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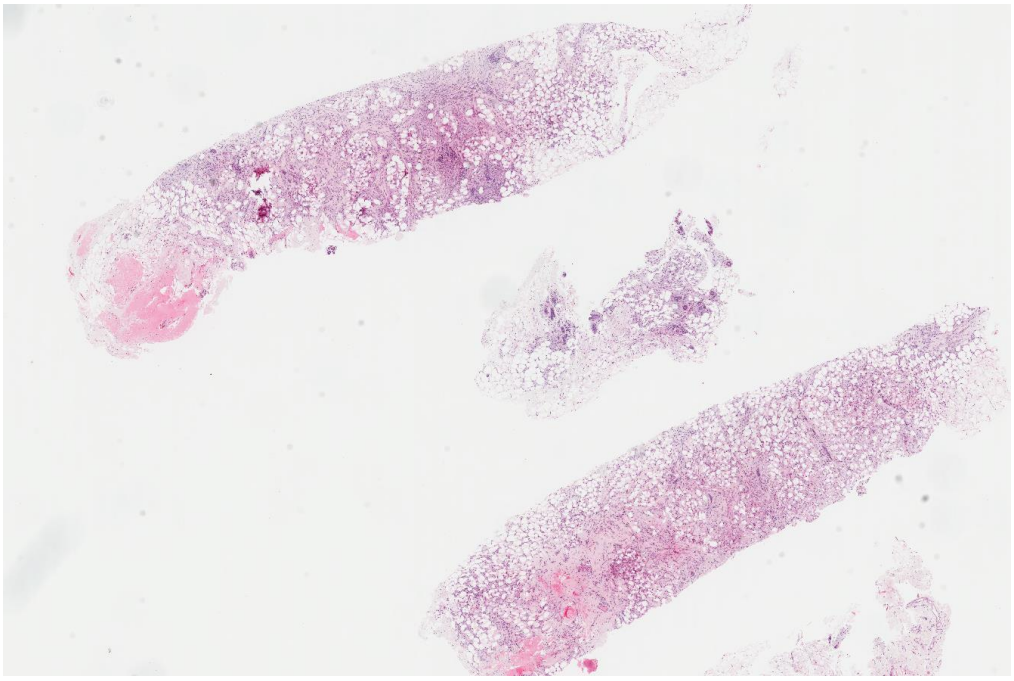
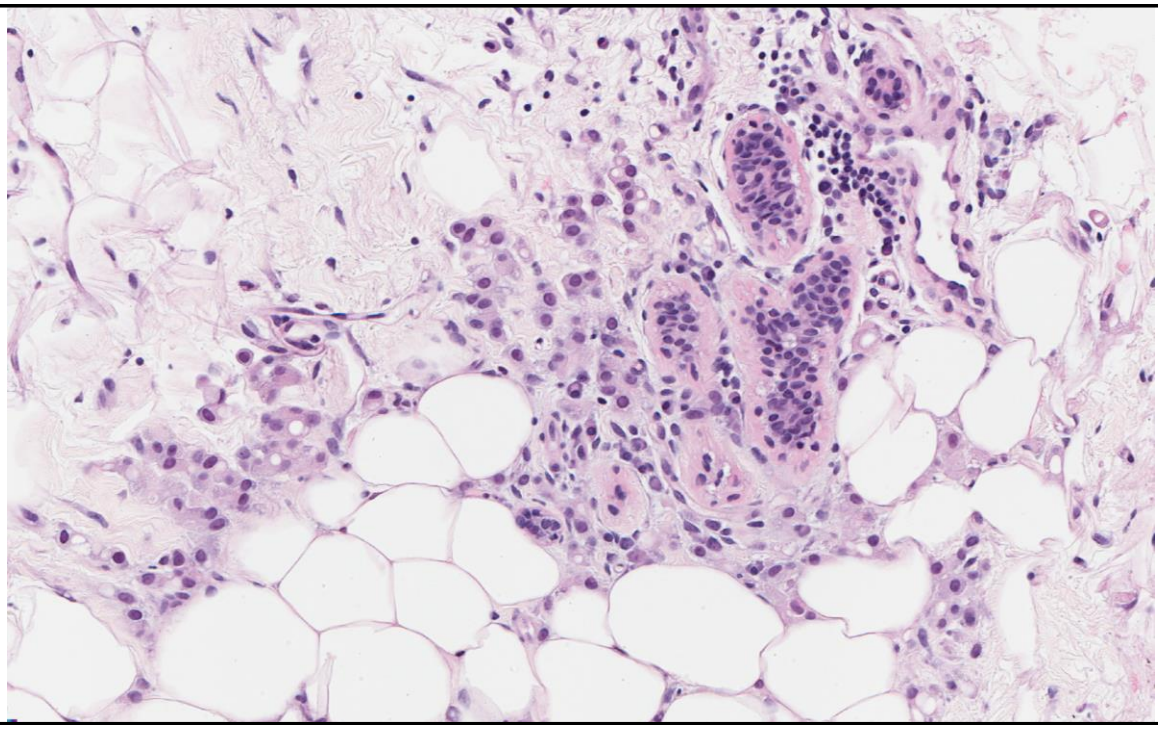
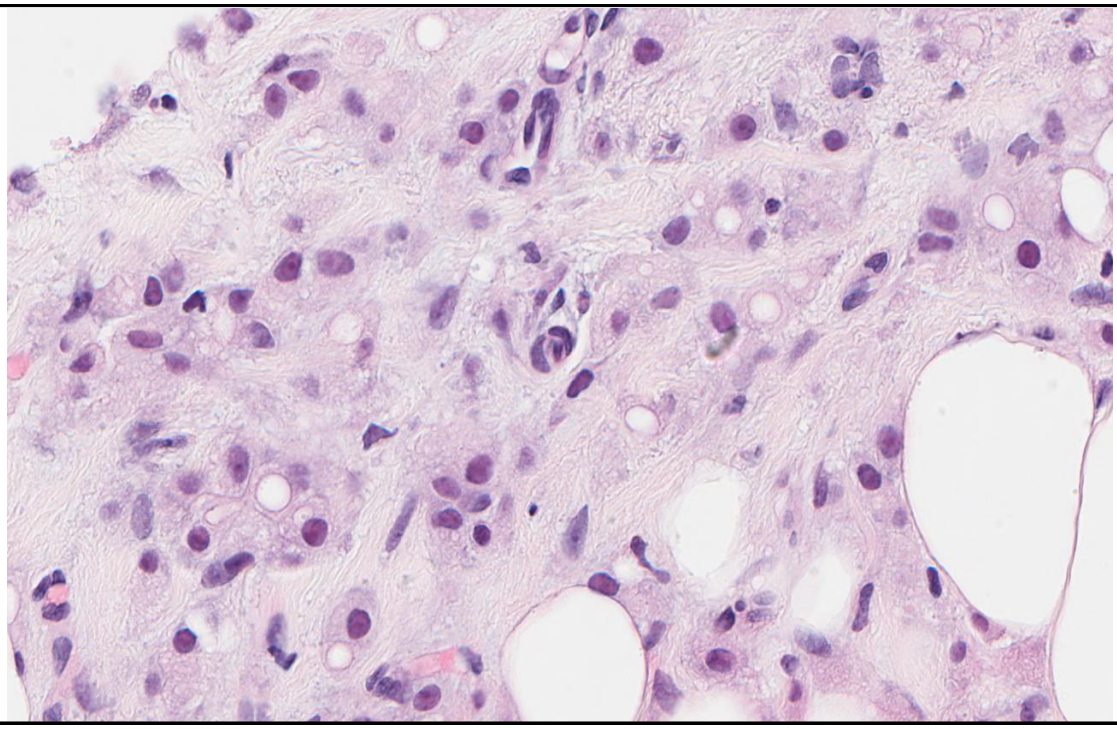
Case A







Differential diagnosis

- Lobular carcinoma
  - ER+
- Carcinoma with Apocrine features
  - ER- negative, often TNBC

Goals of Classification


Diagnostic Classification ☒


Description ☒


Treatment Planning ☑

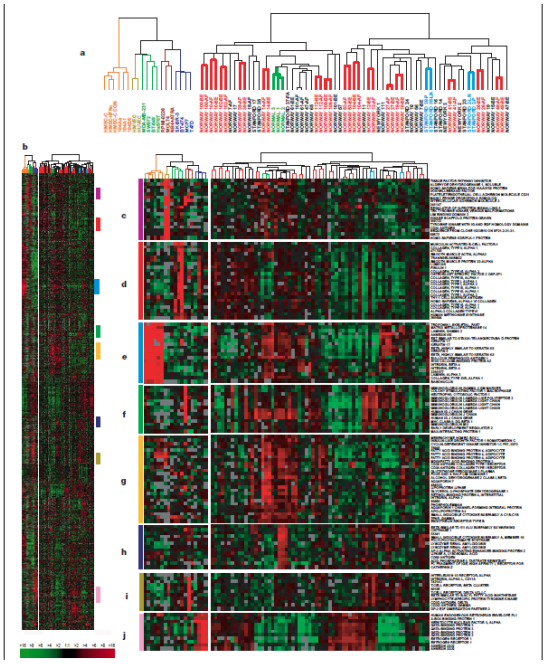

Prediction ☑

Breast Cancer classifications

- All tumors are individuals and have distinct profiles
  - RNA
  - DNA
  - Protein
- Depending on the classification schema
  - Multiple subclasses can identified
- Nothing intrinsic about “intrinsic classification”
  - Classes can change with time and treatment

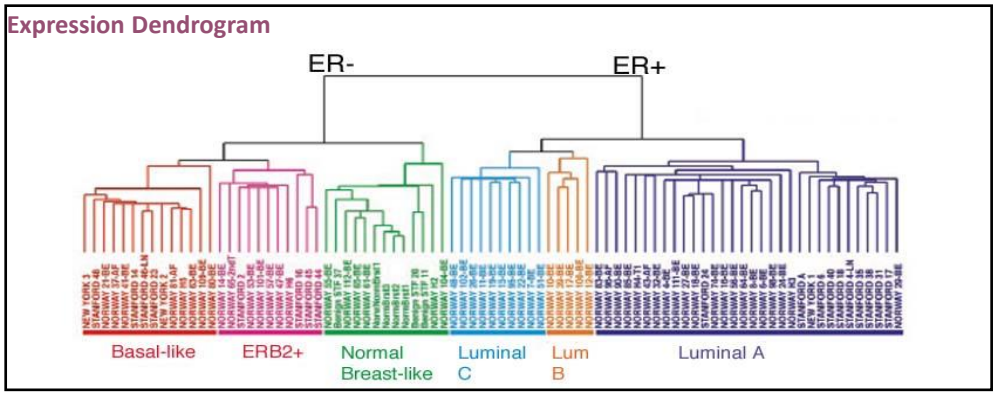
Molecular Portraits

Human breast tumours are diverse in their natural history and in their responsiveness to treatments[1]. Variation in transcriptional programs accounts for much of the biological diversity of human cells and tumours. In each cell, signal transduction and regulatory systems transduce information from the cell's identity to its environmental status, thereby controlling the level of expression of every gene in the genome. Here we have characterized variation in gene expression patterns in a set of 65 surgical specimens of human breast tumours from 42 different individuals, using complementary DNA microarrays representing 8,102 human genes. These patterns provided a distinctive molecular portrait of each tumour. Twenty of the tumours were sampled twice, before and after a 16-week course of doxorubicin chemotherapy, and two tumours were paired with a lymph node metastasis from the same patient. Gene expression patterns in two tumour samples from the same individual were almost always more similar to each other than either was to any other sample. Sets of co-expressed genes were identified for which variation in messenger RNA levels could be related to specific features of physiological variation. The tumours could be classified into subtypes distinguished by pervasive differences in their gene expression patterns.



Sorlie PNAS 2001

Intrinsic classification



Nothing intrinsic about "intrinsic classification"
- Classes can change with time and treatment

Chromosomal aberrations-based classification

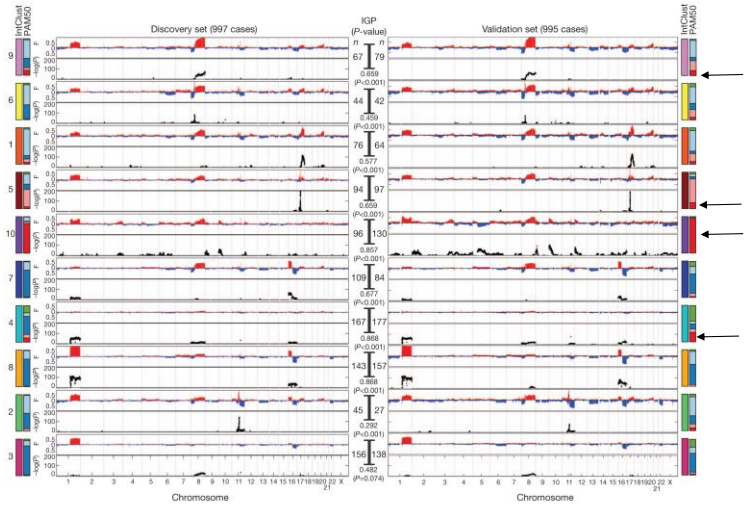
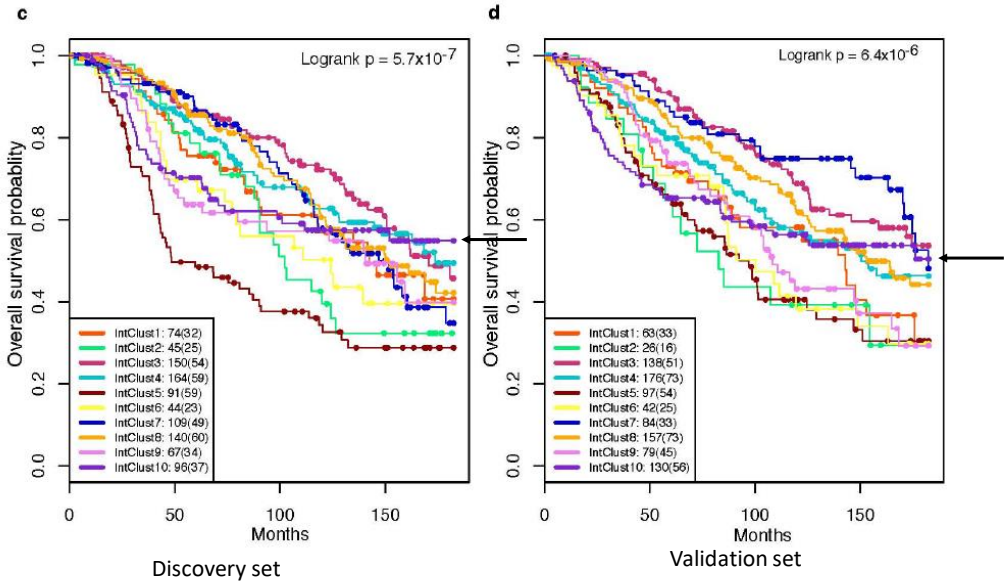


Figure 4 | The integrative subgroups have distinct copy number profiles. Genome-wide frequencies (F, proportion of cases) of somatic CNAs (*y*-axis, upper plot) and the subtype-specific association ($-\log_{10}$ *P*-value) of aberrations (*y*-axis, bottom plot) based on a χ^2 test of independence are shown for each of the 10 integrative clusters. Regions of copy number gain are indicated in red and regions of loss in blue in the frequency plot (upper plot). Subgroups were ordered by hierarchical clustering of their copy number profiles in the discovery cohort ($n = 997$). For the validation cohort ($n = 995$), samples were classified into each of the integrative clusters as described in the text. The number of cases in each subgroup (n) is indicated as is the in-group proportion (IGP) and associated *P*-value, as well as the distribution of PAM50 subtypes within each cluster.

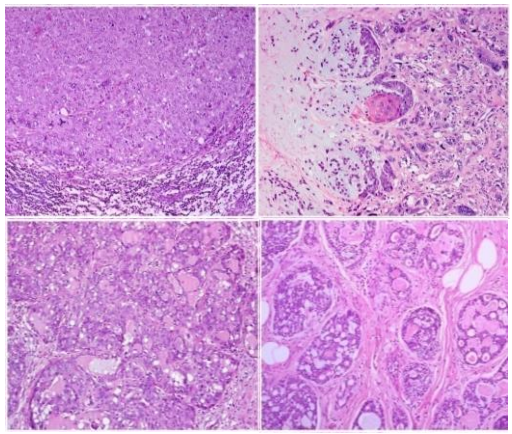
Curtis et al 2012 Nature doi:10:1038/nature10983

Integrated cluster classification



TNBC classifications

- Basal like is not TNBCs
- Histologically heterogeneous
- Marker expression in these cancers is heterogeneous
- Classification schema???



Interrelationship between BLC and TNBC

Previously, the majority (50%–90%) of TNBCs have been classified as basal-like either by IHC or by correlation to the intrinsic molecular breast cancer subtypes (17, 18, 42). A previous TNBC study identified 5 distinct hierarchical clusters in which 91% (88 of 97) of TNBCs identified by IHC correlated to the basal-like subtype (42). However, the study lacked molecular analysis of the tumors and conclusions were limited to clinical outcomes based on pathological markers. The relationship between TNBC and basal-like breast cancer remains controversial (43). The proportion of TNBCs with basal-like GE in our study was 47%, resulting in a higher proportion of TNBCs that correlate with other molecular subtypes: luminal A (17%), normal breast–like (12%), luminal B (6%), HER2 (6%), or unclassified (12%). Our study indicates that TNBC is not limited to tumors with a basal-like phenotype; rather it is a heterogeneous collection of tumors with distinct phenotypes, as evidenced by the diverse GE patterns and varying sensitivity of representative cell lines to the targeted therapies assessed in this study.

Lehmann et al 2011 J Clin Invest

Molecular Subtypes of TNBC

- Six subtypes of TNBCs
- Different molecular pathways
- Different drugs might be effective
  - In vitro
  - In mouse models

Lehmann/ Bauer et al 2011 J Clin Invest

Six subtypes of TNBCs

Basal-like 1
- Cell Cycle
- DNA Replication Reactome
- G_2 Pathway
- RNA Polymerase
- ATR/ BRCA Pathway
- G_1 to S Cell Cycle

Immunomodulatory
- CTLA4 Pathway
- IL12 Pathway
- NK Cell Pathway
- Th1/Th2 Pathway
- IL7 Pathway
- Antigen Processing/ Presentation
- NFKB Pathway
- TNF Pathway
- T Cell Signal Transduction
- DC Pathway
- BCR Signaling Pathway
- NK Cell Mediated Cytotoxicity
- JAK/ STAT Signaling Pathway
- ATR/ BRCA Pathway

Basal-like 2
- EGF Pathway
- NGF Pathway
- MET Pathway
- WNT β-catenin Pathway
- IGF1R Pathway
- Glycolysis/ Gluconeogenesis

Mesenchymal-like
- IGF/ mTOR Pathway
- ECM Pathway
- Regulation of Actin by RHO
- WNT Pathway
- ALK Pathway
- TGFβ Pathway

Mesenchymal Stem-like
- ECM Receptor Interaction
- TCR Pathway
- WNT β-catenin
- Focal Adhesion
- Inositol Phophate Metabolism
- NFKB Pathway
- EGF Pathway
- ALK Pathway
- GH Pathway
- NK Cell Mediated Toxicity
- RAC1 Pathway
- GPCR Pathway
- ERK1/2 Pathway
- Integrin Mediated Adhesion
- ABC Transporters General
- RHO Pathway
- Smooth Muscle Contraction
- Calcium Signaling Pathway
- Adipocytokine Signaling Pathway
- PDGF Pathway
- TGFβ Pathway

Luminal AR
- Pentose/Glucuronate Interconversion
- Glutathione Metabolism
- Tyrosine Metabolism
- Steroid Biosynthesis
- Porphyrin Metabolism
- Androgen and Estrogen Metabolism
- Glycosphingolipid Metabolism
- Flagellar Assembly
- Citrate Cycle TCA
- Phenylalanine Metabolism
- ATP Synthesis
- Starch and Surcrose Metabolism
- Arginine and Proline Metabolism
- Metabolism by Cytochrome P450
- Fructose and Mannose Metabolism
- Fatty Acid Metabolism
- Alanine and Aspartate Metabolism
- Eicosanoid Synthesis
- CHREB Pathway
- Tryptophan Metabolism

Lehmann/ Bauer et al 2011 J Clin Invest

Luminal Androgen receptor

- AR is expressed by a relatively large number of TNBCs
  - In some studies up to 50%
  - Provides a therapeutic target
- Drugs have shown activity and are in multiple trials (single agents or in combinations)
  - Bicalutamide
  - Enzalutamide
  - Abiraterone acetate

Routine practice and Mol. subtypes

- ER positive
  - Lum A: PR+, HER2-; Ki67 (low <20%)
  - Lum B: PR-, HER2+ OR Ki67 (high>20%)
- HER2
  - IHC or FISH
- TNBC
  - Tumor infiltrating lymphocytes
  - Androgen receptor
  - No value of additional markers (as yet!)

Take home messages

- TNBCs/Basal-like CA
  - Group of entities
  - Morphology/molecular characteristics
- Therapy may be subgroup dependent
  - Need additional evidence
- Androgen receptor is a good target