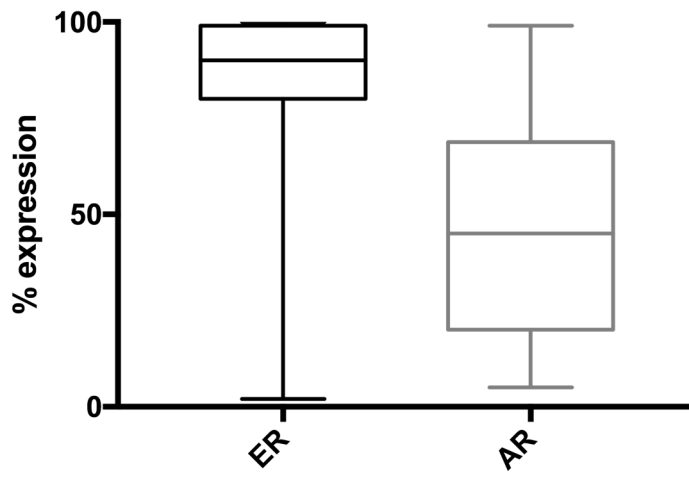
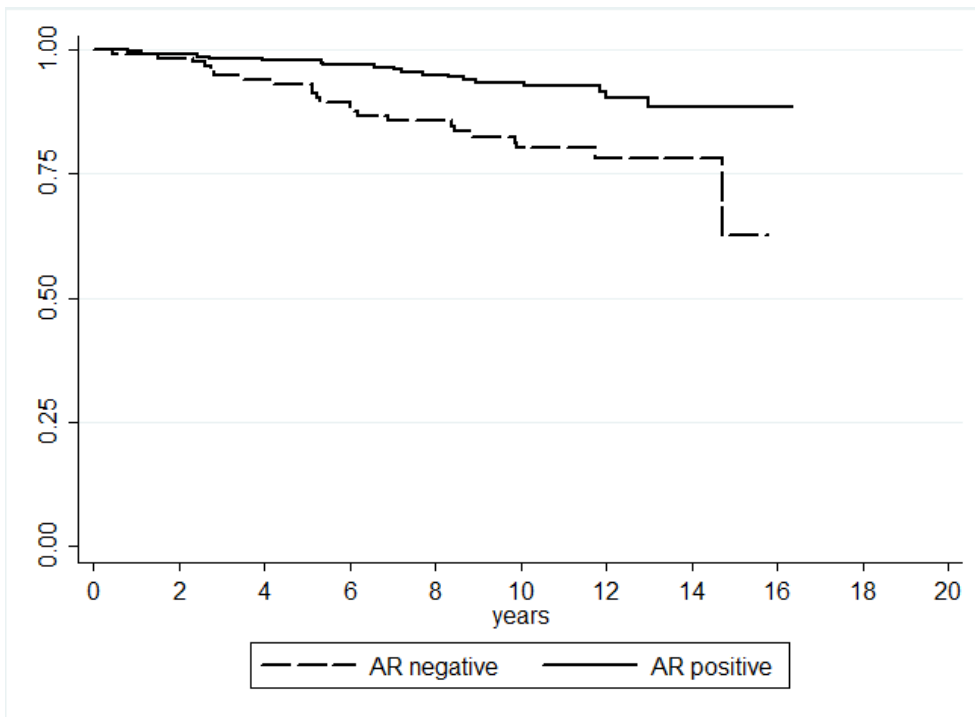


ANNEXES

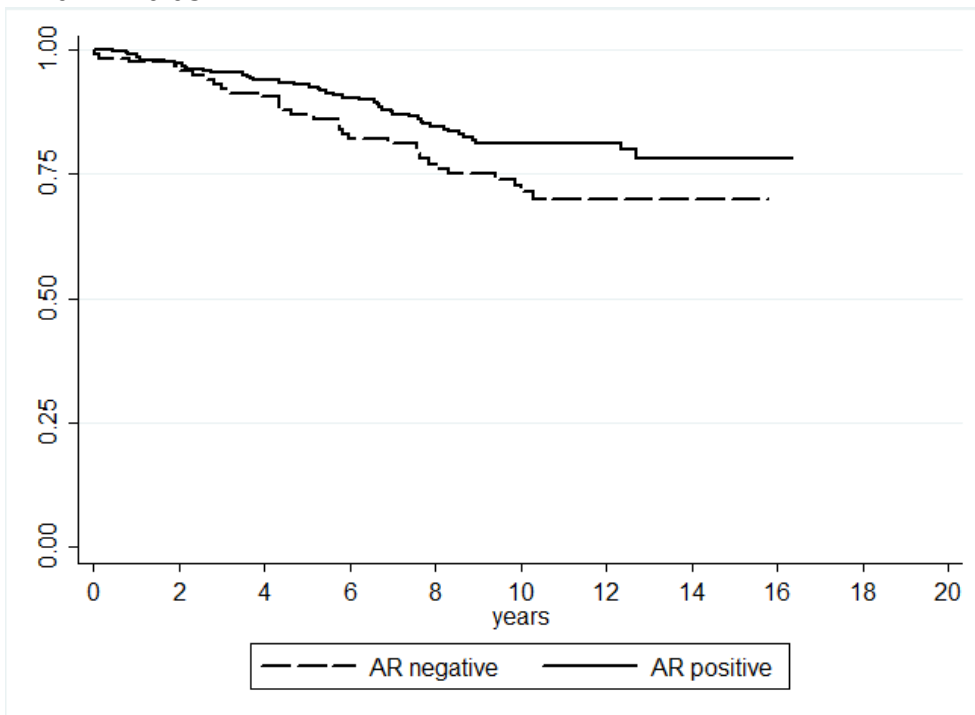
Annex 1. Distribution plots of IHC ER and AR % nuclear staining.



Annex 2. Survival curves for AR+ Vs. AR- BC.

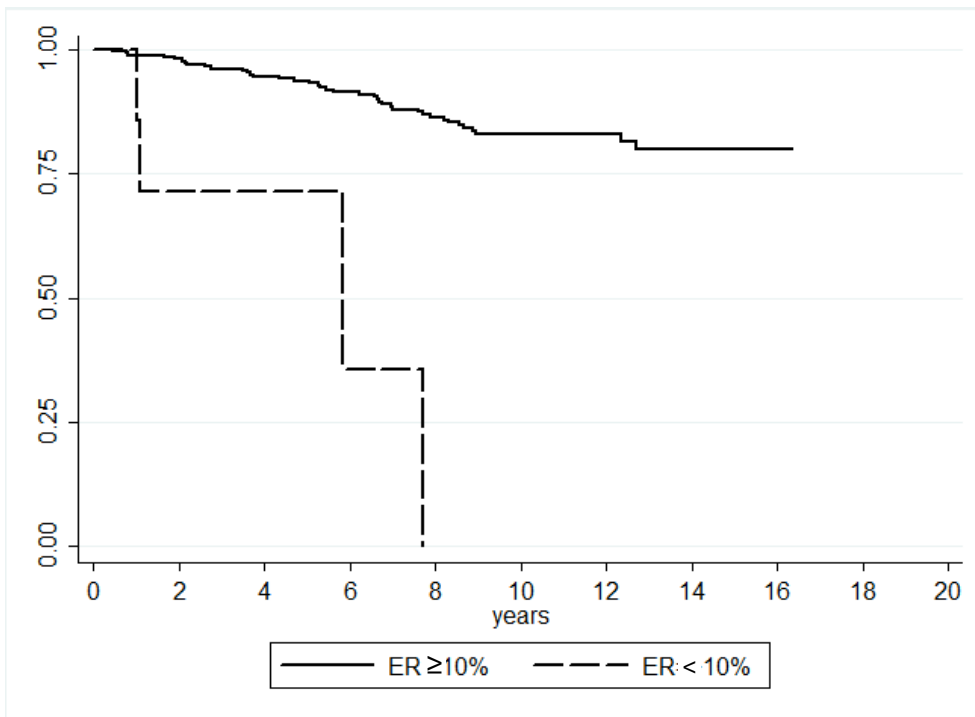


a) Disease Free Interval (DFI). Log-rank test for equality of survivor functions. $Pr > \chi^2 = 0.05$.

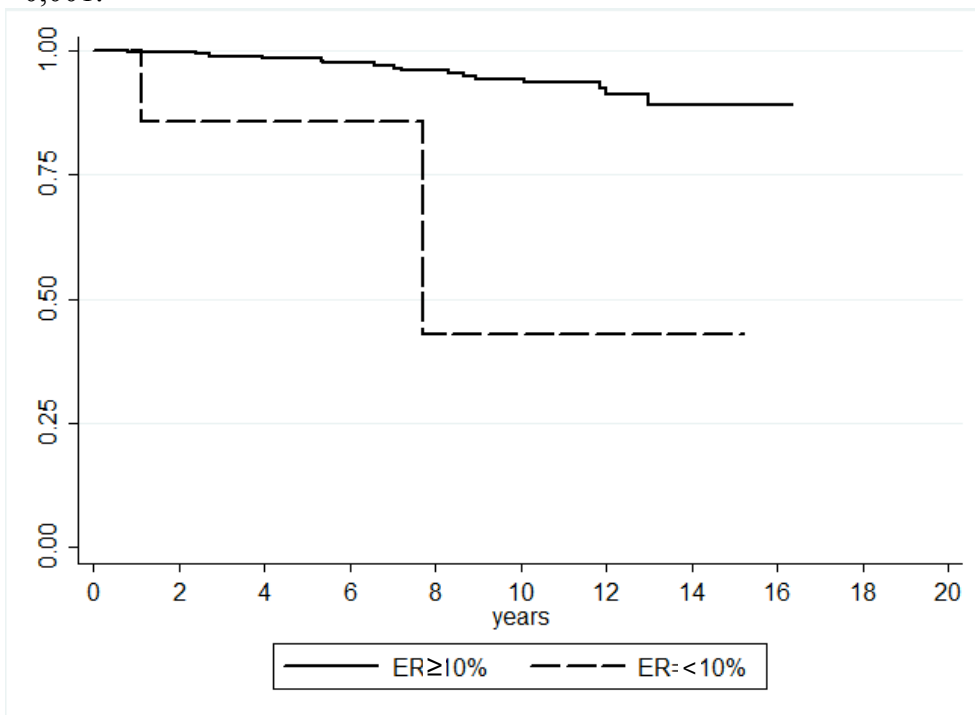


b) Disease Specific Survival (DSS). Log-rank test for equality of survivor functions. $Pr > \chi^2 = 0,0008$.

Annex 3. Survival curves for ER+/AR+ BC cases. Cut-off ER at 10%.



a) Disease Free Interval (DFI). Log-rank test for equality of survivor functions. $Pr > \chi^2 = < 0,001$.



b) Disease Specific Survival (DSS). Log-rank test for equality of survivor functions. $Pr > \chi^2 = < 0,002$.

Annex 4. Primers for real-time PCR

ER α	Sense: 5'-TGT GTC CAG CCA CCA ACC AG- 3' Antisense: 5'- TTC AAC ATT CTC CCT CCT CTT CGG-3'
FOXA1	Sense: 5'-GGG TGG CTC CAG GAT GTT AGG - 3' Antisense: 5'-GGG TCA TGT TGC CGC TCG TAG -3'
AR	Sense: 5'-AAT TGT CCA TCT TGT CGT CTT CGG - 3' Antisense: 5'-GCC TCT CCT TCC TCC TGT AGT TTC -3'
β -ACT	Sense: 5'-GCG AGA AGA TGA CCC AGA TC- 3' Antisense: 5'- GGA TAG CAC AGC CTG GAT AG-3'
β 2- microglobulin	Sense: 5'-AGA TGA GTA TGC CTG CCG TGT G-3' Antisense: 5'-TCA ACC CTC CAT GAT GCT GCT TAC-3'
L13A	Sense: 5'-GCA AGC GGA TGA ACA CCA ACC-3' Antisense: 5'-TTG AGG GCA GCA GGA ACC AC-3'

Annex 5. Clinico-pathological characteristics of BC patients according to FOXA1 expression.

Characteristics		FOXA1 Positive N=405 (85%)	FOXA1 Negative N=74 (15%)	P
<i>Age</i>	≤50	65	21	0.011
	>50	340	53	
<i>Type of surgery (missing 8)</i>	Conservative	238	44	0.0062
	Mastectomy	159	30	
<i>Size (missing 7)</i>	<15 mm	162	14	0.002
	≥15 mm	237	59	
<i>Lymph node involvement (missing 7)</i>	pN0	234	43	0.002
	pN1,2,3	165	30	
<i>Histological grade (missing 9)</i>	1	118	7	<0.001
	2	175	12	
	3	104	54	
<i>Histotype</i>	IDC	256	49	0.005
	ILC	89	6	
	Other	60	19	
<i>Vascular Invasion (missing 113)</i>	No	172	28	0.448
	Yes	138	28	
<i>ER (IHC)</i>	0	52	54	<0.001
	≥1	353	20	
<i>PGR (IHC) (missing 48)</i>	0	75	47	<0.001
	≥1	288	21	
<i>Ki67 (missing 9)</i>	<20	196	9	<0.001
	≥20	202	63	
<i>Her2 (missing 43)</i>	Neg	333	65	0.611
	Pos	33	5	

Annex 6.

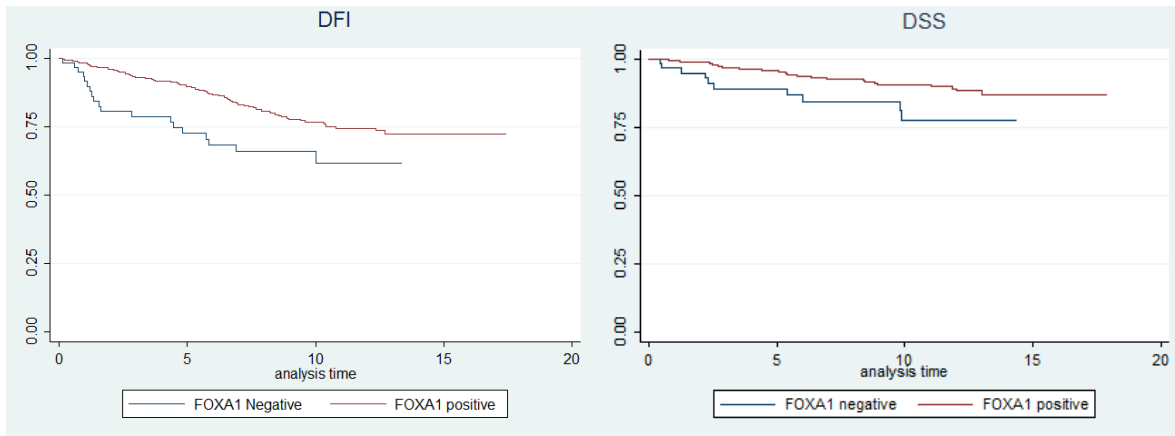
Clinico-pathological characteristics of BC patients according to FOXA1 and AR status.

Characteristics		Total	FOXA1+A R+ (278)	FOXA1+A R- (127)	FOXA1- AR- (66)	<i>P</i> *	FOXA1- AR+ (8)
<i>Age</i>	≤50	86	48	17	21	0.006	0
	>50	393	230	110	45		8
<i>Type of surgery (missing 8)</i>	Conservative	282	159	81	38	0.442	4
	Mastectomy	189	113	44	28		4
<i>Size (missing 7)</i>	<15 mm	176	126	37	9	<0.001	4
	≥15 mm	296	145	91	56		4
<i>Lymph node involvement (missing 7)</i>	pN0	277	163	70	39	0.710	5
	pN1,2,3	195	109	56	27		3
<i>Histological grade (missing 9)</i>	1	125	82	36	5	<0.001	2
	2	187	127	48	8		4
	3	158	58	44	54		2
<i>Histotype</i>	IDC	305	166	91	45	<0.001	3
	ILC	95	72	17	4		2
	Other	79	37	23	17		2
<i>Vascular Invasion (missing 113)</i>	No	200	120	51	23	0.356	6
	Yes	166	91	46	27		2
<i>ER (IHC)</i>	0	106	26	26	52	<0.001	2
	≥1	373	252	101	14		6
<i>PGR (IHC) (missing 48)</i>	0	122	48	26	44	<0.001	4
	≥1	309	194	95	18		2
<i>Ki67 (missing 9)</i>	<20	205	145	52	5	<0.001	3
	≥20	265	126	76	60		3
<i>Her2 (missing 43)</i>	Neg	398	231	102	57	0.105	8
	Pos	38	17	16	5		0
<i>Therapy (missing 15)</i>	Only radiotherapy	18	4	4	8	<0.001	2
	Ormono therapy	229	166	63	8		1
	Chemio-ormono	125	85	32	7		1
	Chemio	81	22	14	41		4
	No Therapy	11	6	3	2		0

<i>Recurrences</i>	No	395	232	104	46	0.036	7
	Yes	84	46	23	20		1
<i>Deaths</i>	No	440	261	115	56	0.049	8
	Yes	39	17	12	10		0

* We were unable to perform any analyses on the FOXA1-/AR+ BC since only 8 patients carried this phenotype, therefore P value corresponds to analyses performed between the other three subgroups.

Annex 7. Kaplan–Meier estimates of DFI and DSS survival according to FOXA1 status in 479 breast tumors.



DFI	FOXA1-	FOXA1+	Log-rank P	DSS	FOXA1-	FOXA1+	Log-rank P
5-Years	66.4	86.1	0.0084	5-Years	87.0	93.6	0.0180
10-Years	59.6	74.1		10-Years	77.2	90.7	

Annex 8. Clinical, pathological and molecular characteristics of HER2 double-equivocal carcinomas

Case*	ER (%)	Ki67 (%)	Histologic type	PT/R/M	G	HER2‡	CEP17‡	HER2/CEP17†	TH (%)	IHC surrogate subtype	Molecular subtype PAM50	ROR score	POR
01-EEE	98	26	IC-NST	PT	2	4.1	3.2	1.3	<10	Lum B	Lum B	71	High
02-EEE	98	15	IC-NST	PT	2	4.2	3.7	1.1	<10	Lum A	Lum B	69	High
03-EEE	98	21	IC-NST	PT	2	5	2.9	1.7	<10	Lum B	Lum B	75	High
04-EEE	98	7	ILC	PT	2	4	3.4	1.1	<10	Lum A	Lum A	18	Low
05-EEE	98	24	IC-NST	PT	2	4.1	2.5	1.7	<10	Lum B	Lum B	76	High
06-EEE	99	20	IC-NST	PT	2	4.6	3.7	1.2	<10	Lum B	Lum B	56	High
07-EEE	95	20	IC-NST	PT	2	4.2	3.1	1.3	<10	Lum B	Lum B	71	High
08-EEE	96	10	IC-NST/ILC	PT	2	4	2.4	1.7	ND	Lum A	Lum A	48	High
09-EEE	99	28	IC-NST	PT	3	5.4	5.1	1.1	<10	Lum B	Lum B	81	High
10-EEE	95	40	IC-NST	PT	3	4.2	3.8	1.1	<10	Lum B	Lum B	62	High
11-EEE	99	35	IC-NST	PT	3	4.7	3.2	1.4	ND	Lum B	Lum B	89	High
12-EEE	80	26	IC-NST	PT	3	4.2	3.4	1.2	<10	Lum B	Lum B	89	High
13-EEE	98	31	IC-NST	PT	3	5	2.6	1.9	<10	Lum B	Lum B	65	High
14-EEE	99	25	IC-NST	PT	3	4.3	3.4	1.3	<10	Lum B	Lum B	99	High
15-EEE	99	17	IC-NST	PT	2	4.1	3.5	1.1	ND	Lum A	HER2-Enr.	62	High
16-EEE	95	26	IC-NST	PT	3	4.5	4.1	1.1	<10	Lum B	Lum B	78	High
17-EEE	95	22	IC-NST	PT	2	4.1	3.9	1.3	ND	Lum B	Lum B	62	High
18-EEE	100	27	IC-NST	PT	1	4	3.8	1.1	ND	Lum B	Lum A	55	High
19-EEE	95	26	IC-NST	PT	3	4.95	2.92	1.7	<10	Lum B	Lum B	52	Int.
20-EEE	95	25	IC-NST	PT	2	4.02	2.45	1.64	<10	Lum B	Lum B	72	High
21-EEE	95	40	IC-NST	M	NA	5.1	3.6	1.4	<10	Lum B	Lum B	NA	NA
22-EEE	98	8	IC-NST	R	2	4.0	3.9	1.0	<10	Lum A	Lum B	NA	NA
23-EEE	95	60	IC-NST	PT	3	4.1	3.9	1.0	<10	Lum B	Lum B	82	High
24-EEE	100	24	IC-NST	M	NA	4.2	2.7	1.5	ND	Lum B	Lum B	NA	NA
25-EEE	90	40	IC-NST	PT	3	4.3	3.6	1.2	ND	Lum B	HER2-Enr.	66	High
26-EEN	95	28	IC-NST	PT	2	4.52	2.32	1.95	<10	Lum B	Lum A	45	High
27-EEN	95	31	IC-NST	PT	2	4.08	2.48	1.64	<10	Lum B	Lum B	84	High
28-EEN	95	45	IC-NST	PT	3	4.65	2.75	1.69	<10	Lum B	Lum B	59	Int.
29-EEN	95	28	ILC	PT	3	4.46	2.25	1.95	<10	Lum B	Lum B	81	High
30-EEN	95	20	IC-NST	PT	2	4.43	2.37	1.87	10	Lum B	Lum A	19	Int.
31-EPP	90	35	IC-NST	PT	3	4.47	2.6	1.72	20	Lum B	Lum B	81	High
32-EPP	90	50	IC-NST	PT	3	4.67	2.35	1.99	29	Lum B	Lum B	73	High
33-EPP	90	18	MPC	PT	2	4.82	2.58	1.87	22	Lum A	Lum A	39	Low
34-EPP	95	40	IC-NST	PT	3	4.75	2.49	1.91	16	Lum B	Lum B	84	High
35-EPP	100	8	ILC	PT	2	4.7	2.4	1.9	28	Lum A	Lum A	23	Int.
36-EPP	99	35	IC-NST	PT	2	4	3.3	1.2	24	Lum B	Lum B	57	Int.
37-EPP	100	30	IC-NST	PT	2	4.5	3.4	1.3	29	Lum B	Lum B	81	High
38-EPP	100	38	IC-NST	PT	2	5.9	3.4	1.73	40	Lum B	Lum B	67	High
39-EPP	100	28	IC-NST	PT	2	4	2.7	1.5	11	Lum B	Lum B	55	Int.
40-EPP	99	25	IC-NST	PT	2	4	3.2	1.2	11	Lum B	Lum B	73	High
41-EPP	99	36	IC-NST	PT	2	4.1	2.8	1.5	16	Lum B	Lum B	86	High
42-EPN	99	5	IC-NST	PT	2	4.3	2.8	1.5	15	Lum A	Lum A	4	Low
43-ENN	60	40	ILC	PT	3	4.24	2.2	1.92	<10	Lum B	Lum B	81	High
44-ENN	95	40	IC-NST	PT	3	4.5	2.33	1.9	<10	Lum B	Lum B	75	High
45-ENN	95	25	IC-NST	PT	2	4.2	2.33	1.8	<10	Lum B	Lum B	53	Int.
46-ENN	95	23	IC-NST	PT	2	4.03	2.13	1.89	<10	Lum B	Lum B	46	Int.
47-ENN	95	55	IC-NST	PT	3	4.5	2.25	1.8	ND	Lum B	Lum B	82	High
48-ENN	98	16	IC-NST	PT	2	4.2	3.9	1.1	ND	Lum A	Lum A	30	Low

* Each letter represent the reading of three independent observers for *HER2* FISH status. E - Equivocal, P – Positive, N – Negative. ‡ Probe counts (signals/cell). † *HER2/CEP17* probe ratio. IC: Invasive Carcinoma. NST: Non Special Type. ILC: Invasive Lobular Carcinoma. PT: Primary Tumor. R: Relapse. M: Metastasis. G: Grade. TH: Tumour Heterogeneity. Lum: Luminal. HER2-Enr.:HER2-Enriched. POR: Probability of Recurrences. Int.: Intermediate. NA: Does not Apply. ND: Not Detected.

Annex 9. List of the 24 gene found to be differentially expressed between two groups of ER+/HER2+ (score 3+) and ER+/HER2- (score 0) BCs. In red those pertaining to the signature of 14 genes used to derive the hierarchical clustering (see Figure 17)

Gene	Chromosomal location	Official Full Name
<i>AGTR1</i>	3q24	angiotensin II receptor type 1
<i>CACNA1H</i>	16p13.3	calcium voltage-gated channel subunit alpha1 H
<i>DSCR6</i>	21q22.13	RIPPLY3: ripply transcriptional repressor 3
<i>DUX3</i>	This gene resides within repeats of the 3.3-kb repeated elements in regions associated with heterochromatin	double homeobox 3
<i>ERBB2</i>	17q12	erb-b2 receptor tyrosine kinase 2
<i>GRB7</i>	17q12	growth factor receptor bound protein 7
<i>GSTM1</i>	1p13.3	glutathione S-transferase mu 1
<i>KRT6A</i>	12q13.13	keratin 6A
<i>MAPT</i>	17q21.31	microtubule associated protein tau
<i>MED24</i>	17q21.1	mediator complex subunit 24
<i>MUCL1</i>	12q13.2	mucin like 1
<i>NOVA1</i>	14q12	NOVA alternative splicing regulator 1
<i>NPY1R</i>	4q32.2	neuropeptide Y receptor Y1
<i>ORMDL3</i>	17q21.1	ORMDL sphingolipid biosynthesis regulator 3
<i>PGAP3</i>	17q12	post-GPI attachment to proteins 3
<i>PNMT</i>	17q12	phenylethanolamine N-methyltransferase
<i>POTEB</i>	15q11.2	POTE ankyrin domain family member B
<i>PPARBP</i>	17q12	MED1: mediator complex subunit 1
<i>PSMD3</i>	17q21.1	proteasome 26S subunit, non-ATPase 3
<i>RAPGEFL1</i>	17q21.1	Rap guanine nucleotide exchange factor like 1
<i>SEZ6L</i>	22q12.1	seizure related 6 homolog like
<i>SORCS1</i>	10q25.1	sortilin related VPS10 domain containing receptor 1
<i>TCAP</i>	17q12	titin-cap
<i>TPRG1</i>	3q28	tumor protein p63 regulated 1