

Data S1. MAT algorithm and DAVID parameters used in the performed comparisons.

MAT algorithm parameters used in the following comparison:

1. FBC (17 cases) vs. MBC (7 cases)  
MAT algorithm parameters: P-value threshold: 0.0001, sliding window: 1400 bp, minimum number of probes in a region: 10.
2. BRCAX FBC (10 cases) vs. BRCAX MBC (6 cases)  
MAT algorithm parameters: P-value threshold: 0.0001, sliding window: 1400 bp, minimum number of probes in a region: 10.
3. BRCAX (16 cases) vs. BRCA1/2 (8 cases)  
MAT algorithm parameters: P-value threshold: 0.0001, sliding window: 1400 bp, minimum number of probes in a region: 10.
4. BRCA1 (4 cases) vs. BRCA2 (3 cases)  
MAT algorithm parameters: P-value threshold: 0.0001, sliding window: 600 bp, minimum number of probes in a region: 10.
5. BRCA1(4 cases) vs. BRCAX (10 cases)  
MAT algorithm parameters: P-value threshold: 0.0001, sliding window: 600 bp, minimum number of probes in a region: 10.
6. BRCA2 (3 cases) vs. BRCAX (10 cases)  
MAT algorithm parameters: P-value threshold: 0.0001, sliding window: 600 bp, minimum number of probes in a region: 10.
7. BRCA1 (4 cases) vs. BRCA2 (3 cases) and BRCAX (10 cases)  
MAT algorithm parameters: P-value threshold: 0.0001, sliding window: 350 bp, minimum number of probes in a region: 10.
8. BRCA2 (3 cases) vs. BRCAX (10 cases) and BRCA1 (4 cases)  
MAT algorithm parameters: P-value threshold: 0.0001, sliding window: 350 bp, minimum number of probes in a region: 10.
9. BRCAX (10 cases) vs. BRCA2 (3 cases) and BRCA1 (4 cases)

MAT algorithm parameters: P-value threshold: 0.0001, sliding window: 350 bp, minimum number of probes in a region: 10.

DAVID parameters used in the following comparison:

A more stringent cut-off associated to DMR was applied to remove not relevant genes and reduced the list of DMRs and corresponding genes used for performing the functional enrichment analyses by DAVID.

1. FBC vs. MBC; cut-off: P-value<8.15x10<sup>-5</sup>.  
The list was reduced to 2846 DMRs corresponding to 2486 genes. David recognized 2395 genes.
2. BRCAX FBC vs. BRCAX MBC; cut-off: P-value<4.26x10<sup>-5</sup>.  
The list was reduced to 1242 DMRs corresponding to 1102 genes. David recognized 1050 genes.
3. BRCAX vs. BRCA1/2; cut-off not applied.  
David recognized 350 genes up to 357.
4. BRCA1 vs. BRCA2; cut-off: MAT score (absolute value)>3.94.  
The list was reduced to 802 DMRs corresponding to 755 genes. David recognized 723 genes.
5. BRCA1 vs. BRCAX; cut-off: MAT score (absolute value)>4.  
The list was reduced to 484 DMRs corresponding to 464 genes. David recognized 453 genes.
6. BRCA2 vs. BRCAX; cut-off: MAT score (absolute value)>4.2.  
The list was reduced to 673 DMRs corresponding to 629 genes. David recognized 613 genes.
7. BRCA1 vs. BRCA2 and BRCAX: P-value<6.78x10<sup>-5</sup>.  
The list was reduced to 861 DMRs corresponding to 819 genes. David recognized 797 genes.
8. BRCA2 vs. BRCA1 and BRCAX: P-value<6.78x10<sup>-5</sup>.  
The list was reduced to 1380 DMRs corresponding to 1251 genes. David recognized 1209 genes.
9. BRCAX vs. BRCA1 and BRCA2: P-value<6.78x10<sup>-5</sup>.  
The list was reduced to 962 DMRs corresponding to 914 genes. David recognized 888 genes.

Figure S1. Dot plots generated by Partek Genomic Suite represent the 20 most differentially methylated regions in FBC vs. MBC comparison. The average value of the probes contained in a differentially methylated region for a given breast cancer case is represented by a circle. Red and blue indicate FBC and MBC cases, respectively. The numbers on the y-axis are  $\Delta$  methylation values. FBC, female breast cancer; MBC, male breast cancer.

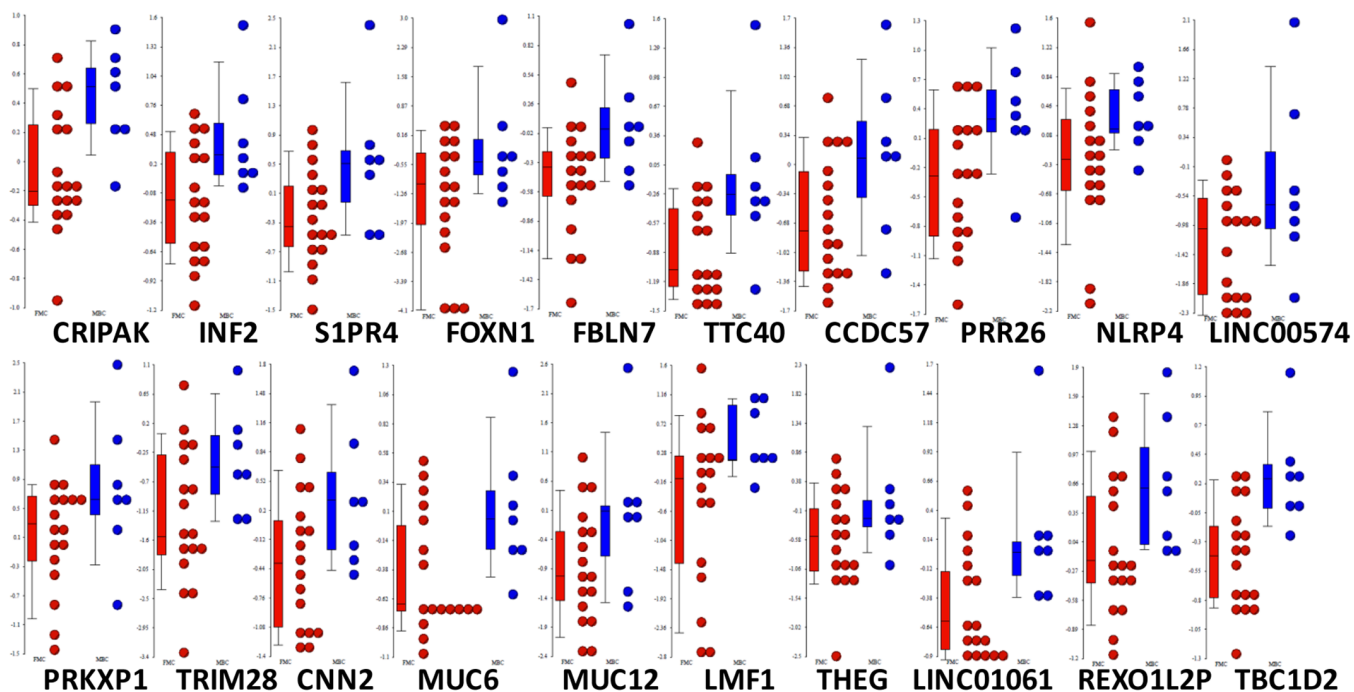


Figure S2. Dot plots generated by Partek Genomic Suite represent the 20 most differentially methylated regions in the FBC vs. MBC comparison (BRCA cases only). The average value of the probes contained in a differentially methylated region for a given breast cancer case is represented by a circle. Red and blue indicate FBC and MBC cases, respectively. The numbers on the y-axis are  $\Delta$  methylation values. FBC, female breast cancer; MBC, male breast cancer.

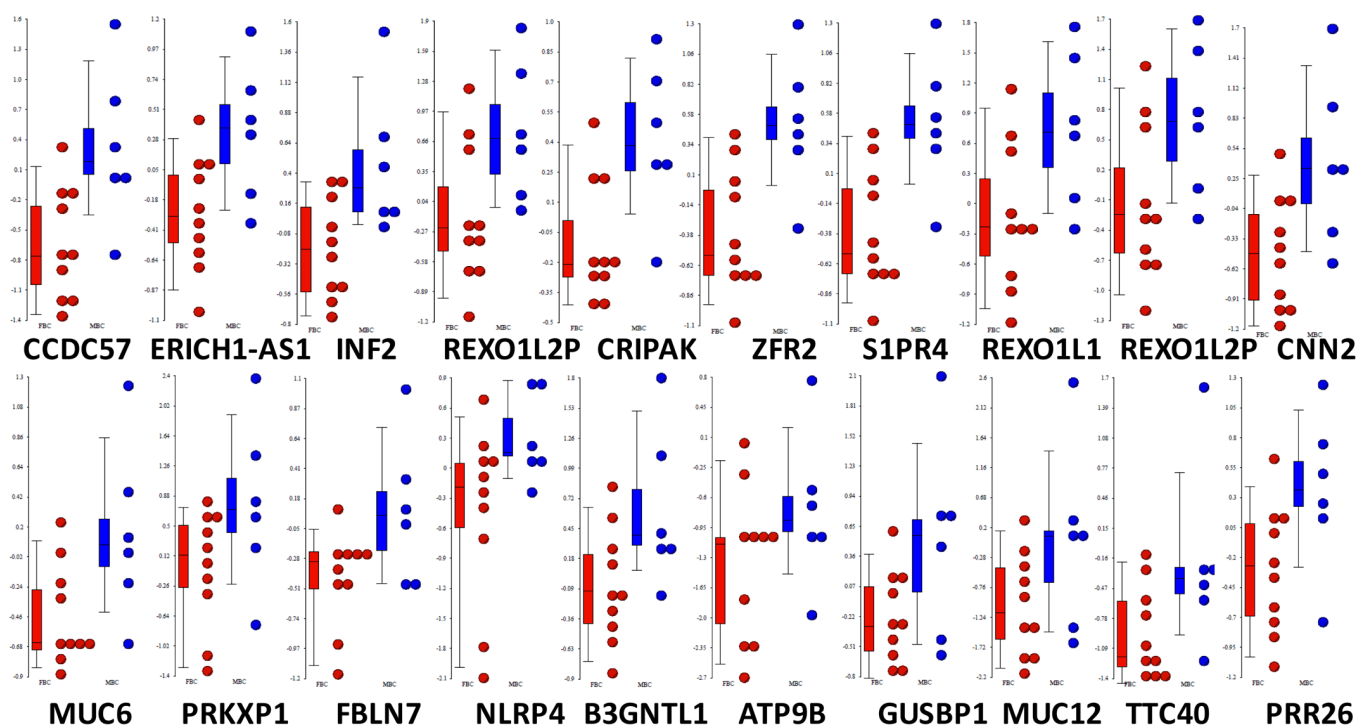


Figure S3. Dot plots generated by Partek Genomic Suite represent the 20 most differentially methylated regions in the BRCA1/BRCA2 vs. BRCA1/BRCA2 comparison. The average value of the probes contained in a differentially methylated region for a given breast cancer case is represented by a circle. Red and blue indicate BRCA1/BRCA2 and BRCA1/BRCA2 cases, respectively. The numbers on the y-axis are  $\Delta$  methylation values.

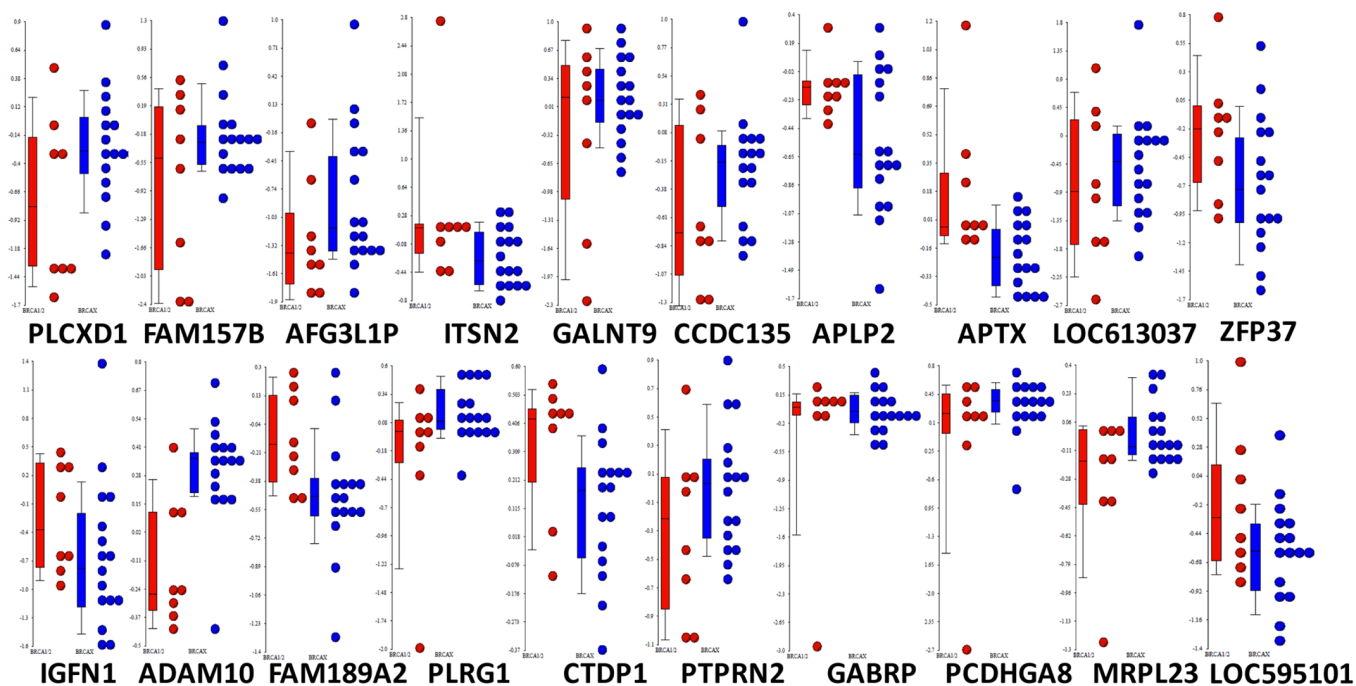


Figure S4. Dot plots generated by Partek Genomic Suite represent the 20 most differentially methylated regions in the BRCA1 vs. BRCA2 comparison (female breast cancer cases only). The average value of the probes contained in a differentially methylated region for a given breast cancer case is represented by a circle. Red and blue indicate BRCA1 and BRCA2 cases, respectively. The numbers on the y-axis are  $\Delta$  methylation values.

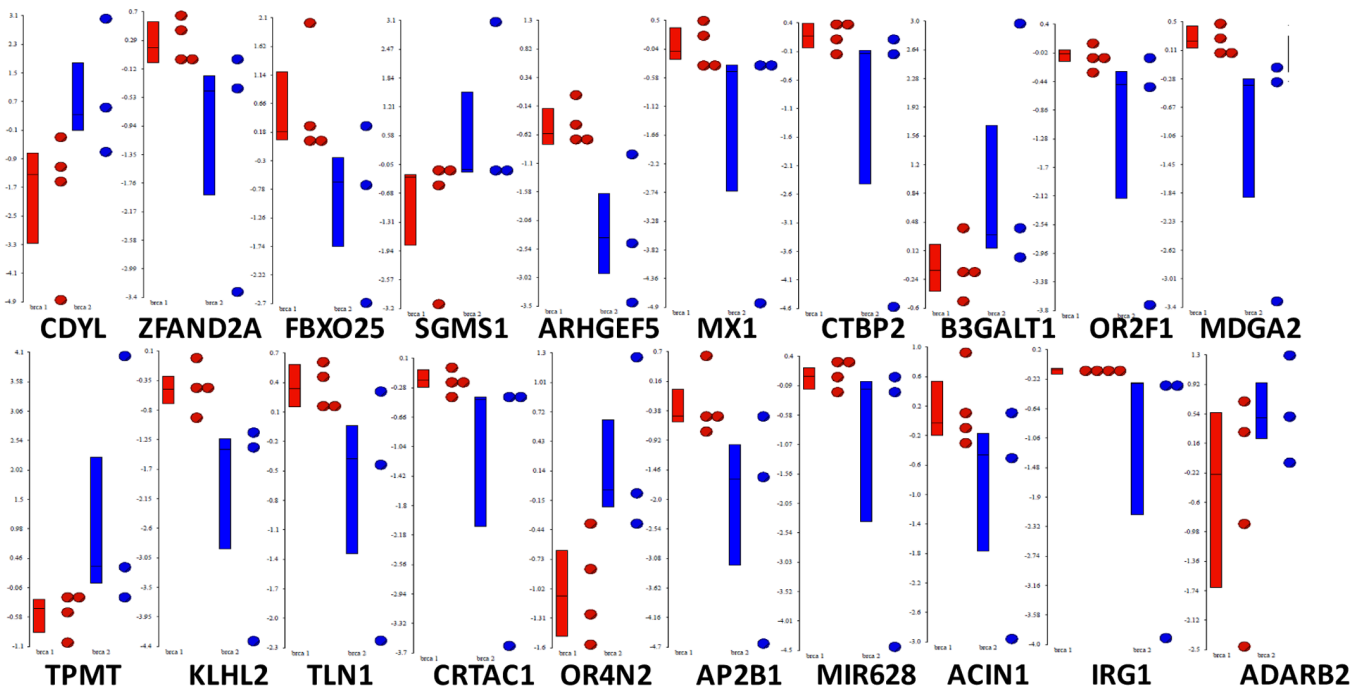


Figure S5. Dot plots generated by Partek Genomic Suite represent the 20 most differentially methylated regions in the BRCA1 vs. BRCA2 comparison (female breast cancer cases only). The average value of the probes contained in a differentially methylated region for a given breast cancer case is represented by a circle. Red and green indicate BRCA1 and BRCA2 cases, respectively. The numbers on the y-axis are  $\Delta$  methylation values.

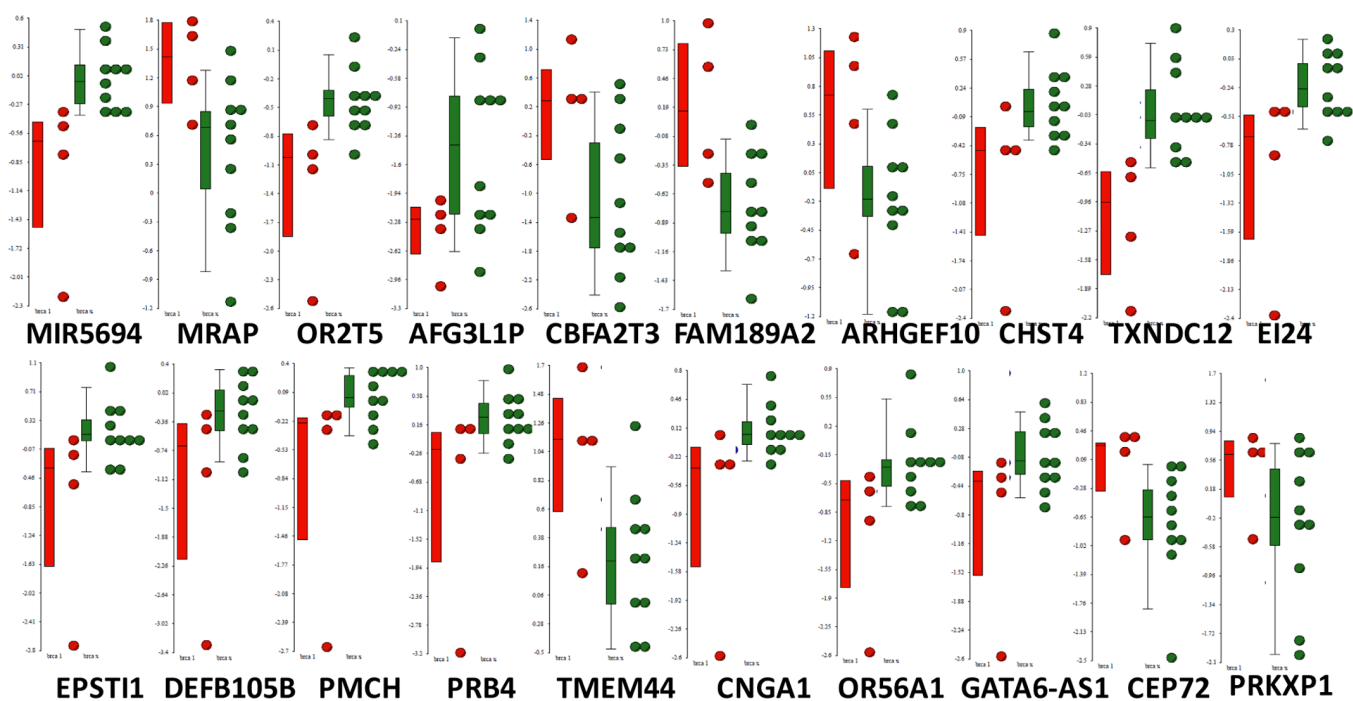


Figure S6. Dot plots generated by Partek Genomic Suite represent the 20 most differentially methylated regions in the BRCA2 vs. BRCAX comparison (female breast cancer cases only). The average value of the probes contained in a differentially methylated region for a given breast cancer case is represented by a circle. Blue and green indicate BRCA2 and BRCAX cases, respectively. The numbers on the y-axis are  $\Delta$  methylation values.

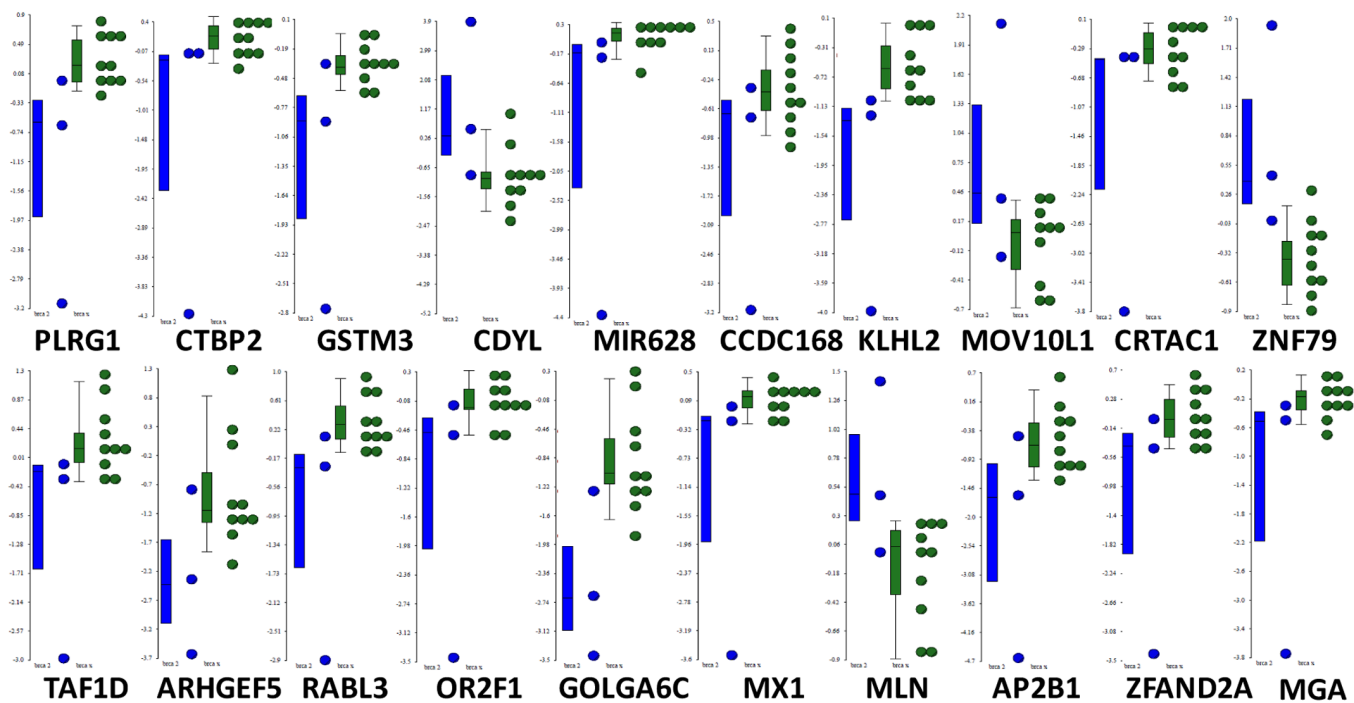


Figure S7. Dot plots generated by Partek Genomic Suite represent the 20 most differentially methylated regions in the BRCA1 vs. BRCA2/X comparison (female breast cancer cases only). The average value of the probes contained in a differentially methylated region for a given breast cancer case is represented by a circle. Red, blue and green indicate BRCA1, BRCA2 and BRCA1 cases, respectively. The numbers on the y-axis are  $\Delta$  methylation values.

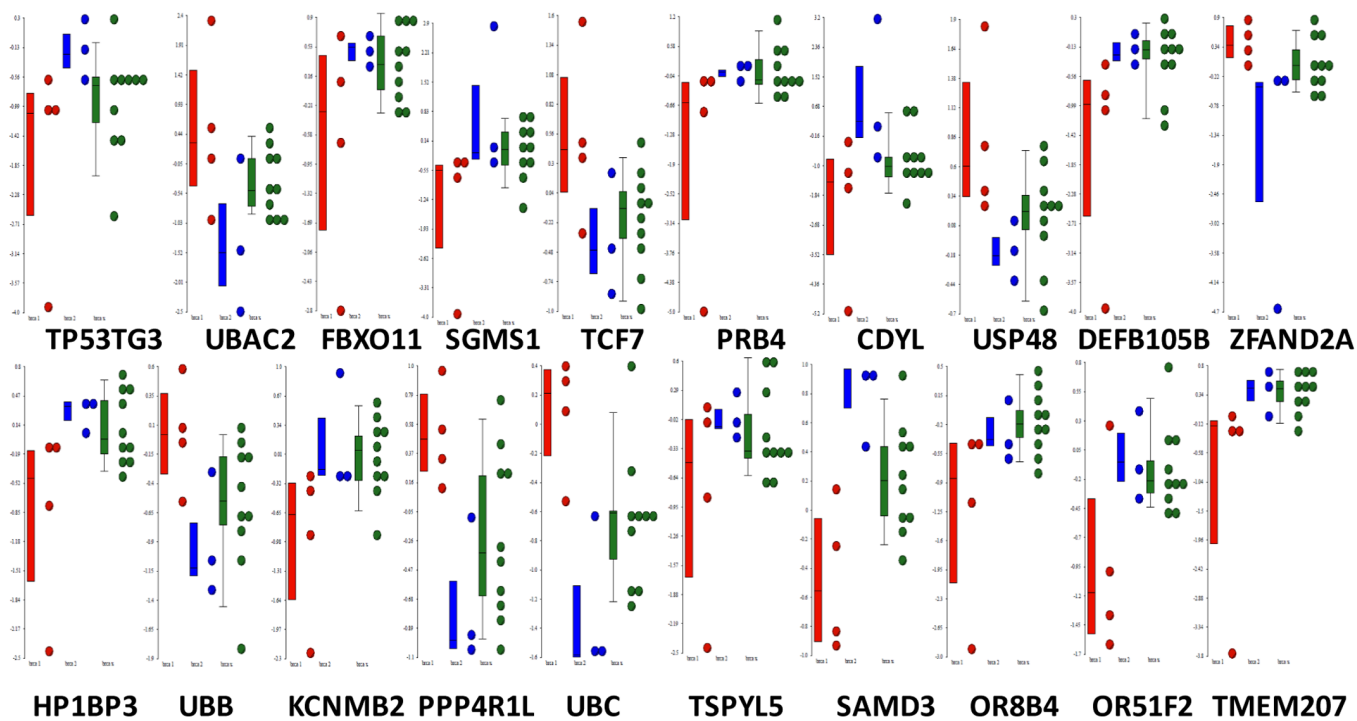




Figure S8. Dot plots generated by Partek Genomic Suite represent the 20 most differentially methylated regions in the BRCA2 vs. BRCA1/X comparison (female breast cancer cases only). The average value of the probes contained in a differentially methylated region for a given breast cancer case is represented by a circle. Red, blue and green indicate BRCA1, BRCA2 and BRCA1X cases, respectively. The numbers on the y-axis are  $\Delta$  methylation values.

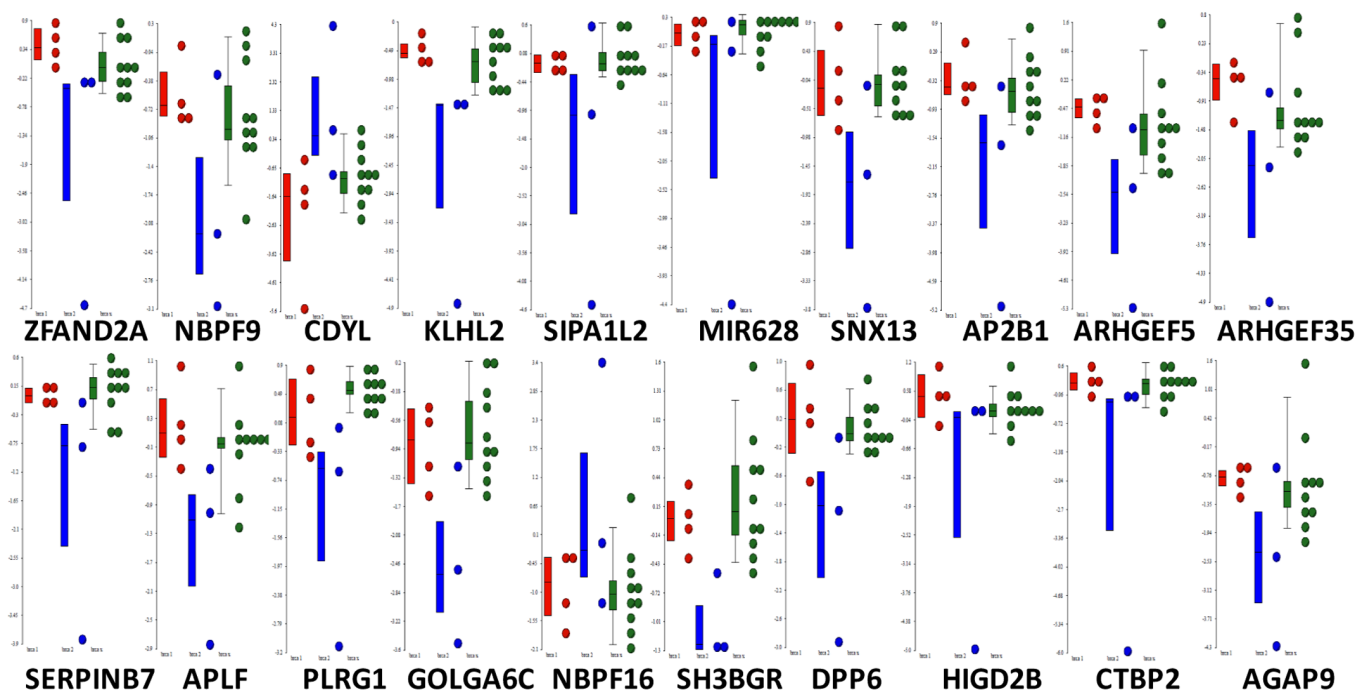


Figure S9. Dot plots generated by Partek Genomic Suite represent the 20 most differentially methylated regions in the BRCA1 vs. BRCA2 comparison (female breast cancer cases only). The average value of the probes contained in a differentially methylated region for a given breast cancer case is represented by a circle. Red, blue and green indicate BRCA1, BRCA2 and BRCA1/2 cases, respectively. The numbers on the y-axis are  $\Delta$  methylation values.

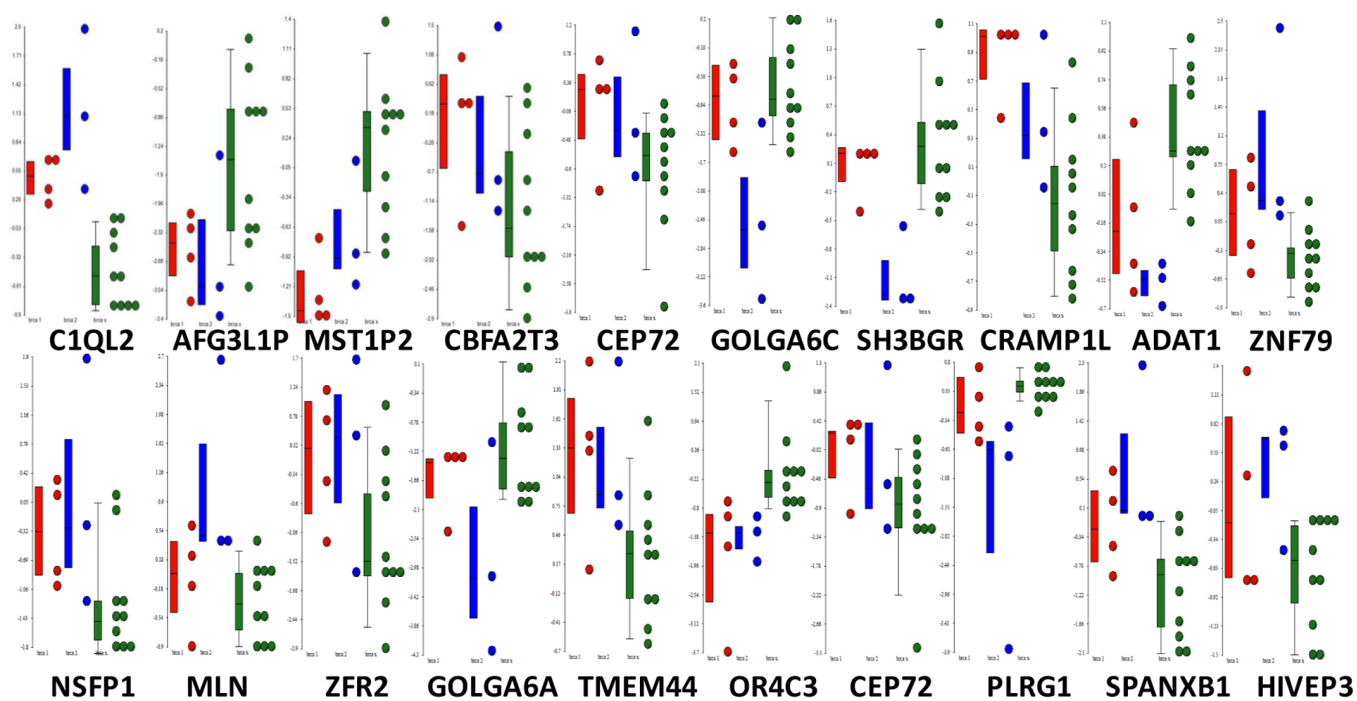


Table SI. Genes corresponding to the 20 most differentially methylated regions.

## A, Comparison N° 1: FBC vs. MBC (17 cases vs. 7 cases)

Gene symbol	P-value	MAT score	Chromosome	Region start at:	Region end at:	DMR length, bp	Probes in region	DMR position
CRIPAK	1.42x10 <sup>-5</sup>	-12.052	chr4	1378294	1383307	5014	131	Promoter
INF2	1.42x10 <sup>-5</sup>	-11.232	chr14	104256668	104260009	3342	74	Promoter
S1PR4	1.42x10 <sup>-5</sup>	-11.073	chr19	3123001	3128649	5649	135	Upstream TSS
FOXN1	1.42x10 <sup>-5</sup>	-10.285	chr17	23867579	23870505	2927	63	Upstream TSS
FBLN7	1.42x10 <sup>-5</sup>	-10.209	chr2	112612054	112614829	2776	68	Promoter
TTC40	1.42x10 <sup>-5</sup>	-10.075	chr10	134525715	134528706	2992	84	Intron
CCDC57	1.42x10 <sup>-5</sup>	-10.070	chr17	77700513	77703776	3264	90	Intron
PRR26	1.42x10 <sup>-5</sup>	-10.026	chr10	682104	687304	5201	144	Intron
NLRP4	1.42x10 <sup>-5</sup>	-9.640	chr19	61052866	61055636	2771	77	Exon
LINC00574	1.42x10 <sup>-5</sup>	-9.277	chr6	169945301	169948324	3024	84	Downstream CDS end
PRKXP1	1.42x10 <sup>-5</sup>	-9.260	chr15	98914126	98916895	2770	74	Exon
TRIM28	1.42x10 <sup>-5</sup>	-9.059	chr19	63741516	63747134	5619	123	Upstream TSS
CNN2	1.42x10 <sup>-5</sup>	-9.049	chr19	983366	988935	5570	104	Exon
MUC6	1.42x10 <sup>-5</sup>	-9.046	chr11	1005022	1010338	5317	145	Exon
MUC12	1.42x10 <sup>-5</sup>	-9.030	chr7	100419514	100436366	16853	435	Exon
LMF1	1.42x10 <sup>-5</sup>	-9.006	chr16	950289	952101	1813	38	Intron
THEG	1.42x10 <sup>-5</sup>	-8.675	chr19	330868	334483	3616	90	Upstream TSS
LINC01061	1.42x10 <sup>-5</sup>	-8.510	chr4	120547714	120551328	3615	87	Promoter
REXO1L2P	1.42x10 <sup>-5</sup>	-8.363	chr8	86883906	86886596	2691	73	Exon
TBC1D2	1.42x10 <sup>-5</sup>	-8.245	chr9	100013396	100017955	4560	84	Exon

## B, Comparison N° 2: FBC vs. MBC (10 cases vs. 6 cases; only BRCA cases were considered)

Gene symbol	P-value	MAT score	Chromosome	Region start at:	Region end at:	DMR length, bp	Probes in region	DMR position
CCDC57	1.42x10 <sup>-5</sup>	-15.070	chr17	77700513	77703854	3342	92	Intron
ERICH1-AS1	1.42x10 <sup>-5</sup>	-12.198	chr8	975683	982493	6811	171	Intron
INF2	1.42x10 <sup>-5</sup>	-12.105	chr14	104256668	104260009	3342	74	Promoter
REXO1L2P	1.42x10 <sup>-5</sup>	-12.065	chr8	86883906	86886596	2691	73	Exon
CRIPAK	1.42x10 <sup>-5</sup>	-12.033	chr4	1378294	1383307	5014	131	Promoter
ZFR2	1.42x10 <sup>-5</sup>	-11.173	chr19	3787538	3790224	2687	72	Intron
S1PR4	1.42x10 <sup>-5</sup>	-11.164	chr19	3123001	3128649	5649	135	Upstream TSS
REXO1L1	1.42x10 <sup>-5</sup>	-11.155	chr8	86753702	86756668	2967	81	Exon
REXO1L2P	1.42x10 <sup>-5</sup>	-11.109	chr8	86760539	86763506	2968	80	Exon
CNN2	1.42x10 <sup>-5</sup>	-11.072	chr19	983297	989018	5722	108	Exon
MUC6	1.42x10 <sup>-5</sup>	-11.046	chr11	1004902	1010303	5402	147	Exon
PRKXP1	1.42x10 <sup>-5</sup>	-11.006	chr15	98914126	98916957	2832	76	Exon
FBLN7	1.42x10 <sup>-5</sup>	-10.785	chr2	112612093	112614829	2737	67	Promoter
NLRP4	1.42x10 <sup>-5</sup>	-10.451	chr19	61052866	61055636	2771	77	Exon
B3GNTL1	1.42x10 <sup>-5</sup>	-10.313	chr17	78605016	78608221	3206	78	Upstream TSS
ATP9B	1.42x10 <sup>-5</sup>	-10.095	chr18	74925996	74929037	3042	73	Upstream TSS
GUSBP1	1.42x10 <sup>-5</sup>	-10.057	chr5	21516934	21520701	3768	104	Intron
MUC12	1.42x10 <sup>-5</sup>	-10.037	chr7	100419514	100436290	16777	433	Exon
TTC40	1.42x10 <sup>-5</sup>	-10.029	chr10	134525817	134528706	2890	81	Intron
PRR26	1.42x10 <sup>-5</sup>	-10.001	chr10	682160	687379	5220	144	Promoter

Table SI. Continued.

## C, Comparison N° 3: BRCA1 vs. BRCA2 (16 cases vs. 8 cases)

Gene symbol	P-value	MAT score	Chromosome	Region start at:	Region end at:	DMR length, bp	Probes in region	DMR position
PLCXD1	1.42x10 <sup>-5</sup>	9.319	chrX	127440	132209	4770	101	Upstream TSS
FAM157B	1.42x10 <sup>-5</sup>	7.770	chr9	140242535	140244023	1489	42	Exon
AFG3L1P	1.42x10 <sup>-5</sup>	6.079	chr16	88588157	88590877	2721	64	Intron
ITSN2	1.42x10 <sup>-5</sup>	-6.040	chr2	24334126	24336975	2850	69	Exon
GALNT9	1.42x10 <sup>-5</sup>	6.015	chr12	131261926	131263649	1724	37	Intron
CCDC135	1.42x10 <sup>-5</sup>	5.556	chr16	56321133	56322917	1785	46	Promoter
APLP2	1.42x10 <sup>-5</sup>	-5.321	chr11	129438343	129441002	2660	61	Upstream TSS
APTIX	1.42x10 <sup>-5</sup>	-5.276	chr9	32977115	32980828	3714	83	Exon
LOC613037	1.42x10 <sup>-5</sup>	5.234	chr16	30141205	30144941	3737	77	Promoter
ZFP37	1.42x10 <sup>-5</sup>	-5.214	chr9	114856371	114859470	3100	88	Promoter
IGFN1	1.42x10 <sup>-5</sup>	-5.162	chr1	199443653	199447899	4247	118	Exon
ADAM10	1.42x10 <sup>-5</sup>	5.155	chr15	56759920	56762787	2868	65	Exon
FAM189A2	1.42x10 <sup>-5</sup>	-5.153	chr9	71133392	71135939	2548	57	Intron
PLRG1	1.42x10 <sup>-5</sup>	5.152	chr4	155690184	155692920	2737	67	Promoter
CTDP1	1.42x10 <sup>-5</sup>	-5.142	chr18	75546721	75549239	2519	54	Intron
PTPRN2	1.42x10 <sup>-5</sup>	5.138	chr7	157844637	157847675	3039	80	Intron
GABRP	1.42x10 <sup>-5</sup>	5.131	chr5	170142178	170144576	2399	61	Promoter
PCDHGA8	1.42x10 <sup>-5</sup>	5.131	chr5	140750411	140753000	2590	68	Intron
MRPL23	1.42x10 <sup>-5</sup>	5.129	chr11	1925752	1927547	1796	50	Intron
LOC595101	1.42x10 <sup>-5</sup>	-5.126	chr16	30251757	30253657	1901	53	Intron

## D, Comparison N° 4: BRCA1 vs. BRCA2 (4 cases vs. 3 cases; only FBC cases were considered)

Gene symbol	P-value	MAT score	Chromosome	Region start at:	Region end at:	DMR length, bp	Probes in region	DMR position
CDYL	8.79x10 <sup>-6</sup>	-8.477	chr6	4754700	4755794	1095	30	Intron
ZFAND2A	8.79x10 <sup>-6</sup>	7.140	chr7	1164076	1165224	1149	33	Exon
FBXO25	8.79x10 <sup>-6</sup>	7.087	chr8	353945	355490	1546	42	Intron
SGMS1	8.79x10 <sup>-6</sup>	-6.622	chr10	51762654	51763658	1005	28	Intron
ARHGEF5	8.79x10 <sup>-6</sup>	6.453	chr7	143685749	143686990	1242	34	Intron
MX1	8.79x10 <sup>-6</sup>	6.408	chr21	41722008	41722744	737	21	Intron
CTBP2	8.79x10 <sup>-6</sup>	6.403	chr10	126789339	126790616	1278	36	Exon
B3GALT1	8.79x10 <sup>-6</sup>	-6.389	chr2	168434171	168435295	1125	31	Exon
OR2F1	8.79x10 <sup>-6</sup>	6.384	chr7	143283723	143284996	1274	36	Upstream TSS
MDGA2	8.79x10 <sup>-6</sup>	6.311	chr14	46885619	46887056	1438	40	Intron
TPMT	8.79x10 <sup>-6</sup>	-6.285	chr6	18261506	18262564	1059	24	Intron
KLHL2	8.79x10 <sup>-6</sup>	6.283	chr4	166353051	166354774	1724	40	Intron
TLN1	8.79x10 <sup>-6</sup>	6.253	chr9	35714749	35715901	1153	33	Exon
CRTAC1	8.79x10 <sup>-6</sup>	6.205	chr10	99781789	99782987	1199	32	Upstream TSS
OR4N2	8.79x10 <sup>-6</sup>	-6.187	chr14	19359477	19360682	1206	35	Upstream TSS
AP2B1	8.79x10 <sup>-6</sup>	6.173	chr17	30935333	30936071	739	22	Upstream TSS
MIR628	8.79x10 <sup>-6</sup>	6.155	chr15	53452317	53453871	1555	43	Intron
ACIN1	8.79x10 <sup>-6</sup>	6.149	chr14	22601032	22602646	1615	42	Exon
IRG1	8.79x10 <sup>-6</sup>	6.109	chr13	76421863	76423193	1331	37	Upstream TSS
ADARB2	8.79x10 <sup>-6</sup>	-6.109	chr10	1731260	1734281	3022	81	Intron

Table SI. Continued.

E, Comparison N° 5: BRCA1 vs. BRCA1X (4 cases vs. 10 cases; only FBC cases were considered)

Gene symbol	P-value	MAT score	Chromosome	Region start at:	Region end at:	DMR length, bp	Probes in region	DMR position
MIR5694	8.79x10 <sup>-6</sup>	-7.002	chr10	122343054	122344351	1298	34	Intron
MRAP	8.79x10 <sup>-6</sup>	6.269	chr21	32594026	32595179	1154	28	Intron
OR2T5	8.79x10 <sup>-6</sup>	-6.245	chr1	246716194	246717309	1116	31	Upstream TSS
AFG3L1P	8.79x10 <sup>-6</sup>	-6.063	chr16	88588573	88590063	1491	42	Exon/intron
CBFA2T3	8.79x10 <sup>-6</sup>	6.061	chr16	87523232	87524291	1060	25	Intron
FAM189A2	8.79x10 <sup>-6</sup>	6.052	chr9	71134105	71135217	1113	30	Exon/intron
ARHGEF10	8.79x10 <sup>-6</sup>	6.029	chr8	1794144	1795326	1183	33	Intron
CHST4	8.79x10 <sup>-6</sup>	-6.028	chr16	70114259	70115464	1206	34	Upstream TSS
TXNDC12	8.79x10 <sup>-6</sup>	-5.957	chr1	52288390	52289251	862	23	Intron
EI24	8.79x10 <sup>-6</sup>	-5.651	chr11	124945252	124946388	1137	29	Intron
EPSTI1	8.79x10 <sup>-6</sup>	-5.493	chr13	42468707	42469775	1069	27	Upstream TSS
DEFB105B	8.79x10 <sup>-6</sup>	-5.341	chr8	7332517	7333571	1055	29	Promoter
PMCH	8.79x10 <sup>-6</sup>	-5.340	chr12	101114188	101115210	1023	28	Promoter
PRB4	8.79x10 <sup>-6</sup>	-5.307	chr12	11357959	11358634	676	19	Upstream TSS
TMEM44	8.79x10 <sup>-6</sup>	5.290	chr3	195832853	195833594	742	21	Intron
CNGA1	8.79x10 <sup>-6</sup>	-5.267	chr4	47633668	47634656	989	27	Exon
OR56A1	8.79x10 <sup>-6</sup>	-5.247	chr11	6007135	6008216	1082	31	Upstream TSS
GATA6-AS1	8.79x10 <sup>-6</sup>	-5.209	chr18	17996287	17997348	1062	0	Downstream CDS end
CEP72	8.79x10 <sup>-6</sup>	5.203	chr5	682311	687015	4705	115	Exon
PRKXP1	8.79x10 <sup>-6</sup>	5.201	chr15	98914126	98916416	2291	60	Exon

F, Comparison N° 6: BRCA2 vs. BRCA1X (3 cases vs. 10 cases; only FBC cases were considered)

Gene symbol	P-value	MAT score	Chromosome	Region start at:	Region end at:	DMR length, bp	Probes in region	DMR position
PLRG1	8.79x10 <sup>-6</sup>	-8.077	chr4	155690335	155691939	1605	45	Promoter
CTBP2	8.79x10 <sup>-6</sup>	-8.050	chr10	126789266	126790650	1385	39	Exon
GSTM3	8.79x10 <sup>-6</sup>	-7.440	chr1	110081516	110082655	1140	32	Exon
CDYL	8.79x10 <sup>-6</sup>	7.332	chr6	4754700	4755574	875	24	Intron
MIR628	8.79x10 <sup>-6</sup>	-7.179	chr15	53452152	53453871	1720	47	Intron
CCDC168	8.79x10 <sup>-6</sup>	-7.177	chr13	102186205	102187402	1198	34	Exon
KLHL2	8.79x10 <sup>-6</sup>	-7.164	chr4	166352915	166354808	1894	45	Intron
MOV10L1	8.79x10 <sup>-6</sup>	7.151	chr22	48946134	48947278	1145	32	Downstream CDS end
CRTAC1	8.79x10 <sup>-6</sup>	-7.115	chr10	99781789	99782916	1128	30	Upstream TSS
ZNF79	8.79x10 <sup>-6</sup>	7.108	chr9	129246102	129247147	1046	30	Exon
TAF1D	8.79x10 <sup>-6</sup>	-7.090	chr11	93109749	93110986	1238	34	Exon
ARHGEF5	8.79x10 <sup>-6</sup>	-7.073	chr7	143685815	143686990	1176	32	Intron
RABL3	8.79x10 <sup>-6</sup>	-7.047	chr3	121889701	121890680	980	27	Exon
OR2F1	8.79x10 <sup>-6</sup>	-7.040	chr7	143283723	143285108	1386	39	Upstream TSS
GOLGA6C	8.79x10 <sup>-6</sup>	-6.798	chr15	73335771	73336977	1207	30	Upstream TSS
MX1	8.79x10 <sup>-6</sup>	-6.638	chr21	41722008	41723019	1012	28	Intron
MLN	8.79x10 <sup>-6</sup>	6.635	chr6	33877921	33879025	1105	32	Intron
AP2B1	8.79x10 <sup>-6</sup>	-6.579	chr17	30935333	30936071	739	22	Upstream TSS
ZFAND2A	8.79x10 <sup>-6</sup>	-6.505	chr7	1164076	1165185	1110	32	Exon
MGA	8.79x10 <sup>-6</sup>	-6.493	chr15	39829192	39830677	1486	42	Exon

Table SI. Continued.

G, Comparison N° 7: BRCA1 vs. BRCA2/X (4 cases vs. 13 cases; female cases only)

Gene symbol	P-value	MAT score	Chromosome	Region start at:	Region end at:	DMR length, bp	Probes in region	DMR position
TP53TG3	7.53x10 <sup>-6</sup>	5.443	chr16	33111909	33112338	430	24	Upstream TSS
UBAC2	7.53x10 <sup>-6</sup>	-5.336	chr13	98764881	98765573	693	20	Intron
FBXO11	7.53x10 <sup>-6</sup>	5.314	chr2	47984071	47984670	600	17	Intron
SGMS1	7.53x10 <sup>-6</sup>	5.244	chr10	51762654	51763397	744	21	Intron
TCF7	7.53x10 <sup>-6</sup>	-5.209	chr5	133479934	133480544	611	18	Intron
PRB4	7.53x10 <sup>-6</sup>	5.204	chr12	11358179	11358634	456	13	Upstream TSS
CDYL	7.53x10 <sup>-6</sup>	5.185	chr6	4754700	4755723	1024	28	Intron
USP48	7.53x10 <sup>-6</sup>	-5.151	chr1	21904981	21905611	631	18	Exon
DEFB105B	7.53x10 <sup>-6</sup>	5.151	chr8	7332672	7333423	752	21	Exon
ZFAND2A	7.53x10 <sup>-6</sup>	-5.144	chr7	1164240	1165012	773	22	Exon
HP1BP3	7.53x10 <sup>-6</sup>	5.139	chr1	20977158	20977742	585	17	Intron
UBB	7.53x10 <sup>-6</sup>	-5.137	chr17	16225879	16226628	750	21	Exon
KCNMB2	7.53x10 <sup>-6</sup>	5.133	chr3	179753093	179753732	640	18	Intron
PPP4R1L	7.53x10 <sup>-6</sup>	-5.091	chr20	56240044	56240680	637	18	Downstream CDS end
UBC	7.53x10 <sup>-6</sup>	-5.051	chr12	123962214	123964416	2203	60	Exon
TSPYL5	7.53x10 <sup>-6</sup>	5.037	chr8	98357340	98357832	493	14	Exon
SAMD3	7.53x10 <sup>-6</sup>	5.031	chr6	130577055	130577634	580	17	Exon
OR8B4	7.53x10 <sup>-6</sup>	5.023	chr11	123800832	123801478	647	18	Upstream TSS
OR51F2	7.53x10 <sup>-6</sup>	5.021	chr11	4799954	4800486	533	15	Promoter
TMEM207	7.53x10 <sup>-6</sup>	5.013	chr3	191653068	191653636	569	16	Upstream TSS

H, comparison N° 8: BRCA2 vs. BRCA1/X (4 cases vs. 14 cases; only FBC cases were considered)

Gene symbol	P-value	MAT score	Chromosome	Region start at:	Region end at:	DMR length, bp	Probes in region	DMR position
ZFAND2A	7.53x10 <sup>-6</sup>	7.213	chr7	1164240	1165012	773	22	Exon
NBPF9	7.53x10 <sup>-6</sup>	7.211	chr1	143330003	143330634	632	18	Intron
CDYL	7.53x10 <sup>-6</sup>	-7.124	chr6	4754700	4755505	806	22	Intron
KLHL2	7.53x10 <sup>-6</sup>	6.743	chr4	166353361	166354596	1236	34	Intron
SIPA1L2	7.53x10 <sup>-6</sup>	6.563	chr1	230650101	230650842	742	21	Intron
MIR628	7.53x10 <sup>-6</sup>	6.518	chr15	53452267	53453871	1605	44	Intron
SNX13	7.53x10 <sup>-6</sup>	6.503	chr7	17948670	17949227	558	15	Upstream TSS
AP2B1	7.53x10 <sup>-6</sup>	6.416	chr17	30935400	30936071	672	20	Upstream TSS
ARHGEF5	7.53x10 <sup>-6</sup>	6.226	chr7	143685994	143686769	776	22	Intron
ARHGEF35	7.53x10 <sup>-6</sup>	6.218	chr7	143520309	143520999	691	20	Intron
SERPINB7	7.53x10 <sup>-6</sup>	6.090	chr18	59595459	59596058	600	17	Intron
APLF	7.53x10 <sup>-6</sup>	6.074	chr2	68549919	68550515	597	17	Intron
PLRG1	7.53x10 <sup>-6</sup>	6.072	chr4	155691006	155691939	934	27	Promoter
GOLGA6C	7.53x10 <sup>-6</sup>	6.070	chr15	73335771	73336461	691	20	Upstream TSS
NBPF16	7.53x10 <sup>-6</sup>	-6.058	chr1	146848305	146848996	692	20	Exon
SH3BGR	7.53x10 <sup>-6</sup>	6.042	chr21	39746184	39746770	587	17	Intron
DPP6	7.53x10 <sup>-6</sup>	6.018	chr7	153375725	153376311	587	16	Intron
HIGD2B	7.53x10 <sup>-6</sup>	6.012	chr15	70764874	70765367	494	14	Exon
CTBP2	7.53x10 <sup>-6</sup>	6.008	chr10	126789512	126790505	994	28	Exon
AGAP9	7.53x10 <sup>-6</sup>	5.791	chr10	47831948	47832573	626	17	Upstream TSS

Table SI. Continued.

I, Comparison N° 9: BRCA1 vs. BRCA2 (10 cases vs. 7 cases; only FBC cases were considered)

Gene symbol	P-value	MAT score	Chromosome	Region start at:	Region end at:	DMR length, bp	Probes in region	DMR position
C1QL2	7.53x10 <sup>-6</sup>	6.063	chr2	119636046	119636549	504	14	Upstream TSS
AFG3L1P	7.53x10 <sup>-6</sup>	-6.004	chr16	88588612	88589950	1339	38	Exon/Intron
MST1P2	7.53x10 <sup>-6</sup>	-5.820	chr1	16853565	16854076	512	15	Downstream CDS end
CBFA2T3	7.53x10 <sup>-6</sup>	5.630	chr16	87523496	87524291	796	22	Intron
CEP72	7.53x10 <sup>-6</sup>	5.553	chr5	684096	684713	618	17	Intron
GOLGA6C	7.53x10 <sup>-6</sup>	-5.474	chr15	73335771	73336461	691	20	Upstream TSS
SH3BGR	7.53x10 <sup>-6</sup>	-5.378	chr21	39746184	39746738	555	16	Intron
CRAMP1L	7.53x10 <sup>-6</sup>	5.255	chr16	1661268	1661900	633	18	Intron
ADAT1	7.53x10 <sup>-6</sup>	-5.217	chr16	74212234	74212727	494	14	Intron
ZNF79	7.53x10 <sup>-6</sup>	5.210	chr9	129246171	129247041	871	25	Exon
NSFP1	7.53x10 <sup>-6</sup>	5.205	chr17	42024441	42025115	675	20	Intron
MLN	7.53x10 <sup>-6</sup>	5.184	chr6	33878221	33878726	506	14	Intron
ZFR2	7.53x10 <sup>-6</sup>	5.179	chr19	3788248	3789265	1018	29	Intron
GOLGA6A	7.53x10 <sup>-6</sup>	-5.123	chr15	72163443	72164089	647	18	Upstream TSS
TMEM44	7.53x10 <sup>-6</sup>	5.114	chr3	195832853	195833423	571	16	Intron
OR4C3	7.53x10 <sup>-6</sup>	-5.089	chr11	48301313	48301654	342	10	Upstream TSS
CEP72	7.53x10 <sup>-6</sup>	5.087	chr5	682521	683231	711	19	Intron
PLRG1	7.53x10 <sup>-6</sup>	-5.066	chr4	155691148	155691939	792	23	Upstream TSS
SPANXB1	7.53x10 <sup>-6</sup>	5.037	chrX	139923796	139924309	514	15	Upstream TSS
HIVEP3	7.53x10 <sup>-6</sup>	5.031	chr1	42275837	42276401	565	16	Upstream TSS

CDS, coding sequence; DMRs, differentially methylated regions; FBC, female breast cancer; MAT, model-based analysis of tiling arrays; MBC, male breast cancer; TSS, transcriptional start sites.



Table SII. HUGO Gene Nomenclature Committee classification of the genes identified to be differentially methylated in the different comparisons considered.

A, FBC vs. MBC		
Variable	Number	Percentage
Total DMR	2846	
Total genes	2486	100.00
Protein coding genes	2173	87.41
Long non coding RNA	53	2.13
MicroRNA	15	0.60
Small nuclear RNA	1	0.04
Small nucleolar RNA	4	0.16
Pseudogene	108	4.34
Complex locus constituent	2	0.08
Protocadherin	2	0.08
Gene readthrough	10	0.40
Unknown	118	4.75

B, FBC vs. MBC (BRCA1 cases only)

Variable	Number	Percentage
Total DMR	1242	
Total genes	1102	100.00
Protein coding genes	919	83.39
Long non coding RNA	22	2.00
MicroRNA	8	0.73
Small nuclear RNA	1	0.09
Small nucleolar RNA	5	0.45
Pseudogene	72	6.53
Complex locus constituent	2	0.18
Protocadherin	2	0.18
Readthrough	6	0.54
Unknown	65	5.90

C, BRCA1 vs. BRCA2 (FBC cases only)

Variable	Number	Percentage
Total DMR	364	
Total genes	357	100.00
Protein coding genes	317	88.80
Long non coding RNA	8	2.24
MicroRNA	5	1.40
Pseudogene	12	3.36
Protocadherin	1	0.28
Readthrough	1	0.28
Unknown	13	3.64

D, BRCA1 vs. BRCA2 (FBC cases only)

Variable	Number	Percentage
Total DMR	802	
Total gene	755	100.00
Protein coding genes	678	89.80
Long non coding RNA	19	2.52
MicroRNA	6	0.79

Table SII. Continued.

RNA small nucleolar	1	0.13
Pseudogene	25	3.31
Protocadherin	2	0.26
Readthrough	3	0.40
Unknown	21	2.78

E, BRCA1 vs. BRCA2 (FBC cases only)

Variable	Number	Percentage
Total DMR	484	
Total genes	464	100.00
Protein coding genes	410	88.36
Long non coding RNA	10	2.16
MicroRNA	1	0.22
Pseudogene	20	4.31
Protocadherin	2	0.43
Readthrough	2	0.43
Unknown	19	4.09

F, BRCA2 vs. BRCA1 (FBC cases only)

Variable	Number	Percentage
Total DMR	673	
Total genes	629	100.00
Protein coding genes	561	89.19
Long non coding RNA	19	3.02
MicroRNA	4	0.64
Pseudogene	15	2.38
Readthrough	3	0.48
Unknown	27	4.29

G, BRCA2/X vs. BRCA1 (FBC cases only)

Variable	Number	Percentage
Total DMR	861	
Total genes	819	100.00
Protein coding genes	736	89.87
Long non coding RNA	21	2.56
MicroRNA	2	0.24
RNA small nucleolar	1	0.12
Pseudogene	28	3.42
complex locus constituent	1	0.12
Protocadherin	1	0.12
Readthrough	5	0.61
Unknown	24	2.93

H, BRCA1/X vs. BRCA2 (FBC cases only)

Variable	Number	Percentage
Total DMR	1380	
Total genes	1251	100.00
Protein coding genes	1121	89.61
Long non coding RNA	35	2.80
MicroRNA	4	0.32
RNA small nucleolar	1	0.08



Table SII. Continued.

Pseudogene	39	3.12
complex locus constituent	1	0.08
Protocadherin	2	0.16
Readthrough	6	0.48
Unknown	42	3.36

## I, BRCA1/2 vs. BRCA1 (FBC cases only)

Variable	Number	Percentage
Total DMR	962	
Total gene	914	100.00
Protein coding genes	820	89.72
Long non coding RNA	33	3.61
MicroRNA	5	0.55
RNA small nucleolar	2	0.22
Pseudogene	23	2.52
Protocadherin	1	0.11
Readthrough	4	0.44
Unknown	26	2.84

DMRs, differentially methylated regions; FBC, female breast cancer; MBC, male breast cancer.

Table SIII. Analysis of the association between the clinicopathological characteristics of patients with breast cancer and the DNA methylation levels of KRT genes<sup>a</sup>.

Variable	KRT1		KRT6A		KRT14		KRT75		KRT78 (i)		KRT78 (ii)		KRT80		KRT81		KRT86		
	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	
<b>ER status</b>																			
Positive, n	6	9	5	10	5	10	7	8	6	9	5	10	6	9	5	10	5	10	10
Negative, n	3	2	3	2	4	1	3	2	3	2	3	2	3	2	4	1	4	1	1
P-value	0.617		0.347		0.127		>0.999		0.617		0.347		0.617		0.127		0.127		0.127
<b>PR status</b>																			
Positive, n	4	9	3	10	3	10	5	8	4	9	4	9	4	9	3	10	3	10	10
Negative, n	5	2	5	2	6	1	5	2	5	2	4	3	4	2	6	1	6	1	1
P-value	0.160		0.062		0.017 <sup>b</sup>		0.350		0.160		0.356		0.160		0.017 <sup>b</sup>		0.017 <sup>b</sup>		0.017 <sup>b</sup>
<b>HER2 status</b>																			
Positive, n	4	2	3	3	3	3	5	1	4	2	2	4	5	1	4	2	4	2	2
Negative, n	4	8	5	7	6	6	5	7	5	7	6	6	4	8	5	7	5	7	7
P-value	0.321		>0.999		>0.999		0.151		0.620		0.638		0.131		0.620		0.620		0.620
<b>Ki67 status</b>																			
Positive, n	5	5	4	6	6	4	6	4	5	5	6	4	6	4	6	4	6	4	4
Negative, n	4	5	4	5	3	6	4	5	4	5	2	7	3	6	3	6	3	6	6
P-value	>0.999		>0.999		0.370		0.656		>0.999		0.170		0.370		0.370		0.370		0.370
<b>Molecular subtypes<sup>c</sup></b>																			
Luminal A, n	3	7	3	7	3	7	3	7	3	7	4	6	2	8	2	8	2	8	8
Luminal B, n	2	2	1	3	1	3	3	1	1	3	2	2	3	1	2	2	2	2	2
HER2-positive, n	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0	0
Triple negative, n	2	2	2	2	3	1	2	2	2	2	2	2	2	2	3	1	3	1	1
P-value	0.651		0.175		0.288		0.044 <sup>b</sup>		0.081		0.837		0.390		0.655		0.130		0.130

<sup>a</sup>The DNA methylation level of KRT genes was categorized into two groups: High DNA methylation level and low DNA methylation level. The median of  $\Delta$  methylation values was selected as the cut-off point. Fisher's exact test was used to determine the statistical significance between two categorical variables. <sup>b</sup>P<0.05. <sup>c</sup>One-way ANOVA and Tukey's pairwise comparison tests were used to determine the statistical differences of mean  $\Delta$  methylation values among the different molecular subtypes. Two differentially methylated regions were detected for KRT78 gene, indicated as (i) and (ii). ER, estrogen receptor; KRT, keratin; PR, progesterone receptor.

Table SIV. Significantly enriched annotation terms found by DAVID in the performed comparisons.

## A, Significant enriched annotation terms found by DAVID in FBC vs. MBC comparison (only BRCA cases were considered)

Category	Term	Genes	Count	P-value	Benjamini
GO: BP	GO:0051056 regulation of small GTPase mediated signal transduction	ABR, AGAP3, AGAP6, AGAP9, ARAP1, ARAP3, ARFGAP3, ARHGEF10, ARHGEF16, ARHGEF3, ARHGEF5, DGKZ, EPO, GMIP, HRAS, IQSEC1, KNDC1, LPAR2, NUP62, RAPGEF3, RASA3, RASA4CP, RASGRP2, RGL2, TBC1D16, TBC1D2, TBC1D22A, TBC1D25, TBC1D29, TBC1D3B, TBC1D3F, TBC1D3G, TIAM2, USP6	34	0.000368	0.010
GO: MF	GO:0030695 GTPase regulator activity	ABR, AGAP3, AGAP6, AGAP9, ARAP1, ARAP3, ARFGAP3, ARHGAP11B, ARHGAP23, ARHGAP35, ARHGAP40, ARHGEF10, ARHGEF16, ARHGEF3, ARHGEF5, BCRP2, DOCK2, DOCK6, GMIP, IQSEC1, KNDC1, MYO9B, RAPGEF3, RASA3, RASA4CP, RASGRP2, RGL2, RGS12, RPH3AL, SH3BP1, SRGAP1, SYTL2, SYTL3, TBC1D16, TBC1D2, TBC1D22A, TBC1D25, TBC1D29, TBC1D3B, TBC1D3F, TBC1D3G, TIAM2, USP6	43	0.000530	0.011
GO: MF	GO:0060589 nucleoside-triphosphatase regulator activity	ABR, AGAP3, AGAP6, AGAP9, AHS2, ARAP1, ARAP3, ARFGAP3, ARHGAP11B, ARHGAP23, ARHGAP35, ARHGAP40, ARHGEF10, ARHGEF16, ARHGEF3, ARHGEF5, BCRP2, DOCK2, DOCK6, GMIP, IQSEC1, KNDC1, MYO9B, RAPGEF3, RASA3, RASA4CP, RASGRP2, RGL2, RGS12, RPH3AL, SH3BP1, SRGAP1, SYTL2, SYTL3, TBC1D16, TBC1D2, TBC1D22A, TBC1D25, TBC1D29, TBC1D3B, TBC1D3F, TBC1D3G, TIAM2, USP6	44	0.000404	0.011
GO: MF	GO:0060090 molecular adaptor activity	ANK1, BAIAP2, BAIAP2L1, BAIAP2L2, EPO, GAB1, GRAP, GRB7, KHDRBS1, MTSS1L, OBSL1, PDCD6, SH3BP2, SRC	14	0.000339	0.014
GO: MF	GO:0005096 GTPase activator activity	ABR, AGAP3, AGAP6, AGAP9, ARAP1, ARAP3, ARFGAP3, ARHGAP11B, ARHGAP23, ARHGAP35, ARHGAP40, BCRP2, DOCK2, GMIP, MYO9B, RASA3, RASA4CP, RGS12, SH3BP1, SRGAP1, TBC1D16, TBC1D2, TBC1D22A, TBC1D25, TBC1D29, TBC1D3B, TBC1D3F, TBC1D3G, TIAM2, USP6	30	0.000205	0.017
GO: MF	GO:0008047 enzyme activator activity	ABR, AGAP3, AGAP6, AGAP9, AHS2, ARAP1, ARAP3, ARFGAP3, ARHGAP11B, ARHGAP23, ARHGAP35, ARHGAP40, BCRP2, CTAGE9, DOCK2, GHRL, GMIP, GUCA1A, IGF3, MMP16, MYO9B, RASA3, RASA4CP, RGS12, SH3BP1, SRGAP1, TBC1D16, TBC1D2, TBC1D22A, TBC1D25, TBC1D29, TBC1D3B, TBC1D3F, TBC1D3G, TIAM2, USP6	36	0.000236	0.038
GO: MF	GO:0008093 cytoskeletal adaptor activity	ANK1, BAIAP2, BAIAP2L1, BAIAP2L2, MTSS1L, OBSL1	6	0.000339	0.045
GO: BP	GO:0046578 regulation of Ras protein signal transduction	ABR, AGAP3, AGAP6, AGAP9, ARAP1, ARAP3, ARFGAP3, ARHGEF10, ARHGEF16, ARHGEF3, ARHGEF5, DGKZ, EPO, GMIP, HRAS, IQSEC1, LPAR2, NUP62, TBC1D16, TBC1D2, TBC1D22A, TBC1D25, TBC1D29, TBC1D3B, TBC1D3F, TBC1D3G, TIAM2, USP6	28	0.000530	0.071

Table SIV. Continued.

## B, Significant enriched annotation terms found by DAVID in BRCA1 vs. BRCA2 comparison (only FBC cases were considered)

Category	Term	Genes	Count	P-value	Benjamini
GO: MF	GO:0019787: small conjugating protein ligase activity	ATG3 <sup>a</sup> , FBXO11 <sup>a</sup> , FBXO25, FBXO3 <sup>a</sup> , FBXO4 <sup>a</sup> , MALT1 <sup>a</sup> , NEDD4 <sup>a</sup> , NEDD4L, RBBP6 <sup>a</sup> , RNF128, RNF6 <sup>a</sup> , UBE2G1 <sup>a</sup> , UBE2MP1 <sup>a</sup> , UBE2S, UBE2T, UBE4A <sup>a</sup> , UHRF2, WWP1 <sup>a</sup>	18	0.000147	0.05

## C, Significant enriched annotation terms by DAVID in BRCA1 vs. BRCA2 comparison (only FBC cases were considered).

Category	Term	Genes	Count	P-value	Benjamini
GO: BP	GO:0051240 positive regulation of multicellular organismal process	AGT <sup>a</sup> , BMPR2 <sup>a</sup> , CD40LG <sup>a</sup> , CHRM3, CPS1 <sup>a</sup> , GRIK1 <sup>a</sup> , IL20RB, LGI1 <sup>a</sup> , NMU <sup>a</sup> , PEX5 <sup>a</sup> , PMCH <sup>a</sup> , RARA, SLC1A3 <sup>a</sup> , SLC24A2 <sup>a</sup> , SMAD3, TPM1 <sup>a</sup> , TRAF2, UBB, UBC	19	0.000163	0.032

## D, Significant enriched annotation terms found by DAVID in BRCA2 vs. BRCA2 comparison (only FBC cases were considered)

Category	Term	Genes	Count	P-value	Benjamini
KEGG pathway	hsa05220 Chronic myeloid leukemia	AKT2, CDKN1B, CTBP2 <sup>a</sup> , E2F3 <sup>a</sup> , GAB2 <sup>a</sup> , GRB2 <sup>a</sup> , LOC407835 <sup>a</sup> , PIK3R1, PIK3R3 <sup>a</sup> , SHC2	10	0.000278	0.0372
GO: MF	GO:0008047 enzyme activator activity	AFAP1L2, AGAP4 <sup>a</sup> , AGAP9 <sup>a</sup> , APOA4, ARHGAP17, ARHGAP42, ARHGAP44 <sup>a</sup> , ARHGAP5, ARHGAP6 <sup>a</sup> , BNIP2, FAM13B, FRS2 <sup>a</sup> , IGF1BP3, ITSN1, MALT1, PRLR <sup>a</sup> , RALGAPA2, RALGAPB <sup>a</sup> , RASAL1, RGS12 <sup>a</sup> , SIPA1L2 <sup>a</sup> , STARD13 <sup>a</sup> , TBC1D2, TBC1D25, TBC1D31 <sup>a</sup>	25	0.000177	0.0378
GO: MF	GO:0060589 nucleoside-triphosphatase regulator activity	AGAP4 <sup>a</sup> , AGAP9 <sup>a</sup> , ANXA2 <sup>a</sup> , ARHGAP17, ARHGAP42, ARHGAP44 <sup>a</sup> , ARHGAP5, ARHGAP6 <sup>a</sup> , ARHGEF10, ARHGEF5 <sup>a</sup> , BNIP2, CDC42SE1 <sup>a</sup> , FAM13B, FER <sup>a</sup> , ITSN1, ITSN2, PSD3 <sup>a</sup> , RALGAPA2, RALGAPB <sup>a</sup> , RASAL1, RASGRF2 <sup>a</sup> , RGS12 <sup>a</sup> , SIPA1L2 <sup>a</sup> , STARD13 <sup>a</sup> , SYTL4 <sup>a</sup> , TBC1D2, TBC1D25, TBC1D31 <sup>a</sup> , TNIK <sup>a</sup>	29	0.000146	0.0466

## E, Significant enriched annotation terms found by DAVID in BRCA1 vs. BRCA2/X comparison (only FBC cases were considered)

Category	Term	Genes	Count	P-value	Benjamini
GO: MF	GO:0008092 cytoskeletal protein binding	AATF <sup>a</sup> , ANG <sup>a</sup> , CALD1, CCDC88A, CENPJ <sup>a</sup> , CLASP1, CLMN <sup>a</sup> , CNN3 <sup>a</sup> , DAAM2 <sup>a</sup> , DIXDC1 <sup>a</sup> , DYNLL2, EZR <sup>a</sup> , FMN2, FRMD3, GABARAPL1 <sup>a</sup> , IQGAP2, KLHL2 <sup>a</sup> , LIMCH1 <sup>a</sup> , LMO7 <sup>a</sup> , MAPRE1 <sup>a</sup> , MKL2 <sup>a</sup> , MTUS2, MYH3, MYO16 <sup>a</sup> , MYO1H <sup>a</sup> , MYO3A <sup>a</sup> , PACSIN2, PALLD <sup>a</sup> , PKD2 <sup>a</sup> , PRNP, RAB11FIP5 <sup>a</sup> , RAB27A <sup>a</sup> , SSH1 <sup>a</sup> , SYNE1, SYNE2 <sup>a</sup> , TLN1 <sup>a</sup> , TMOD3 <sup>a</sup> , TMOD4, TNNI3K, TPM1 <sup>a</sup> , VPS41	41	0.000648	0.0477

## F, Significant enriched annotation terms found by DAVID in BRCA2 vs. BRCA1/X comparison (only FBC cases were considered)

Category	Term	Genes	Count	P-value	Benjamini
KEGG pathway	hsa04660 T cell receptor signaling pathway	AKT2 <sup>a</sup> , CD40LG <sup>a</sup> , CD8B <sup>a</sup> , FYN <sup>a</sup> , GRB2, IL10, LOC407835, MALT1 <sup>a</sup> , MAPK9, NCK2 <sup>a</sup> , NFATC2 <sup>a</sup> , NRAS, PIK3CA, PIK3CG, PIK3R1 <sup>a</sup> , PIK3R3, PTPRC	17	0.000106	0.0346
KEGG pathway	hsa05214 Glioma	AKT2 <sup>a</sup> , CALM2, CAMK2A <sup>a</sup> , E2F3, GRB2, LOC407835, NRAS, PIK3CA, PIK3CG, PIK3R1 <sup>a</sup> , PIK3R3, SHC2 <sup>a</sup> , TGFA	13	0.000430	0.0350

Table SIV. Continued.

Category	Term	Genes	Count	P-value	Benjamini
KEGG pathway	hsa05213 Endometrial cancer	AKT2 <sup>a</sup> , FOXO3B <sup>a</sup> , GRB2, ILK, LOC407835, NRAS, PIK3CA, PIK3CG, PIK3R1 <sup>a</sup> , PIK3R3, TCF7 <sup>a</sup>	11	0.000136	0.0368
KEGG pathway	hsa04012 ErbB signaling pathway	AKT2 <sup>a</sup> , CAMK2A <sup>a</sup> , GRB2, HBEGF, LOC407835, MAPK9, NCK2 <sup>a</sup> , NRAS, PIK3CA, PIK3CG, PIK3R1 <sup>a</sup> , PIK3R3, SHC2 <sup>a</sup> , STAT5B, TGFA	15	0.000925	0.0376
KEGG pathway	hsa04722 Neurotrophin signaling pathway	AKT2 <sup>a</sup> , CALM2, CAMK2A <sup>a</sup> , CSK, FOXO3B <sup>a</sup> , FRS2, GRB2, LOC407835, MAP2K5 <sup>a</sup> , MAPK9, MAPKAPK2, NRAS, PIK3CA, PIK3CG, PIK3R1 <sup>a</sup> , PIK3R3, RPS6KA2 <sup>a</sup> , SHC2 <sup>a</sup> , YWHAB, ZNF274	20	0.000239	0.0389
KEGG pathway	hsa05220 Chronic myeloid leukemia	ACVR1B, AKT2 <sup>a</sup> , CTBP2, E2F3, GRB2, HDAC2 <sup>a</sup> , LOC407835, NRAS, PIK3CA, PIK3CG, PIK3R1 <sup>a</sup> , PIK3R3, SHC2 <sup>a</sup> , STAT5B	14	0.000763	0.0413
KEGG pathway	hsa05223 Non-small cell lung cancer	AKT2 <sup>a</sup> , E2F3, FOXO3B <sup>a</sup> , GRB2, LOC407835, NRAS, PIK3CA, PIK3CG, PIK3R1 <sup>a</sup> , PIK3R3, TGFA	11	0.000183	0.0425

G, Significant enriched annotation terms found by DAVID in BRCA1 vs. BRCA2 comparison (only FBC cases were considered)

Category	Term	Genes	Count	P-value	Benjamini
GO: MF	GO:0030695: GTPase regulator activity	AGAP9 <sup>a</sup> , ANXA2 <sup>a</sup> , ARFGAP3, ARHGAP11A <sup>a</sup> , ARHGAP23, ARHGAP32 <sup>a</sup> , ARHGAP5, ARHGAP6 <sup>a</sup> , ARHGAP9, ARHGEF10, ARHGEF12 <sup>a</sup> , ARHGEF5 <sup>a</sup> , ASAP1 <sup>a</sup> , BNIP2, CHN2 <sup>a</sup> , DOCK3, HERC1 <sup>a</sup> , IQSEC3, KNDC1, MCF2L <sup>a</sup> , MYO9B, PREX1 <sup>a</sup> , PRR5, PRR5-ARHGAP8, RALGAPA2, RAPGEF3 <sup>a</sup> , RASA4CP <sup>a</sup> , RASGRF1, RIMS2 <sup>a</sup> , SIPA1L2 <sup>a</sup> , TBC1D15 <sup>a</sup> , TBC1D16, TBC1D25, TBC1D31 <sup>a</sup> , TBC1D3B, TBC1D3F, TBC1D8, TNIK <sup>a</sup> , TRIO	37	0.000546	0.0210086
GO: MF	GO:0005096: GTPase activator activity	AGAP9 <sup>a</sup> , ARFGAP3, ARHGAP11A <sup>a</sup> , ARHGAP23, ARHGAP32 <sup>a</sup> , ARHGAP5, ARHGAP6 <sup>a</sup> , ARHGAP9, ARHGEF12 <sup>a</sup> , ASAP1 <sup>a</sup> , BNIP2, CHN2 <sup>a</sup> , MYO9B, PREX1 <sup>a</sup> , PRR5, PRR5-ARHGAP8, RALGAPA2, RASA4CP <sup>a</sup> , SIPA1L2, TBC1D15 <sup>a</sup> , TBC1D16, TBC1D25, TBC1D31 <sup>a</sup> , TBC1D3B, TBC1D3F, TBC1D8	24	0.000107	0.0273196
GO: MF	GO:0060589: nucleoside-triphosphatase regulator activity	AGAP9 <sup>a</sup> , ANXA2 <sup>a</sup> , ARFGAP3, ARHGAP11A <sup>a</sup> , ARHGAP23, ARHGAP32 <sup>a</sup> , ARHGAP5, ARHGAP6 <sup>a</sup> , ARHGAP9, ARHGEF10, ARHGEF12 <sup>a</sup> , ARHGEF5 <sup>a</sup> , ASAP1 <sup>a</sup> , BNIP2, CHN2 <sup>a</sup> , DOCK3, GRPEL2 <sup>a</sup> , HERC1 <sup>a</sup> , IQSEC3, KNDC1, MCF2L <sup>a</sup> , MYO9B, PREX1 <sup>a</sup> , PRR5, PRR5-ARHGAP8, RALGAPA2, RAPGEF3 <sup>a</sup> , RASA4CP <sup>a</sup> , RASGRF1, RIMS2 <sup>a</sup> , SIPA1L2 <sup>a</sup> , TBC1D15 <sup>a</sup> , TBC1D16, TBC1D25, TBC1D31 <sup>a</sup> , TBC1D3B, TBC1D3F, TBC1D8, TNIK <sup>a</sup> , TRIO	38	0.000387	0.0296572

<sup>a</sup>Hypomethylated genes reporting a negative MAT-score. GO, Gene Ontology; BP, Biological Process; MF, Molecular Function; FBC, female breast cancer; MBC, male breast cancer; DAVID, Database for Annotation, Visualization and Integrated Discovery.