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CLINICAL ONCOLOGY

Breast cancer intrinsic subtypes

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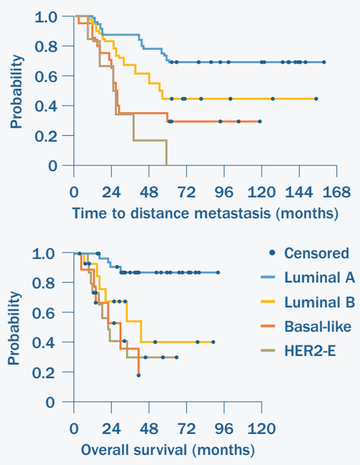
Breast cancer consists of many diseases. This heterogeneity is visible at the histological, clinical, genetic and genomic level. Genomic studies have identified four intrinsic subtypes of breast cancer: basal-like, luminal A and B, and HER2-enriched. The basal-like tumours are identified by high expression of *KRT5/6A*, *ID4*, and *FOXC1* (basal epithelial-like cluster). The luminal epithelial-like cluster is characterized by high expression of *ER*, *GATA3*, *XBP1*, and *FOXA1*. Luminal A tumours have the highest expression of luminal epithelial genes when compared with luminal B tumours; luminal A and B tumours show, respectively, low and high proliferation rates. The HER2-enriched subtype, although expressing the luminal-epithelial cluster, is defined by amplification of genes on 17q12 including *HER2/ERBB2*. Recent studies have described the somatic mutations and DNA copy-number landscape of breast cancers, showing a good concordance between these genetic alterations and the genetic intrinsic subtypes. Here, we present an overview of the common genetic and genomic events seen in breast tumours.

Clinical outcomes

The intrinsic subtypes of breast cancer can predict prognosis.[1,2] Luminal A tumours tend to have the most favourable outcomes, while luminal B, HER2-enriched, and basal-like tumours have worse prognosis. At the clinical level, there is correlation between the three established clinical biomarkers—ER, PR, and HER2—and the intrinsic subtypes. Luminal A tumours tend to be ER+, PR+, HER2–. Luminal B tumours are likely to be ER+, PR+/–and sometimes HER2+.[3] The HER2-enriched tumours are usually HER2+/ER–. The basal-like subtype tends to be triple negative (ER–, PR–, HER2–). Despite this correlation, the intrinsic subtypes cannot be accurately identified using these markers.[3] Nonetheless, most luminal A and B tumours are ER+ and/or PR+, and thus candidates for endocrine therapy; most HER2-enriched cancers are HER2+ and thus candidates for anti-HER2 therapies, and most basal-like tumours are ER–, PR–, and HER2– and therefore candidates for chemotherapy regimens.



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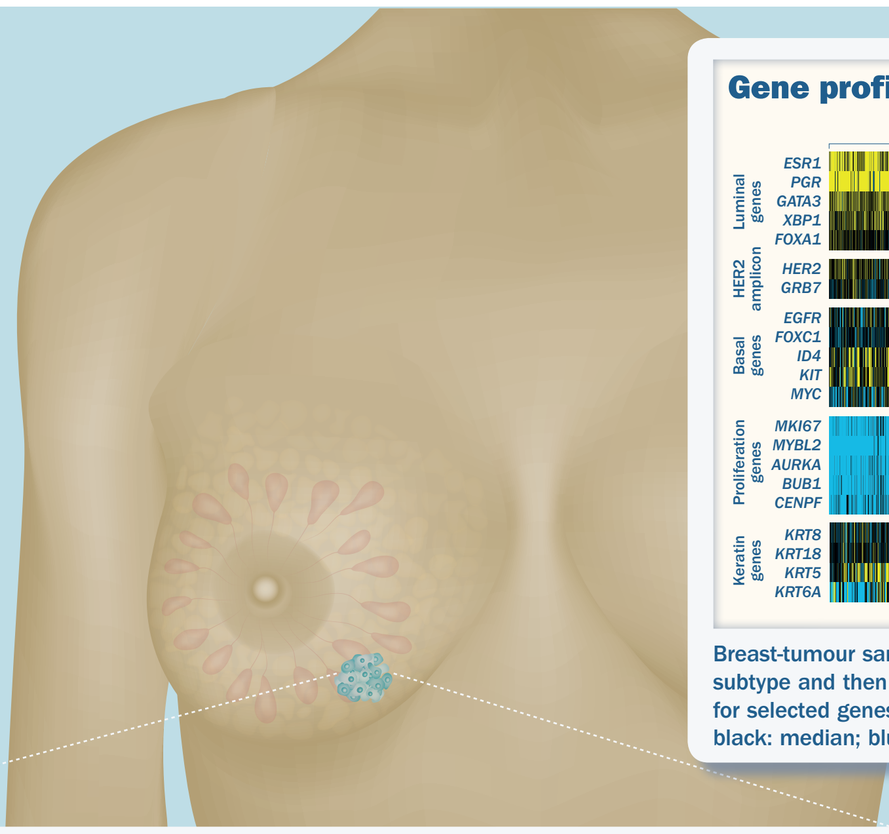
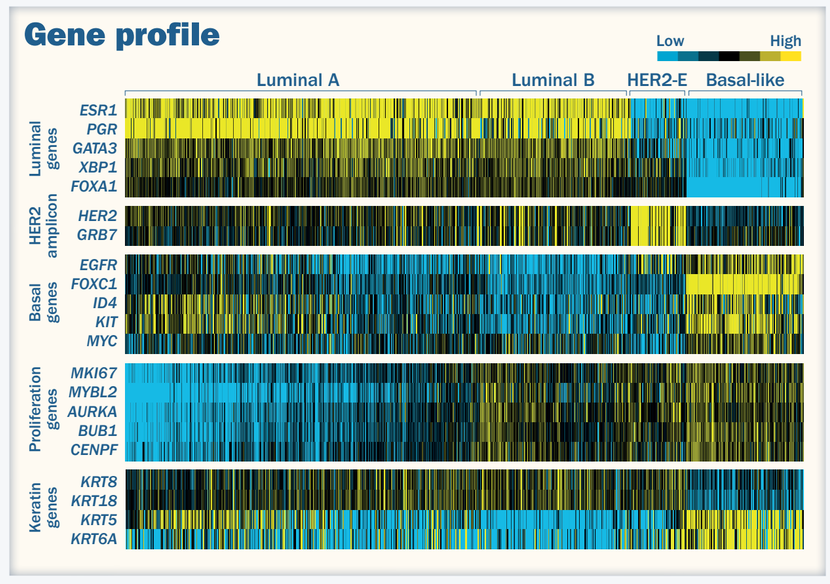


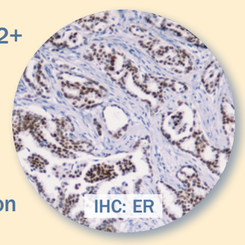
Gene profile



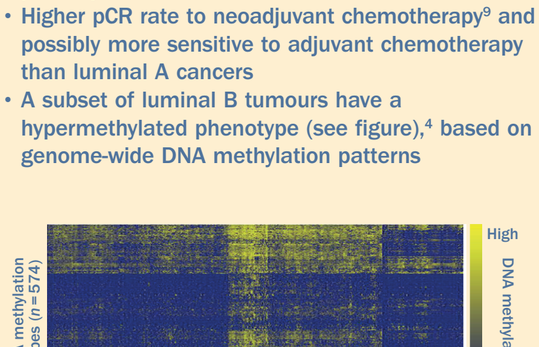
Breast-tumour samples from TCGA ($n=792$) were ordered according to intrinsic subtype and then by correlation to the subtype centroid.[4] Gene-expression data for selected genes are shown. Yellow: higher than median gene expression; black: median; blue: lower than median.

Luminal A

90% ER+, 89% PR+, 14% HER2+

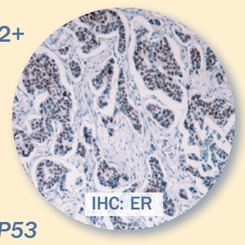


- Mostly diploid; few copy number changes; 1q gain and 16q loss
- Low pathological grade; high morphological differentiation; low proliferation rates
- Recurrently mutated genes (>5%): *PIK3CA*, *CDH1*, *MAP3K1*, *GATA3*, *MAP2K4*, *FOXA1*, *TP53*, *RUNX1*, *CBFB*, *NBL1*, *CTCF*, *NCOR1*, *PTEN*, *CDKN1B*, *AKT1*, *TBX3*, *ARID1A*, and *NF1*
- Typically responsive to endocrine therapy
- Usually less responsive to (neo)adjuvant chemotherapy
- Highest number of recurrently mutated genes, but the lowest total number of mutations and copy number changes, suggesting that these alterations are likely to be driver mutations (see figure, black line indicates a non-silent mutation)



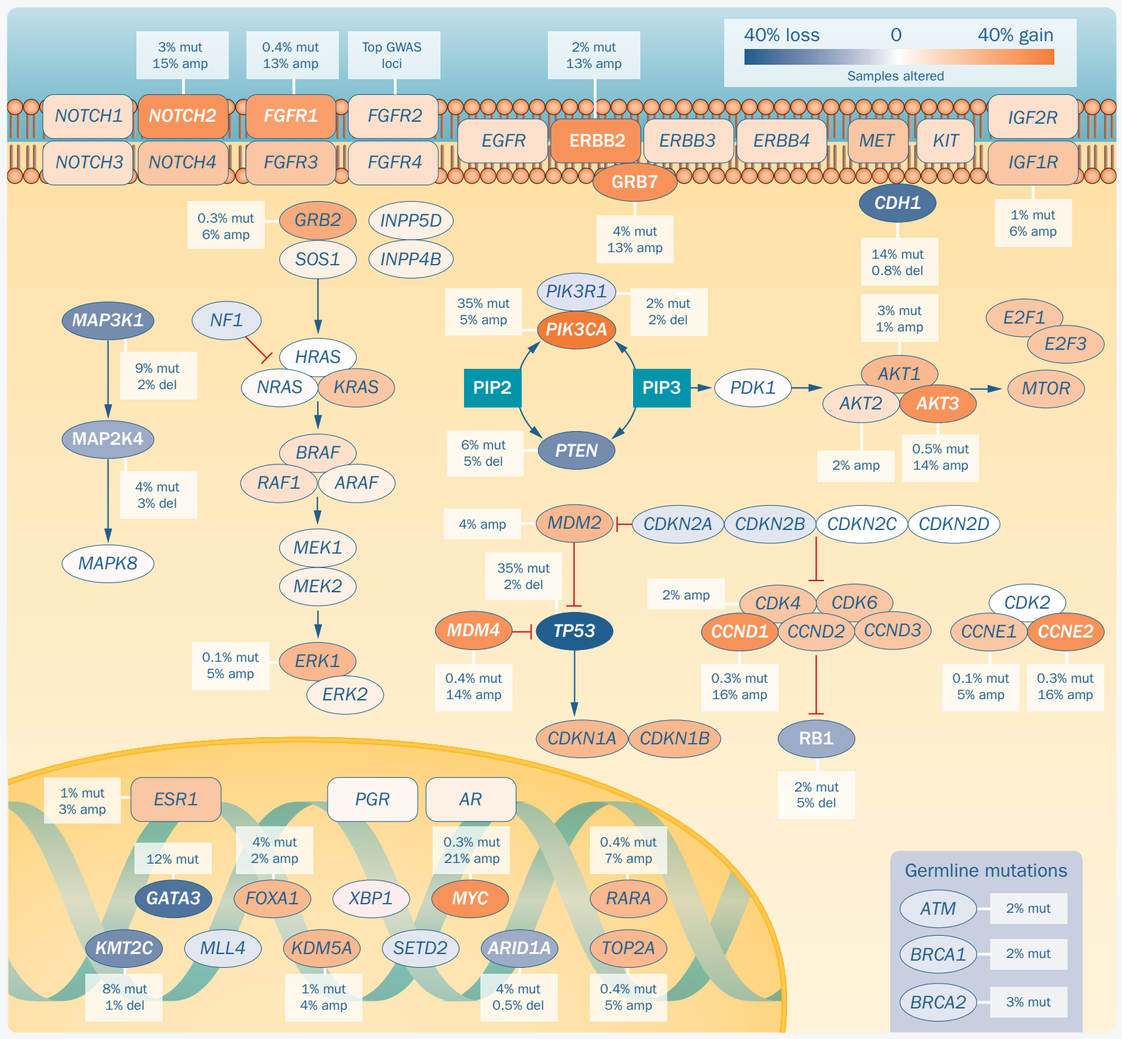
Luminal B

98% ER+, 82% PR+, 24% HER2+



- Mostly aneuploid, with many high-level focal amplifications (11q13 [Cyclin D1, 56%]; 8p11–12 [FGFR1, 23%])
- Recurrently mutated genes: *PIK3CA*, *GATA3*, *PTEN*, and *TP53*
- The quantitative level of PR is lower in luminal B relative to luminal A, while Ki-67 is higher in luminal B relative to luminal A[3]
- Typically responsive to endocrine therapy, possibly less so than luminal A cancers
- Higher pCR rate to neoadjuvant chemotherapy[9] and possibly more sensitive to adjuvant chemotherapy than luminal A cancers
- A subset of luminal B tumours have a hypermethylated phenotype (see figure),[4] based on genome-wide DNA methylation patterns

Hypermethylation phenotype in luminal B samples



Common genetic alterations

TCGA data on breast tumour DNA copy number and somatic mutations were used to identify the frequency of each genetic alteration across 792 patients (all cancer subtypes).[4]

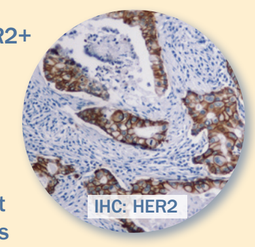
Each gene is shaded according to the overall frequency of alteration. Orange indicates a high level of amplification and/or likely gain-of-function mutations; blue represents homozygous deletions and/or likely loss-of-function mutations.

Three germline mutation rates are shown—taken from a subset of 500 TCGA samples previously published.[4]

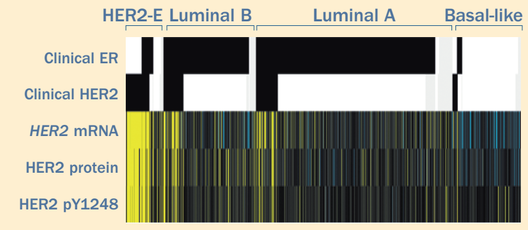
Biomarker	Potential treatment	Evidence
Luminal A and B		
ER+ and/or PR+ by IHC	Endocrine therapy	Meta-analysis
PIK3CA mutation	PI3K inhibitors	Data from phase I and II trials
FGFR1 amplification	FGFR inhibitors	Data from phase I and II trials
Germline *BRCA1/BRCA2* variants	PARP inhibitors	Data from phase I and II trials
GATA3 mutation	Endocrine therapy	Retrospective analysis of trials
MDM2 amplification	MDM2 inhibitors	Preclinical evidence
TP53 mutation	Sensitivity to chemotherapy	Retrospective analysis of trials
HER2 mutation	HER2 inhibitors	Preclinical evidence
CCND1/CDK4/CDK6 amplified	CDK4/6 inhibitors	Preclinical evidence
AKT1 mutation	AKT inhibitors	Preclinical evidence
IGF1R amplification	IGFR inhibitors	Preclinical evidence
HER2-enriched		
HER2 amplification or HER2 IHC+	HER2 inhibitors	Data from phase III trials
HER2 mutation	HER2 inhibitors	Preclinical evidence
PIK3CA mutation	PI3K inhibitors	Data from phase I and II trials
PTEN mutation/loss	PI3K/mTOR inhibitors	Retrospective analysis of trials
PIK3R1 mutation	PI3K inhibitors	Preclinical evidence
FGFR4 amplification	FGFR inhibitors	Preclinical evidence
Basal-like		
Germline *BRCA1/BRCA2* mutation	PARP inhibitors	Data from phase I and II trials
NOTCH1/NOTCH3 amplification/mutation	γ-Secretase inhibitors	Preclinical evidence
AKT3 amplification	AKT inhibitors	Preclinical evidence
EGFR amplification	EGFR inhibitors	Preclinical evidence
NF1 deletion, *KRAS* amplification	MEK inhibitors	Phase I and II trials in other diseases
TP53 mutation	Sensitivity to chemotherapy	Retrospective analysis of trials
PIK3R1/PTEN/INPP4B mutation/loss	PI3K inhibitors	Preclinical evidence
MET amplification/mutation	MET inhibitors	Preclinical evidence

HER2-enriched

38% ER+, 20% PR+, 72% HER2+

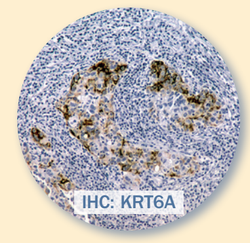


- High levels of *HER2/ERBB2* amplification
- Mostly aneuploid with high chromosomal instability
- Highest single nucleotide mutation rate,[4] but small list of recurrently mutated genes (*TP53* [71%] and *PIK3CA* [35%])
- Linked to APOBEC-mediated mutational profile[5]
- Mostly high pathological grade, typically ER– (62%)
- High rate of brain metastases
- Typically responsive to (neo)adjuvant trastuzumab in combination with chemotherapy[6]
- Sensitive to adjuvant anthracyclines[7] and taxanes[8]
- HER2-enriched tumours that are also clinically HER2+ show high levels of HER2 protein and phosphoprotein suggesting active HER2 signalling (see figure)

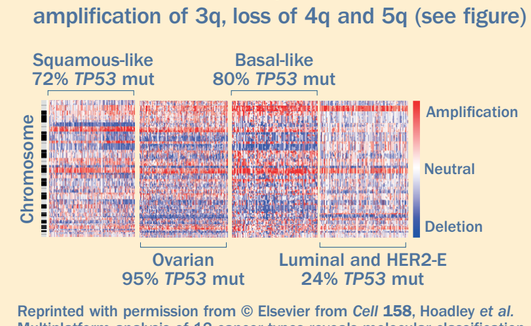


Basal-like

8% ER+, 7% PR+, 7% HER2+



- Includes 70–80% of TNBC[10]
- High metastasis rate[11]
- Associated with younger age; high frequency in those of African descent[12]
- Associated with *BRCA1* germline mutations[2]
- *TP53* is the only recurrently mutated gene (>10%)
- Highest pCR rate to neoadjuvant chemotherapy[9]
- TILs are prognostic within this subtype[13]
- In a 12 tumour-type analysis, the basal-like subtype formed a unique group[14] (distinct from other breast cancers), showing similar characteristics to ovarian cancer, squamous cancers of the lung, head and neck, with frequent *TP53* mutations, amplification of 3q, loss of 4q and 5q (see figure)



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Abbreviations

amp	amplification
APOBEC	apolipoprotein B mRNA editing enzyme
del	deletion
ER	oestrogen receptor
ER+	oestrogen receptor positive
ER–	oestrogen receptor negative
HER2+	HER2 positive
HER2–	HER2 negative
HER2-E	HER2-enriched molecular subtype
IHC	immunohistochemistry
KRT	cytokeratin
mut	mutation
pCR	pathological complete response
PR	progesterone receptor
PR+	progesterone receptor positive
TCGA	The Cancer Genome Atlas
TIL	tumour-infiltrating lymphocyte
TNBC	triple-negative breast cancer

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