 0,008 0,008 0,002 0,025 0,025 0,025	AD FC -18 -17 -4,7 -4,5 -3,8 -3,7 -3,7 -3,7 -3,7 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5	H vs IDC Gene Symbol PNT POSTN HIST2122AA4,3 TOP2A COL1A1 BGN COL1A1 BGN COL1A1 BGN COL1A2 MK167 MK1244-1,2 PPP1R14BP3 AC093850.2 KPNA2 COLA2 COLA2 COLA2 COLA3 COLA3 COLA3 COLA4 HIST1HZBI HIST21HZBI LRRC15 CCT3	P 9E-04 0,022 0,001 0,045 0,004 0,004 0,012 0,007 0,006 0,002 0,007 0,002 0,002 0,007 0,002 0,002 0,001 0,017 0,022 0,001 0,012 0,002 0,002 0,001 0,012 0,000 0,002 0,000000	FC 74 4,6 3,7 3,6 2,9 2,8 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5	Gene Symbol CPB1 CPB1 FR15-206M1.7 IG1A1 ERBB2: MIR4728 KRT14 KRT15 FOS STEAP4 EGR1 IG3 PTN SFRP1 KRT6B AC0D AC0D AC0D AC0D CPTN CPHLP	P 0,041 0,014 0,014 0,013 0,014 0,014 0,010 0,019 0,004 0,004 0,004 0,000 0,000 0,000 0,001 0,001 0,011 0,04 0,011 0,014 0,004 0,004 0,004 0,004 0,004 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,001 0,001 0,000 0,000 0,000 0,000 0,000 0,001 0,000 0,001 0,000 0,001 0,001 0,001 0,001 0,000 0,001 0,001 0,001 0,000 0,001 0,001 0,001 0,001 0,001 0,001 0,001 0,001 0,001 0,001 0,001 0,002	DC FC -5.1 -3.7 -3.3 -3.9 -2.8 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.4 -2.3 -2.3 -2.3 -2.3 -2.3 -2.2 -2.2 -2.2	IS vs IDC CENF CENF RPI-706015.7 MKI67 ATAD2 KIF11 ZBTB18.ZNP238 CCT3 SNRPD1 CADM1 LMNB1 RNU5F-1 HIST21ZaC BTRS CKAP2 ANP32E CCNA2 TPX2 KIF23 SIG20.2	P 0,017 0,04 0,044 0,019 0,037 0,007 0,019 0,005 0,039 0,035 0,039 0,035 0,039 0,035 0,039 0,035 0,039 0,035 0,017 0,047 0,001 0,041 0,017 0,0000000000	
Gene Symbol PI15 NPV1R NOVAR CGF0 CGF0 SCARNA8 RP1-530191 SNORD5 SNORD5 SNORD5 SNORD5 SNORD5 SNORD5 SNORD126 SN	P 0,015 5E-04 0,02 0,015 0,037 0,038 0,005 0,038 0,005 0,038 0,001 0,022 0,04 0,048 0,004 1 0,029 0,004 0,029 0,0029 0,0029	AE FC -5.5 -3.8 -2.7 -2.5 -2.4 -2.3 -2.3 -2.3 -2.3 -2.3 -2.3 -2.2 -2.2	DH vs DCIS Gene Symbol IF16 CRIP1F6 CDSr02 CDSr02 CDSr02 MIR6152 MIR6152 CTC CCCL10 CSCL10	P 0,006 0,004 0,037 0,034 0,02 5E-04 0,038 0,048 0,003 0,032 0,036 0,005 0,014 0,043 0,044 0,044 0,044 0,044 0,044 0,017 0,045 6E-04	FC 3.3 3.1 2.4 2.3 2.2 2 2 2 2 2 2 2 2 2 2 2 2 2	Gene Symbol SCGB2A2 PIP PISO19,1 TNN ANKR030A, KRT14 RP11-53019,2 SCGB2A1 ANPOD MGP KRT5 ANPEP GLRA3 SCGB102 EGR1 SLC39A6 SERPINA3 PLAT STEAP4 SFRP1	P 0.024 0.02 0.003 5E-05 0.047 0.025 0.025 0.025 0.025 0.025 0.001 0.008 0.008 0.0025 0.001 0.008 0.0025 0.001	AD FC -18 -7.2 -4.5 -4.3 -3.7 -3.5 -3.4 -3.3 -3.4 -3.3 -3.4 -3.3 -3.5 -3.4 -3.3 -3.5 -3.4 -3.3 -3.2 -2.9 -2.9 -2.9 -2.9	H vs IDC Gene Symbol FNI POSTN POSTN IIST212AA4.3 TOP2A COLLA COLLA ATT78030.2 MEI07 MEI07 MEI24-11.2 PPP1R14BP3 AC093850.2 COLLA2 COL	P 9E-04 0,022 0,001 0,045 0,045 0,004 0,005 0,022 0,007 0,022 0,007 0,022 0,007 0,022 0,007 0,022 0,001 0,015 0,023 0,011	FC 74 4.6 3.7 3.6 3.1 2.9 2.8 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5	Gene Symbol CPB1 R11:2066411.7 IG1IA1 ERBE2, MI4728 KR14 KR15 KR15 EGR1 IGJ FOSB APOD KRT6B MGP TM45F18 TNFSF10 TA45F18	P 0.041 0.041 0.031 3E-06 0.013 0.036 0.019 0.004 0.004 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.001	DCC FC -5.1 -5.1 -3.3 -3.1 -3.1 -3.1 -3.1 -2.9 -2.8 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.2 -2.2	IS vs IDC Gene Symbol CENTP RP11-706015.7 ANLA MEMO AVEVI 2BTB18: ZNP238 CCT3 CADMI LMNB1 RNU5F-1 HIST2HZAC EPRS OLR1 CKAP2 ANP32E CCNA2 TPX2 KIP23 ISG201.2 PARPI	P 0.017 0.04 0.04 0.037 0.007 0.024 0.024 0.024 0.024 0.024 0.025 0.035 0.035 0.035 0.035 0.044 0.003 0.003 0.003 0.003 0.003 0.003 0.003 0.003 0.004	
Gene Symbol PI3 PY1R NOVAI CLIC6 SCARNA8 SCARNA8 SCARNA8 SNORD35 SNORD35 SNORD35 SNORD35 SNORD35 SNORD42 PI6R SNORD42 PI6R SNORD42 PI6R SNORD42 SNORD42 PI6R SNORD42 S	P 0,015 5E-04 0,007 0,037 0,037 0,037 0,038 0,005 0,035 0,005 0,005 0,005 0,005 0,002 0,004 0,041 0,029 0,004 0,029 0,004 0,029	AD FC 	H vs DCIS Gene Symbol Fife CRIP1P4 CISor754 CDK12 PLK2 MIR612, NEAT1 FIT1 OAS2 FI27 CLTC CXCL10 CXCL10 CXCL10 CXCL10 TSPVL5 CST1 DVNT1 IDN14 BST2 EZR SNORA.29 TCP1 HK2 FZR SNORA.29 TCP1 HK2 FZR SNORA.29 TCP1 HK2 CK2 SNORA.29 CP1 FZR SNORA.29 CP1 FZR SNORA.29 FZP S	P 0.006 0.004 0.034 0.02 5E-04 0.01 5E-04 0.038 0.048 0.003 0.038 0.038 0.038 0.032 0.036 0.005 0.036 0.001 0.041 0.041 0.041 0.041	FC 3.3 2.4 2.3 2.2 2 2 2 2 2 2 2 2 2 2 2 2 2	Gene Symbol SCORDA2 PPP PIT5 RP11-53019.1 PTN ANKRD30A KKT14 SNORD115-4 RP11-53019.2 SCORD215-4 RP11-53019.2 SCORD215-4 SNORD115-4 SCORD15-4 SCORD2 SCORD2 EGR1 SLC39A6 SERPINA3 PLAT STEAP4 SFRP1 FOS	P 0,024 0,003 0,003 5E:05 0,047 2E:04 0,027 0,013 0,001 0,025 0,025 0,025 0,025 0,025 0,027 0,013 0,001 0,008 0,008 0,003 0,018	AD FC -18 -17 -4,7 -4,5 -3,8 -3,7 -3,7 -3,7 -3,7 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5	H vs IDC Gene Symbol PNT POSTN HIST2122AA4,3 TOP2A COL1A1 BGN COL1A1 BGN COL1A1 BGN COL1A2 MK167 MK1244-1,2 PPP1R14BP3 AC093850.2 KPNA2 COLA2 COLA2 COLA2 COLA3 COLA3 COLA3 COLA4 HIST1HZBI HIST21HZBI LRRC15 CCT3	P 9E-04 0,022 0,001 0,045 0,002 0,007 0,005 0,002 0,007 0,006 0,004 0,001 0,007 0,002 0,002 0,002 0,003 1 0,026 0,003 1 0,026 0,003 0,001	FC 74 4,6 3,7 3,6 2,9 2,8 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5	Gene Symbol CPB1 CPB1 GIA1 ERBB2: MIR4728 KRT14 KRT15 FOS STEAP4 EGR1 IGJ PTN SFRP1 IGJ PTN SFRP1 GJ FOS STEAP4 EGR1 GJ FOS STEAP4 FOS STEAP4 TAST8 TVASF18 TV	P 0,041 0,014 0,014 0,013 0,014 0,014 0,010 0,019 0,004 0,004 0,004 0,000 0,000 0,000 0,001 0,001 0,011 0,04 0,011 0,014 0,004 0,004 0,004 0,004 0,004 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,001 0,001 0,000 0,000 0,000 0,000 0,000 0,001 0,000 0,001 0,000 0,001 0,001 0,001 0,001 0,000 0,001 0,001 0,001 0,000 0,001 0,001 0,001 0,001 0,001 0,001 0,001 0,001 0,001 0,001 0,001 0,002	DC FC -5.1 -3.7 -3.3 -3.9 -2.8 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.4 -2.3 -2.3 -2.3 -2.3 -2.3 -2.2 -2.2 -2.2	IS vs IDC CENTF CENTF RP1-7060015.7 ANLN MKI67 ATAD2 KIF11 ZBTB18.ZNP238 CCT3 SNRPD1 CADM1 LMNB1 RNU5F-1 HIST21ZAC EPRS1 CKAP2 ANP32E CCNA2 TPX2 KIF23 SIG20.2 PARP1 ROS1	P 0,017 0,04 0,019 0,037 0,024 0,019 0,007 0,024 0,019 0,039 0,039 0,014 0,001 0,039 0,014 0,001 0,017 0,017 0,017	
Gene Symbol PI15 NPV1R NOVAI CLICG GT10 SCIEB/2 SNORD05 SNORD5 SN	P 0,015 5E-04 0,015 0,037 0,037 0,038 0,005 0,038 0,005 0,038 0,001 0,022 0,041 0,048 0,048 0,044 0,048 0,049 0,044 0,044 0,049 0,005	AED FC 3.8 -3.6 -3.6 -3.7 -2.5 -2.4 -2.3 -2.3 -2.2 -2.4 -2.3 -2.2 -2.2 -2.2 -2.2 -2.2 -2.1 -2.1 -2.1	DH vs DCIS   Gene Symbol   IFi6   CRIP1P4   CDSG751   CDSG752   PIR62   MIR02: NEATI   HT52   HR02: NEATI   HT52   CICIC   CXCL10   TSPYL5   CSTI   DYNLTI   HF14   IDH2   BST2   EZR   SNORA29: TCPI   HR27   PABFC1   ACSE1	P 0,006 0,004 0,037 0,037 0,037 0,037 0,038 0,038 0,049 0,043 0,043 0,049 0,044 0,048 0,048 0,048	FC 3.3 2.4 2.3 2.2 2 2 2 2 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.7 1.7 1.6 6 1.6 1.6 1.6 1.5 1.5 1.5 1.5	Gene Symbol SCGB2A2 PIP PI153309,1 PI153309,1 PI153309,1 PI153309,1 PI15309,2 PI15309,	P 0.024 0.02 0.003 5E:05 0.047 0.02 2E:04 0.025 2E:04 0.025 0.025 0.025 0.025 0.025 0.025 0.025 0.001 0.008 0.008 0.008 0.003	AD FC -18 -17 -15 -7,2 -4,3 -3,4 -3,7 -3,7 -3,7 -3,5 -3,4 -3,3 -3,5 -3,4 -3,3 -3,5 -3,4 -3,3 -3,2 -2,9 -2,9 -2,9 -2,9 -2,9 -2,9 -2,9 -2	H vs IDC Gene Symbol FNI POSTN POSTN INST212AA4.3 TOP2A COL1A1 BOR ACT 178030.2 MEI07 MEI07 MEI24-112 PPP1E14BP3 AC003850.2 COL1A2 CXCL10 COL3A1; MIR3606 COL3A1; MIR3606 HISTIH3A-J SULF1 THBS2 CENFF HISTIH2BI LRRC15 CCT3 KIF11	P 9E-04 0,022 0,001 0,045 0,025 0,002 0,005 0,022 0,007 0,022 0,007 0,017 0,027 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,015 0,022	FC 74 4,6 3,7 3,6 3,7 2,9 2,8 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5	Gene Symbol CPB1 R11-206M1.7 IG1A1 ERBB2, MIR-728 KRT14 KRT3 FG8 STCAP4 EGR1 GJ FG3 FG9 FG3 FG9 FG9 FG9 FG9 FG9 FG9 FG9 FG9 FG9 FG9	P 0,041 0,041 0,031 3E-06 0,013 0,036 0,019 0,036 0,019 0,046 0,004 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,001 0,004 0,014 0,041 0,041 0,041 0,041 0,041 0,041 0,041 0,041 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,031 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,032 0,034 0,031 0,032 0,032 0,032 0,034 0,034 0,032 0,034 0,032 0,034 0,032 0,034 0,032 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,034 0,032 0,036 0,032 0,004 0,001 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,002 0,003 0,004 0,001 0,00200000000	DCC FC 6-4 -51 -3,7 -3,3 -3,1 -3,1 -3,1 -3,1 -3,1 -2,8 -2,8 -2,7 -2,7 -2,7 -2,7 -2,4 -2,3 -2,3 -2,3 -2,2 -2,2 -2,2 -2,2	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN MK167 ATAD2 KH711 ZBTB18.72NF238 GENE CADMI LMNB1 RNU5F-1 HIST2H2AC HIST2H2AC GENE CCNA2 TPX2 CCNA2 TPX2 KH73 ISC20L2 PARP1 RCS1 RBM8A	P 0,017 0,04 0,019 0,037 0,007 0,024 0,024 0,024 0,024 0,024 0,024 0,024 0,024 0,024 0,024 0,024 0,024 0,024 0,024 0,017 0,017 0,017 0,017 0,017	
Gene Symbol PI3 PP3R NOVA1 CLIC6 SCARNA8 SCARNA8 SNORD35 SNORD35 SNORD35 SNORD31 SNORD	P 0,015 5E-04 0,007 0,027 0,037 0,038 0,005 0,038 0,001 0,028 0,041 0,029 0,004 0,029 0,004 0,029 0,002 0,029 0,015 0,029 0,015	AD FC 5.5 -3.8 -2.7 -2.5 -2.4 -2.3 -2.3 -2.3 -2.3 -2.2 -2.2 -2.2 -2.2	H vs DCIS Gene Symbol IFG CRIP1P4 CDSr754 CDSr754 CDSr12 PLK2 MIR612, NEAT1 IFT1 OAS2 IF127 CLTC CXCL10 CXCL10 CXCL10 CXCL10 CXCL10 CXCL10 DYNLT1 IF144 IDM2 BZZ SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 HK2 SNORA.29 TCP1 SNORA.29 TCP1 SNORA.29	P 0,006 0,004 0,037 0,032 5E:04 0,032 5E:04 0,032 0,032 0,036 0,048 0,003 0,036 0,048 0,048 0,044 0,041 0,041 0,041 0,043 0,044 0,041 0,043	FC 33 31 2,4 2,3 2,2 2 2 2 2 2 2 2 2 2 2 2 2 2 1,9 1,9 1,9 1,9 1,9 1,9 1,9 1,9 1,9 1,7 1,6 1,6 1,6 1,6 1,5 1,5 1,5 1,5 1,5 1,5 1,5 1,5 1,5 1,5	Gene Symbol SCGB2A2 PPP PIT5 RP11-53019.1 PTN ANKR030A KRT14 SNORD115.4 RP11-53019.2 SCGB2A1 ARDD KRT5 SCGB2A1 ARDD KRT5 SCGB2A1 SCGBA2 SCGB2A1 SCGBA3 SCGB12 FLAT STEAP4 STEAPA STEAPA STEAPA STEAPA STEAPA	P 0,024 0,003 0,003 0,0047 2E-04 0,025 0,027 0,013 0,001 0,027 0,013 0,001 0,028 0,002 0,025 0,025 0,025 0,025 0,025 0,025 0,027 0,013 0,003 0,003 0,003 0,003 0,003 0,003 0,003 0,003 0,004 0,005 0,004 0,005 0,004 0,005 0,004 0,005 0,004 0,005 0,00000000	AD FC -13 -17 -15 -17 -4,5 -3,7 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5 -3,5	H vs IDC Gene Symbol PNT POSTN HIST2H2AA4,3 TOP2A COL1A1 BGN COL1A1 BGN COL1A1 BGN COL1A1 BGN COL1A2 MEI67 MEI244-1,2 PPP1E14BP3 AC003850.2 KPNA2 COL1A3 SULF1 HIS2 COL3 KIF11 EPRS	P 9E-04 0.022 0.001 0.045 0.022 0.05 0.022 0.007 0.006 0.007 0.020 0.031 0.027 0.031 0.027 0.031 0.027 0.031 0.032 0.031 0.032 0.032 0.032 0.031 0.032 0.032 0.032 0.032 0.032 0.033 0.032 0.033 0.032 0.033 0.032 0.033 0.032 0.033 0.032 0.033 0.032 0.033 0.032 0.033 0.032 0.033 0.032 0.033 0.031 0.032 0.032 0.033 0.031 0.032 0.032 0.032 0.032 0.033 0.031 0.032 0.032 0.032 0.032 0.033 0.031 0.032 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.032 0.031 0.031 0.032 0.0310000000000	FC 7.4 4.6 3.7 3.6 2.9 2.8 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5	Gene Symbol CPB1 CPB1 F11-206M11.7 GIA1 ERBB2: MIR4728 KRT14 KRT15 FOS STEAP4 EGR1 IGJ PTN PIX2 SFRP1 GJ PTN PIX2 SFRP1 APOB APOB APOB APOB TNSF10 TN	P 0,041 0,014 0,031 3E-06 0,011 0,036 0,010 0,004 0,004 0,004 0,004 0,004 0,004 0,000 0,000 0,000 0,000 0,000 0,000 0,001 0,001 0,001 0,004 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,001 0,000 0,001 0,000 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,003 0,001 0,003 0,002 0,002 0,003 0,003 0,003 0,003 0,003 0,003 0,003 0,003 0,004 0,003 0,003 0,004 0,001 0,003 0,001 0,003 0,001 0,003 0,001 0,003 0,001 0,000 0,001 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000 0,000000	DC FC -5,1 -3,3 -3,1 -3,1 -3,1 -3,1 -3,1 -3,1 -3	IS vs IDC CENTF CENTF RP1-T060015.7 ANLAN MKI67 ATAD2 KIF11 ZBTD18: ZNP238 CCT3 SNRPD1 CADM1 LMNB1 RNU5F-1 HIST2H2AC CRAP2 CCNA2 CCN	P 0,017 0,04 0,019 0,037 0,024 0,019 0,007 0,024 0,019 0,006 0,035 0,039 0,035 0,039 0,035 0,039 0,035 0,047 0,035 0,047 0,035 0,047 0,017 0,014 0,035 0,017 0,014 0,017 0,014 0,017 0,014 0,017 0,014 0,017 0,014 0,017 0,014 0,019 0,017 0,024 0,019 0,017 0,019 0,017 0,024 0,019 0,019 0,017 0,024 0,019 0,007 0,019 0,007 0,00000000	
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Gene Symbol PI15 NPV1R NOV1R CLIC6 SCRNAB SC	P 0,015 5E-04 0,015 0,015 0,015 0,037 0,037 0,038 0,005 0,038 0,001 0,029 0,004 0,041 0,029 0,0029 0,0029 0,020 0,0200000000	AEC FC 5-5-5 -5-5-5 -5-5 -2-5-5 -2-4 -2-3 -2-5 -2-3 -2-3 -2-2 -2-2 -2-2 -2-2	DH vs DCIS Gene Symbol FF16 CRIP1P4 CI5of54 CDK12 PIR2 MIR02: NEATI HTT PIR2 HT2 CICC CXCL10 TSPYL5 CST1 DYNLT1 PIR4 IDH2 BST2 EZR SNORA29: TCP1 NORA29: TCP1 RAF4 PABPC1 ACSL1 B2M STAT1	P 0,006 0,004 0,037 0,037 5E-04 0,02 5E-04 0,038 0,048 0,048 0,048 0,049 0,044 0,045 6E-04 0,048 0,048	FC 33 2,4 2,2 2 2 2 2 1,9 1,9 1,9 1,9 1,9 1,9 1,9 1,9 1,9 1,9	Gene Symbol SCGB2A2 PIP PI1-53019,1 PT1-53019,1 PT1-53019,2 SCGD15-4 SNOD15	P 0,024 0,023 0,003 0,003 0,047 0,025 0,025 0,027 0,013 0,001 0,008 0,006 0,025 0,001 0,003 0,00000000	AE FC -18 -17 -15 -17 -15 -17 -15 -17 -15 -17 -17 -15 -17 -17 -17 -15 -17 -17 -17 -17 -15 -17 -17 -17 -17 -17 -17 -17 -17 -17 -17	H vs IDC Gene Symbol FNI POSTN INST212AA4.3 TOP2A COLIA1 BON CUTA1 BON CUTA1 BON CUTA1 BON CUTA1 BON CUTA2 COLIA2 CO	P 9E-04 0,022 0,001 0,045 0,002 0,007 0,006 0,002 0,007 0,006 0,002 0,007 0,002 0,007 0,002 0,002 0,002 0,004 0,011 0,012 0,022 0,001 0,012 0,001 0,012 0,001 0,012 0,001 0,001 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,002 0,001 0,002 0,004 0,002 0,004 0,002 0,004 0,002 0,007 0,002 0,007 0,002 0,007 0,002 0,000000	FC 74 4,6 3,7 3,6 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5 2,5	Gene Symbol CPB1 R11-206M1.7 IGIA1 ERBB2, MIR-728 KRT14 KRT3 FCS SCAP4 ECR1 ECR1 ECR1 ECR1 ECR1 ECR1 ECR1 ECR1	P 0,041 0,014 0,031 3E-06 0,010 0,036 0,010 0,036 0,004 0,004 0,004 0,004 0,002 0,002 0,002 0,002 0,002 0,002 0,001 0,041 0,041 0,041 0,041 0,041 0,041 0,041 0,041 0,032 0,031 0,032 0,004 0,031 0,031 0,032 0,004 0,031 0,031 0,032 0,004 0,031 0,032 0,004 0,004 0,004 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,001 0,002 0,002 0,001 0,004 0,002 0,000000	DCC FC -5- -5- -5- -3.7 -3.3 -3.1 -3.1 -3.1 -3.1 -3.1 -3.9 -2.9 -2.8 -2.7 -2.7 -2.7 -2.7 -2.7 -2.7 -2.4 -2.3 -2.3 -2.3 -2.2 -2.2 -2.2 -2.2 -2.2	IS vs IDC Gene Symbol CENPF RP11-706015.7 ANLN MK167 ATAD2 KIF11 SCOD1 SCOD1 SCOD1 SCOD1 COD1 COD1 COD1 COD1 COD1 COD1 COD1	P 0,017 0,044 0,019 0,037 0,024 0,037 0,037 0,017 0,019 0,035 0,047 0,030 0,047 0,030 0,047 0,048 0,047	

Figure 4: Comparison of the gene expression among different subgroups. Venn-diagram (A) representing differentially expressed ncRNAs in each subgroup of BC progression as compared to normal breast lesions. (B) The top 30 ( $\pm$  1.5-fold and p < 0.05) differentially regulated genes when compared to gene expression in normal breast lesions or inter groups comparisons (C). Green = Downregulation, Red= upregulation. Normal: benign breast tissue; ADH: Atypical ductal hyperplasia; DCIS: Ductal carcinoma *in situ*; IDC: Invasive ductal carcinoma.

degrade the extracellular matrix as a preparatory step to matrix invasion. This data is in concordance with a previous studies. [3, 18]. An increase in the angiogenesisrelated pathways [19] such as changes in the extracellular matrix, endothelial cell proliferation, migration, VEGF signaling, and actin cytoskeleton signaling at the DCIS stage was also observed. Once the cells were prepared to switch to the IDC stage, in addition to the genes involved in extracellular matrix re-organization and epithelial cell proliferation, upregulation of genes involved in stress environment, i.e. genes involved in survival in a stress environment (eNOS pathway, NRF2 mediated oxidative response, GADD45 pathway etc), inflammatory processes (Th2 pathway, chemokine signaling, NFkB pathway, IL-17 signaling), growth factor signaling (EGF signaling) and transcription initiation and mitosis (TOP2A) was observed. These data are in concordance with the literature, which highlights an increase in inflammatory processes [20], DNA replication [21] and survival in stress environment [22] to be associated with BC progression. Furthermore, we have also observed a linear progression in the cellular functions (cell growth, proliferation, development and movement) as the tumor develops from ADH to IDC, and this is also shown by a study by Hou et al., 2016 [23].

In addition, a significant number of non-coding RNAs (ncRNAs) were pinpointed as significantly modulated (Figure 5A). Many studies highlighted the role of ncRNA in BC initiation and progression [24, 25]. In our study, the more significant regulated ncRNAs were *SNORD115* (breast lesion), *SNORD116* (MCF10A), *SNORD114, SNORD78* and *miR205*. SNORD proteins are members of the non-coding small nucleolar RNA (sno-RNA) family with C/D box and are associated with DNA methylation. This gene family usually found in gene clusters, has roles in RNA nucleotide modification and mRNA splicing [26]. Sno-RNA can also generate miRNAs which can affect expression of many genes [27]. Deregulation of sno-RNA expression has been seen in

many cancers [24, 25]. Kishore and Stamm reported that SNORD115 was essential for correct splicing of a serotonin receptor Htr2c, whose expression has been correlated with breast tumor progression [26]. Our results showed an increase in SNORD115 in ADH and DCIS, and a similar modulation of SNORD116 was seen in MCF10A cell lines. Reports suggest that SNORD115 and SNORD116 affect each other's activity and hence modulate the expression of their target genes [13]. As previously published, Falaleeva et al (2015) showed that the over-expression of SNORD115 and SNORD116 altered the pathways related to cellular response to DNA damage, regulation of cellular response to stress, post transcriptional regulation of gene expression, mitotic cell cycle progression, cytokine signaling and TNF signaling [13]. This is in agreement with our results characterizing the Normal to IDC transition in breast tissue lesions. These data display the initial role of SNORD115/116 as a preparatory signal for cancer progression towards IDC. A decrease in SNORD114 expression, which is located at the MEG3-MEG8 loci in the genome, was also observed in our study [28, 29]. Previous studies have shown a suppression of MEG3 gene in various tumors [30, 31] and a downregulation of MEG8 gene, which is essential for stem cell growth and proliferation, thus resulting into a cancer cell [29]. In addition, we have found an increase in SNORD78 (2.4 fold, p-value = 1.3E-03) and a decrease in miR205 expression (-2.5 fold, p-value = 1.6E-03) in IDC subgroup when compared to normal, which are in concordance with the literature, suggesting that SNORD78 expression was associated with tumorigenesis [32], while miR205 could supress cell growth and invasion in BC [33]. Validation of SNORD115 and SNORD114 gene expression by qPCR in breast tissue lesions confirmed these modulations. MCF10A cell lines also showed similar patterns.

In addition to ncRNAs, we found differentially regulated protein coding genes belonging to molecular pathways responsible for BC progression. Indeed,



**Figure 5: Validation of the difference in gene expression by qPCR.** Based on the changes in the top 30 genes depicted in Figure 5B and 5C, 7 genes were selected and validated by qPCR in tissue samples (N=3). The expression data is the ratio of query gene to 3 housekeeping genes (*ATP50, HPRT1* and *GAPDH*). The graph is representative of two independent experiments. Normal: benign breast tissue; ADH: Atypical ductal hyperplasia; DCIS: Ductal carcinoma *in situ*; IDC: Invasive ductal carcinoma.

SFRP1, PI15, RELN, POSTN, SPP1, FN1, TOP2A, ANLN, CENPF and LRRC15 could represent potential signatures corresponding to each subgroup. Out of these, SFRP1, PI15 and RELN were downregulated as the tumor progresses toward malignancy. On the other hand, POSTN, SPP, TOP1, ANLN, CENPF and LRRC15 were upregulated at the IDC stage (Figure 6).

Four of these genes namely SFRP1, PI15, SPP1 and *FN1* have been then confirmed by qPCR. We observed a significant decrease in SFRP1 as the tumor cancer progresses towards IDC. The SFRP1 (Secreted Frizzled Related Protein 1) protein is a negative regulator of the Wnt pathway [34]. As described earlier, this protein harbours a cysteine rich domain which is homologous to frizzled receptor [34]. After being secreted by the cell the protein remains associated with the membrane and can interact with other proteins in the extracellular space. Upon binding to the WNT protein, SFRP1 inhibits the ligand receptor binding and hence circumvents WNT signaling which therefore behaves both as oncogenic as well as a tumor suppressor signal depending on the context. In BC, downregulation of SFRP1 protein is associated with tumor progression and poor prognosis [35], which is in agreement with our results. Furthermore, we found that a decrease in PI15 (Peptidase inhibitor 15) gene correlated with tumor progression. This gene encodes a trypsin inhibitor protein. Interestingly, several studies have shown that food supplements containing trypsin inhibitors might be beneficial in fighting breast and other cancers by inhibiting trypsin used by cancer cells to invade the basement membrane [36].

POSTN (Periostin) is a secreted extracellular matrix glycoprotein which binds to integrins and supports the adhesion and migration of epithelial cells [37]. POSTN has a role in tissue development, regeneration, wound healing as well as epithelial mesenchymal transition [38]. Hence, its increase observed in the invasive subgroup is in agreement with these former observations. POSTN has been reported to play a role in many cancers and has been seen in cancer associated fibroblasts of IDC and highgrade tumors [39] which again is in accordance with our data.

SPP1 (Secreted Phosphoprotein 1) also known as Osteopontin is involved in the attachment of osteoclasts to mineralized bone. It is present in cell membrane and is also a cytokine responsible for upregulation of INF $\gamma$ and IL-12 [40]. SPP1 is associated with aggressiveness of cancer, increases in tumor promoting inflammation and activates invasion and metastasis [41], which is in perfect agreement with our findings. Based on our data, we found an increase in the inflammatory pathway at the IDC stage. In addition, a significant upregulation of FN1 (Fibronectin1), a glycoprotein found in dimeric or multimeric form in the extracellular matrix, was noted



**Figure 6: Molecular changes associated with breast cancer progression.** Stages of BC progression where decrease in tumor suppressor gene, snoRNA regulation and increase in genes responsible for extracellular matrix organisation is associated with breast cancer progression. The triangles represent the changes at each subgroup of BC progression.

in IDC transition. FN1 is involved in cell adhesion and migration, wound healing, invasiveness and metastasis. In BC, FN1 is secreted by both the stromal and epithelial cells and is a marker of increased invasiveness and metastatic potential [42].

Moreover, other genes were also pinpointed in our study (*RELN, TOP2A, ANLN, CENPF* and *LRRC15*) and were also documented in the literature regarding their expression in BC [43–47].

Downregulation of RELN (Reelin), a secreted extracellular matrix protein, is considered a poor prognosis for BC [43]. TOP2A (Topoisomerase (DNA) II Alpha) is involved in chromosome condensation, chromatid separation, and the relief of torsional stress that occurs during DNA transcription and replication. Its upregulation and aberrant expression was observed in many cancers including BC [44]. The upregulation of TOP2A in our study can be associated with increased mitotic division seen in the IDC subgroup. ANLN (Anillin Actin Binding Protein), which plays a role in cell growth, migration and cytokinesis, has been shown to be associated with poor prognosis in BC patients and is considered an important player for cell division [45]. As for CENPF (Centromere Protein F), this protein has a major role in chromosome segregation during mitosis and has been associated with chromosomal instability in primary BC patients and therefore poor prognosis [45]. The upregulation of LRRC15 (Leucine Rich Repeat Containing 15) gene, as observed in IDC when compared to DCIS lesion, is considered to play a major function in BC invasiveness [46]. These studies were in concordance with our findings.

The present study could truly serve in early diagnosis in clinical setting and further characterization could also identify potential and specific targets for each subgroup of BC. Indeed, our analysis highlights involvement of tumor suppressor genes and snoRNAs as initial modulators of breast cell transformation into ADH lesion, signifying bi-directional signaling in the breast cell. As the cell proceeds towards DCIS, extracellular matrix proteins prevail while an increase in signaling associated with increased invasiveness, metastasis, cell division and survival is observed at the IDC stage.

The genes identified in the present study could aid clinicians to make a priority-based decision for intervention. For example, if a patient shows expression of PI15 but lacks the expression of SPP1 and FN1, then this patient could be called for follow-up without the need of immediate surgery. On the other hand, reverse of this situation calls for immediate surgical intervention. The present study provides an opportunity for early detection which is quick and cost-effective in addition further investigation could provide a new and specific target for each subgroup of BC progression.

A study by Hou et al. 2016 [23] has carried out a systemic analysis of genes involved in breast cancer

development by carrying out comparative analysis of gene expression in normal, DCIS and IDC stages. This study is however missing one of the important stages of breast cancer progression, that is ADH [48, 49], which is often confused with low grade DCIS. In summary, the present study is the first thoroughly analyzed gene expression in a whole continuum of breast lesions of varying severity, and has led to the identification of a specific human gene signature that could be a potential signature for different stages of cell malignancy development, from normal breast tissue to invasive cells. These genes could therefore be further characterized in breast samples and could be developed as biomarkers for the prognosis of BC progression and invasiveness.

# **MATERIALS AND METHODS**

#### **Breast tissue samples**

The breast lesion tissue samples were collected from the tissue bank located at the Centre des maladies du sein Deschênes-Fabia of Hôpital du St-Sacrement, Quebec, Canada. All breast tissue samples deposited in the bank were from women (n=20) with no hormonotherapy or chemotherapy treatment before surgery. All breast diseases were confirmed by an experienced pathologist, and all tumor characteristics were routinely collected from medical reports: size, histologic type, grade, lymph node involvement and receptor status (ER, PR and HER2). Formalin-fixed paraffin-embedded (FFPE) blocks containing normal (classified as normal breast tissue), ADH, DCIS or IDC epithelial tissue were selected by a senior pathologist specialized in breast pathologies. Normal tissues were collected from women coming for biopsy. These patients did not had any sign of breast lesions at the time of surgery. High grade DCIS was selected to avoid any contamination with ADH given that ADH and low-grade DCIS share many architectural and cytological features, and risk of invasive BC is higher in high grade DCIS. Since high grade DCIS was selected, we did the same for IDC. Five independent samples corresponding to each stage of BC progression were selected for gene expression analysis. All selected DCIS and IDC were positive for estrogen and progesterone receptors and were of high grade. The mean age of selected women for this study was 53±4 years.

#### MCF10A cell lines

The MCF10A cell line subtypes were developed to represent different stages of BC progression [8, 9]. These cell lines were used in parallel to compare *in vitro* MCF10A cell line data with breast lesion clinical data. Two biological replicates of each MCF10A (normal/ benign), MCF10AT (ADH), MCF10DCIS (DCIS) and MCF10CA1a (IDC) cells were used for analyses.

#### **Tissue microarray**

For each of the 20 participants, a tissue microarray (TMA) was done to ensure that RNA is assessed on samples containing breast tissue with at least 90% epithelial content. Hematoxylin and eosin (H&E)-staining was performed on first and last tissue sections for review and tissue was validated by an experienced pathologist to ensure consistency of the breast tissue of interest throughout the block (5 normal, 5 ADH, 5 DCIS, 5 IDC).

#### **RNA** isolation

Total RNA from breast tissue samples as well as MCF10A cell lines were isolated with Qiagen RNeasy Mini Kit (Qiagen, Hilden, Germany). Preparation of RNA samples for whole-genome expression analysis was performed using the SensationPlus<sup>TM</sup> FFPE Amplification Kit (Affymetrix, Thermo Fisher Scientific Waltham, Massachusetts, United States).

#### Human transcriptome array analysis (HTA)

HTA analysis was performed on these samples using the GeneChip<sup>™</sup> Human Transcriptome Array 2.0 (ThermoFisher Scientific, Massachusetts, United States). HTA hybridization, washing, staining and scanning were performed following the GeneChip<sup>™</sup> Human Transcriptome Array 2.0 protocol of the genomic platform located at the CHU de Quebec Research Centre, Laval University.

#### Statistical analyses

Identification of differentially expressed gene isoforms between subgroups of lesion or MCF10A cell line series (normal, ADH, DCIS and IDC) was carried out by ANOVA analysis between 4 groups and obtained data were further analyzed with the Transcriptome Analysis Console (TAC) Software (Affymetrix). To do so, normalized intensities between subgroups of lesions or cell lines were compared using One-way Between-Subject ANOVA, and multi-testing correction was performed using Benjamini-Hochberg Step-Up False Discovery Rate (FDR) controlling procedure [50]. Then for statistically significant results, expression analysis was performed for all pairing groups while linear regression was applied for a tissue subtype along the continuum of lesions (normal/ADH/DCIS/IDC) to reveal progressive and significant differences, which is dependent on the lesion aggressiveness level. Finally, the latter expression analysis was repeated regardless of p-values obtained by ANOVA analysis to reveal gene signature for each subgroup. P-values < 0.05 were considered as significant with a FDR of 5%.

# Pathways, networks, and clustering analysis

In order to identify biological pathways differentially expressed between prognostic subgroups, we performed an enrichment analysis of upregulated and downregulated genes (FDR < 0.05) using ClueGO, Metascape server (Sanford Burnham, UCSD, GNF, http://metascape.org) and three different pathways analysis tools: the KEGG (Kyoto Encyclopedia of Genes and Genomes) database, the panther classification system (http://pantherdb.org/) and the Ingenuity Pathway Analysis (IPA®, QIAGEN Redwood City, www.giagen.com/ingenuity). Default settings in IPA for expression dataset analyses were used for functional analysis. Gene lists were uploaded using NCBI Entrez gene IDs or gene symbols and submitted for IPA Core Analysis. IPA calculates p-values that reflect the statistical significance of association between the genes and the networks by Fisher's exact test. P-values <0.05 were considered significant. Gene ontology and KEGG pathways enrichment of transcripts significantly and differentially expressed were performed using Gene Set Enrichment Analysis (GSEA) tools with default parameters, while FDR q-values below 0.01 were used.

# Quantitative real-time PCR (q-PCR) analysis

Quantitative PCR was performed using SyBr Green technology as described previously [51]. Briefly, oligoprimer pairs that allow the amplification of ~200 base pairs (bp) of the indicated specific mRNA were designed by GeneTools software and their specificity was verified by blasting the GenBank database. The sequence of primers is indicated in Supplementary Table 3. Data calculation and normalization were performed using the secondderivative and double-correction method [52], with three housekeeping genes (*ATP50*, *HPRT1* and *GAPDH*). The mRNA levels were expressed as number of copies/µg of total RNA calculated using corresponding standard curves.

# **Author contributions**

FD and CD designed the research protocol. CK and GO conducted experiments. SJ and CD contributed samples. CK, GO and YL performed data analysis. CK, YL, FD and CD drafted manuscript. Critical revision of the manuscript was done by all authors.

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# **CONFLICTS OF INTEREST**

The authors declare that they have no conflicts of interest.

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